

INVENTORY OF PROJECTS

PROGRESS REPORT: IMPLEMENTATION  
OF A PUBLIC HEALTH ACTION PLAN TO  
COMBAT ANTIMICROBIAL RESISTANCE

PROGRESS THROUGH 2007

## FOCUS AREA I: SURVEILLANCE

ACTION ITEM #1: DETERMINE WHICH ORGANISMS AND SUSCEPTIBILITY TO SPECIFIC ANTIMICROBIAL DRUGS SHOULD BE UNDER SURVEILLANCE AND CREATE A MECHANISM FOR PERIODIC UPDATING OF THIS LIST.

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### PROJECT TITLE: PUBLIC HEALTH SURVEILLANCE

- **Agency:** CDC, USDA, FDA, DoD, VA
- **Description:** Organisms currently under public health surveillance for antimicrobial resistance include: *Campylobacter*, *E. coli* O157:H7, Gram negative and Gram positive organisms causing health care associated infections, group A *Streptococcus*, group B *Streptococcus*, *Haemophilus influenzae*, *Helicobacter pylori*, HIV, Influenza, Malaria, *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, Salmonella, Shigella, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Trichomonas vaginalis*, and Vancomycin Resistant Enterococcus. Organisms are added to this list when resistance emerges as a public health problem, as tools are developed for detecting resistance, and when there is capacity at the appropriate level. On August 30, 2006, FDA cleared a new test for the detection of vancomycin resistant Enterococci (VRE) by detecting vanA and vanB genes using an automated real-time PCR Instrument. It is indicated for use for patients at risk for VRE colonization.
- **Results:** Ongoing. See Executive Summary and Surveillance Data (to be released following public comment period, summer 2007).

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### PROJECT: CDC ANTIMICROBIAL RESISTANCE SURVEILLANCE ACTIVITIES MEETING

- **Agency:** CDC
- **Description:** The CDC Office of Antimicrobial Resistance, in response to the recently held Antimicrobial Resistance Task Force consultants meeting, convened an internal AR surveillance meeting to explore ways for programs to strengthen and enhance their current surveillance efforts. By sharing successes and failures and exploring potential collaborations, we may be able to increase the impact and utility of our overall surveillance programs.
- **Results:** Meeting held May 15, 2008 at CDC. Approximately 100 attended from the agency. System/activity overviews presented included: GISP, GASP Collaborations, ABCs, NARMS, NHSN, Fungal Surveillance, AIDS, HIV/AIDS, Hepatitis, Malaria, and Neglected Tropical diseases and International Emerging Infectious Diseases.

**\*\*TOP PRIORITY\*\***

ACTION ITEM #2: WITH PARTNERS, DESIGN AND IMPLEMENT A NATIONAL AR SURVEILLANCE PLAN.

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PROJECT TITLE: EXPANSION AND ENHANCEMENT OF THE NATIONAL ANTIMICROBIAL RESISTANCE MONITORING SYSTEM (NARMS) FOR ENTERIC BACTERIA

- **Agency:** CDC, FDA, USDA
- **Description:** NARMS is a collaboration among FDA (Center for Veterinary Medicine), CDC and U.S. Department of Agriculture. The NARMS program has three components or “arms” (human, retail, and animal) from which select foodborne bacteria are characterized from human clinical cases, retail meats, and food animals at federally inspected slaughter and processing plants. . Additionally, ten state laboratories, who also participate in FoodNet, submit a proportion of *Campylobacter* isolates to the CDC NARMS laboratory. Currently, nine participating FoodNet states plus Pennsylvania test grocery store meat products for the presence of select enteric bacteria and corresponding antimicrobial susceptibility profiles. *Salmonella* slaughter isolates recovered from chickens, turkeys, cattle, and swine were submitted to the NARMS animal program through the USDA Food Safety and Inspection Service (FSIS) *Salmonella* HACCP Verification Testing Program.
- **Results:** NARMS now includes all 50 states, providing national surveillance for antimicrobial resistance among select foodborne pathogens. *Campylobacter* sampling in the nine FoodNet states has been changed to allow for burden estimates and a plan for further expanding to more sites is underway. Five additional sites send enterococci and *E. coli* isolated from outpatient stools to CDC NARMS for antimicrobial susceptibility testing. FDA, CDC, & USDA NARMS staff also met in Atlanta September 17-18, 2007 for a strategic planning conference to discuss how to implement the recommendations put forward in the FDA Science Board summary report.

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PROJECT TITLE: COORDINATION OF SURVEILLANCE EFFORTS

- **Agency:** CDC, FDA
- **Description:** Coordinate surveillance activities.
- **Results:** The NARMS program just completed in 2007 an extensive review by the FDA Science Board, focusing on 4 major areas: sampling strategies, data reporting and harmonization, coordinated research, and international surveillance activities. FDA responded to the Board’s recommendations, and is prioritizing recommendations for improving the program. A strategic planning meeting was held at CDC, September 17-18, 2007 focusing on how best to implement the Science Board recommendations where appropriate. NARMS scientists are also currently partnering with scientists at the University of Maryland to investigate the presence of MRSA in retail meats in the greater Washington DC area. Findings of this MRSA retail meat study may direct a larger study with the FoodNet program looking at a larger sample size obtained from the National Antimicrobial Resistance Monitoring System.

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PROJECT TITLE: ENHANCED SURVEILLANCE FOR MULTIDRUG-RESISTANT (MDR TB) AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR TB) IN THE UNITED STATES. SUPPLEMENTAL FUNDED PROJECT FOR 4 TB PROGRAMS.

- **Agency:** CDC
- **Description:** The purpose of this pilot exercise is to provide additional surveillance data for TB cases reported as MDR or XDR. Data not currently collected on the Report of a Verified Case of TB (RVCT), such as additional drug susceptibility test results, culture results, treatment and outcome data and information about hospitalization, are requested from 4 TB programs (CA, NYC, FL, TX), which provide about 55% of the reported MDR TB cases in the U.S. The results of this pilot will provide important additional clinical and diagnostic information on MDR TB. It will also inform CDC on how a nationwide supplemental registry for MDR/XDR TB would work, what information we can expect to collect, and the usefulness and reliability of that information.
- **Results:** Data collection is ongoing and should be completed by May 2008. Analysis and reporting will occur in Summer 2008.

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PROJECT TITLE: TREATMENT PRACTICES, OUTCOMES AND COST OF MULTIDRUG-RESISTANT (MDR TB) AND EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR TB) IN THE UNITED STATES.

- **Agency:** CDC
- **Description:** The purpose of this proposed project is to provide detailed observational data on the current treatment characteristics, outcomes and costs of multidrug resistant (MDR) and extensively drug resistant XDR TB cases in the United States. The study collects treatment, outcome, and cost data which are generalizable to the U.S. population of MDR and XDR TB cases. The objectives of the project are to describe the clinical and case management practices currently employed to manage MDR TB and XDR TB cases, determine the frequency and contributing factors of further acquired drug resistance during treatment among MDR TB cases, describe factors associated with favorable MDR/XDR TB patient outcomes, and determine costs and payer sources for treatment and case management of MDR and XDR TB for a population representative of the US MDR TB case population.
- **Results:** Project is being announced by CDC for extramural funding in Spring 2008. Selection process for awards will begin June, 2008.

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PROJECT TITLE: FEDERAL TB TASK FORCE RESPONSE TO EXTENSIVELY DRUG-RESISTANT (XDR) TB

- **Agency:** CDC
- **Description:** In November of 2006, the Federal TB TF convened to discuss the possible U.S. government response to the global threat of XDR TB. It was decided that the TB TF would draft an action plan describing the potential U.S. government (USG) response to XDR domestically and internationally. The TB TF divided into 8 workgroups to draft each section (Surveillance, epidemiology and outbreak investigation; laboratory; infection control; clinical and programmatic; research; communications and education; partnerships; and cost

analysis). The 1992 National Action Plan to Combat MDR TB was used as a model. In April 2007, an initial draft was completed and is undergoing review.

- **Results:** A draft of the plan has been entered into multiple agency USG clearance.

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PROJECT TITLE: AN ANALYSIS OF MOLECULAR EPIDEMIOLOGY OF MULTI-DRUG RESISTANT *M. TUBERCULOSIS* IN THE UNITED STATES

- **Agency:** CDC
- **Description:** The purpose of this research project is to develop a comprehensive national tuberculosis (TB) genotyping registry for TB case-patients with multidrug-resistant *M. tuberculosis* (MDR-TB) and to assess the molecular epidemiology of MDR-TB in the United States (U.S.). Through this investigation, the Division of TB Elimination (DTBE) at the Centers for Disease Control and Prevention (CDC) will work with 14 selected U.S. TB Epidemiologic Studies Consortium (TBESC) sites to collect epidemiologic and genotyping data from all MDR-TB case-patients in the U.S. This will be a five-year cross-sectional population based study design where recruitment and data collection are handled prospectively starting on October 1, 2005 through 2010.
- **Results:** Project is currently enrolling patients at all 14 sites.

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PROJECT TITLE: NATIONAL TUBERCULOSIS SURVEILLANCE SYSTEM (NTSS)

- **Agency:** CDC
- **Description:** Ongoing collection, analysis, and communication of national tuberculosis surveillance information; expanded in 1993 to include the frequency and type of antimicrobial resistance, enabling strategically focused tuberculosis control and elimination efforts. The expanded national TB surveillance system has proven its usefulness in assisting in the evaluation of the success of TB control efforts and monitoring the status of the epidemic, particularly through the collection of data on initial drug susceptibility. Information on the use of initial regimens of four first-line drugs, directly observed therapy, and completion of therapy in one year or less have been used as measures to evaluate program success. As future efforts towards TB elimination increase, both existing and new surveillance systems at the national, state, and local levels will become even more critical to monitor the burden and impact of TB, evaluate the success of control and prevention efforts, and direct planning and policy development.
- **Results:** Data collection and analysis are gathered on a continuous basis. The proportion of patients with primary MDR TB decreased from 2.4% to 1.0% in 2001. After an increase to 1.2% in 2002, the proportion has decreased to 0.9% in 2006. In 2006, the percentage of U.S.-born persons with MDR was 0.4 %. The percentage of foreign-born persons with MDR was much greater, at 1.3%. Of the total number of reported MDR TB cases, the proportion occurring in foreign-born persons increased from 25% in 1993 to 80% in 2006. The CDC annual TB surveillance report, Reported Tuberculosis in the United States, 2006, provides detailed summaries of anti-TB drug resistance from the national surveillance data. This report and other publications and recommendations based on these data are available on the internet. <http://www.cdc.gov/tb/surv/surv2006/default.htm>

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PROJECT TITLE: GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP)

- **Agency:** CDC, DoD
- **Description:** Sentinel surveillance system for monitoring antimicrobial resistance of *Neisseria gonorrhoeae* in the US, established in 1986. Male urethral gonococcal isolates are submitted for susceptibility testing together with clinical and demographic patient data each month from STD clinics in 25-30 cities in the US. GISP data has demonstrated the ongoing and increasing spread of fluoroquinolone-resistance *N. gonorrhoeae* and the emergence of *N. gonorrhoeae* with decreased susceptibility to azithromycin in the U.S. Currently, there is only one class of antibiotics that is recommended and available for treatment of all gonococcal infections in the US; and with the continued decrease in the capacity for local/state public health laboratories to maintain culture capacity and to perform local antimicrobial susceptibility testing, GISP data have become even more important.
- **Results:** GISP data are published in an annual report and periodically in the MMWR and other peer-reviewed journals. GISP annual reports from 1998-2005, as well as important reference and link resources can be found at <http://www.cdc.gov/std/gisp>. GISP data were used to update and revise the 2007 CDC's Sexually Transmitted Diseases Treatment Guidelines (*Update to CDC's STD Treatment Guidelines, 2006: Fluoroquinolones NO Longer Recommended for Treatment of Gonococcal Infections*. MMWR, April 13, 2007, 54 (14).) Location-specific (city, state, region) alerts and guidelines are regularly updated on the CDC's GISP website.

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PROJECT TITLE: AZITHROMYCIN RESISTANCE IN SYPHILIS IN THE UNITED STATES

- **Agency:** CDC
- **Description:** This sentinel surveillance project for monitoring azithromycin-resistant syphilis in the United States was initiated in early 2008. Residual clinical specimens from genital ulcers and other moist lesions from men and women, along with demographic data, are submitted to CDC from STD clinic sites in 11 cities. Specimens are tested by PCR for *Treponema pallidum*. When positive, the DNA is screened for mutations in 23S RNA associated with resistance to azithromycin. The objectives are to monitor and track the epidemiology of azithromycin-resistant syphilis for each participating geographic locale.
- **Results:** Specimen and data submission is underway.

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PROJECT TITLE: SURVEILLANCE FOR HIV DRUG RESISTANCE

- **Agency:** CDC
- **Description:** CDC maintains a national surveillance system that provides data for national, state, and local public health HIV prevention program planning and evaluation. The variant, atypical, and resistant HIV surveillance (VARHS) system is an extension of CDC's HIV/AIDS reporting system in select surveillance areas. It uses remnant HIV diagnostic sera or plasma to amplify and sequence relevant genes of the HIV pol region and collects electronic amino acid sequence data from private laboratories performing genotyping to evaluate HIV-1 drug resistance and HIV-1 subtypes and associated factors among persons newly diagnosed and

reported with HIV. Data will be useful for future evaluations of trends associated with the transmission of HIV drug resistant mutations and subtype distribution. Ongoing data collection and analyses through routine surveillance also will inform HIV prevention and treatment program planning and vaccine development efforts and alert to the spread or clustering of atypical strains.

- **Results:** National surveillance for HIV drug resistance is ongoing. Currently (2008), eleven (11) surveillance areas participate.

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PROJECT TITLE: SURVEILLANCE FOR EMERGING ANTIMICROBIAL RESISTANCE  
CONNECTED TO HEALTHCARE (SEARCH)

- **Agency:** CDC
- **Description:** The SEARCH program started as a network of voluntary participants (i.e., hospitals, private industries, professional organizations, and state health departments) to enhance detection and reporting of vancomycin-resistant *Staphylococcus aureus* (VRSAs). All U.S. healthcare organizations and practitioners are encouraged to report such isolates to CDC through SEARCH and, after notifying their state health department, to send the isolates to CDC for confirmatory testing.
- **Results:** As of April 2008, CDC has confirmed ten VRSA's in the U.S.

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PROJECT TITLE: ENHANCED COLLECTION AND ELECTRONIC TRANSFER OF DATA ON  
ANTIMICROBIAL USE AND RESISTANCE (AUR)

- **Agency:** CDC
- **Description:** A cooperative study of enhanced collection, compilation, and transmission of data on antimicrobial use and resistance from automated laboratory instrumentation systems in healthcare settings to CDC and other public health systems using architecture fully compatible with the Public Health Information Network (PHIN). This will create a database that will facilitate benchmarking and performance feedback to promote local AR improvement efforts; development of regional, state, and national data about patterns of use and resistance; and evaluation of prevention programs.
- **Results:** During 2007, microbiology, pharmacy and admission/discharge/transfer (ADT) data in the electronic HL7 Version 3 message format were received from 5 pilot healthcare facilities. The validation of these data in the medications-associated module of the National Healthcare Safety Network continue. In December 2007, collaboration with the National Center for Public Health Informatics (NCPHI) BioSense Project was undertaken to leverage their infrastructure to expand to additional pilot healthcare facilities using a more widely accepted message format called HL7 V2.5.

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PROJECT TITLE: SURVEILLANCE FOR INVASIVE METHICILLIN-RESISTANT  
*STAPHYLOCOCCUS AUREUS* THROUGH THE ACTIVE BACTERIAL CORE SURVEILLANCE  
(ABCS), EMERGING INFECTIONS PROGRAM

- **Agency:** CDC
- **Description:** ABCs, part of CDC's Emerging Infections Program, conducts ongoing, active, population-based surveillance for invasive pathogens, including MRSA, in selected areas of the United States. Population-based surveillance occurs at 9 ABCs sites (California, Colorado, Georgia, Maryland, Minnesota, New York, Oregon and Tennessee) for both community-associated and healthcare-associated invasive MRSA disease. Data collected are used to determine incidence rates for invasive MRSA disease, detect at-risk populations, and explore strain characteristics through collection of MRSA isolates.
- **Results:** In 2008, two surveillance sites expanded. Maryland now includes the Baltimore metro area and Minnesota includes 2 counties for a total population under surveillance of approximately 18 million persons. All cases of invasive MRSA reported during 2005 and 2006 were analyzed, population based incidence rates were calculated and annual summaries were completed (<http://www.cdc.gov/ncidod/dbmd/abc/survreports.htm>). A preliminary analysis of trends in invasive disease between 2005 and 2006 were performed.

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PROJECT TITLE: SURVEILLANCE OF MULTI-DRUG RESISTANT INFECTIONS THROUGH NATIONAL HEALTHCARE SAFETY NETWORK (NHSN)

- **Agency:** CDC
- **Description:** Surveillance of healthcare associated infections and their antimicrobial resistance patterns.
- **Results:** The first NHSN Antimicrobial Resistance Report has been submitted to peer review for publication. Analysis of trends includes incidence of MRSA central line bloodstream infection. Development and implementation of a new module to monitor multi-drug resistant pathogens is scheduled to be launched in July 2008.

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PROJECT TITLE: ASSESSING PREVENTION MEASURES FOR ANTIMICROBIAL RESISTANT INVASIVE PNEUMOCOCCAL DISEASE

- **Agency:** CDC
- **Description:** *Streptococcus pneumoniae* is a common cause of pneumonia, meningitis, and otitis media in the U.S. Incidence of drug-resistant *S. pneumoniae* increased steadily during the 1990s but then decreased after the introduction of pneumococcal conjugate vaccine (PCV7) in 2000. CDC's Active Bacterial Core surveillance (ABCs) has followed trends in invasive pneumococcal disease (IPD) to evaluate the impact of PCV7 introduction. This project has five goals: 1. Assess and improve use of pneumococcal conjugate vaccines; 2. Evaluate trends in outpatient antibiotic use for drugs likely to select for DRSP; 3. Monitor trends in DRSP using conventional and molecular means to inform the development of new pneumococcal vaccines and monitor effect of prevention measures; 4. Develop PCR-based approaches for detecting antibiotic resistant pneumococci; 5. Provide ABCs data to partners developing or evaluating prevention measures.
- **Results:** Held monthly conference calls with ACIP Pneumococcal Working Group to identify key areas of existing pneumococcal vaccine recommendations in need of updating; 2.



Analyzed IMS data on antibiotic use to characterize geographic differences in antibiotic use and the relationship between use and resistance (compiled from ABCs data); 3. Characterized over 500 serotype 19A strains and determined that this serotype, the one serotype with the greatest increase in IPD incidence, is becoming much more genetically diverse and antibiotic resistant; 4. Partnered with colleagues in the UK and around the U.S. (e.g., Cleveland, Boston) to describe molecular mechanisms of antibiotic resistance; 5. Provided ABCs data to multiple external partners, including colleagues from Emory and Harvard Universities, GlaxoSmithKline, the Swedish Institute of Health Economics, and the Clinical and Laboratory Standards Institute.

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PROJECT TITLE: NATIONAL MOLECULAR SURVEILLANCE OF ANTIBIOTIC-RESISTANT  
*STREPTOCOCCUS PNEUMONIAE*

- **Agency:** CDC
- **Description:** The Respiratory Diseases Branch (RDB) and our collaborators at the Emory Rollins School of Public Health will establish a national laboratory for the molecular surveillance of invasive *Streptococcus pneumoniae* (*Spn*). We will provide front-line information concerning established and newly emerging antibiotic resistance mechanisms, clonal types, and serotypes of ABCs *Spn* isolates. We will monitor effects of currently used vaccines and antibiotics on the emergence and distribution of antibiotic-resistant strains.
- **Results:** Since introduction of the 7 valent conjugate vaccine (PCV7), serotype 19A has become the predominant invasive serotype and the primary source of antibiotic resistance; multilocus sequence typing (MLST) indicates that this is due to the emergence of new resistant strains. We have characterized at the molecular level the first example recorded in nature of a serotype switch event (resulting in 19A serotype) with concurrent conversion to penicillin-nonsusceptibility due to a single genetic event. We have also noted increases in antibiotic-nonsusceptible strains of other serotypes not targeted by PCV7 and are completing MLST analysis of these isolates. An increase in beta-lactam resistance has been documented over the past 2 years and this is probably due to the increase in penicillin nonsusceptibility among serotype 19A.

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PROJECT TITLE: NATIONAL SURVEILLANCE FOR THE IMPACT OF PNEUMOCOCCAL  
CONJUGATE VACCINE USE AND APPROPRIATE ANTIBIOTIC USE CAMPAIGNS ON  
DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

- **Agency:** CDC
- **Description:** CDC's Active Bacterial Core surveillance (ABCs) is a high-quality, active, population-based system operating in 10 states with a population of over 20 million persons under surveillance. ABCs has tracked drug-resistant *S. pneumoniae* since 1995, collecting approximately 3000 invasive disease strains yearly for susceptibility testing and serotyping. Data analyses by serotype can evaluate the ongoing impact of conjugate vaccine use on resistance; by linking to data on antibiotic use inferences can also be made about a possible impact of appropriate use measures. ABCs is CDC's main system for tracking drug-resistant pneumococcus and the impact of interventions.

- **Results:** In 2006, approximately 3000 cases of invasive disease were identified through ABCs and serotyping and susceptibility testing of isolates is nearing completion.

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PROJECT TITLE: ANTIMICROBIAL RESISTANT NEONATAL SEPSIS IN THE ERA OF PROPHYLAXIS FOR GBS INFECTION

- **Agency:** CDC
- **Description:** Increased use of antibiotic prophylaxis during labor and delivery to prevent perinatal group B streptococcal (GBS) disease has decreased the rate of early-onset GBS infections by 81%, but a potentially alarming increase has been detected in ampicillin resistance among selected other neonatal pathogens, especially in the low birth weight or preterm newborn. Because higher mortality is associated with ampicillin resistant gram negative infections, preliminary data on these was investigated. CDC's Emerging Infections Program network, through ABCs, provides an opportunity to monitor longer term, wider-spread trends in sepsis in the first week of life and correlate ampicillin-resistant *E. coli* infections with maternal receipt of intrapartum antibiotics. Enhancement of the neonatal sepsis surveillance activities in four EIPs address the impact of recent recommendations for use of vancomycin for penicillin allergy among women who carry group B streptococcus resistant to clindamycin.
- **Results:** ABCs surveillance since 1998 shows that *E. coli* is the number 2 pathogen causing invasive neonatal sepsis, after group B streptococcus. In 2006, our most recent year of analyzed surveillance, some surveillance areas have a higher incidence of *E. coli* sepsis than GBS sepsis. This is due to declines in GBS sepsis. *E. coli* sepsis incidence appears stable with a trend towards an increased incidence among preterm incidence. In 2005 and 2006 46% of *E. coli* isolates identified by ABCs had documented ampicillin resistance. Analysis found that exposure to at least four hours of intrapartum antibiotic prophylaxis was protective among term infants. Among preterm infants, exposure to intrapartum antibiotics was not associated with *E. coli* sepsis and for ampicillin-resistance *E. coli* sepsis. Preterm delivery was the strongest single risk factor for *E. coli* sepsis and for ampicillin-resistance *E. coli* sepsis, with an adjusted population attributable risk of 59%. To date in ABCs neonatal sepsis surveillance only 1 case infant had a sterile site MRSA isolate identified.

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PROJECT TITLE: CHARACTERIZATION OF MUTATIONS IN GROUPS A AND B STREPTOCOCCI CAUSING DECREASED SUSCEPTIBILITY TO PENICILLIN.

- **Agency:** CDC
- **Description:** Our primary objective is to screen invasive GAS and GBS isolates collected by the Active Bacterial Core surveillance (ABCs), a multistate population-based surveillance system, for susceptibility to beta-lactam agents and to characterize isolates that express unusually high MICs. These organisms could be accumulating combinations of mutations required for full resistance to penicillin. In *S. pneumoniae*, changes within 3 key penicillin binding protein (PBP) genes, *pbp1a*, *pbp2x*, and *pbp2b* lead to resistance to beta-lactam agents. Our immediate objective is to examine key PBP gene sequences from 41 national surveillance isolates (40 GBS, 1 GAS) identified so far with elevated

MICs to identify the molecular genetic basis of these phenotypes. All isolates will be tested for potential beta- lactamase activity.

- **Results:** Three different penicillin binding protein (PBP) gene mutants in invasive GBS isolates are putatively responsible for the elevated MICs to beta lactam antibiotics. Wild type MICs were restored after PBP gene replacement with the wild type allele. Identical results were obtained through introducing the wild type PBP gene allele into this mutant on a multicopy plasmid.

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PROJECT TITLE: SURVEILLANCE AND DETECTION OF ANTIMICROBIAL RESISTANT INVASIVE FUNGAL INFECTIONS AMONG STEM CELL AND LUNG TRANSPLANT RECIPIENTS

- **Agency:** CDC
- **Description:** Goals of this project are to detect and monitor trends in emerging antimicrobial resistance among invasive fungal infections, and develop a collection of such strains for applied research by CDC and other researchers. There are currently six transplant centers involved in a sentinel network collecting surveillance data and fungal isolates, related to invasive fungal infections among persons who have received stem cell or lung transplants. This population is at highest risk for anti-fungal resistant *Candida* spp. and mold infections. There is no current system to track emerging anti-fungal resistance among fungal infections nationally.
- **Results:** University of Pittsburgh, Washington University, Cleveland Clinic, University of Alabama, University of Michigan, and the University of Pennsylvania are currently contributing to surveillance. Patient enrollment into the cohort began in April 2006. Patients are being followed for 18 months. A total of 437 patients have been enrolled to date. There have been a total of 23 invasive fungal infections, susceptibility analysis is ongoing.

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PROJECT TITLE: MRSA DISEASE IN ALASKA

- **Agency:** CDC
- **Description:** Laboratory surveillance was established to collect isolates from the first 5 MRSA infections each month in two sites: rural southwest where MRSA comprises 85% of all *S. aureus* infections and at the Alaska Native Medical Center in- and outpatient services, where 50% of *S. aureus* infections are due to MRSA.
- **Results:** Isolates of MRSA from southwest Alaska are predominantly ST1 or USA400. This differs from the predominant strain in the rest of the US which is ST8 or USA300. Typing of surveillance strains from urban Anchorage is pending.

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PROJECT TITLE: ALASKA SENTINEL SURVEILLANCE FOR ANTIMICROBIAL RESISTANCE IN *HELICOBACTER PYLORI* ISOLATES FROM ALASKA NATIVES

- **Agency:** CDC

- **Description:** The Alaska *H. pylori* surveillance is a sentinel lab-based system that serves hospitals located in five regions of Alaska. Gastric biopsies are obtained from patients undergoing routine diagnostic esophagogastroduodenoscopy (EGD), and sent to the CDC Arctic Investigations Program (AIP) laboratory for *H. pylori* culture and antimicrobial susceptibility testing. Among Alaska Natives, 80% of adults have *H. pylori* infection and gastric cancer mortality are 2-4 times higher than the general US population.
- **Results:** *Ongoing specimen collection and analysis.* Most recent summary publication "Alaska sentinel surveillance for antimicrobial resistance in Helicobacter pylori isolates from Alaska native persons, 1999-2003." *Helicobacter* 2006; 11: 581-88. Metronidazole resistance was found in 44% of persons, clarithromycin resistance in 31%, and amoxicillin resistance in 2% persons. The proportion of resistant isolates has been stable over this time period. In 2006, we added levofloxacin susceptibility testing and found 10% of isolates resistant, with resistance associated with prior fluoroquinolone use. Ref: *Clin Infect Dis.* 2007 Jan 15;44(2):e5-8. Epub 2006 Dec 7.

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PROJECT TITLE: ENHANCED SURVEILLANCE OF INFLUENZA VIRUSES FOR RESISTANCE TO LICENSED DRUGS AND DEVELOPMENT OF TESTS FOR RAPID DETECTION OF DRUG-RESISTANT STRAINS WITH PANDEMIC POTENTIAL

- **Agency:** CDC
- **Description:** Improved molecular tests for rapid diagnosis of mutants resistant to both the old and new drugs are needed for pandemic preparedness as well as for interpandemic control of influenza. This project studies avian influenza viruses of different subtypes, which will improve pandemic preparedness. In addition, it will evaluate existing biochemical tests and develop new molecular techniques for detecting influenza A and B mutants resistant to neuraminidase inhibitors (NIs), which will improve surveillance for drug-resistant variants among human influenza viruses.
- **Results:** In 2006, surveillance data for resistance to licensed drugs (M2 blockers: amantadine and rimantadine) in human isolates from the US and other countries was reviewed. In the US the percentage of influenza A(H3N2) viruses resistant to amantadine/rimantadine was much higher (14%) than in previous years. Continued analysis of different subtypes of influenza virus isolates resistant to amantadine/rimantadine did not reveal their antigenic difference from viruses sensitive to the drugs.

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PROJECT TITLE: DEVELOPMENT OF A DOD AR SURVEILLANCE PLAN CONSISTENT WITH THE NATIONAL AR SURVEILLANCE PLAN

- **Agency:** DoD
- **Description:** Establish an overarching framework for facilitating the implementation, operation, and evaluation of activities in AR surveillance within DoD.
- **Results:** In February 2007 DoD & CDC sponsored a US Medicine Institute for Health Studies (USMI) roundtable meeting entitled, "Addressing Antimicrobial Resistance"; an

executive summary, transcript and speaker presentations are available on the USMI website at <http://www.usminstitute.org/index.html> (from the home page, click on the tab "Roundtable" and scroll down to this date). New ways to capture microbiological (including resistance) clinical lab data from military treatment facilities' electronic medical records, standardization of Acinetobacter PFGE techniques with improved specimen sharing among certain medical centers, and a significant research effort by DoD and NIAID focusing on infections (e.g., wounds, burns, etc) with multidrug resistant organisms at collaborating medical centers are areas of progress in 2007.

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PROJECT TITLE: DOD ANTIMICROBIAL RESISTANCE SURVEILLANCE NETWORK

- **Agency:** DoD
- **Description:** Under a Cooperative Research and Development Agreement (CRADA) with private industry, developing a DoD-wide AR surveillance network for identifying AR occurrences and trends within the military population. The cornerstones of this mechanism are: 1) the provision of daily, independent quality-assurance review and feedback of a military laboratory's susceptibility test results by experts in the field, 2) the continuous generation of up-to-date antibiograms based on an individual medical facility's AR patterns, 3) access to validated information on antimicrobial resistance occurrences and trends in the facility's geographic region for evaluating their implications for military personnel, and 4) facilitation of DoD-wide monitoring of AR trends to improve evidence-based decision and policy making on antibiotic usage and patient care, and 5) to enhance DoD ability to identify and respond to AR events of military significance in a timely manner.
- **Results:** Ongoing. Electronic antimicrobial susceptibility testing quality assurance and analysis system TSN from Focus-Bio-Innova (now Eurofins Medinet) is being used in 4 DoD pilot sites, 3 in the US and 1 in Europe. Expansion to additional sites has been proposed. TSN is viewed by its parent company as "mature" and is not seeking to add additional sites, but has not ruled out additional DoD participation. Linkage of these sites into a DoD network (pilot sites plus DoD-GEIS) for information aggregation, sharing and analysis of AR trends was accomplished in 2006.

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PROJECT TITLE: EMERGING PATHOGENS INITIATIVE (EPI)

- **Agency:** VA
- **Description:** The Veterans Health Administration (VHA) currently has an ongoing and well-defined AR surveillance plan (the EPI, a laboratory-based automated surveillance system). The VHA uses standardized definitions and methods to set local parameters for surveillance in the EPI system. EPI data regarding some AR organisms have been returned to the Veterans Integrated Service Networks with reporting station specific data included. National quartiles have also been provided for use at the Network and local level. Confidentiality is a key element in any activity undertaken by the VHA. Great effort has been put forth to maintain confidentiality of the Emerging Pathogens Initiative surveillance data set. Access is strictly limited for any data with unique identifiers.

- **Results:** Currently over 158 VHA facilities across the country transmit data to the EPI monthly. The data collected by the EPI are being reviewed by the Infectious Diseases Program Office and reported to the Veterans Integrated Service Networks (VISNs = VA regional offices). Enhancements that acquire additional information on antimicrobial resistance of specified organisms were distributed to reporting stations in July 2004 and continue to function as requested with ongoing enhancements to acquire even more information have been requested and are currently in process. Review of process for reporting information back to VISNs was undertaken and determined it should continue with annual reports; this review is still in process and will continue.

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PROJECT TITLE: REVIEW OF COMMERCIALY AVAILABLE COMPUTER SOFTWARE TO BE USED FOR INFECTION PREVENTION, CONTROL AND CONTAINMENT

- **Agency:** VA
- **Description:** VA is actively reviewing computer off-the-shelf software products to assist in infection control processes for prevention and control of infectious diseases including antimicrobial resistant organisms; computer-assisted decision support systems will be a key element in VA's choice of product.
- **Results:** Review and evaluation of off-the-shelf products remains in process for issue of antibiotic resistance, as well as having features that will assist in evaluation of healthcare-associated infection analysis. At this time, one vendor product has been selected for further development nationwide that will include antibiogram monitoring and possibly decision support regarding antibiotic choices. Provided successful pilot and beta-site testing, systemwide implementation would be anticipated within 3 years.

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ACTION ITEM #3: DEVELOP STANDARDS AND METHODOLOGIES.

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PROJECT TITLE: ANALYTICAL METHODS DEVELOPMENT FOR ECOLOGICALLY RELEVANT PHARMACEUTICALS AND METABOLITES

- **Agency:** EPA
- **Description:** Evaluate sample volumes, sample preservation options, and extraction techniques for LC/MS/MS analyses in order to achieve the detection limits necessary to measure environmentally relevant or informatically predicted levels of the 65 pharmaceuticals in water, sediment, and tissues.
- **Results:** Manuscript on LC/MS/MS and water extraction methods by the end of FY07. Manuscript on LC/MS/MS and sediment and tissue extraction methods by the end of FY08. FY10 Report on chemical methods developed for ecologically relevant pharmaceuticals.

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PROJECT TITLE: DEVELOPMENT AND SINGLE LAB VALIDATION OF METHODS FOR PHARMACEUTICALS AND PERSONAL CARE PRODUCTS

- **Agency:** EPA

- **Description:** Project designed to develop and refine methods of detection for pharmaceuticals, pesticides, steroids and hormones. Several antibiotics are included in the most recently published method. Ultimately the goal is to produce refined methods with high accuracy and precision.
- **Results:** Ongoing. "Method 1694: Pharmaceuticals and Personal Care Products in Water, Soil, Sediment, and Biosolids by HPLC/MS/MS" was published in December of 2007. This publication includes methods for numerous antibiotics.

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PROJECT TITLE: DEVELOPMENT OF CLSI/NCCLS TESTING STANDARDS

- **Agency:** FDA
- **Description:** Campylobacter is one of the primary foodborne pathogens under surveillance in NARMS. Additionally, many bacteria that cause disease in aquatic animals require growth conditions that vary substantially from routine terrestrial bacterial pathogens, thus the need for development of standardized testing methods.
- **Results:** Completed development of a standardized in vitro susceptibility testing method for Campylobacter including the determination of quality control ranges for fourteen antimicrobial agents of human and veterinary importance. This method was incorporated into the Clinical and Laboratory Standards Institute (CLSI) M45-A guideline "Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria". Also completed a multi-laboratory study to evaluate the use of disk diffusion for screening Campylobacter isolates for resistance to ciprofloxacin and erythromycin which has been incorporated in the CLSI M45 guideline. Completed development of standardized in vitro susceptibility testing methods for bacteria isolated from aquatic animals. These methods were incorporated into the Clinical and Laboratory Standards Institute (CLSI) M42-A guideline "Methods for Broth Dilution Susceptibility Testing of Bacteria Isolated from Aquatic Animals", and M49-A guideline "Methods for Antimicrobial Disk Susceptibility Testing of Bacteria Isolated from Aquatic Animals".

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PROJECT TITLE: ANTIMICROBIAL SUSCEPTIBILITY TESTING FOR *LISTERIA*

- **Agency:** USDA
- **Description:** Methodologies and standards for antimicrobial susceptibility testing of *Listeria* are being developed and implemented.
- **Results:** A new *Listeria* broth microdilution plate was constructed and tested in 2007. A manuscript has been submitted for publication. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

ACTION ITEM #4: ADDRESS ADDITIONAL SURVEILLANCE ISSUES UNIQUE TO AR.

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PROJECT TITLE: ESTIMATING THE PUBLIC HEALTH AND ECONOMIC BURDEN OF DISEASE CAUSED BY DRUG RESISTANT GROUP A STREPTOCOCCUS



- **Agency:** CDC
- **Description:** The goal of this project is to estimate the burden of disease caused by Drug-Resistant Group A streptococcus (GAS). The project will draw from estimates of the prevalence of resistance among GAS isolates from CDC's Active Bacterial Core surveillance as well as the scientific literature on resistance. Burden of disease will be estimated from national databases of health care visits and hospitalizations as well as ABCs data on disease rates.
- **Results:** Progress has been made on two components of the study. Approximately 900 invasive GAS isolates obtained from CDC's active surveillance (ABCs) during 2006 have been received at CDC; antibiotic susceptibility testing of these is nearly complete. Preliminary estimates of the burden of noninvasive GAS infections (e.g., skin infections such as cellulitis and impetigo, pharyngitis) obtained from two national databases (National Ambulatory Medical Care Survey or NAMCS and the National Hospital Ambulatory Medical Care Survey or NHAMCS) have been calculated: annual visits for GAS cellulitis=1.4-5.0 million; GAS pharyngitis=4.4-9.0 million. Next steps: complete antibiotic susceptibility testing of ABCs 2007 GAS isolates; finalize national estimates of noninvasive GAS disease; calculate annual burden of macrolide resistant invasive GAS infections as identified through ABCs and use sensitivity estimates to generate high and low estimates of the total annual number of resistant noninvasive GAS infections.

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PROJECT TITLE: NATIONAL BURDEN OF ANTIMICROBIAL RESISTANT NEONATAL SEPSIS

- **Agency:** CDC
- **Description:** Neonatal sepsis, including bloodstream infections, meningitis, pneumonia and clinical sepsis, is a leading cause of illness in early life that can result in long-term disability and death. The emergence of antimicrobial resistance among common neonatal pathogens, particularly *Escherichia coli* and *Staphylococcus aureus*, threatens successful treatment of these infections and has raised concerns about overuse of intrapartum antibiotics. Recent studies have detected vaginal MRSA colonization in up to 11% of pregnant women late in pregnancy. However, there are no precise estimates of the overall burden of disease caused by drug-resistant neonatal pathogens upon which to base clinical guidelines and policy decisions. This project is a collaboration between 3 CDC centers, Emory University, and the National Institute of Child Health and Development's (NICHD) neonatal network. Through CDC's Active Bacterial Core surveillance (ABCs) and NICHD's neonatal network, we will conduct active surveillance for early-onset neonatal sepsis from 2007-2009.
- **Results:** Accomplishments to date include identification of 175 neonatal sepsis cases in the participating ABCs areas in 2007 (data not finalized) suggesting a slight decline in overall incidence from 2006. No additional early-onset MRSA cases in ABCs were confirmed in 2007. The NICHD 2007 data are not finalized; from 2006-first 6 months of 2007 NICHD identified 221 early-onset sepsis cases; GBS was the leading cause (33%) followed by *E. coli* (27%). From ABCs we documented that 32% of births in the era of universal GBS screening are exposed to intrapartum antibiotics; penicillin and ampicillin are the most common agents (77%) followed by clindamycin. For newborns only sepsis



associated hospitalizations declined from 25-21 hospitalizations /1000 live births; for all infants <3 months of age, sepsis-associated hospitalizations declined from 35-31 hospitalizations/1000 live births.

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PROJECT TITLE: POPULATION-BASED SURVEILLANCE FOR ANTIMICROBIAL RESISTANCE AMONG *CANDIDA* BLOODSTREAM INFECTIONS.

- **Agency:** CDC
- **Description:** Conduct population-based surveillance for antimicrobial resistance among *candida* bloodstream infections in Baltimore and surrounding area and Atlanta and surrounding area (limited by funding to two sites). Sites will collect epidemiologic data and submit candida isolates to CDC for speciation and susceptibility results. Surveillance will be conducted for two years and compared with previous surveillance data from the same areas in order to assess changing trends. There are no national surveillance programs for monitoring susceptibility in *candida* infections.
- **Results:** Approximately 100 isolates have been received to date from Atlanta metropolitan area sites. Demographic and detailed clinical data collection for case patients is also underway in the Atlanta area. Of 70 cases for whom data have been received, 50% have candidemia due to *C. albicans*, and 30% have candidemia due to *C. glabrata* (12% of candidemia cases were due to *C. glabrata* in 1992-1993 Atlanta metropolitan area candidemia surveillance). Species confirmation is underway at CDC, and susceptibility testing will be performed. Isolate collection has recently begun in Baltimore City and Baltimore County. More funding is being sought in order to expand the surveillance network.

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PROJECT TITLE: CLINICAL OUTCOMES IN MULTI-DRUG RESISTANT NON-TYPHI *SALMONELLA* SEROTYPES

- **Agency:** CDC
- **Description:** Enhanced surveillance for non-Typhi *Salmonella* to investigate the impact of multi-drug resistance on clinical outcomes.
- **Results:** 8 of 10 sites completed 2 years of data/isolate collection. Participants submitted approximately 350 isolates for susceptibility testing to NARMS lab at CDC. Participants and CDC epidemiologists conducted teleconferences to finalize analysis scheme.

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PROJECT TITLE: IMPLEMENTATION OF THE COLLABORATION IN ANIMAL HEALTH AND FOOD SAFETY EPIDEMIOLOGY (CAHFSE).

- **Agency:** USDA
- **Description:** Collaboration in Animal Health, Food Safety, and Epidemiology (CAHFSE) is a comprehensive USDA program designed to address animal health and food safety issues, including antimicrobial resistance, utilizing continual tracking of the selected data

points. This program includes on-farm sample collection and data and risk factor analysis (APHIS), research efforts with molecular and phenotypic characterization of isolates, pathogenesis and development of intervention strategies (ARS), and in-plant efforts for sample collection, data analysis and risk assessment (Food Safety and Inspection Service (FSIS)).

- **Results:** As of 2007, a total of 1209 on-farm swine fecal samples from 31 farms were analyzed for Salmonella. A total of 516 of these samples were analyzed for the presence of Campylobacter, *E. coli*, and enterococci. The incidence of Salmonella, Campylobacter, *E. coli*, and enterococci was 7%, 27%, 87%, and 60%, respectively. The incidence of Salmonella, *E. coli*, and enterococci was consistent with previous years, while the level of Campylobacter was almost 50% less than in previous years. The predominant serotypes of Salmonella were S. Derby, *S. Typhimurium* 5(-), S. Heidelberg, and, S. Mbandaka.

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PROJECT TITLE: PARTICIPATION IN THE REGIONAL DAIRY QUALITY MANAGEMENT ALLIANCE (RDQMA).

- **Agency:** USDA
- **Description:** The mission of the RDQMA is to assure a healthful and safe food supply by advocating the adoption of best management practices (BMPs), which promote animal health and welfare, improve productivity and profitability of dairy farms and encourages environmental stewardship. The RDQMA utilizes the New York State Cattle Health Assurance Program (NYSCHAP) herd risk assessment model and this model has been adopted for use in all participating states. The USDA is responsible for addressing specific issues such as Johne's Disease, salmonellosis, antimicrobial resistance and mastitis/milk quality. The RDQMA is being considered as the pilot program prior to implementation of a dairy component of the CAHFSE program.
- **Results:** Ongoing. Blood, manure, weekly bulk milk tank samples, environmental samples, management data surveys, economic data, nutrient management data and carcass data are being gathered from 2 farms in the northeastern US. Samples are being analyzed for the presence of Mycobacterium avium spp. paratuberculosis, Salmonella spp., *E. coli* 0157:H7 and generic *E. coli*, Listeria monocytogenes, Campylobacter, and Enterococci. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. This program is in the early stages of data collection.

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PROJECT TITLE: IMPLEMENTATION OF A DAIRY PILOT PROGRAM IN THE MIDWEST.

- **Agency:** USDA
- **Description:** Prior to implementation of a dairy component of the CAHFSE program, and in addition to the RDQMA described above, APHIS and ARS have undertaken a pilot study on 5 dairy farms in the midwest for comparison to the RDQMA program. Currently, samples are being cultured for Salmonella, Campylobacter, *E. coli* and Enterococci, (zoonotic and commensal bacteria). Sera are being banked for future testing. Samples and health/management data are being collected from each farm monthly.

- **Results:** Completed-2007. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. From the APHIS dairy study, a total of approximately 500 fecal and environmental samples were analyzed for Salmonella with one-fourth of these sampled for the other bacteria. The incidence of Salmonella, E. coli, and enterococci was consistent with previous years, while the level of Campylobacter was almost 50% less than in previous years. The predominant serotypes of Salmonella from swine samples were S. Derby, S. Typhimurium 5(-), S. Heidelberg, and, S. Mbandaka.

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PROJECT TITLE: IMPLEMENTATION OF USDA VETNET.

- **Agency:** USDA
- **Description:** USDA VetNet was established in 2003 and was modeled after PulseNet USA, the national molecular subtyping network for food-borne disease surveillance. The objectives of USDA VetNet are to use PFGE to subtype zoonotic pathogens submitted to the animal arm of the National Antimicrobial Resistance Monitoring System (NARMS), compare USDA VetNet and PulseNet PFGE patterns, and to use the comparative data for surveillance and investigation of food-borne illness outbreaks. Whereas PulseNet subtypes seven food borne disease-causing bacteria: E. coli O157:H7, nontyphoidal Salmonella, Shigella, Listeria monocytogenes, Campylobacter, Yersinia pestis, and Vibrio cholerae, VetNet, at present, subtypes nontyphoidal Salmonella serotypes and Campylobacter from animals including diagnostic specimens, healthy farm animals, and carcasses of food-producing animals at slaughter.
- **Results:** Ongoing. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. VetNet has two functioning databases including the NARMS Salmonella and Campylobacter databases. The Salmonella database contains over 13,000 Salmonella isolates, while the Campylobacter database contains over 900 Campylobacter isolates. Both databases contain the PFGE Tagged Image File Format (TIFF) images, demographic information, and the antimicrobial resistance profiles assigned by NARMS.

**\*\* TOP PRIORITY \*\***

ACTION ITEM #5: DEVELOP AND IMPLEMENT PROCEDURES FOR MONITORING ANTIMICROBIAL USE IN HUMAN MEDICINE, AGRICULTURE, VETERINARY MEDICINE, AND CONSUMER PRODUCTS.

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PROJECT TITLE: COMPREHENSIVE DEMONSTRATION PROJECT: BUILDING REGIONAL COALITIONS TO PREVENT METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN HEALTHCARE FACILITIES

- **Agency:** CDC
- **Description:** This project supports the development and implementation of comprehensive programs to reduce the incidence of MRSA infections in states and/or large regional networks acute phase and nonacute phase healthcare facilities. The Pittsburgh Regional Healthcare Initiative (PRHI) was recruited as a collaborating partner

for this project. PRHI is a coalition of regional healthcare facilities and civic, corporate, and healthcare leaders in the Pittsburgh area dedicated to improving the quality of healthcare delivery in southwestern Pennsylvania.

- **Results:** 2007 milestones include: 1) National Veteran's Health Affairs MRSA Prevention Initiative-building on the work at VA Pittsburgh, a national pilot program was initiated in August 2006 to determine if results could be replicated in 17 other VA hospitals; CDC's NHSN is being used to measure the impact. In January 2007 plans were announced to initiate MRSA prevention programs in all VA hospitals. CDC continues to actively participate in that national task force. 2) Plexus Institute Initiative (funded by Robert Wood Johnson Foundation-another expansion of Pittsburgh VA work, this project examines use of a social/cultural change improvement model ("positive deviance") applied to MRSA prevention in 6 funded sites. CDC is providing in-kind support and assistance. 3) Maryland Patient Safety Center Initiative has initiated a regional voluntary MRSA prevention program of 16 Maryland Hospitals that will implement MRSA prevention initiatives using the "positive deviance" change model. CDC is providing in-kind support and assistance in using NHSN as the outcome measurement tool.

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PROJECT TITLE: NATIONAL AMBULATORY MEDICAL CARE SURVEY (NAMCS) AND NATIONAL HOSPITAL AMBULATORY MEDICAL CARE SURVEY (NHAMCS)

- **Agency:** CDC
- **Description:** NAMCS is an annual national survey that collects data on the utilization of ambulatory medical care services provided by office-based physicians in the United States. Findings are based on a sample of visits to nonfederally employed office-based physicians who are primarily engaged in direct patient care. NAMCS monitors trends in prescription of antimicrobial drugs in the physician office setting. NHAMCS is an annual national survey that collects data on the utilization of ambulatory medical care services provided by hospital emergency and outpatient departments in the United States. Findings are based on a sample of visits to emergency departments and outpatient clinics. NHAMCS monitors trends in prescription of antimicrobial drugs in hospital emergency and outpatient departments.
- **Results:** During 2007, presented poster on "Antimicrobial Use at Respiratory-related U.S. Ambulatory Care Visits Before and After Issuance of Performance Measures for Community-acquired Pneumonia" at the 2007 Annual Meeting of the Infectious Diseases Society of America. Antimicrobial prescribing in ambulatory care settings decreased from 154 antimicrobials per 1,000 visits in 1993-94 to 123 antimicrobials per 1,000 visits in 2005-06 (down by 20%). This decline was observed in all age groups, except for persons 15-24 years of age. Among children and adolescents under 15 years of age, decreasing trends in antimicrobial prescribing rates were found in the physician office and emergency department (ED) settings, but not in the hospital outpatient department (OPD). For persons 15 years of age and over, antimicrobial prescribing rates increased by 29% in the OPD and 15% in the ED; no change was observed in physician offices.

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PROJECT TITLE: PRESCRIPTION DATABASES

- **Agency:** DoD
- **Description:** Use of the prescription database (PDTs) is being piloted for gastrointestinal and respiratory outbreak detections.
- **Results:** 17 additional VA hospitals nationwide are now participating in a pilot program to evaluate the reproducibility of the initial results, and the group has elected to use CDC's National Healthcare Safety Network (NHSN) for data collection. Data submission is underway in those hospitals.

ACTION ITEM #6: IDENTIFY AND EVALUATE METHODS FOR COLLECTING (E.G., OPTIMAL SAMPLING METHODS) AND DISSEMINATING THE SURVEILLANCE DATA ON ANTIMICROBIAL DRUG USE.

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PROJECT TITLE: MONITORING TRENDS IN PRESCRIPTIONS OF ANTIMICROBIALS IN THE ALASKA NATIVE HEALTH CARE SYSTEM

- **Agency:** CDC
- **Description:** In Alaska, where many patients are seen and treated in locations far from a hospital and where substantial delays may occur in transporting ill patients to definitive care, little is known about changes in prescribing rates. We have developed a method for extracting prescriptions from the Indian Health Service to measure rates of antimicrobial prescriptions over time.
- **Results:** Final analysis and write-up of prescribing data from Anchorage and Bristol Bay regional clinical services for 1992- 2004. The overall visit-based prescribing rate of oral antimicrobials in <18 year olds was lower than rates reported from a similar age group in US but decreases in prescribing rates seen in other regions of the US since the mid-1990's have not been seen in Alaska.

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PROJECT TITLE: EMERGING PATHOGENS INITIATIVE (EPI)

- **Agency:** VA
- **Description:** Resistance data are being gathered in the EPI, an automated surveillance system, at the reporting site level and can be used for comparisons based on geographic areas and can be linked to ICD-9-CM diagnostic codes. In addition, drug use data can be linked to laboratory testing and diagnoses for a significant emerging disease.
- **Results:** This item is already underway in the VHA with reporting from facilities across the country. Enhancements that acquire additional information on antimicrobial resistance of specified organisms were distributed to reporting stations in July 2004 and continue to function as requested. Request for enhancements to capture ICD-9-CM coding from outpatient encounters associated with presence of antimicrobial resistance has been submitted, as has request for ability to delineate differences of data from sites that have consolidated administrative services and reporting mechanisms.

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PROJECT TITLE: REVIEW OF COMMERCIALY AVAILABLE COMPUTER SOFTWARE TO BE USED FOR INFECTION PREVENTION, CONTROL AND CONTAINMENT

- **Agency:** VA
- **Description:** VA is actively reviewing computer off-the-shelf software products to assist in infection control processes for prevention and control of infectious diseases including antimicrobial resistant organisms; computer-assisted decision support systems will be a key element in VA's choice of product.
- **Results:** Commercially available software are being tested in clinical settings including some VA medical centers. At this time, one vendor product has been selected for further development nationwide that will include antibiogram monitoring and possibly decision support regarding antibiotic choices.

ACTION ITEM #7: WORK WITH ACCREDITING AGENCIES TO ADDRESS ANTIMICROBIAL DRUG-USE AS PART OF QUALITY ASSURANCE IN HEALTH CARE DELIVERY SYSTEMS.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK-DEVELOPMENT AND TESTING OF HEALTH PLAN EMPLOYER DATA AND INFORMATION SET (HEDIS) MEASURES FOR APPROPRIATE ANTIBIOTIC USE

- **Agency:** CDC
- **Description:** HEDIS is a performance measurement tool used by purchasers and consumers to compare many of the nation's leading health plans. In this project, CDC epidemiologists collaborate with experts in the development and testing of HEDIS measures to develop and test one or more measures of appropriate antimicrobial use in children. Measures include rate of prescribing antimicrobial drugs for acute upper respiratory infections and bronchitis; rate of prescribing antimicrobial drugs for pharyngitis where no throat culture or rapid streptococcal antigen test was performed; and episodes of otitis media treated with a recommended first-line agent. When the measure is incorporated into HEDIS, the measure and its impact on physician and patient awareness of appropriate antimicrobial use will be evaluated. Additionally, two new measures were developed and tested during 2004 for adults; the treatment of acute bronchitis and all upper respiratory infections.
- **Results:** NCQA was presented with specifications for two potential measures relating to Appropriate Antibiotic Prescribing for Respiratory Infections for Children. Two measures for children were agreed upon, developed and tested following NCQA's specifications. In 2003 these two measures; one on pharyngitis and one on upper respiratory infections were pilot tested. NCQA reviewed and accepted these measures and they were incorporated into the 2004 HEDIS set. The two adult measures were included in the HEDIS set beginning in 2006. The 2006 pilot year of the acute bronchitis measure showed that on average, both Commercial and Medicaid plans showed high rates of inappropriate antibiotic use (66% and 70%, respectively). The antibiotic utilization measure was not approved for public reporting because of the type of information

collected (e.g. total number of antibiotics prescribed not broken down by diagnosis); the committee approved this measure for 2008 HEDIS.

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PROJECT TITLE: SURGICAL SITE INFECTION ANTIBIOTIC PROPHYLAXIS PLAN IN CONJUNCTION WITH THE JOINT COMMISSION ORYX AGGREGATE

- **Agency:** VA
- **Description:** VHA has introduced surgical site antibiotic prophylaxis (including both timing and appropriateness of choices, as well as timely cessation) as a performance measure for VHA systems nationwide. These performance measures constitute 50% of the annual evaluation for Executive Career Field (ECF) performance plans for VHA regional directors and individual medical center directors.
- **Results:** In Federal Fiscal Year 2005, VHA introduced surgical site antibiotic prophylaxis as a performance measure for VHA systems nationwide--ongoing into FY 2008 (considered a "mission critical" measure. Data from VHA's Office of Quality and Performance reveal that for Performance Measures SIP1a (Prophylactic antibiotic started timely) comparing national numbers from the third and 4th quarters from FY 2005, FY 2006 and FY 2007, the percent starting timely was 78.7%, 88.6% and 90.6%, respectively. Additionally, for the measure of SIP10a (Correct Antibiotic ALL surgeries) comparing national numbers for fourth quarter FY 2006 and FY 2007, percent with correct antibiotics was 93.7% and 95.8%, respectively.

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PROJECT TITLE: COMMUNITY-ACQUIRED PNEUMONIA PERFORMANCE MEASURES IN CONJUNCTION WITH THE JOINT COMMISSION ORYX AGGREGATE

- **Agency:** VA
- **Description:** Along with b above, VHA Office of Quality and Performance has initiated quality measures for timing, diagnostics and treatment of community-acquired pneumonia.
- **Results:** Data from VHA's Office of Quality and Performance reveal that for Performance Measures CAP11 (Initial antibiotic started within 8 hours of presentation) comparing national numbers from 2005, 2006, and 2006, percent of community acquired pneumonia cases admitted to inpatient status received initial antibiotics within 8 hours of presentation for 73.5%, 88.9% and 94.4% of the time respectively. For CAP12 (Initial antibiotic started within 4 hours), the numbers are 44.4%, 68.7% and 80.9%, respectively for FY 2005, 2006 and 2007. CAP14 (Appropriate initial antibiotic for immunocompromised, non-ICU admissions) was 69.7%, 82.2% and 89.0%, respectively for FY 2005, 2006 and 2007. And, CAP10 (Blood culture obtained before initial dose of antibiotic) for community acquired pneumonia admitted, quarters 2, 3 and 4 for FY 2005, 2006, and 2007 respectively, revealed rates of 87.5%, 90.3% and 92.7%, respectively.

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PROJECT TITLE: TRANSFORMATIONAL MEASURES FOR VHA-INFECTION RATE REDUCTION



- **Agency:** VA
- **Description:** VHA Office of Quality and Performance has espoused as Transformational Measure 1, Infection Rate Reduction which included central line-associated bloodstream infections, ventilator-associated pneumonias and methicillin-resistant Staphylococcus aureus prevention. Transformational measures are incremental measures designed to support long term strategic goals. They are visionary and identify areas of significant system impact, but may not be attainable in a single performance year.
- **Results:** Formally adopted as transformational measures for FY 2008. Ventilator-associated pneumonia and central-line-associated bloodstream infections in the ICUs have been in effect since FY 2006 through the VA Inpatient Evaluation Center (IPEC). MRSA Prevention Initiative started in FY 2007. All are ongoing. Transformational measures indicates that no definitive measures have been selected, but the issue is of such significance to the organization that individual ones are being reviewed for inclusion in the next set of performance measures.

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PROJECT TITLE: PARTICIPATION IN THE INSTITUTE FOR HEALTHCARE IMPROVEMENT'S 5 MILLION LIVES CAMPAIGN

- **Agency:** VA
- **Description:** Relative to antibiotic resistance the individual campaigns 'Reduce Methicillin-Resistant Staphylococcus aureus (MRSA) Infection,' 'Prevent Surgical Site Infections,' 'Prevent Central Line-Associated Bloodstream Infections,' and 'Prevent Ventilator-Associated Pneumonia' have been espoused.
- **Results:** Establishment of performance measures as part of the annual evaluation for the Executive Career Field (ECF) performance plans for VHA regional directors and individual medical center directors. These will be transformational measures for the organization. Transformational measures indicates that no definitive measures have been selected, but the issue is of such significance to the organization that individual ones are being reviewed for inclusion in the next set of performance measures.

ACTION ITEM #8: ENSURE THAT CLINICAL LABORATORIES THAT PROVIDE DATA FOR AR SURVEILLANCE PURPOSES HAVE ACCESS TO AND ROUTINELY PARTICIPATE IN PERTINENT TRAINING AND PROFICIENCY TESTING PROGRAMS WITH GOOD PERFORMANCE AND INDICATE AR TESTING METHODOLOGIES IN THEIR SURVEILLANCE REPORTS (E.G., SPECIFIC AUTOMATED METHODS OR MANUAL TECHNIQUES).

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PROJECT TITLE: QUALITY HIV DRUG RESISTANCE GENOTYPING SERVICES TO PEPFAR COUNTRIES (INTERNATIONAL LABORATORY BRANCH, DIVISION OF GLOBAL AIDS, NCHHSTP).

- **Agency:** CDC



- **Description:** Purpose of this ongoing project is to provide the best possible quality data and services to PEPFAR countries on HIV drug resistance surveillance and monitoring.
- **Results:** Ongoing. Our laboratory is the only laboratory within CDC which has been accredited by College of American Pathologists (CAP). Any data we provided to the PEPFAR countries have been generated by certified technologists or scientists and the assays we used have been validated in our lab based on CAP standards. We routinely participated CAP, WHO and AccuTest PT programs for our assays. For the past two years, we have provide genotyping and analytic services for the surveillance of transmitted HIV DR in recently-HIV-infected populations for Tanzania, Malawi, Kenya, China and Botswana. The surveillance results indicate that transmitted HIV DR in recently-infected population are low, less than 5%. Two of the survey results from the Tanzania and Malawi have been published in peer-reviewed scientific journal--Antiviral Therapy, 2008.

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PROJECT TITLE: PERTINENT TRAINING

- **Agency:** FDA
- **Description:** Continue to ensure validity of antimicrobial susceptibility information derived from NARMS.
- **Results:** Developed both an antimicrobial susceptibility testing quality control and quality assurance program for the three arms of NARMS, human, slaughter plants, and retail meat. NARMS also participates in the WHO-Global Salm-Surv External Quality Assurance System (EQAS). The EQAS supports the assessment of the quality of serotyping and antimicrobial susceptibility testing of Salmonella in all participating laboratories. The NARMS program has also developed two secondary antimicrobial testing plates for Salmonella and *E. coli*; a fluoroquinolone panel and extended-spectrum cephalosporin panel.

ACTION ITEM #10: WORKING WITH PARTNERS, INCLUDING NATIONAL COMMITTEE FOR CLINICAL LABORATORY STANDARDS (NCCLS), FURTHER DEVELOP, REFINE, AND PROMOTE STANDARDIZED CLINICAL, EPIDEMIOLOGIC, AND LABORATORY METHODS FOR DOCUMENTING AND ASSESSING THE SIGNIFICANCE OF DRUG RESISTANCE AMONG YEASTS AND MOULDS, PARASITES, AND VIRUSES.

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PROJECT TITLE: ADOPTATION AND IMPLEMENTATION OF WHO METHODOLOGIES ON HIV DRUG RESISTANCE IN PEPFAR COUNTRIES (INTERNATIONAL LABORATORY BRANCH, DIVISION OF GLOBAL AIDS, NCHHSTP).

- **Agency:** CDC
- **Description:** Aim of the project is to harmonize the CDC-supported HIV drug resistance surveillance in PEPFAR countries is in line with the WHO recommended methodologies. To ensure the data generated can be compared and analyzed.

- **Results:** By adopting the WHO methodologies for transmitted HIV drug resistance survey, termed Threshold Survey (TS). We have shared data generated from 3 countries with WHO and make data analysis from different countries a reality. With the close collaboration on protocol developments and harmonization with WHO ResNet, data generated from CDC from PEPFAR countries have become part of the HIV drug resistance database at WHO. We have submitted data from Tanzania, Malawi and Kenya. For the first time in HIV DR surveillance history, all the data generated from PEPFAR and WHO-supported countries can be analyzed and compared which make a global HIV DR surveillance database a reality.

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PROJECT TITLE: POPULATION-BASED, NATIONAL/REGIONAL SURVEY FOR TB DRUG RESISTANCE

- **Agency:** CDC
- **Description:** In 2008, the fourth report of ongoing population-based, national/regional survey for TB drug resistance sponsored by the WHO and the International Union Against TB and Lung Disease (IUATLD) will be issued, representing up to 85 countries and >50,000 patients. The Division of TB Elimination, via both the Mycobacteriology Laboratory Branch and the International Research and Programs Branch, has contributed substantially to this massive, sustained surveillance effort by: 1) providing scientific and technical leadership, quality assurance, and training to national and regional TB labs; 2) conducting surveys and surveillance programs in several countries which contribute data to the WHO/IUATLD program; and 3) leading in the development of international standard case and outcome definitions and surveillance procedures for MDR TB.
- **Results:** Ongoing, data on new cases were available for 72 countries and 2 special administrative regions (SARs) of China. DST results were available for 62, 746 patients. The proportion of resistance to at least one antituberculosis drug (any resistance) ranged from 0% in two Western European countries to 56.3% in Baku, Azerbaijan. The proportion of MDR ranged from 0% in eight countries to 22.3% in Baku, Azerbaijan and 19.4% in the Republic of Moldova. Data on previously treated cases were available for 66 countries and 2 SARs of China. In total, DST results were available for 12, 977 patients. Resistance to at least one anti-tuberculosis drug (any resistance) ranged from 0% in three European countries to 85.9%, in Tashkent, Uzbekistan. The highest proportions of MDR were reported in Tashkent, Uzbekistan (60.0%), and Baku, Azerbaijan (55.8%). Thirty five countries and two SARs were able to report data on XDR-TB either through routine surveillance data or through drug resistance surveys. In total, data were reported on 4, 012 MDR-TB cases, and among those 301 or 7.0% XDR-TB cases were detected.

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PROJECT TITLE: MULTINATIONAL, PROSPECTIVE COHORT STUDY OF MDR TB TREATMENT TO DETERMINE THE ADDED BENEFIT OF THE PROGRAMMATIC APPROACHES IN PREVENTING ACQUIRED RESISTANCE TO 2ND-LINE DRUGS.

- **Agency:** CDC

- **Description:** Prospective cohort study of MDR TB treatment to determine the added benefit of the programmatic approaches in preventing acquired resistance to 2nd-line drugs.
- **Results:** Enrollment has now grown to 20 sites in 10 countries, ending in June 2008 with follow-up ending June 2010. This study demonstrated that large, multinational clinical and epidemiological studies of MDR TB with long-term follow-up are indeed possible and affordable and provided the first substantial data on the baseline prevalence and distribution of 2nd-line drug resistance and genotypes among MDR TB cases in several countries. The Division of TB Elimination has also implemented programmatic and clinical research projects to address principal issues during several international outbreaks of MDR TB.

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PROJECT TITLE: DEVELOPMENT OF A NOVEL, RAPID VIABILITY BASED ASSAY FOR YEAST ANTIFUNGAL SUSCEPTIBILITY TESTING.

- **Agency:** CDC
- **Description:** The goals of this project: (1) Development of a yeast antifungal susceptibility testing method (AFST) using the viability dye FUN1 in a flow cytometry based assay to generate objective results in under 6 hours. Results of conventional AFST methods are available in 24 hours and are often subjective. (2) To adapt the flow cytometry based system to a fluorescent plate reader format for AFST. This will allow routine clinical microbiology including state health laboratories to use this methodology in a cost-efficient, objective and user-friendly fashion. (3) To perform a multi-center study to evaluate the inter-laboratory reproducibility of this novel AFST assay
- **Results:** Ongoing. Assay parameters including dye concentrations, appropriate incubation temperature/ time, interpretation and analyses of results for representative *Candida* and *Cryptococcus* isolates have been established. Several domestic and international laboratories identified to participate in the multi-center study. Antifungal susceptibilities of 20 *C. albicans* and 10 *C. neoformans* isolates to amphotericin B and fluconazole have been generated using the new flow cytometry based assay. Results were comparable with the established CLSI AFST method.

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PROJECT TITLE: IN-VITRO ANTIMICROBIAL SUSCEPTIBILITY TESTING

- **Agency:** FDA
- **Description:** Develop quality control standards for the in-vitro antimicrobial susceptibility testing of bacterial pathogens isolated from aquatic animals and aquaculture foods.
- **Results:** Completed development of standardized in vitro susceptibility testing methods for bacteria isolated from aquatic animals. These methods were incorporated into the Clinical and Laboratory Standards Institute (CLSI) M42-A guideline "Methods for Broth Dilution Susceptibility Testing of Bacteria Isolated from Aquatic Animals", and M49-A guideline "Methods for Antimicrobial Disk Susceptibility Testing of Bacteria Isolated from Aquatic Animals".

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PROJECT TITLE: DEVICES CONTAINING ANTIMICROBIALS GUIDANCE

- **Agency:** FDA
- **Description:** Draft guidance document for industry: how the Center for Devices and Radiologic Health (CDRH) intends to regulate devices containing antimicrobial agents, and what information regarding efficacy and resistance CDRH wants to see in premarket applications (interim until rulemaking is completed).
- **Results:** Draft guidance published in October 2007. Comments received and reviewed with final guidance to issue soon.

ACTION ITEM #15: PROVIDE AN ACCESSIBLE, CENTRALIZED SOURCE OF AR DATA FROM MAJOR SURVEILLANCE SYSTEMS INVOLVING ANIMAL AND HUMAN POPULATIONS. IN CONSULTATION WITH STAKEHOLDERS, DETERMINE HOW TO REPORT AR DATA IN A WAY THAT IS VALID AND USEFUL TO INTERESTED PARTIES (E.G., CLINICIANS, PUBLIC HEALTH OFFICIALS, VETERINARIANS, AND RESEARCHERS). INCLUDE SUFFICIENT DETAIL IN SURVEILLANCE REPORTS TO PERMIT LOCAL ANALYSIS AND COMPARISON WITH TRENDS IN DRUG USE AND MEDICAL AND AGRICULTURAL PRACTICES.

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PROJECT TITLE: SURVEILLANCE FOR *STREPTOCOCCUS PYOGENES* AMONG MILITARY TRAINEES

- **Agency:** DoD
- **Description:** Increasing resistance of *S. pyogenes* to macrolide antibiotics is a concern. Furthermore, during military-recruit training exercises, penicillin-allergic patients are often given erythromycin when mass prophylaxis is recommended. If resistant organisms are present or develop in this population, *S. pyogenes* infections (latent or overt) may not be treated effectively. Recruits could be reservoirs of resistant pathogens for military populations. This project conducts antimicrobial susceptibility and gene typing on *S. pyogenes* isolates collected from recruits at 9 military training centers and monitors for *S. pyogenes* resistance rates.
- **Results:** Ongoing. Reports of susceptibility test results and summary statements are being provided to primary care facilities, and are accessible to DoD staff at [www.geis.fhp.osd.mil](http://www.geis.fhp.osd.mil). Generated data show moderate antibiotic resistance through 2007. National DoD surveillance data for antibiotic resistance and emm gene type of group A streptococcal isolates from eight basic-training military sites was published in the Journal of Clinical Microbiology, Vol 48, October 2003. All isolates remain susceptible to penicillin, and macrolide resistance remained steady at approximately 10%. NHRC assisted in *S. pyogenes* outbreak investigations at 3 recruit training centers in 2006-07. Data from this surveillance was presented to the Defense Health Board (formerly the Armed Forces Epidemiology Board) in December 2006 and September 2007. Additional publication: Crum NF, Russell KL, Kaplan EL, Wallace MR, Wu J, Ashtari P, Morris DJ,

Hale BR. Pneumonia outbreak associated with group a Streptococcus species at a military training facility. Clin Infect Dis. 2005 Feb 15;40(4):511-8.

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PROJECT TITLE: MULTILOCUS SEQUENCE ANALYSIS OF *STREPTOCOCCUS PNEUMONIAE* ISOLATES

- **Agency:** DoD
- **Description:** DoD data from 1981 to 1991 suggest that *S. pneumoniae* may cause about 12% of military pneumonia hospitalizations. Multilocus sequence typing characterizes isolates of bacterial species using the sequences of internal fragments of 7 house-keeping genes. This highly discriminatory molecular typing method is used to track the global spread of virulence, to provide a direct comparison of isolates of multidrug-resistant *S. pneumoniae*, to define serotypes of isolates, estimate recombinational parameters, and identify discrete clonal complexes.
- **Results:** A pneumococcal isolate from a fatal case of meningitis was investigated using this technique, allowing the discovery of a non-vaccine serotype not commonly found among meningitis cases. During 2003 a conjunctivitis outbreak of *S. pneumoniae* was identified and analyzed. This work enabled the identification of a novel strain responsible for the outbreak and provided epidemiologic information on the causative isolate's resistance pattern. Further analyses of pneumococcal strains from Egypt is in process in hopes of providing valuable epidemiologic data for prevention and treatment options. Publications: Wasfy MO, et. al.. Antimicrobial susceptibility and serotype distribution of Streptococcus pneumoniae causing meningitis in Egypt, 1998-2003. *J Antimicrob Chemother.* 2005 Jun;55(6):958-64. Crum NF, Barrozo CP, Chapman FA, Ryan MA, Russell KL. An outbreak of conjunctivitis due to a novel unencapsulated Streptococcus pneumoniae among military trainees.

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PROJECT TITLE: INVESTIGATIONS OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) OUTBREAKS OCCURRING ON MILITARY BASES.

- **Agency:** DoD
- **Description:** Hospital acquired MRSA outbreaks are well known, but recent reports have caused concern about community acquired MRSA infections. Investigations into this recent trend have been conducted at several military bases. Laboratory work has involved culture identification followed by antibiotic resistance testing. The presence of the panton valentine leukocidin gene which is a known virulence factor has been shown in many of these investigations. The multilocus sequence typing method has also been used to identify global virulent clones by characterizing the isolates with the sequencing of 7 house-keeping genes. Further molecular analyses have been utilized to discover the specific SCCmec type of these MRSA's, which is the mobile genetic element that mediates the methicillin resistance.
- **Results:** BAMC investigators have conducted a randomized trial to look at mupirocin intranasal treatment and reduced MRSA carriage. Unfortunately, there was no reduction in carriage within the treated group. BAMC has also been collecting and characterizing

MRSA isolates from across the MHS.NHRC has been testing MRSA isolates for over 15 years within military populations in the San Diego area. Molecular characterization has shown the emergence of distinct community-acquired MRSA strains that were genetically unrelated to nosocomial MRSA isolates from the same community.

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PROJECT TITLE: INVESTIGATION OF MULTI-DRUG RESISTANT *ACINETOBACTER BAUMANNI* IN US SERVICE MEMBERS

- **Agency:** DoD
- **Description:** *Acinetobacter baumannii* is an opportunist, with pathogenicity usually associated with high infectious doses or contamination of deep or necrotic wounds. Its importance as a nosocomial agent is due to its high rate of multi-antibiotic resistance. A review of *A. baumannii* infection in wounded US service persons is underway to determine 1) the number and location of patients involved, 2) what risk factors are common to the patients (e.g., military unit or geographic proximity before injury, type and site of wound causing hospitalization, specimen source, type and location of all medical and surgical treatment, exposure to other patients with *A. baumannii* infection), 3) the phenotypic strain(s) of *A. baumannii* involved, 4) genotyping of strains currently involved in hospitals at NNMC and WRAMC, and 5) sequencing isolates to conduct molecular epidemiology study with Tim Read at Naval Medical Research Center
- **Results:** DoD GEIS has established a strategic initiative to monitor changes in *Acinetobacter* isolates recovered from large medical centers. The medical centers that are participating are WRAMC, BAMC, LRMC and NNMC. WRAIR is coordinating the effort and serving as a focal point for sharing data. An epidemiologist is reviewing the data and providing monthly reports to critical MHS responsible officials to help raise awareness and augment infection control. This system will expand to other MDROs in the future. GEIS is also funding an in theater study at a combat support hospital to try to identify the common source of *Acinetobacter* infections.

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PROJECT TITLE: ELECTRONIC DATA CAPTURE OF CLINICAL MICROBIOLOGICAL AND AR DATA IN EXISTING MILITARY TREATMENT FACILITY MEDICAL RECORDS, USING HL7 MESSAGE DATA, FOR SURVEILLANCE OF ANTIMICROBIAL RESISTANCE (NEW EFFORT)

- **Agency:** DoD
- **Description:** Surveillance of antimicrobial resistance and monitoring trends in emerging AR are important to military and public health. Empirical treatment guided by validated sensitivity and resistance data can lead to improved patient outcomes and a reduction in the emergence of resistance. However, it is difficult to establish this capability effectively across a spectrum of military medical facilities located in the US and in many foreign countries. A prior approach to developing such a system has been tried through a partnership with TSN (described in another part of this report); this was successful but has not expanded beyond four medical centers.

- **Results:** The Navy and Marine Corps Public Health Center, Portsmouth, VA, is testing a newer approach using Health Level 7 (HL7) data generated from the military health system. HL7 microbiology data were restructured for analysis using WHONET© to produce detailed reports characterizing antibiotic resistance in beneficiaries served by four military treatment facility (MTF) laboratories. A total of 32,264 isolates were identified from clinical specimens collected from July 2005 to October 2007. The efficiency and scope of DoD-level electronic surveillance, using this approach, will augment existing institutional-level surveillance techniques. This method can be expanded to include many more military centers and clinics - it is the first methodology to provide the possibility of timely AR surveillance and analysis of clinical microbiology laboratory data in the military population; this approach can lead to improvements in health outcomes, reduced healthcare costs and earlier recognition of adverse trends in antibiotic sensitivity.

ACTION ITEM #16: PROVIDE HEALTHCARE SYSTEM ADMINISTRATORS AND OTHER DECISION MAKERS WITH DATA ON THE IMPACT OF DRUG-RESISTANT ORGANISMS (E.G., OUTCOME, TREATMENT COSTS) AND ON EFFECTIVE PREVENTION AND CONTROL MEASURES.

PROJECT TITLE: RESEARCH DEMONSTRATION (U18): CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS (CERTS) PROGRAM: A NATIONAL INITIATIVE TO INCREASE AWARENESS OF THE BENEFITS AND RISKS OF NEW, EXISTING, OR COMBINED USES OF THERAPEUTICS THROUGH EDUCATION AND RESEARCH.

- **Agency:** AHRQ
- **Description:** The Harvard Pilgrim Healthcare CERT supports nine collaborating systems within an HMO Research Network to study antibiotic use in children and resistance and cost-effectiveness.
- **Results:** Enhanced surveillance of invasive pneumococcal disease (NPD) in Massachusetts began in October 2001 and remains ongoing. Nonvaccine serotypes caused 72%-91% of invasive pneumococcal disease annually in children less than 5 years of age between 2002 and 2005. Serotype 19A has emerged as the most frequent cause of IPD in Massachusetts. A multidrug-resistant clone (ceftriaxone, amoxicillin, azithromycin and trimethoprim-sulfamethoxazole) (MLST 320) was first identified in Massachusetts in 2005. Three years after the introduction of pneumococcal conjugate vaccine for universal administration to children less than 2 in Massachusetts, a significant increase in invasive disease due to serotype 19A was observed. Although MLST 199 remains the most frequent sequence type among invasive isolates (of 19A), a multidrug-resistant sequence type, not previously identified in Massachusetts, has become an important cause of invasive disease (Pelton SI et al. *Pediatr Infect Dis J.* 2007; 26:468-72.).

ACTION ITEM #17: EXPAND AND ENHANCE COORDINATION OF SURVEILLANCE FOR DRUG-RESISTANCE IN ENTERIC BACTERIA IN SICK AND HEALTHY HUMANS AND IN SICK AND HEALTHY ANIMALS ON FARMS, AT SLAUGHTER, AND AT RETAIL.



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PROJECT TITLE: FDA SCIENCE BOARD REVIEW OF THE NARMS PROGRAM

- **Agency:** CDC, FDA, USDA
- **Description:** A scientific review designed to help the program identify how it can enhance the coordination among the three arms to provide a more comprehensive look at drug resistance in enteric bacteria was initiated.
- **Results:** In 2007, the NARMS program underwent an extensive review by the FDA Science Board, focusing on 4 major areas: sampling strategies, data reporting and harmonization, coordinated research, and international surveillance activities. FDA responded to the Board's recommendations, and is prioritizing recommendations for improving the program. A strategic planning meeting was held at CDC, September 17-18, 2007 focusing on how best to implement the Science Board recommendations where appropriate.

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PROJECT TITLE: INTEGRATED (HUMAN, ANIMAL, RETAIL) NATIONAL ANTIBIOTIC RESISTANCE MONITORING SYSTEM FOR ENTERIC BACTERIA (NARMS) REPORT

- **Agency:** CDC, FDA, USDA
- **Description:** An integrated summary of human, animal, and retail meat NARMS data for annual publication
- **Results:** CVM released the FY 2003 executive report, which summarizes data on Salmonella and Campylobacter isolates from all three components of the program in an integrated format, on CVM's website on February 5, 2007. The joint FDA, CDC and USDA FY 2004 Executive Summary of NARMS data will become available Summer 2007. The fourth annual NARMS retail meat report provides 2005 data on the prevalence of antimicrobial resistant foodborne pathogens and commensal bacteria among retail meat and poultry samples, comprising results from nearly 4,800 samples, was released in December, 2007.

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PROJECT TITLE: ANTIMICROBIAL RESISTANT BACTERIA IN FEED INGREDIENTS

- **Agency:** FDA
- **Description:** Assess the prevalence of antimicrobial resistant bacteria in feed ingredients, primarily rendered product. This work will be done in conjunction with FDA field personnel. Results will be coordinated with NARMS. Expand NARMS into retail foods of animal origin.
- **Results:** Initial surveys of rendered products and plant based proteins completed. CVM continues to screen feeds and feed commodities for the presence of antimicrobial resistant Enterococcus and E. coli.

ACTION ITEM #18: EVALUATE THE USEFULNESS OF MONITORING SENTINEL HUMAN POPULATIONS (E.G., FARM, ABATTOIR, FRUIT AND VEGETABLE, AND FOOD



PROCESSING PLANT WORKERS) AND PERSONS IN THE GENERAL COMMUNITY FOR INFECTION OR COLONIZATION WITH RESISTANT ENTERIC BACTERIA.

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PROJECT TITLE: NARMS ENTEROCOCCI AND *E COLI* SURVEILLANCE STUDY

- **Agency:** CDC
- **Description:** Determine the susceptibility patterns for isolates of Enterococci and *E coli* isolated from stool samples of healthy persons or outpatients from the community. Determine the risk factors associated with resistant and susceptible bacteria.
- **Results:** Four states are sending isolates of enterococci and two states for *E. coli* to NARMS CDC lab collected from stool of healthy volunteers or outpatients who report no hospitalization. Interviews are being conducted to determine specific environmental, medical, and food exposures previous to the culture. In 2007 susceptibility data were published in NARMS 2004 human isolate report.

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PROJECT TITLE: ANTIMICROBIAL RESISTANT BACTERIA IN SENTINEL HUMAN POPULATIONS

- **Agency:** FDA
- **Description:** Evaluate abattoir workers for carriage of antimicrobial resistant bacterial pathogens.
- **Results:** CVM funded a cooperative research agreement to academic investigators at the University of Maryland to characterize antimicrobial resistance and genetic relatedness among enterococcal isolates from retail poultry, and healthy and ill humans. The study is complete and data analysis is in progress. CVM scientists also partnered with scientists in the Mexican Resist-Vet surveillance program to determine the prevalence of *Salmonella* species and quinolone-resistant non-type specific *E .coli* from human clinical cases, asymptomatic children, and raw retail meats.

ACTION ITEM #19: CONDUCT PILOT STUDIES TO ASSESS THE EXTENT OF ENVIRONMENTAL CONTAMINATION BY ANTIMICROBIAL DRUG RESIDUES AND DRUG-RESISTANT ORGANISMS THAT ENTER THE SOIL OR WATER FROM HUMAN AND ANIMAL WASTE. IF CONTAMINATION IS DETECTED, CONDUCT APPROPRIATE SURVEILLANCE IN WASTE, SURFACE AND GROUND WATER, AND SOIL FROM AGRICULTURAL AREAS IN WHICH WASTE IS USED FOR FERTILIZER, AND CONDUCT STUDIES TO DETERMINE POTENTIAL IMPACT ON HUMAN AND ANIMAL HEALTH.

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PROJECT TITLE: INVESTIGATING ENVIRONMENTAL SINKS OF MACROLIDE ANTIBIOTICS, AND ILLICIT DRUGS, WITH ANALYTICAL CHEMISTRY

- **Agency:** EPA

- **Description:** Research to determine what, if any, environmental sinks the macrolide antibiotics and illicit drugs (e.g., methamphetamine, MDMA) apportion to. This will include: source waters, wastewaters, biosolids, wetland plants, sediments, and possibly fish tissue. Antibiotics being analyzed include azithromycin, roxithromycin, and clarithromycin.
- **Results:** Ongoing. Preliminary data suggests that there are reservoirs of the macrolides other than wastewater and biosolids (i.e., wetland plant/roots and sediments). Some correlation between prescribed use of macrolides and environmental findings, but presence of Roxithromycin, which is not used in the U.S., suggests other means are used for obtaining antibiotics.

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PROJECT TITLE: OCCURRENCE, TRANSPORT, AND FATE OF PHARMACEUTICALS AND OTHER EMERGING CONTAMINANTS PRESENT IN WASTEWATER

- **Agency:** EPA
- **Description:** At ten locations, samples were collected upstream and at two sites downstream from the wastewater treatment plant discharge, as well as from the effluent pipe. Of the 110 compounds investigated in effluents and surrounding surface waters, 78 were detected at least once. Different chemicals exhibited diverse environmental persistence.
- **Results:** This project supplied information on the occurrence and fate of pharmaceuticals and other wastewater derived compounds. This information is being applied in other projects that are (1) evaluating the compounds for use as indicators of human fecal contamination; and (2) ascertaining which chemicals are present in finished drinking water.

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PROJECT TITLE: PERSISTENCE OF CONTAMINANTS FROM WASTEWATER DISCHARGES DURING DRINKING WATER TREATMENT: IDENTIFICATION OF COMPOUNDS AND DEGRADATION/DISINFECTION BYPRODUCTS, EVALUATION OF REMOVAL, AND POTENTIAL EXPOSURE

- **Agency:** EPA
- **Description:** Compounds in wastewater, including antibiotics, discharged from a treatment plant or septic system have the potential to end up in surface or groundwater that may ultimately be used as a source of drinking water. Two different sampling plans will be implemented to determine the presence of these chemicals in drinking water. In Phase 1, the source and finished waters of 9 - 15 drinking water treatment plants, known to be impacted by wastewater, will be sampled. The samples will be analyzed using existing USGS methods for pharmaceuticals and wastewater compounds, as well as by two new methods currently under development at the USGS. The first new method will consist of pharmaceuticals not currently included in the existing methods; the second will focus on chlorination and degradation byproducts of wastewater contaminants. Phase 2 will be a more intensive investigation of two to four drinking water treatment facilities.

- **Results:** Ongoing. This work will assist the USEPA's Office of Water in determining which compounds should be included in future Unregulated Contaminant Monitoring Regulation (UCMR) sampling plans. Knowledge of the occurrence and persistence of these compounds will become increasingly important in the future as the demands on potable water sources increase and communities turn to approaches such as water reuse to supplement their drinking water supply.

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PROJECT TITLE: DEFINING THE ROLE OF SALMONELLA NEWPORT IN CONTAMINATED OYSTERS

- **Agency:** USDA
- **Description:** Research to test the ability of Salmonella to survive in oysters and to track the source of Salmonella in surface waters
- **Results:** Overall prevalence of 7.4% of Salmonella in oysters with up to 78% in some bays. Majority is one genotype of *S. newport*. Funded by CSREES, NRI program (Univ of AZ)

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PROJECT TITLE: ENHANCE OVERALL UNDERSTANDING OF PATHOGENS THAT POSE A FOOD-SAFETY RISK PARTICULARLY FROM THE ENVIRONMENT.

- **Agency:** USDA
- **Description:** Pilot study to determine the contribution waterways play in movement of bacteria originating from animal production facilities in particular.
- **Results:** A mobile microbiology trailer has been designed and equipped. In the summer of 2005, collection will start in the southeastern US with the intent to visit all 50 states within the next 5 years. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: ENHANCE OVERALL UNDERSTANDING OF PATHOGENS THAT POSE A FOOD-SAFETY RISK AND TO ROUTINELY MONITOR CRITICAL DISEASES IN FOOD-ANIMAL PRODUCTION, AND DEVELOP A MODEL FOR FUTURE SURVEILLANCE EFFORTS ON A NATIONAL LEVEL.

- **Agency:** USDA
- **Description:** CAHFSE will enable USDA to identify and implement mitigation strategies for animal health and food safety issues in a timely manner thereby averting adverse economic, animal well-being, and public health consequences. Further, it will provide comprehensive science based answers regarding animal health and public health, it will serve as a model for future surveillance efforts on a national level, and it will complement information obtained from both the National Antimicrobial Resistance Monitoring System (NARMS) and USDA VetNet programs. These data are being used by the swine industry to develop management recommendations for producers.

- **Results:** This program is being expanded to all commodities and has been endorsed by the Animal Ag Coalition and other commodity groups. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

ACTION ITEM #20: GATHER INFORMATION ON THE RELATIONSHIP BETWEEN ANTIMICROBIAL PESTICIDE AND HERBICIDE USE AND THE EMERGENCE OF DRUG-RESISTANCE BY MONITORING.

## FOCUS AREA II: PREVENTION AND CONTROL

ACTION ITEM #21: IDENTIFY FACTORS THAT PROMOTE OR IMPEDE APPROPRIATE DRUG USE IN HOSPITALS, EXTENDED CARE FACILITIES, AND OUTPATIENT SETTINGS IN COLLABORATION WITH PARTNERS.

PROJECT TITLE: RESEARCH PROJECTS (R01): 1. IMPROVING ANTIBIOTIC USE IN ACUTE CARE TREATMENT (IMPAACT) TRIAL. 2. IMPLEMENTING EVIDENCE-BASED GUIDELINES FOR TREATING NHAP.

- **Agency:** AHRQ
- IMPAACT has examined patient, physician, and hospital factors relating to appropriate antimicrobial use and has tested different types of interventions to improve antimicrobial use in eight emergency departments located across the United States. 2. This quasi-experimental study is designed to test the translation of multidisciplinary guidelines on evaluating and treating nursing home-acquired pneumonia (NHAP) into practice in multiple nursing facilities.
- **Results:** Antimicrobial overuse is very common in emergency departments (EDs), especially for acute bronchitis. Emergency departments affiliated with ED training programs appear to prescribe fewer unnecessary antimicrobials (Gonzales R et al. Acad Emerg Med 2006; 13:288-94.). EDs located in hospitals with restrictive inpatient formularies prescribe fewer fluoroquinolones (Aspinall SL et al. Am J Manag Care 2007; 13:241-8.). A patient and physician educational intervention reduces overuse of antimicrobials, although significant room for improvement remains (Metlay JP et al. Ann Emerg Med 2007;50:221-30). 2. The intervention is complete. A no-cost extension was obtained to complete data analysis. Findings from the baseline study year that suggest that guideline compliance is related to nurse and CNA staffing and turnover are in press in J Gerontol A Biol Sci Med Sci.

PROJECT TITLE: RESEARCH DEMONSTRATION AND DISSEMINATION PROJECT (R18): IMPROVING OTITIS MEDIA CARE WITH HER-BASED CLINICAL DECISION SUPPORT AND FEEDBACK.

- **Agency:** AHRQ

- **Description:** Otitis media is the second commonest disease in childhood and the most common reason for antibiotic prescriptions in the United States. Physicians tend to overuse antibiotics for otitis media because it can be hard to diagnose, medical care is often fragmented across multiple sites and clinicians, and some physicians are not aware of national guidelines that recommend more judicious use of these medicines.
- **Results:** The Children's Hospital of Philadelphia primary care network has been organized as a Pediatric Research Consortium with >180,000 children managed by >300 practitioners from 28 practices in three states. The project will use the Children's Hospital electronic health record to integrate care across time and to supply physicians with the knowledge they need about how to treat a patient at the point of care. Randomly allocating practices into usual care, full intervention, and full intervention without feedback, the project will assess the effects of intervention on quality, resource use, and clinician adoption of the technology.

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PROJECT TITLE: RESEARCH DEMONSTRATION (U18): CENTERS FOR EDUCATION AND RESEARCH ON THERAPEUTICS (CERTS) PROGRAM: A NATIONAL INITIATIVE TO INCREASE AWARENESS OF THE BENEFITS AND RISKS OF NEW, EXISTING, OR COMBINED USES OF THERAPEUTICS THROUGH EDUCATION AND RESEARCH.

- **Agency:** AHRQ
- **Description:** The University of Pennsylvania Center for Education and Research on Therapeutics has undertaken studies investigating the association between antibiotic use and antibiotic resistance, including the impact of different methods of categorizing prior antibiotic use. 2. The Harvard Pilgrim Healthcare CERT supports nine collaborating systems within an HMO Research Network to study antibiotic use in children and has evaluated the impact of a 16-community trial to promote judicious antibiotic use in Massachusetts.
- **Results:** Inaccurate communication of patient data, particularly microbiological data, during prior-approval calls is associated with an increased risk of inappropriate antimicrobial recommendations from an antimicrobial stewardship program (ASP). Clinicians and ASP practitioners should work to confirm that critical data have been communicated accurately prior to use of that data in prescribing decisions (Linkin DR et al. Infect Control Hosp Epidemiol 2007; 28:1374-81.). 2. A substantial downward trend in antibiotic prescribing occurred, even in the absence of intervention. The intervention had no additional effect among children aged 3 to <24 months but was responsible for a 4.2% decrease among those aged 24 to <48 months and a 6.7% decrease among those aged 48 to <72 months. The intervention effect was greatest among Medicaid-insured children and for broad-spectrum agents. A sustained, multifaceted, community-level intervention was only modestly successful at decreasing overall antibiotic use beyond substantial secular trends (Finkelstein JA et al. Pediatrics 2008;121:e15-23.).

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PROJECT TITLE: HIV DRUG RESISTANCE AND CLINICAL EPIDEMIOLOGY

- **Agency:** CDC

- **Description:** DHAP's Epidemiology Branch conducts a number of activities to assess the clinical relevance of HIV resistance. The Epi Branch will continue collecting commercial HIV genotype and phenotype antiretroviral resistance testing results from the convenience sample of ca. 3,000 active adult participants enrolled in the HIV Outpatient Study (HOPS) and the Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (the "SUN" Study) and ca. 1,000 children and young adults in the Longitudinal Epidemiologic Study to Gain Insight into HIV and AIDS in Children and Youth (LEGACY). These data will be used to assess modifiable factors for reducing risk of developing clinically relevant antiretroviral resistance.
- **Results:** To summarize the data thus far:
  - Among everyone in Legacy: 887 genotype tests from among 536 participants (1.65 test per participant); 310 phenotype tests from among 226 participants (1.37 test per participant); and 85 virtual phenotype tests from among 68 participants (1.25 test per participant)
  - In HOPS, since 1997, clinicians have ordered (and results available): 3,420 genotype tests from among 1,995 patients (1.71 tests per patient) and 1,269 phenotype tests from among 819 patients (1.55 tests per patient)
  - In the SUN study since March 2004, 701 participants have been enrolled into the study; of these 346 genotype tests have been completed among 235 participants (1.5 per patient) and 26 phenotype tests have been completed among 20 participants (1.3 per patient).

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PROJECT TITLE: LABELING RULE

- **Agency:** FDA
- **Description:** The new labeling is intended to educate physicians and the public about the resistance problem and to encourage physicians to prescribe systemic antibacterial drugs only when clinically necessary.
- **Results:** The Final Labeling Rule was published in the Federal Register on February 6, 2003. The rule went into effect February 6, 2004. Announcement of Labeling Rule (<http://fda.gov/bbs/topics/NEWS/2003/NEW00869.html>)

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PROJECT TITLE: APPROPRIATE USE OF ANTIMICROBIALS

- **Agency:** VA
- **Description:** The VHA has a national formulary, develops and implements care guidelines, and provides extraordinary educational opportunities for staff to deal with questions concerning appropriate use of antibiotics. This is an ongoing activity, but the effort will continue to be enhanced by further collaboration with federal agencies and other partners (including the private sector) since appropriate antibiotic usage involves many components such as physician education, education of the public, appropriate drug advertising, control of over-the-counter antibiotic use, and many other items that require

intervention both inside and outside of the federal systems. Local VA facilities pilot and use standardized computerized medical records, templating and ordering for medication ordering (including antimicrobials) that incorporate use of clinical pathways for infectious diseases processes (e.g., pneumonia, peri-operative antimicrobial use) ; these all help to direct providers or care to preferred diagnostic and therapeutic strategies.

- **Results:** Ongoing. Infectious Diseases Field Advisory Committee has representation on the national Antimicrobial Medical Advisory Panel (MAP) for pharmacy. Local sites update pathways and order sets based on local feedback from front line providers and as newer regional and national recommendations are available; also as formulary choices change (either local, regional or national) there updates also can occur.

ACTION ITEM #22: DEVELOP APPROPRIATE DRUG USE POLICIES AND EVALUATE THE IMPACT (INCLUDING ON PRESCRIBING PATTERNS, RESISTANCE RATES, PATIENT OUTCOMES, AND COST) OF IMPLEMENTING THESE POLICIES IN HOSPITALS AND OTHER HEALTH CARE DELIVERY SETTINGS. IDENTIFY WAYS TO INCREASE ADHERENCE TO APPROPRIATE USE POLICIES PROVEN TO BE BENEFICIAL IN COLLABORATION WITH PARTNERS.

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PROJECT TITLE: APPROPRIATE USE OF ANTIMICROBIALS

- **Agency:** VA
- **Description:** The VHA has a national formulary, develops and implements care guidelines, and provides extraordinary educational opportunities for staff to deal with questions concerning appropriate use of antibiotics.
- **Results:** Ongoing. Infectious Diseases Field Advisory Committee has representation on the national Antimicrobial Medical Advisory Panel (MAP) for pharmacy

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PROJECT TITLE: SURGICAL SITE INFECTION ANTIBIOTIC PROPHYLAXIS PLAN

- **Agency:** VA
- **Description:** b. VHA has introduced surgical site antibiotic prophylaxis (including both timing and appropriateness of choices, as well as timely cessation) as a performance measure for VHA systems nationwide. These performance measures constitute 50% of the annual evaluation for Executive Career Field (ECF) performance plans for VHA regional directors and individual medical center directors.
- **Results:** In Federal Fiscal Year 2005, VHA introduced surgical site antibiotic prophylaxis as a performance measure for VHA systems nationwide--ongoing into FY 2008 (considered a "mission critical" measure

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PROJECT TITLE: COMMUNITY-ACQUIRED PNEUMONIA PERFORMANCE MEASURES

- **Agency:** VA

- **Description:** Along with b above, VHA Office of Quality and Performance has initiated quality measures for timing, diagnostics and treatment of community-acquired pneumonia.
- **Results:** Implemented FY 2006 and ongoing into FY 2008 considered a "mission critical" measure.

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PROJECT TITLE: D. TRANSFORMATIONAL MEASURES FOR VHA-INFECTION RATE REDUCTION

- **Agency:** VA
- **Description:** VHA Office of Quality and Performance has espoused as Transformational Measure 1, Infection Rate Reduction which included central line-associated bloodstream infections, ventilator-associated pneumonias and methicillin-resistant Staphylococcus aureus prevention. Transformational measures are incremental measures designed to support long term strategic goals. They are visionary and identify areas of significant system impact, but may not be attainable in a single performance year.
- **Results:** Formally adopted as transformational measures for FY 2008. Ventilator-associated pneumonia and central-line-associated bloodstream infections in the ICUs have been in effect since FY 2006 through the VA Inpatient Evaluation Center (IPEC). MRSA Prevention Initiative started in FY 2007. All are ongoing.

ACTION ITEM #24: HELP INDIVIDUAL HOSPITALS AND HEALTHCARE SYSTEMS ANALYZE HOW THE AVAILABILITY OF AR DATA AND COMPUTER-ASSISTED DECISION SUPPORT SYSTEMS INFLUENCES PRESCRIBER BEHAVIOR, HEALTH OUTCOMES, AND COSTS. THIS PLAN MAY INCLUDE THE PROVISION OF COMPUTER SOFTWARE AND THE ESTABLISHMENT OF PROJECTS THAT INVOLVE THE MEDICARE PEER REVIEW ORGANIZATIONS (PROS).

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PROJECT TITLE: EMERGING PATHOGENS INITIATIVE (EPI)

- **Agency:** VA
- **Description:** Data on antimicrobial resistance with quartile rankings in the VHA nationwide are provided to the Networks, including reporting site-specific data by using the EPI, an automated surveillance system. This will be an ongoing initiative since it is not entirely clear what the best method for AR feedback will be in the final analysis.
- **Results:** Ongoing at VA sites across the country. Enhancements that acquire additional information on antimicrobial resistance of specified organisms were distributed to reporting stations in July 2004

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PROJECT TITLE: B. AHRQ 1 UC1 HS014237 TOWARD A SAFETY CULTURE: REDUCING NOSOCOMIAL INFECTIONS



- **Agency:** VA
- **Description:** VA personnel led a regional research study sponsored by AHRQ designed to look at rapid-cycle implementation strategies of evidence-based practices that are known to reduce health care associated infections.
- **Results:** b. Primary study accrual has completed and review however reporting of results is ongoing. This regional cooperative project received the 2005 Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Ernest Amory Codman award and demonstrated findings of: i) reduced central line infections by 50 percent. ii) increased adherence to evidence-based practices to 95 percent from 30 percent. iii) created a new model for facilitating improvement as a community, with an increased chance of success, sharing of successful strategies, reducing rework across the sites, and speeding the implementation process.

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PROJECT TITLE: INPATIENT EVALUATION CENTER (IPEC)

- **Agency:** VA
- **Description:** c. The IPEC is a national program to improve outcomes (risk adjusted mortality and length of stay) in VA ICUs and eventually in inpatient care through feedback of outcomes and implementation of evidenced-based practices.
- **Results:** Implemented nationwide during FY 2006. Ongoing. Due to its ease of use and navigation, the IPEC data entry portal has also been used for data entry for the Methicillin-resistant *Staphylococcus aureus* (MRSA) Prevention Initiative

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PROJECT TITLE: REVIEW OF COMMERCIALY AVAILABLE COMPUTER SOFTWARE TO BE USED FOR INFECTION PREVENTION, CONTROL AND CONTAINMENT

- **Agency:** VA
- **Description:** VA is actively reviewing computer off-the-shelf software products to assist in infection control processes for prevention and control of infectious diseases including antimicrobial resistant organisms; computer-assisted decision support systems will be a key element in VA's choice.
- **Results:** Review and evaluation of off-the-shelf products remains in process for issue of antibiotic resistance, as well as having features that will assist in evaluation of healthcare-associated infection analysis. At this time, one vendor product has been selected for further development nationwide that will include antibiogram monitoring and possibly decision support regarding antibiotic choices. Provided successful pilot and beta-site testing, system wide implementation would be anticipated within 3 years.

\*\* TOP PRIORITY \*\*

ACTION ITEM #25: CONDUCT A PUBLIC HEALTH EDUCATION CAMPAIGN TO PROMOTE APPROPRIATE ANTIMICROBIAL USE AS A NATIONAL HEALTH PRIORITY. THE HEALTH CAMPAIGN SHOULD INVOLVE MANY PARTNERS.

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PROJECT TITLE: "GET SMART: KNOW WHEN ANTIBIOTICS WORK" NATIONAL MEDIA CAMPAIGN

- **Agency:** CDC, FDA
- **Description:** This national media education campaign was developed to promote appropriate antimicrobial drug use in the community for upper respiratory infections, e.g., to decrease patient requests for antibiotics for illnesses for which they offer no benefit. Target audiences are parents of young children and healthy adults. The campaign uses a variety of health communication materials based on concepts tested in focus groups, and its effectiveness will be evaluated when support is available.
- **Results:** Ogilvy Public Relations Worldwide was awarded the media contract in September 2001 to implement a three phase media plan. Phase I focused on research and development while Phase II culminated with a nationwide launch of the media campaign. The TV PSA generated 86.5 million impressions; the radio PSA 160 million impressions; the print ads were viewed by 185 million; and traffic to the Get Smart website substantially increased (unique visitors jumped from just 4,927 in August 2003 to 28,604 in December 2004). Phase III of the media plan involved continuing the outreach efforts implemented in Phase II. During the final phase, appropriate antibiotic use messages and media were developed and tested for Spanish speaking parents of young children, English speaking healthy adults 21- 49, and American Indian/Native American groups, in an effort to expand the campaign's reach. The new materials were released as part of a media re-launch in early 2005. In FY2006, TV and Radio PSAs were made available for download on the Get Smart website.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK - MULTICULTURAL OUTREACH/DIVERSITY INITIATIVE

- **Agency:** CDC
- **Description:** Several projects are in development or implementation stages to increase awareness of antibiotic resistance and appropriate antibiotic use among minority communities and those who do not speak English. Projects include: development of educational materials for Spanish-speakers and American Indian/Native American (AI/NA) communities, train-the-trainer sessions with Latino and AI/NA community members, speaking engagements, promotora outreach in California, and development of partnerships to further develop and sustain the initiative.
- **Results:** The Spanish and AI/NA materials were launched as part of the Phase III media release (see media campaign). Numerous presentations and train-the-trainer sessions have been conducted with Latino interest associations and the Indian Health Service Community Health Representative members. A contest was conducted in early 2006

among the CHRs to distribute educational materials and appropriate antibiotic use messages to AI/NA audiences. Since early 2005, this initiative has developed 17 new partnerships. In FY 2006, Get Smart worked with the Indian Health Service to disseminate culturally-appropriate messages/tools to American Indian communities. In FY2008, with CDC assistance, the Get Smart New Mexico program will develop a curriculum for American Indian communities.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK - PHARMACY INITIATIVE

- **Agency:** CDC
- **Description:** Several projects are in development or implementation stages to increase awareness among consumers about antibiotic adherence, and to educate pharmacists about counseling consumers/clients on appropriate antibiotic use. Projects include: hospital pharmacist CE program, distribution of adherence messages for consumers, and development of partnerships to develop and sustain initiative.
- **Results:** Pharmacist CE: In FY07, Get Smart campaign partner, Society of Infectious Diseases, continued development of a CE program for hospital pharmacists to teach about the issue of antibiotic resistance and give tools to communicate with consumers. Upon final CDC clearance, the program will be hosted online by CE provider, Pharmacy Choice (rxschool.com). In fall 2008, a 5th-year pharmacy student will do a 5 week rotation with the Get Smart campaign and revise the hospital pharmacist CE into a CE for community pharmacists.  
Adherence piece distribution: the antibiotic adherence education piece has been developed, tested, printed and distributed to key partners in the pharmacy setting. Get Smart is working to partner with more pharmacy chains, especially the ones which distribute free or low cost antibiotics.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK ON THE FARM

- **Agency:** CDC
- **Description:** Conduct a public health education campaign to promote appropriate antimicrobial use as a national health priority, involving many partners.
- **Results:** Completed. 10 funded state-based campaigns completed state-based projects addressing appropriate antimicrobial use. This work resulted in 7 peer-reviewed publications, 8 oral/poster presentations, 2 publicly accessible web pages, 2 behavioral surveys, 9 electronic veterinary curricular modules addressing treatment in food animal species, and printed materials that were distributed to over 50,000 food animal producers.

**\*\* TOP PRIORITY \*\***

**ACTION ITEM #26: IN COLLABORATION WITH MANY PARTNERS, DEVELOP AND FACILITATE THE IMPLEMENTATION OF EDUCATIONAL AND BEHAVIORAL**

## INTERVENTIONS THAT WILL ASSIST CLINICIANS IN APPROPRIATE ANTIMICROBIAL PRESCRIBING.

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### PROJECT TITLE: MENTORED CLINICAL SCIENTIST AWARD (K08): IMPROVING CARE FOR ACUTE RESPIRATORY INFECTION

- **Agency:** AHRQ
- **Description:** The recipient is developing and implementing an electronic medical record-based template for acute respiratory infection (ARI) visits, the ARI Smart Form. The ARI Smart Form will standardize documentation of care and give clinicians easy access to clinical information, patient-education materials, and clinical decision support with a goal of reducing inappropriate antibiotic prescribing.
- **Results:** The ARI Smart Form underwent usability testing in Summer 2005 and was pilot-tested in Fall 2005 (Linder JA et al. AMIA Annu Symp Proc 2007: pp. 468-72.). A full randomized controlled trial in some 24 practices took place during the 2005-2006 cold and influenza season (manuscript in preparation). The recipient has also developed and is testing a performance measurement tool for comparing providers' antibiotic prescribing for ARIs, the ARI Quality Dashboard (Jung E et al. In: Teich JM et al. AMIA Annual Symposium Proceedings; November 10-14, 2007; Washington DC. Washington DC: American Medical Informatics Association; 2007; p. 1035.).

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### PROJECT TITLE: CAMPAIGN TO PREVENT ANTIMICROBIAL RESISTANCE IN HEALTHCARE SETTINGS

- **Agency:** CDC
- **Description:** The Campaign to Prevent Antimicrobial Resistance in Healthcare Settings (the Campaign) was launched in March 2002. The Campaign's overall goal is to reduce antimicrobial resistance (AR) by decreasing inappropriate antimicrobial use and improving adherence to proven infection control precautions. Five 12-step Programs with evidence-based action steps have been developed to target physicians who provide care to the following populations: hospitalized adults, dialysis patients, surgical patients, hospitalized children, and long-term care residents. Didactic tools and materials also have been developed and tested and accompany each of the 12-step Programs to promote the implementation of the recommended steps. In addition, materials have been developed that focus on the prevention of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).
- **Results:** The Campaign is currently undergoing an overhaul in an attempt to better focus the messages and action steps to enhance its impact. The Campaign now has a medical director and a dedicated public health advisor. Major 2007 activities included: 1) Funded eight states through the Epidemiology and Laboratory Capacity (ELC) mechanism to conduct educational activities to prevent AR in healthcare settings and CA-MRSA. 2) Collaborated with AMA and IDSA to develop a clinical management algorithm to assist outpatient healthcare providers with the diagnosis and treatment of patients with MRSA skin and soft tissue infections. 3) Co-branded with the Massachusetts Department of

Public Health a series of four posters to address prevention of MRSA among athletes. 4) Developed a series of eight posters targeted at general audiences with prevention messages for MRSA. 5) Collaborated with the National Collegiate Athletic Association to develop a series of six posters to address prevention of MRSA among athletes.

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PROJECT TITLE: REPORTING ANTIMICROBIAL SUSCEPTIBILITY DATA TO CLINICIANS

- **Agency:** CDC
- **Description:** Assist CLSI to produce guidelines for clinical microbiology laboratories on how to report unique resistance patterns, improve detection of inducible resistance, and how to compile and report summaries of cumulative antimicrobial susceptibility data (antibiograms) in a standardized manner to aid in clinical decisions.
- **Results:** More extensive explanations of resistance patterns or cautions in prescribing antimicrobial agents are being incorporated into the Clinical and Laboratory Standards Institute (CLSI) guidelines, which are updated annually. Numerous seminars, teleconferences and educational efforts were presented by DHQP microbiologists to educate clinicians and microbiologists about which antimicrobial agents to override on a patient's report and when further characterization of the pathogen (MRSA, *C. difficile*, multidrug-resistant gram negative rods) would or would not impact the selection of antimicrobial therapy.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK-  
STATE-BASED MULTIFACETED INTERVENTIONS FOR CLINICIANS AND PATIENTS TO  
PROMOTE THE APPROPRIATE USE OF ANTIBIOTICS FOR OUTPATIENT UPPER  
RESPIRATORY INFECTIONS

- **Agency:** CDC
- **Description:** The campaign assists states in implementing broad-based multi-faceted health communication and behavioral interventions to promote appropriate antibiotic use for outpatient upper respiratory infections. State health departments develop broad-based coalitions (e.g., state medical societies, healthcare delivery organizations, healthcare purchasers, consumer groups), use CDC educational materials, develop materials of their own, launch campaigns targeting providers and the general public, and evaluate various aspects of their local campaigns and/or appropriate antibiotic use knowledge, behaviors, and attitudes. Controlled trials have demonstrated success of this program in decreasing inappropriate prescribing; also, nationwide antibiotic prescribing rates for children are declining.
- **Results:** In FY05, 31 local programs were funded (29 program, 2 travel-only). In FY06, 34 local programs were funded (25 program, 9 travel-only). In FY07, 31 programs were funded (20 program, 11 travel). In FY08, 15 program were funded (14 program, 1 carryover, 0 travel). The Get Smart campaign maintains a comprehensive website that funded sites can utilize to gain access to campaign resources and educational tools and to learn more about national campaign activities. The Get Smart campaign conducts regularly scheduled phone calls to provide technical assistance as well as document

ongoing activities. In November 2007, Get Smart hosted a meeting for its funded state programs.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK-DEVELOPMENT AND DISTRIBUTION OF EVALUATION MANUAL FOR PROGRAMS PROMOTING APPROPRIATE ANTIBIOTIC USE IN THE COMMUNITY

- **Agency:** CDC
- **Description:** CDC distributes funds to state and local health departments to develop local campaigns to promote appropriate antibiotic use, and all funded sites are required to include an evaluation component. However, with limited resources, the vast majority of sites do not adequately evaluate the success of their work. In addition, our grantees have repeatedly requested assistance in planning and implementing these evaluations. Data gathered during evaluation enables managers and staff to create the best possible programs, identify lessons learned, make modifications as needed, monitor progress toward program goals, and judge the success of the program in achieving its short-term, intermediate, and long-term outcomes.
- **Results:** During FY 2004, meetings with the evaluation manual working group focused on reviewing manual content, coordinating writing styles, and planning for the completion and distribution of the manual. Completed drafts of two appropriate antibiotic use case studies, sent them to program coordinators of some of our funded sites to solicit feedback, and revised the case studies accordingly. The manual was finalized and cleared in fall 2005. The manual underwent final revisions and proofreading in early 2006 and was released to all CDC-funded state programs and other interested parties in April 2006 via electronic message board, Epi X. In FY2007, a hard copy of the manual was provided to all interested groups. The manual is also available for download on the Get Smart website. A Program Evaluation Officer has been hired as a contractor to assist Get Smart and its funded sites with all program evaluation activities.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK-MEDICAL PROFESSIONAL CURRICULA PROMOTING APPROPRIATE USE OF ANTIBIOTICS

- **Agency:** CDC
- **Description:** Developing and promoting three appropriate antibiotic use curricula for providers:
  1. Curriculum for medical students regarding appropriate antibiotic use. Topics include extent of antibiotic resistance, diagnostic techniques, and appropriate antibiotic use. Case studies focus on diagnosis, treatment, and provider-patient communication. This course is designed to meet the needs of a variety of medical schools with components that can be used separately or as a whole.
  2. Curriculum for primary care residents on appropriate antibiotic use based on the medical school curriculum.
  3. Curriculum for family practice and pediatric residents for diagnosing otitis media.

#### 4. Continuing Education course for MDs, PAs, and NPs

- **Results:** Medical school curriculum, ongoing: The curriculum is intended to be distributed nationally in FY2008. 2) Primary care residents curriculum, ongoing: The Oregon Health and Science University developed a curriculum for primary care residents based on the medical school curriculum. The study team extended the pilot testing phase of the project due to difficulties recruiting primary care residents for testing. After testing and refinement, the curriculum will be used in additional Oregon programs, and later made available nationally. 3) Otitis media curriculum, completed The Children's Hospital of Pittsburgh has developed a curriculum for family practice and pediatric residents to improve training in the diagnosis and treatment of otitis; available at: <http://pedsed.pitt.edu/>. 4) Get Smart funded the Colorado Get Smart campaign to develop and promote an online video-based CE course for acute respiratory infections; it will be available in early FY2009.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK - INFLUENZA ANTIVIRAL EDUCATION FOR PHYSICIANS AND PATIENTS (IN COLLABORATION WITH THE INFLUENZA DIVISION)

- **Agency:** CDC
- **Description:** Develop and promote educational materials for providers and patients about recognizing flu and appropriate use of antivirals, which will in turn decrease inappropriate use of antibiotics. This will consist of evaluating the effectiveness of materials and key messages; conducting focus groups, surveys, and in-depth interviews, and incorporating key messages into web and print materials.
- **Results:** A contract has been awarded to the Academy for Educational Development to conduct this project with oversight from CDC. All research will take place by fall 2008. New materials will be available by Winter 2008/09.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK- NEW MESSAGE DEVELOPMENT INVOLVING ADVERSE DRUG EVENTS AND HEALTHCARE QUALITY PROMOTION.

- **Agency:** CDC
- **Description:** In FY2007, Get Smart convened an External Review Panel to assess the progress of the Get Smart program. While the expert panel stated that significant inroads had been made, they recommended that more should be done. They recommended shifting the focus of Get Smart's messages to include patient safety and healthcare quality promotion.
- **Results:** Get Smart staff will develop, test and implement new messages that highlight quality promotion and patient safety (e.g. adverse drug events). The staff will work with the Oak Ridge Institute for Science and Education, which has been awarded a contract to develop materials and conduct formative research. Focus groups with the general public and in-depth-interviews with physicians will be conducted in FY2008. New materials



should be available in early FY2009. CDC's Division of Healthcare Quality Promotion is a partner in this effort.

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PROJECT TITLE: PERFORMANCE MEASURES FOR SURGICAL ANTIBIOTIC PROPHYLAXIS AND ANTIBIOTIC THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA HAVE BEEN ROLLED OUT WITHIN THE LAST YEAR OR ARE IN PROCESS.

- **Agency:** VA
- **Description:** VHA Office of Quality and Performance has instituted nationwide measures related to antibiotic prescribing regarding timing of antibiotic prophylaxis relative to surgical procedures. Additionally, plans are in process to gather performance data on use of appropriate antibiotics relative to surgical prophylaxis, as well as with regard to treatment of hospitalized patients with community-acquired pneumonias.
- **Results:** Office of Quality and Performance measures began implementation in FY 2005 and continue through FY 2006 with plans for additional measures in FY 2008.

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PROJECT TITLE: DEVELOPMENT OF NATIONAL ICU INPATIENT EVALUATION CENTER (IPEC)

- **Agency:** VA
- **Description:** The IPEC is a national program to improve outcomes (risk adjusted mortality and length of stay) in VA ICUs and eventually in inpatient care through feedback of outcomes and implementation of evidenced-based practices. Currently two of the initiatives deal with issues related to infection prevention--catheter-related bloodstream infections and ventilator-associated pneumonias--both of which may involve resistant organisms. These data are reported back immediately to the local facilities who can track their rates over time and compliance with performance, as well as see the national mid-range statistical analysis results.
- **Results:** IPEC program initiated nationwide during FY 2006 with initial data demonstrating a decrease in ventilator-associated pneumonias and central catheter related bloodstream infections nationwide for each of the past two years.

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PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** In January 2007 VHA administration took strong directive action in plan to address infection with MRSA nationwide as a prototype agent for multidrug resistance issues; this national plan employs a bundle approach which includes hand hygiene, contact precautions, active surveillance culturing and cultural change. Seventeen VA medical centers ("beta-sites") across the country are also participating in a cooperative evaluation of this process with the Centers for Diseases Control and Prevention (CDC)

- **Results:** Initiated FY 2007 (all acute care facilities to have at least one unit active in program by March 15, 2007, with all acute care inpatient units participating in the prevention initiative as of December 31, 2007. Data collection has begun for measures of prevalence of MRSA upon admission to the medical center facility along with prevalence upon admission to each unit within a medical center facility, healthcare-associated infection rate with MRSA and MRSA transmission rates. Ongoing.

ACTION ITEM #27: EXPLORE WAYS TO INTEGRATE APPROPRIATE USE INFORMATION INTO ANTIMICROBIAL PACKAGE INSERTS AND PROMOTIONAL MATERIALS, TO PROVIDE SUCH INFORMATION TO PATIENTS WITH EACH PRESCRIPTION, AND TO PROVIDE CLEAR GUIDANCE TO INDUSTRY TO ENSURE THAT PROMOTION OF ANTIMICROBIALS DIRECTED TOWARDS CONSUMERS ENCOURAGES APPROPRIATE USE AND DISCOURAGES INAPPROPRIATE USE.

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PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK - PHARMACY INITIATIVE: PATIENT MONOGRAPH PROJECT

- **Agency:** CDC
- **Description:** In 2005, Get Smart developed a partnership with Catalina Health Resource, the largest distributor of prescription packaging advertising in the U.S. The antibiotic adherence message developed as part of the Pharmacy Initiative was placed as ads with antibiotic prescriptions nationwide.
- **Results:** During fall 2005, the Get Smart adherence PSA ran for 6 weeks nationally, due to donations of space from Catalina Health Resource. 13,000 pharmacies were reached along with over 1.25 million people, valuing \$1.4 million in advertising cost. A larger scale paid campaign took place in fall 2006, from partner donations received through CDC Foundation. Catalina Health Resource completed a second campaign in Michigan to compliment the Roundup pilot program, lasting 3 months (January 2006-April 2006) in Michigan pharmacies, with nearly 350,000 impressions statewide. There is currently no support for this activity.

ACTION ITEM #28: ARTICULATE FACTORS THAT SUPPORT THE CURRENT APPROACH OF REQUIRING PRESCRIPTION-ONLY DISPENSING FOR ALL SYSTEMIC (E.G., NONTOPICAL) ANTIMICROBIAL DRUGS USED IN CLINICAL MEDICINE.

ACTION ITEM #30: CONVENE AN ADVISORY PANEL OR OTHER EXPERT GROUP IN INVOLVING STAKEHOLDERS AND PARTNERS TO CONSIDER ISSUES RELATED TO RESISTANT PATHOGENS THAT CAUSE SERIOUS INFECTIONS FOR WHICH AVAILABLE TREATMENTS OPTIONS ARE VERY LIMITED OR NONEXISTENT.

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PROJECT TITLE: ANTIMICROBIAL DRUG DEVELOPMENT PUBLIC WORKSHOP (SPONSORED BY FDA, IDSA AND ISAP)

- **Agency:** FDA, CDC, NIH

- **Description:** Workshop provided information for and gained perspective from advocacy groups, industry and others on various aspects of antimicrobial drug development, including clinical trial design issues.
- **Results:** Workshop held April 15-16, 2004. Discussed the use of pharmacodynamic information in appropriate dose selection in clinical trials of anti-infective agents, and summarized the issues with developing antimicrobial drugs by allowing data from one serious disease to be supportive of data in another less serious disease such that sponsors would only have to perform one trial instead of two in the less serious disease. CDER resistance web site to access workshop transcripts (<http://www.fda.gov/cder/drug/antimicrobial/default.htm>)

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PROJECT TITLE: EXPERTS MEETING: COMMUNITY-ONSET METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*: IMPLICATIONS FOR ANTIMICROBIAL THERAPY AND POTENTIAL PREVENTION STRATEGIES

- **Agency:** CDC
- **Description:** CDC convened a two-day meeting of approximately 20-25 experts to discuss issues surrounding the diagnosis, treatment, and prevention of community-associated MRSA infections (CA-MRSA). Participants included clinical experts and epidemiologists from academic institutions and public health agencies with expertise in CA-MRSA and other Staphylococcal infections, as well as representatives from relevant professional societies.
- **Results:** Strategies for the clinical management of MRSA in the community, based on discussions held at this meeting, in conjunction with additional data was posted on the CDC website in March 2006: [www.cdc.gov/ncidod/dhqp/ar\\_mrsa\\_ca\\_04meeting.html](http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca_04meeting.html). In 2007, based on these strategies, CDC, the American Medical Association, and the Infectious Diseases Society of America, developed a treatment algorithm for the outpatient management of MRSA skin and soft tissue infections: [www.cdc.gov/ncidod/dhqp/ar\\_mrsa\\_ca\\_skin.html](http://www.cdc.gov/ncidod/dhqp/ar_mrsa_ca_skin.html).

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PROJECT TITLE: APPROPRIATE USE OF ANTIMICROBIALS

- **Agency:** VA
- **Description:** The VHA has a national formulary, develops and implements care guidelines, and provides extraordinary educational opportunities for staff to deal with questions concerning appropriate use of antibiotics. This is an ongoing activity, but the effort will continue to be enhanced by further collaboration with federal agencies and other partners (including the private sector) since appropriate antibiotic usage involves many components such as physician education, education of the public, appropriate drug advertising, control of over-the-counter antibiotic use, and many other items that require intervention both inside and outside of the federal systems.
- **Results:** Ongoing. Infectious Diseases Field Advisory Committee has representation on the national Antimicrobial Medical Advisory Panel (MAP) for pharmacy.

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PROJECT TITLE: NATIONAL MRSA SUMMIT AND MRSA IMPLEMENTATION TASK FORCE

- **Agency:** VA
- **Description:** National MRSA Summit with VA and non-VA experts to come to consensus on implementation. This Summit was used to compliment much work done by the National MRSA Prevention Initiative Implementation Task Force; it also helped to determine future issues for the Task Force and National Program Office.
- **Results:** MRSA Summit held May 2-3, 2007; work of Implementation Task Force will be ongoing. Subworkgroups for special patient populations of nursing home/long-term care/community living centers, spinal cord injury and polytrauma units have been formed, along with subworkgroups to address issues of patient education, employee education, decolonization and duration of contact precautions.

ACTION ITEM #31: CONVENE A WORKING GROUP TO EXAMINE THE IMPACT OF FEDERAL REIMBURSEMENT POLICIES FOR HOME PARENTAL ANTIMICROBIAL TREATMENT, APPROPRIATE ANTIMICROBIAL USE, AND APPROPRIATE USE OF ANTIMICROBIAL SUSCEPTIBILITY TESTING. WHERE NEEDED, THE WORKING GROUP WILL MAKE RECOMMENDATIONS FOR MODIFYING THESE POLICIES.

ACTION ITEM #32: DEVELOP AND SUBMIT MEASURES FOR APPROPRIATE ANTIMICROBIAL USE TO THE NATIONAL COMMITTEE FOR QUALITY ASSURANCE FOR INCLUSION IN HEALTH PLAN EMPLOYER DATA AND INFORMATION SET (HEDIS), WHICH PROVIDES COMPARATIVE DATA ON MANAGED CARE ORGANIZATIONS

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PROJECT TITLE: A SURGICAL SITE INFECTION ANTIBIOTIC PROPHYLAXIS PLAN

- **Agency:** VA
- **Description:** VHA has introduced surgical site antibiotic prophylaxis as a performance measure for VHA systems nationwide. These performance measures constitute 50% of the annual evaluation for Executive Career Field (ECF) performance plans for VHA regional directors and individual medical center directors. The particular performance measures relative to surgical site infection antibiotic prophylaxis include percent of the cases the drug began timely, percent of the cases the appropriate drug was given, and percent of the cases the drug was discontinued timely.
- **Results:** For Federal Fiscal Year 2005, VHA has introduced surgical site antibiotic prophylaxis as a performance measure for VHA systems nationwide. Refinement with additional measure of appropriate antibiotic choices chosen for FY 2008,

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PROJECT TITLE: COMMUNITY-ACQUIRED PNEUMONIA TREATMENT

- **Agency:** VA
- **Description:** VHA Office of Quality and Performance has also added community-acquired pneumonia treatment timing measures and in pursuing appropriate antibiotic choice measures.
- **Results:** During FY 2006 these measures have been introduced and are being refined. Ongoing FY 2008

ACTION ITEM #33: EVALUATE THE POTENTIAL IMPACT OF IMPROVED DIAGNOSTIC TESTS, INCLUDING RAPID POINT-OF-CARE TESTS ON ANTIMICROBIAL DRUG USE AND PATIENT CARE, AND ASSESS THEIR FINANCIAL IMPLICATIONS. TAKE INTO ACCOUNT TESTS THAT DISTINGUISH BETWEEN BACTERIAL AND VIRAL INFECTIONS, TESTS THAT IDENTIFY RESISTANT PATHOGENS, AND TESTS THAT DISTINGUISH COMMON CLINICAL ENTITIES SUCH AS BACTERIAL SINUSITIS AND ACUTE BACTERIAL OTITIS MEDIA FROM ILLNESSES WITH SIMILAR MANIFESTATIONS FOR WHICH ANTIMICROBIALS ARE NOT BENEFICIAL.

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PROJECT TITLE: RESEARCH CAREER AWARD (K08): RANDOMIZED TRIAL OF SINUS CT FOR ACUTE SINUSITIS.

- **Agency:** AHRQ
- **Description:** Sinusitis is a common medical disease with a tremendous economic impact on health care. The investigator sought to determine the most cost-effective strategy for the management of acute sinusitis from the societal and payers' perspectives. A Markov disease simulation model compared four treatment strategies: (1) no antibiotic, (2) empiric antibiotic, (3) CT-based antibiotic, and (4) clinical guideline-based antibiotic.
- **Results:** Empiric antibiotic treatment was the most cost-effective from the societal perspective. Clinical guideline-based treatment was the most cost-effective strategy from the payers' perspective (\$38,515/quality-adjusted life year). Cost and effectiveness of antibiotics, time lost from work, and prevalence of acute bacterial sinusitis were influential variables. Empiric antibiotic treatment is a cost-effective strategy from the short-term societal perspective. However, antibiotic resistance will lead to increased costs and reduced efficacy of this strategy in the long term. Clinical guidelines provide a low-cost method of targeting therapy (Anzai Y et al. Am J Rhinol. 2007; 21:444-51.).

ACTION ITEM #38: IDENTIFY FACTORS THAT PROMOTE TRANSMISSION OF DRUG-RESISTANT PATHOGENS IN HEALTHCARE FACILITIES, IN EXTENDED CARE FACILITIES, AND IN COMMUNITY SETTINGS, INCLUDING DAYCARE CENTERS IN THE COMMUNITY AT LARGE. THESE MAY INCLUDE CHARACTERISTICS OF THE FACILITIES AND OF THE POPULATIONS THEY SERVE.

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PROJECT TITLE: LONG TERM CARE INFECTION SURVEILLANCE

- **Agency:** VA
- **Description:** A national VA taskforce developed a prototype web-based point prevalence survey which was subsequently beta-tested and used for the actual survey. CDC-based definitions of infections were used. Long term plans are to develop and improve standardized infection surveillance of VHA nursing homes. Develop a nursing home care educational session for use with VHA nursing home care units.
- **Results:** National nursing home survey was completed in Fall 2005. Data analysis and review are ongoing, with report released by the Office of the Inspector General. Publication of article in Am J Infect Control. 2006 Mar;34(2):80-3. Ongoing evaluation of surveillance methodologies and standards are actively being pursued, along with development of education session(s) for use by personnel within VHA nursing home care units (e.g., conference which may be multi-purposed with development of web-based sessions/components from this). Results of first national point-prevalence survey of all VA long-term care facilities released by the Office of the Inspector General for VA. A second national point-prevalence survey was completed January 2008 and analysis is ongoing at this time. Also, first national VA conference on Infection Prevention and Control in Long Term Care completed January 2008.

\*\* TOP PRIORITY \*\*

ACTION ITEM #39: EVALUATE THE EFFECTIVENESS (INCLUDING COST-EFFECTIVENESS) OF CURRENT AND NOVEL INFECTION-CONTROL PRACTICES FOR HEALTH CARE AND EXTENDED CARE SETTINGS AND IN THE COMMUNITY. PROMOTE ADHERENCE TO PRACTICES PROVEN TO BE EFFECTIVE.

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PROJECT TITLE: TASK ORDER: TESTING TECHNIQUES TO RADICALLY REDUCE ANTIBIOTIC-RESISTANT BACTERIA (METHICILLIN-RESISTANT) STAPHYLOCOCCUS AUREUS, OR MRSA.

- **Agency:** AHRQ
- **Description:** The overall purpose of this task order is to measurably reduce hospital-acquired MRSA infections in acute-care facilities or hospitals and document how this was done, in order to help others achieve success in similar settings.
- **Results:** The informatics group has continued to focus on data entry and improving data reporting ability. In addition, the project directors are currently focusing on fashioning a weekly metrics report from each hospital that includes admission and discharge cultures, hand hygiene observations, and barrier isolation observations. One participating hospital can provide all of the above data. The other five hospitals as yet only have internal data that they use to report within their group. Intervention, training, and assessment activities are under way at the collaborating sites.

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PROJECT TITLE: CENTERS OF EXCELLENCE IN HEALTHCARE EPIDEMIOLOGY  
(PREVENTION EPICENTERS)

- **Agency:** CDC
- **Description:** Academic medical centers conduct research to improve infection control practices. Current projects address improving antimicrobial use in acute care facilities, the epidemiology of transmission of resistant organisms in the ICU setting, and exploring novel approaches to preventing transmission.
- **Results:** Recent and ongoing activities include: 1) completed a pilot multi-center evaluation of the use of novel approaches to routine skin antisepsis (daily chlorhexidine baths) to reduce transmission of antimicrobial resistant organisms among ICU patients. This has been expanded to a multi-center cluster-randomized trial. 2) Ongoing study of assessment of colonization pressure in ICUs as a predictor of transmission of MRSA and VRE. 3) Evaluation of the risk of invasive sequelae following acquisition of MRSA and VRE colonization during hospitalization. 4) Examining inter-facility and inter-community transmission of MRSA in hopes that increased communication between facilities, electronic alerts, and infection control measures at point of transport can disrupt transmission and prevent the clonal establishment of MRSA within the targeted communities. 5) Using electronic health information to generate electronic alerts for patients at high risk for MRSA carriage. 6) Using electronic databases to measuring antimicrobial utilization in ICUs.

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PROJECT TITLE: SIX SIGMATM PROCESS TO PROMOTE HAND HYGIENE IN VA  
MEDICAL FACILITIES.

- **Agency:** VA
- **Description:** National VA effort to use the Six Sigma<sup>TM</sup> process in the hand hygiene promotion effort. Pilot project at 3 VA medical facilities, with products from the testing to be distributed nationwide to all VA medical facilities.
- **Results:** Six Sigma process regarding hand hygiene being tested at 3 VA medical facilities. Published as "Using the six sigma process to implement the Centers for Disease Control and Prevention Guideline for Hand Hygiene in 4 intensive care units." J Gen Intern Med. 2006 Feb;21 Suppl 2:S35-42. with authors Eldridge NE, Woods SS, Bonello RS, Clutter K, Ellingson L, Harris MA, Livingston BK, Bagian JP, Danko LH, Dunn EJ, Parlier RL, Pederson C, Reichling KJ, Roselle GA, Wright SM.

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PROJECT TITLE: METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS PATTERNS IN  
VA.

- **Agency:** VA
- **Description:** MRSA laboratory data collected nationwide from VA medical facilities to identify antibiotic resistance patterns.



- **Results:** Abstracts presented at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2007, Baltimore MD authors: G Roselle, R Jain, S Kralovic, L Simbartl about MRSA, at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2006, Chicago, IL authors: S Kralovic, L Danko, L Simbartl, G Roselle about MRSA, at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2005, Los Angeles, CA authors: S Kralovic, L Danko, L Simbartl, G Roselle about Clostridium difficile. Invited presentation of the MRSA Prevention Initiative at the annual meeting of the Association of Professionals in Infection Control and Epidemiology scheduled for June 2008.

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PROJECT TITLE: AHRQ 1 UC1 HS014237 TOWARD A SAFETY CULTURE: REDUCING NOSOCOMIAL INFECTIONS

- **Agency:** VA
- **Description:** VA personnel led a regional research study sponsored by AHRQ designed to look at rapid-cycle implementation strategies of evidence-based practices that are known to reduce health care associated infections
- **Results:** Primary study accrual has completed and review and reporting of results is ongoing. This regional cooperative project received the 2005 Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Ernest Amory Codman award and demonstrated findings of: i) reduced central line infections by 50 percent. ii) increased adherence to evidence-based practices to 95 percent from 30 percent. iii) created a new model for facilitating improvement as a community, with an increased chance of success, sharing of successful strategies, reducing rework across the sites, and speeding the implementation process.

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PROJECT TITLE: TOYOTA PRODUCTION SYSTEM (TPS) PROCESS TO REDUCE INFECTION

- **Agency:** VA
- **Description:** Through a demonstration project sponsored by CDC, VA facilities in Pittsburgh along with other health care institutions in the region participated in evaluation of a methodology (Toyota Production System process) for implementing change in infection control practices.
- **Results:** Has demonstrated decrease with sustained success in resistant Staphylococcus aureus within facility Abstract presented at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2006, Chicago, IL authors R Muder, E McCray, C Cunningham, P Perreiah, C Squier, R Sinkowith-Cochran, J Jernigan. Ongoing

ACTION ITEM #43: CONDUCT A PUBLIC HEALTH CAMPAIGN TO PROMOTE HAND HYGIENE AND OTHER HYGIENIC PRACTICES, AS WELL AS OTHER BEHAVIORS THAT PREVENT THE TRANSMISSION OF INFECTIOUS ORGANISMS, IN COLLABORATION WITH PROFESSIONAL SOCIETIES AND STAKEHOLDERS. THIS CAMPAIGN MAY BE

COORDINATED WITH THE PUBLIC HEALTH EDUCATION STRATEGY TO PROMOTE APPROPRIATE ANTIMICROBIAL USE DESCRIBED IN ACTION ITEM #25: PREVENTION AND CONTROL.

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PROJECT TITLE: INFECTION -DON'T PASS IT ON CAMPAIGN

- **Agency:** VA
- **Description:** The Veterans Administration campaign, "Infection: Don't Pass It On" is a national campaign launched in the fall of 2004. The major focus of this ongoing campaign is hand hygiene, respiratory etiquette, and preparedness for infectious disease emergencies.
- **Results:** Initiated Fall 2004 and ongoing. 2005 winner of Excellence in Public Health Award from the National Public Affairs Association. During Association of Professionals in Infection Control and Epidemiology National Conference June 2006 in Tampa, FL, presented as a general concurrent session.

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PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** Nationally directed MRSA Prevention Initiative incorporating a bundle approach consisting of hand hygiene, contact isolation, active surveillance culturing and cultural change/transformation.
- **Results:** Directive signed Jan 12, 2007 by Under Secretary for Health and all sites with acute care facilities have initiated at least one care unit (preferably an ICU) as of March 1, 2007

ACTION ITEM #44: FACILITATE AND SUPPORT THE ACTIVITIES OF INFECTION CONTROL PROGRAMS IN HEALTH CARE SETTINGS AS A COMPONENT OF MEDICAL CARE. PROMOTE INFECTION CONTROL EDUCATION AT ALL STAGES OF TRAINING AND PRACTICE FOR ALL HEALTH CARE WORKERS WHO HAVE CONTACT WITH PATIENTS.

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PROJECT TITLE: INFOMERCIALS TAPED AND AIRED ON VA KNOWLEDGE NETWORK. VIEWED BY VHA EMPLOYEES.

- **Agency:** VA
- **Description:** 2-3 minute "infomercials" covering issues relating to influenza, PPD's and bloodborne pathogens
- **Results:** Completed. Airing of infomercials ongoing.

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PROJECT TITLE: NATIONAL CENTER FOR HEALTH PROMOTION MONTHLY TOPICS

- **Agency:** VA
- **Description:** Some of the monthly topics address specific diseases and some address specific infectious diseases preventive measures
- **Results:** Information on the following, rotation of monthly disease prevention and health promotion which regularly include infectious diseases topics. Dissemination point for annual influenza-pneumococcal vaccination toolkit information.

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PROJECT TITLE: PLANNED LONG TERM CARE CONFERENCE IN SEPTEMBER 2006

- **Agency:** VA
- **Description:** Issues of antibiotic resistance discussed.
- **Results:** Completed January 2008.

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PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** Nationally directed MRSA Prevention Initiative incorporating a bundle approach consisting of hand hygiene, contact isolation, active surveillance culturing and cultural change/transformation.
- **Results:** Directive signed Jan 12, 2007 by Under Secretary for Health and all inpatient acute care units have established the MRSA Prevention Initiative nationwide in VHA. Ongoing

ACTION ITEM #45: SUPPORT ONGOING PUBLIC HEALTH EDUCATION CAMPAIGNS ON FOOD SAFETY, SUCH AS FDA AND USDA'S FIGHT BAC PROGRAM, WHOSE AIMS ARE TO EDUCATE FOOD PRODUCERS, RETAILERS, AND CONSUMERS ABOUT FOOD SAFETY PRACTICES THAT REDUCE FOODBORNE INFECTIONS (INCLUDING AR INFECTIONS).

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PROJECT TITLE: INNOVATIVE FS PROGRAM FOR LOW LITERACY FOOD HANDLERS

- **Agency:** USDA
- **Description:** Using enhanced and distance education programs
- **Results:** Ongoing. Funded by CSREES, NIFSI program. (univ of connecticut) See csrees website.

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PROJECT TITLE: SCIENCE-TECHNOLOGY BASED FS EDUCATION PROGRAMS ON SAFE FOOD HANDLING

- **Agency:** USDA
- **Description:** Focused on consumers with use of collected data, databases
- **Results:** Ongoing. Funded by CSREES, NIFSI program. (univ of mo) See CSREES website.

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PROJECT TITLE: GOOD AGRICULTURAL PRACTICES ON LINE COURSE FOR PRODUCE SAFETY

- **Agency:** USDA
- **Description:** Will also assess impact of training
- **Results:** Ongoing. Funded by CSREES, NIFSI program (Cornell) See CSREES website.

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PROJECT TITLE: RISK ANALYSIS BASED FOOD DEFENSE CERTIFICATION PROGRAM

- **Agency:** USDA
- **Description:** For professional and academic programs
- **Results:** Ongoing. Funded by CSREES, NIFSI program (univ of md) See CSREES website.

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PROJECT TITLE: FOOD SAFETY TRAINING PROGRAMS FOR ETHNIC VENDORS

- **Agency:** USDA
- **Description:** Evaluate programs and implement changes, particularly for Asian and Mexican foods
- **Results:** Ongoing. Funded by CSREES, NIFSI program. (univ of fl) See csrees website.

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PROJECT TITLE: FIGHT BAC!® CAMPAIGN

- **Agency:** CDC, FDA, USDA
- **Description:** This national program emphasizes the four basic safe handling behaviors: Clean, Separate, Cook, and Chill.
- **Results:** Ongoing: For over 10 years, USDA, FDA, and CDC, have served as the Federal liaisons to The Partnership for Food Safety Education, the public/private partnership that created the Fight BAC!® Campaign

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PROJECT TITLE: USDA/FSIS SAFE HANDLING OUTREACH INITIATIVES

- **Agency:** USDA
- **Description:** Examples of FSIS' efforts include media events, consumer brochures, public service announcements for keeping food safe during power outages, food safety camps for children, development of 5 brochures on food safety for at-risk audiences: people with cancer, HIV/AIDS, diabetes, transplant recipients, and older adults. FSIS provides a toll-free telephone service, the USDA Meat and Poultry Hotline, to help prevent foodborne illness by answering consumer questions about the safe preparation and handling of food.
- **Results:** Ongoing.

ACTION ITEM #47: SUPPORT COMMUNITY-BASED PROGRAMS THAT PROMOTE AND FACILITATE AVAILABILITY OF RECOMMENDED VACCINATIONS FOR ADULTS AND CHILDREN.

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PROJECT TITLE: ANNUAL INFLUENZA/PNEUMOCOCCAL VACCINE TOOLKIT

- **Agency:** VA
- **Description:** Influenza/Pneumococcal Vaccine Toolkits were developed to enhance local influenza/pneumococcal immunization programs throughout VA, and contain promotional items along with directive containing most recent influenza vaccine recommendations
- **Results:** Updated toolkits are sent to VA facilities nationwide in the fall of each year for 2003-2004 season, 2004-2005 season, 2005-2006 season, 2006-2007 season, and 2007-2008 season. Planning for the toolkit for the 2008-2009 season toolkit is underway.

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PROJECT TITLE: ANNUAL INFLUENZA VACCINATION DIRECTIVE

- **Agency:** VA
- **Description:** Provide to the field facilities central direction for the consistent use of influenza vaccination and treatment strategies nationwide within VHA.
- **Results:** Each year a Directive is signed and delivered to the local VA medical centers giving guidance and direction on each new years influenza vaccine and antiviral medications for the treatment of influenza disease including potential influenza viral resistance. This has been ongoing since 1992 and continues--most recent directive was released for 2007-2008 influenza season.

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PROJECT TITLE: PNEUMOCOCCAL AND INFLUENZA VACCINATION AS PERFORMANCE MEASURES

- **Agency:** VA

- **Description:** For many years VHA has included the delivery of both influenza vaccination and pneumococcal vaccination to at-risk populations (based on CDC recommendations) as a key performance measure for patient care. Performance measures constitute 50% of the annual evaluation for Executive Career Field (ECF) performance plans for VHA regional directors and individual medical center directors. Directive measures each year are signed by VHA Under Secretary for Health regarding annual influenza immunizations for patients, and also encouraging healthcare worker participation.
- **Results:** Ongoing. Additional measures for missed opportunities with inpatient admissions currently admitted for high-risk illnesses, including pneumonia have been added to the performance measures for FY 2008.

ACTION ITEM #48: IDENTIFY VACCINES USEFUL IN PREVENTING DRUG-RESISTANT INFECTIONS AND REDUCING ANTIMICROBIAL DRUG USE AND EVALUATE NOVEL METHODS FOR IMPROVING COVERAGE WITH THESE VACCINES.

PROJECT TITLE: ABCS SPECIAL PROJECTS ON PNEUMOCOCCAL RESISTANCE: PREVENTION USING VACCINE AND RISK FACTORS FOR FLUOROQUINOLONE RESISTANCE

- **Agency:** CDC
- **Description:** This proposal sought funding to complete two ongoing case-control studies being conducted in ABCs areas. The purpose of the first project is to evaluate the effectiveness of pneumococcal conjugate vaccine in children 3-59 months of age. The study began enrolling in FY 2001 and by the end of FY 2003 had enrolled 3031 children in eight ABCs areas; in FY 2004, study personnel will be enrolling children 24-59 months of age for one additional year to meet an objective of assessing effectiveness specifically for that age group. The purpose of the second project is to identify risk factors for invasive disease in adults caused by fluoroquinolone-resistant pneumococci. Cases are adults with invasive pneumococcal disease caused by a fluoroquinolone-resistant strain; 2 controls are selected for each case from subsequent cases caused by susceptible strains in adults. This study is ongoing in 9 ABCs areas and, based on our sample size estimates, will continue until Spring 2005.
- **Results:** The vaccine effectiveness studies have been completed. For the vaccine effectiveness study, PCV7 was shown to be highly effective at reducing invasive pneumococcal disease caused by vaccine serotypes and antimicrobial resistant strains (Whitney et al, Lancet 2007). For the second study, nursing home residence and exposure to fluoroquinolones in the 3 months prior to disease were risk factors for infection with fluoroquinolone-resistant invasive pneumococcal disease.

PROJECT TITLE: *H. INFLUENZAE* TYPE B (HIB) VACCINE

- **Agency:** FDA

- **Description:** Monitoring of polysaccharide conjugated vaccines, including regular inspections of the production facilities, review and conduct of Lot Release studies, and review of amendments to the current Biologic License Application.
- **Results:** Ongoing. Several licensed vaccines. Continued vaccine supply essential to maintaining the near elimination of resistant *H. influenzae* disease in the U.S.

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PROJECT TITLE: PNEUMOCOCCAL VACCINE

- **Agency:** FDA
- **Description:** Monitoring and guidance provided to current manufacturer of a seven-valent conjugate vaccine. Ongoing. One licensed conjugate vaccine for the prevention of invasive disease and acute otitis media in infants and small children. Studies suggest decrease in AR among *S. pneumonia* isolates coincident with wide spread use of conjugate vaccine in infants. One licensed multivalent polysaccharide vaccine for the elderly. Facilitating clinical development of a more immunogenic vaccine for the elderly.
- **Results:** Ongoing. One licensed polysaccharide and one licensed conjugate vaccine for the prevention of invasive disease and acute otitis media. Studies suggest decrease in antimicrobial resistance among *S. pneumonia* isolates coincident with wide spread use of conjugate vaccine in infants. One licensed multivalent polysaccharide vaccine for the elderly.

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PROJECT TITLE: INFLUENZA VACCINE

- **Agency:** FDA
- **Description:** Regulatory and research support of annual trivalent inactivated and live intranasal influenza vaccine development, production and licensure, including additional manufacturers and novel technologies. Facilitating expanding indication to additional age groups and select immunocompromised populations.
- **Results:** Influenza immunization is currently recommended for children 6 to 59 months old. At the February 2008 ACIP meeting, there was discussion and vote to included children through 18 years old. Five seasonal influenza vaccines are licensed and distributed in the U.S. These vaccines include Medimmune (FluMist®), Sanofi (Fluzone®), Chiron (Fluvrin®), ID Biomedical (FlulavalO), and GSK (Fluarix®).

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PROJECT TITLE: PANDEMIC INFLUENZA VACCINE

- **Agency:** FDA
- **Description:** Regulatory and research activities to support development, licensure and rapid widespread availability of vaccines for pandemic influenza.
- **Results:** 10 INDs were submitted for vaccines against potential pandemic influenza virus strains H5N1, H7N3, and H9N2, or against seasonal influenza. \* Nov 2007: CBER co-chaired and participated in an FDA-EMEA meeting to discuss evaluation of



pandemic/prepandemic influenza vaccines for licensure/marketing authorization. \* Dec 2007: CBER participated in an FDA-NIH-WHO workshop on Immune Correlates of Protection Against Influenza A Viruses in Support of Pandemic Vaccine Development to (1) identify gaps in current abilities to develop and evaluate pandemic influenza vaccines; (2) facilitate implementation of a global research agenda to improve efficacy assessment of pandemic influenza vaccines.

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PROJECT TITLE: IMPROVE USE OF VACCINES RELATED TO PRUDENT USE OF ANTIBIOTICS

- **Agency:** VA
- **Description:** Dept. of Veterans Administration, VHA Directive 2001-053. Influenza Vaccine – Recommendations for 2001-2002. Published and placed on VA Intranet website 8/28/01. Infomercials were aired on VA Knowledge Network regarding influenza vaccine. Performance Measurement Program, 2001 and 2002 VHA Performance Measurement System Technical Manuals list Influenza Immunization and Pneumococcal Immunization as Preventive Care Quality Performance Measures, with specific recommendations for these immunizations for Nursing Home Care Units within VHA system.
- **Results:** The VHA is already in the forefront of immunization practices as is evidenced by the pneumococcal and influenza vaccine usage rates compared to the national averages. In addition, influenza vaccine use increases each year in the VHA as emphasis on this program continues. Therefore, this action item is already under way and will continue to be an area of emphasis area for the VA.

ACTION ITEM #49: EVALUATE THE NATURE AND MAGNITUDE OF THE IMPACT OF USING VARIOUS ANTIMICROBIAL DRUGS AS GROWTH PROMOTANTS IN DIFFERENT SPECIES, USING CURRENT ANIMAL HUSBANDRY PRACTICES. USE THIS INFORMATION TO ASSIST IN RISK-BENEFIT ASSESSMENTS OF SUCH USE.

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PROJECT TITLE: POTENTIAL PUBLIC HEALTH AND FOOD SAFETY IMPACTS ASSOCIATED WITH USE OF ANTIBIOTIC GROWTH PROMOTERS

- **Agency:** USDA
- **Description:** The objective of this proposal is to use molecular epidemiologic approaches to determine whether eliminating the use of antibiotic growth promoters has adverse effects on public health, reduces the health of swine, and whether antibiotic growth promoters mediate their effects by alteration of the intestinal bacterial microflora.
- **Results:** Funded, CSREES, NRI in 07. Isaacson, University of MN

ACTION ITEM #50: CONDUCT ADDITIONAL RESEARCH TO FURTHER DEFINE THE EFFECTS OF USING VARIOUS VETERINARY DRUGS ON THE EMERGENCE OF RESISTANT BACTERIA THAT INFECT OR COLONIZE FOOD ANIMALS OF DIFFERENT

SPECIES, USING VARIOUS ANIMAL HUSBANDRY PRACTICES. IDENTIFY RISK FACTORS AND PREVENTIVE MEASURES TO HUMANS.

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PROJECT TITLE: DISSEMINATION OF CEPHALOSPORIN RESISTANCE GENES

- **Agency:** USDA
- **Description:** Experimentally determine the frequency with which bla<sub>cm</sub>-2 and adjacent plasmid genes are transferred to previously susceptible e coli strains, and perform observational studies in calves and cows to determine the effects of ceftifur therapy on the frequency, diversity, and persistence of cmy-2 resistance in commensal e.coli populations
- **Results:** Funded, CSREES, NRI in 07. Sischo, Washington State Univ

ACTION ITEM #51: CONDUCT EPIDEMIOLOGIC AND LABORATORY STUDIES TO ASSESS THE RISK OF DEVELOPMENT AND TRANSFER OF RESISTANCE RELATED TO THE USE OF ANTIMICROBIAL DRUGS IN FOOD AND NON-FOOD PLANTS, AND IDENTIFY RISK FACTORS AND POTENTIAL PREVENTIVE MEASURES.

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PROJECT TITLE: ANTIBIOTICS USED AS PESTICIDES IN ORCHARDS

- **Agency:** CDC
- **Description:** In the United States, apple and pear orchards are treated with streptomycin or oxytetracycline sprays to control Erwinia amylovora bacteria (fireblight). We evaluated design protocols and methods to determine: 1) if there is a correlation between antibiotic treatment and resistance in bacteria from fruit samples; 2) if antibiotic-resistant bacteria on fruit are related to bacteria of human health concern; and 3) if they carry genetic elements for antibiotic resistance that could be transferred to other bacteria. Thirty composite fruit washes from hanging and dropped apples and pears treated with oxytetracycline, streptomycin, gentamicin, oxolinic acid or water were collected from 2 commercial and 2 research orchards. Bacterial abundance, and proportion resistant to treatment antibiotic, were determined for gram-negative (eosin-methylene blue medium), gram-positive (bile esculin agar) and environmental bacteria (R2A).
- **Results:** Bacteria resistant to treatment antibiotics were prevalent in each orchard, but extreme variability in bacterial numbers, and varying management practices in commercial and research orchards, confounded any association between treatment and proportion resistant. We are presently conducting focused analyses from the blossom stage to the fruit stage for bacteria with developed antibiotic resistance. Sample collection and most analyses for this experiment have been completed. We are presently evaluating the results of work completed to date. A manuscript will be prepared once analysis is completed.

ACTION ITEM #52: DEVELOP RAPID TESTS FOR INSPECTING FRESH COMMODITIES LIKE FRUIT FOR EVIDENCE OF CONTAMINATION WITH BACTERIA THAT ARE RESISTANT TO ANTIBIOTICS.

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PROJECT TITLE: RAPID METHODS DEVELOPMENT

- **Agency:** FDA
- **Description:** Validated culture methods for foodborne pathogens in animal feeds.
- **Results:** Completed development and instillation of cultural methods to be used in screening feeds and feed commodities for the presence of the *Bacillus cereus* group. CVM continues to screen feeds and feed commodities for the presence of antimicrobial resistant *Enterococcus* and *E. coli*. CVM continues to collaborate with USDA-Agricultural Marketing Service to determine DNA fingerprint patterns and antimicrobial susceptibilities among *Salmonella* and *E. coli* isolates recovered from produce obtained from the microbiological data program plan.

ACTION ITEM #53: EVALUATE THE EFFECT OF CURRENT FOOD PROCESSING AND DISTRIBUTION METHODS ON THE EMERGENCE AND SPREAD OF DRUG-RESISTANT ORGANISMS.

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PROJECT TITLE: NARMS RETAIL FOOD

- **Agency:** FDA
- **Description:** Monitor prevalence of antimicrobial resistant zoonotic pathogens and commensal organisms among foods of animal origin.
- **Results:** NARMS retail was initiated in 2002, as of 2008, 9 FoodNet sites plus Pennsylvania are participating. The 2005 NARMS retail meat annual report was recently published and can be found at <http://www.fda.gov/cvm/NARMSReport2005.htm>. FDA is currently involved in publishing the 2006 annual report.

ACTION ITEM #54: IDENTIFY AND EVALUATE NEW FOOD PASTEURIZATION STRATEGIES.

ACTION ITEM #55: ASSESS THE RISK OF AN EMERGENCE AND SPREAD DUE TO ENVIRONMENTAL CONTAMINATION BY ANTIMICROBIAL DRUGS OR BY RESISTANT BACTERIA IN ANIMAL AND HUMAN WASTE. COLLECT INFORMATION ON WHETHER ENVIRONMENTAL CONTAMINATION BY ANTIMICROBIAL DRUGS CAN LEAD TO THE DEVELOPMENT OF RESISTANCE IN BACTERIA THAT LIVE IN SOIL OR WATER.

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PROJECT TITLE: ANIMAL PRODUCTION STUDIES

- **Agency:** FDA
- **Description:** Determine dynamics of resistance development in naïve animal populations exposed to antimicrobial agents.
- **Results:** Completed animal studies focusing on the development and persistence of bacteria resistance after exposure to specific antimicrobials. Two studies have been completed in poultry: the first focused on fluoroquinolone resistance development in *Campylobacter* after exposure to veterinary approved fluoroquinolones, while the second concentrated on the emergence and carriage of streptogramin resistance in enterococci exposed to the veterinary streptogramin, virginamycin. Also, partnered with academic investigators at the University of Minnesota and Iowa State University in characterizing potential links between antimicrobial resistant E. coli recovered from foods and human extraintestinal pathogenic E. coli infections (e.g. UTIs, septicemia).

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PROJECT TITLE: DEFINING THE ROLE OF SALMONELLA NEWPORT IN CONTAMINATED OYSTERS

- **Agency:** USDA
- **Description:** Early studies show prevalence of Salmonella spp in oysters and bays in US. A majority of isolates are MDR Salmonella newport which match pulsenet. Hypothesis is the presence of this genotype in oysters suggests the role of dairy sheds. Information will help with intervention strategies
- **Results:** Funded by NRI, CSREES. Joens, University of AZ.

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PROJECT TITLE: ENHANCE OVERALL UNDERSTANDING OF PATHOGENS THAT POSE A FOOD-SAFETY RISK PARTICULARLY FROM THE ENVIRONMENT.

- **Agency:** USDA
- **Description:** Pilot study to determine the contribution waterways play in movement of bacteria originating from animal production facilities in particular.
- **Results:** A mobile microbiology trailer has been designed and equipped. In the summer of 2005, collection will start in the southeastern US with the intent to visit all 50 states within the next 5 years. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

ACTION ITEM #57: WORK WITH VETERINARY AND AGRICULTURAL COMMUNITIES TO HELP EDUCATE USERS OF VETERINARY AND AGRICULTURE ANTIMICROBIALS ABOUT AR ISSUES, AND PROMOTE THE IMPLEMENTATION AND EVALUATION OF GUIDELINES THAT ADDRESS THESE ISSUES.

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PROJECT TITLE: FUND AND DEVELOP STATE-BASED EDUCATIONAL PROGRAMS TO PROMOTE APPROPRIATE ANTIMICROBIAL DRUG USE

- **Agency:** CDC
- **Description:** Several states are developing state based education programs in collaboration with agricultural industry groups to educate veterinarians and animal producers on appropriate antimicrobial drug use. Funding for these projects is provided by the Get Smart: Know When Antibiotics Work on the Farm program.
- **Results:** Continuing development of educational materials with partners at Tacoma-Pierce County Health Department in Tacoma Washington. A KAP survey of dairy producers was completed and educational materials were distributed to all of the state's dairy producers. The project is now evaluating six dairy farms for antibiotic use best practices. All other state programs were discontinued due to lack of funds.

**\*\* TOP PRIORITY \*\***

ACTION ITEM #58: IN CONSULTATION WITH STAKEHOLDERS, REFINE AND IMPLEMENT THE PROPOSED FDA FRAMEWORK FOR APPROVING NEW ANTIMICROBIAL DRUGS FOR USE IN FOOD-ANIMAL PRODUCTION AND, WHEN APPROPRIATE, FOR RE-EVALUATING CURRENTLY APPROVED VETERINARY ANTIMICROBIAL DRUGS.

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PROJECT TITLE: RISK ASSESSMENT

- **Agency:** FDA
- **Description:** Risk assessment: Conduct an analysis of the relationship between emergence of streptogramin-resistant *Enterococcus faecium* (Synercid) in humans and use of streptogramins (virginiamycin) in food-producing animals.
- **Results:** Draft risk assessment published November 23, 2004; public comment period through February 25, 2005. The Center for Veterinary Medicine (CVM) conducted a thorough review and analysis of all the comments submitted to the Docket. Considerable attention was given to the potential impacts of suggested changes on risk estimates, particularly in light of new information in the scientific literature. However, there was insufficient basis to warrant revision of the original risk assessment. CVM will continue to monitor the scientific literature, the results of surveillance studies, the usage patterns of Synercid (and other future streptogramin drugs) in hospital and health care settings, and other relevant data that may affect the findings of the risk assessment and will revisit the

risk assessment at a time dictated by the availability of new data and scientific developments in streptogramin resistance.

ACTION ITEM #59: STRONGLY ENCOURAGE INVOLVEMENT OF VETERINARIANS IN DECISIONS REGARDING THE USE OF SYSTEMIC ANTIMICROBIAL DRUGS IN ANIMALS, REGARDLESS OF THE DISTRIBUTION SYSTEM THROUGH WHICH THE DRUG IS OBTAINED (E.G., REGARDLESS OF WHETHER A PRESCRIPTION IS REQUIRED TO OBTAIN THE DRUG).

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PROJECT TITLE: EDUCATIONAL MATERIALS

- **Agency:** FDA
- **Description:** Develop outreach materials on judicious use targeted to food animal producers.
- **Results:** CVM has developed a series of booklets that explain antimicrobial prudent use principles in depth for beef, dairy, swine, poultry, and more recently aquatic veterinarians. CVM has also produced a nine-minute animation explaining how antimicrobial resistance both emerges and proliferates among bacteria and can be found on the CVM web site <http://www.fda.gov/cvm/antiresistvideo.htm>.

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PROJECT TITLE: AR USE BY VETERINARIANS

- **Agency:** FDA
- **Description:** Develop a Web-based decision support system for use by veterinarians to select and use antimicrobial agents appropriately.
- **Results:** Provided funding for development of Veterinary Antimicrobial Decision Support System; five year contract awarded late 2001. The Veterinary Antimicrobial Decision System continues to be revised and improved. Feedback from users on the data used as well as modeling and interpretation methods are currently being solicited.

ACTION ITEM #62: ESTABLISH AN ONGOING MECHANISM TO OBTAIN PERIODIC INPUT FROM EXTERNAL EXPERTS ON AR ISSUES. THIS PROCESS WILL INCLUDE ENSURING INPUT FROM STAKEHOLDERS AND PARTNERS (E.G., STATE AND LOCAL HEALTH AGENCIES, THE PRIVATE SECTOR, AND THE PUBLIC) IN DEVELOPING AND REVIEWING FEDERAL EFFORTS TO ADDRESS ANTIMICROBIAL RESISTANCE.

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PROJECT TITLE: ANTIBIOTIC RESISTANCE TASK FORCE

- **Agency:** ARHQ, CDC, CMS, DoD, HRSA, USAID, VA, EPA, FDA, NIH, USDA
- **Description:** Annual Progress Report and Public Meeting.

- **Results:** 2001 - 2007, annual progress reports issued consisting of inventory of projects that address Action Plan items. Held eighth annual public meeting June 25, 2008, Bethesda, MD. December 2007, convened consultants meeting to discuss issues relating to revising the Action Plan.

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PROJECT TITLE: ANTIBIOTIC RESISTANCE TASK FORCE ACTION PLAN UPDATE

- **Agency:** ARHQ, CDC, CMS, DoD, HRSA, USAID, VA, EPA, FDA, NIH, USDA
- **Description:** The Task Force is currently working on Revising and Updating The Action Plan to Combat antimicrobial Resistance.
- **Results:** On December 12 and 13, 2007, the Interagency Task Force on Antimicrobial Resistance, held a consultants meeting in Atlanta, Georgia to obtain input and recommendations for revising and updating "A Public Health Action Plan to Combat Antimicrobial Resistance." In addition to over fifty consultants from the United States, nine international consultants from Canada, Denmark, France, Germany, The Netherlands, and United Kingdom participated in the meeting. The consultants included experts from human and veterinary medicine, the pharmaceutical and diagnostics industries, animal husbandry industry, clinical microbiology, epidemiology, infectious disease and infection control specialists, and state and local public health departments. The consultants reviewed the 2001 Action Plan in detail and made a series of recommendations for the Interagency Task Force to consider. A revised Action Plan should be available for public comment in the Fall of 2008.

**\*\* TOP PRIORITY \*\***

ACTION ITEM #63: SUPPORT DEMONSTRATION PROJECTS TO EVALUATE COMPREHENSIVE STRATEGIES THAT USE MULTIPLE INTERVENTIONS TO PROMOTE APPROPRIATE DRUG USE AND REDUCE INFECTION RATES.

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PROJECT TITLE: PREVENTION OF INFECTION CAUSED BY MMETHICILLIN OR QXACILLIN RESISTANT STAPHYLOCOCCUS AUREUS (PRIMO): RECURRENT CA-MRSA PREVENTION TRIAL

- **Agency:** CDC
- **Description:** Primary Objectives are as follows: 1. Test the efficacy and safety of a body decolonization regimen at preventing recurrent CA-MRSA infections among persons with recurrent CA-MRSA infection, 2. Test the efficacy of an environmental decolonization regimen at preventing recurrent CA-MRSA infections in persons with recurrent CA-MRSA infections
- **Results:** Protocol approved, enrollment initiated in June 2007 and is ongoing.



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PROJECT TITLE: COMPREHENSIVE DEMONSTRATION PROJECT: BUILDING REGIONAL COALITIONS TO PREVENT METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA) IN HEALTHCARE FACILITIES

- **Agency:** CDC
- **Description:** This project supports the development and implementation of comprehensive programs to reduce the incidence of MRSA infections in states and/or large regional networks acute phase and nonacute phase healthcare facilities. The Pittsburgh Regional Healthcare Initiative (PRHI) was recruited as a collaborating partner for this project. PRHI is a coalition of regional healthcare facilities and civic, corporate, and healthcare leaders in the Pittsburgh area dedicated to improving the quality of healthcare delivery in southwestern Pennsylvania.
- **Results:** 2007 milestones include: 1) National Veteran's Health Affairs MRSA Prevention Initiative-building on the work at VA Pittsburgh, a national pilot program was initiated in August 2006 to determine if results could be replicated in 17 other VA hospitals. In January 2007 plans were announced to initiate MRSA prevention programs in all VA hospitals. CDC continues to actively participate in that national task force. 2) Plexus Institute Initiative (funded by Robert Woods Johnson Foundation)-another expansion of Pittsburgh VA work, this project examines use of a social/cultural change improvement model ("positive deviance") applied to MRSA prevention at 6 funded sites. CDC is providing in-kind support and assistance. 3) Maryland Patient Safety Center Initiative has initiated a regional voluntary MRSA prevention program of 16 Maryland Hospitals that will implement MRSA prevention initiatives using the "positive deviance" change model. CDC is providing in-kind support and assistance in using NHSN as the outcome measurement tool.

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PROJECT TITLE: AHRQ 1 UC1 HS014237 TOWARD A SAFETY CULTURE: REDUCING NOSOCOMIAL INFECTIONS

- **Agency:** VA
- **Description:** VA personnel are leading a regional research study sponsored by AHRQ designed to look at rapid-cycle implementation strategies of evidence-based practices that are known to reduce health care associated infections
- **Results:** Primary study accrual has completed and review and reporting of results is ongoing. This regional cooperative project received the 2005 Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Ernest Amory Codman award and demonstrated findings of: i) reduced central line infections by 50 percent. ii) increased adherence to evidence-based practices to 95 percent from 30 percent. iii) created a new model for facilitating improvement as a community, with an increased chance of success, sharing of successful strategies, reducing rework across the sites, and speeding the implementation process.

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PROJECT TITLE: TOYOTA PRODUCTION SYSTEM (TPS) PROCESS TO REDUCE INFECTION

- **Agency:** VA
- **Description:** Through a demonstration project sponsored by CDC, VA facilities in Pittsburgh along with other health care institutions in the region participated in evaluation of a methodology (Toyota Production System process) for implementing change in infection control practices
- **Results:** Has demonstrated decrease with sustained success in resistant *Staphylococcus aureus* within facility Abstract presented at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2006, Chicago, IL authors R Muder, E McCray, C Cunningham, P Perreiah, C Squier, R Sinkowith-Cochran, J Jernigan. Ongoing and has led to both a further in depth evaluation process of 17 VHA medical centers nationwide and to nationwide implementation of a VHA MRSA Prevention Initiative.

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PROJECT TITLE: POSITIVE DEVIANCE

- **Agency:** VA
- **Description:** Use of Positive Deviance model to assist with national MRSA Prevention Initiative
- **Results:** Abstracts demonstrating use of positive deviance for cultural change at the Pittsburgh VA as part of its' successful MRSA reduction efforts presented at the Society for Healthcare Epidemiology of America Annual Scientific Conference April 2007, Baltimore, MD authors R. Muder, C Cunningham, C Squier, E McCray, R Jain, R Sinkowitz-Cocharn, J Lloyd, J Jernigan on the first abstract and J Jacob, R Muder, C Cuningham, E McCray, C Squier, C Mehta, R Jain, R Sinkowitz-Cochran, J Lloyd and J Jernigan on the second abstract Ongoing

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PROJECT TITLE: INPATIENT EVALUATION CENTER (IPEC)

- **Agency:** VA
- **Description:** The IPEC is a national program to improve outcomes (risk adjusted mortality and length of stay) in VA ICUs and eventually in inpatient care through feedback of outcomes and implementation of evidenced-based practices. Currently two of the initiatives deal with issues related to infection prevention--catheter-related bloodstream infections and ventilator-associated pneumonias--both of which may involve resistant organisms These data are reported back immediately to the local facilities who can track their rates over time and compliance with performance, as well as see the national mid-range statistical analysis results.
- **Results:** IPEC program initiated nationwide during FY 2006 with initial data demonstrating a decrease in ventilator-associated pneumonias and central catheter related bloodstream infections nationwide within the past year.

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PROJECT TITLE: METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** Establishment of a national MRSA Prevention Initiative for all VA Medical Centers. In January 2007 VHA administration took strong directive action in plan to address infection with MRSA nationwide as a prototype agent for multidrug resistance issues; this national plan employs a bundle approach which includes hand hygiene, contact precautions, active surveillance culturing and cultural change. Seventeen VA medical centers ("beta-sites") across the country are also participating in a cooperative evaluation of this process with the Centers for Diseases Control and Prevention (CDC).
- **Results:** Implemented January 2007. By December 31, 2007 all inpatient acute care units nationwide in VHA had begun the initiative. Ongoing with evaluation for expansion into additional settings such as the long-term care/nursing home/community living center area. National data collection has begun for areas of prevalence of MRSA infection/colonization on admission, healthcare-associated infection with MRSA and MRSA transmission.

ACTION ITEM #64: UTILIZE FEDERAL HEALTH CARE SYSTEMS (E.G., DOD, VA) AS MODELS FOR AR SURVEILLANCE AND PREVENTION AND CONTROL ACTIVITIES INVOLVING APPROPRIATE DRUG USE, OPTIMIZED DIAGNOSTIC TESTING, INFECTION CONTROL, AND VACCINATION PRACTICE.

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PROJECT TITLE: SIX SIGMATM PROCESS TO PROMOTE HAND HYGIENE IN VA MEDICAL FACILITIES.

- **Agency:** VA
- **Description:** National VA effort to use the Six Sigma™ process in the hand hygiene promotion effort. Pilot project at 3 VA medical facilities, with products from the testing to be distributed nationwide to all VA medical facilities.
- **Results:** National VA effort to use the Six Sigma™ process in the hand hygiene promotion effort. Pilot project at 3 VA medical facilities, with products from the testing to be distributed nationwide to all VA medical facilities.

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PROJECT TITLE: AHRQ 1 UC1 HS014237 TOWARD A SAFETY CULTURE: REDUCING NOSOCOMIAL INFECTIONS

- **Agency:** VA
- **Description:** VA personnel are leading a regional research study sponsored by AHRQ designed to look at rapid-cycle implementation strategies of evidence-based practices that are known to reduce health care associated infections

- **Results:** Primary study accrual has completed and review and reporting of results is ongoing. This regional cooperative project received the 2005 Joint Commission on Accreditation of Healthcare Organizations (JCAHO) Ernest Amory Codman award and demonstrated findings of: i) reduced central line infections by 50 percent. ii) increased adherence to evidence-based practices to 95 percent from 30 percent. iii) created a new model for facilitating improvement as a community, with an increased chance of success, sharing of successful strategies, reducing rework across the sites, and speeding the implementation process.

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PROJECT TITLE: INFLUENZA AND PNEUMOCOCCAL VACCINATIONS AS PERFORMANCE MEASURES

- **Agency:** VA
- **Description:** VHA has included the delivery of both influenza vaccination and pneumococcal vaccination to at-risk populations as a key performance measure for patient care.
- **Results:** Ongoing FY For Federal Fiscal Year 2006, VHA has introduced timing of antibiotics for community-acquired pneumonia for inpatients and is pursuing measures for appropriate antibiotic choices.

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PROJECT TITLE: INPATIENT EVALUATION CENTER (IPEC)

- **Agency:** VA
- **Description:** The IPEC is a national program to improve outcomes (risk adjusted mortality and length of stay) in VA ICUs and eventually in inpatient care through feedback of outcomes and implementation of evidenced-based practices. Currently two of the initiatives deal with issues related to infection prevention--catheter-related bloodstream infections and ventilator-associated pneumonias--both of which may involve resistant organisms. These data are reported back immediately to the local facilities who can track their rates over time and compliance with performance, as well as see the national mid-range statistical analysis results.
- **Results:** IPEC program initiated nationwide during FY 2006 with initial data demonstrating a decrease in ventilator-associated pneumonias and central catheter related bloodstream infections nationwide within the past year.

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PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** Nationally directed MRSA Prevention Initiative incorporating a bundle approach consisting of hand hygiene, contact isolation, active surveillance culturing and cultural change/transformation.

- **Results:** Directive signed Jan 12, 2007 by Under Secretary for Health and all inpatient acute care units have established the MRSA Prevention Initiative nationwide in VHA. Ongoing

ACTION ITEM #65: FOR ALL HEALTHCARE SYSTEMS FOR WHICH FEDERAL FUNDS ARE PROVIDED, IDENTIFY AND PROMOTE STRATEGIES TO ESTABLISH AR PREVENTION AND CONTROL ACTIVITIES AS PART OF QUALITY MONITORING PROGRAMS.

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PROJECT TITLE: QUALITY ASSURANCE PROGRAMS

- **Agency:** VA
- **Description:** The Office of Quality and Performance's Performance Measurement Program, which supports the VHA Strategic Plan, serves as a vehicle for effecting change in a balanced fashion. The Performance Plan operationalizes the premise that better quality, access, and satisfaction are often more efficient. Example, improved rates of inexpensive pneumococcal vaccinations may result in decreased antibiotic use. Immunization rates are assessed through a contract chart review system and are part of managers' perf. standards, and, therefore, used as part of the VHA quality-monitoring program. Excellent immunization rates in VHA have resulted from this program.
- **Results:** The VA Under Secretary for Health's hand hygiene memorandum was issued to VA medical facilities nationwide on 12/15/03. The study "Toward a Safety Culture" is in process.

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PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE

- **Agency:** VA
- **Description:** For the National MRSA Prevention Initiative (noted above in #64), the Office of Quality and Performance has sponsored support of 17 beta-testing sites for this initiative to determine if quality measures related any or all components of the bundle approach may be amenable to further analysis by quality monitors.
- **Results:** In progress with evaluation beginning with initiation of beta-test sites in Summer 2006. Ongoing collaboration with the Centers for Diseases Control and Prevention (CDC).

**FOCUS AREA III: RESEARCH**

ACTION ITEM #67: ADDITIONAL RESEARCH, INCLUDING HIGH RISK AND HIGH PAYOFF RESEARCH IN NONTRADITIONAL FIELDS, IS NEEDED.

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PROJECT TITLE: AR MECHANISMS OF *S. PNEUMONIAE* (ALASKA)

- **Agency:** CDC

- **Description:** PCR methodologies are used to assist ongoing population-based surveillance of invasive disease in Alaska. We rapidly screen *S. pneumoniae* isolates for genetic determinants of resistance; monitoring the emergence, spread, persistence, and decline of multidrug-resistance organisms by molecular-based typing capabilities to include multilocus sequence typing (MLST).
- **Results:** Serotype 19A has emerged as the most frequent cause of IPD in Alaska. Sequence type 199 remains the most frequent sequence type among 19A isolates and was present prior to the recent increase in aerotype 19A disease among rural Alaska Native children. Recent identification of a multidrug-resistant Sequence type 320 isolate is of concern as it has emerged as the second most common clonal group in the rest of the U.S.

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PROJECT TITLE: DEFENSE THREAT REDUCTION AGENCY (DTRA) BIOTHREAT REDUCTION PROGRAM (BTRP)

- **Agency:** DoD
- **Description:** The BTRP is a DTRA project to engage former soviet weapons scientists in public health activities and health related scientific research. The program concentrates on the states of the Former Soviet Union (FSU), especially the "stans". DTRA funds projects which develop collaborations between US scientists and FSU scientists to address critical questions about diseases caused specifically by bioterror agents but is expanding to other public health threats.
- **Results:** DTRA is funding the construction of a human and agriculture research institute in the Republic of Georgia. The plan is for the laboratory to become another DoD overseas facility with funding by GEIS, other DoD agencies and other US government agencies. The GEIS portion of the work will concentrate on disease surveillance including antimicrobial resistance.

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PROJECT TITLE: DNA MICROARRAY PROFILING OF ANTIBIOTIC RESISTANCE GENES.

- **Agency:** FDA
- **Description:** Develop DNA microarray techniques and DNA chips for characterizing antibiotic resistance genes for multiple bacterial pathogens.
- **Results:** CVM scientists partnered with academic investigators at the North Carolina State University and Ohio State University in using microarray technologies to detect antimicrobial resistance and virulence genes obtained through foodborne bacteria collected via the NARMS program. Scientists from the Center for Food Safety and Applied Nutrition and the Center for Veterinary Medicine collaborated with researchers from the J. Craig Venter Institute in sequencing the genomes of 17 Salmonella serovars of public health importance. The strains chosen for genomic analysis were selected based on an extensive examination of their potential to provide information needed for examining pathogenicity, transmission, origin, ecology, evolution, and dissemination of antimicrobial resistance.

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PROJECT TITLE: STUDIES ON THE MECHANISM OF FLUOROQUINOLONE (FQ) RESISTANCE AND MOLECULAR SCREENING FOR RESISTANCE DETERMINANTS IN CAMPYLOBACTER, *E. COLI*, AND SALMONELLA

- **Agency:** FDA
- **Description:** Isolate and characterize FQ resistant Campylobacter, *E. coli* and Salmonella from chicken and turkey farms.
- **Results:** 21 FQ resistant campylobacter were isolated from chicken liver samples and characterized by PCR-RFLP and Pulsed field gel electrophoresis (PFGE). Seventy-eight campylobacters were isolated from turkey litter samples and characterized for the presence of galE gene, PCR-RFLP and PFGE. Quinolone resistance determining regions (QRDR) from campylobacters and *E. coli* were PCR amplified and sequenced for the detection of silent mismatched mutations. The FQ resistant *E. coli* strains isolated from chicken and turkey litter were typed by ribotyping. Completed in vivo studies examining the development of fluoroquinolone resistance among Campylobacter from chickens administered approved fluoroquinolones. Continue to characterize at the molecular level, resistant Salmonella, Campylobacter and *E. coli* as part of the NARMS retail program.

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PROJECT TITLE: FATE AND DEGRADATION OF ANTIMICROBIALS, OXYTETRACYCLINE (OTC) AND SULFADIMETHOXINE-ORMETOPRIM (ROMET 30) FROM AQUACULTURE ENVIRONMENTAL SAMPLES

- **Agency:** FDA
- **Description:** To isolate and characterize OTC and Romet 30 resistant *Aeromonas* spp., *Pseudomonas*, *Citrobacter* and *E. coli*. From aquaculture and catfish tissues.
- **Results:** 30 OTC resistant *Aeromonas* spp. have been isolated. These isolates have been characterized by PFGE. These investigations are still in progress.

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PROJECT TITLE: BLOOD BORNE PATHOGENS

- **Agency:** FDA
- **Description:** Develop rapid assays to identify blood borne pathogens using nucleic acid based tests (NAT) and a TaqMan assay to detect bacterial contamination in whole blood and platelets. The sequences used in these primer sets are conserved in 19 bacterial species.
- **Results:** Ongoing research to develop a DNA microarray based pathogen chip that could detect all pathogenic bacteria that contaminate blood and blood products. Project Mgr (PI) filed a TQR on 20, July 2007 for work April -June, and co-PI responded to FDA reviewer comments on 27 August 2007. Progress reported in optimizing techniques to eliminate contamination bacterial DNA from reagents using psoralen/UV treatment and reduce PRC-inhibiting substances, as well as developing a basic PCR-based "universal" method and more specific methods for detecting Gram-positive and Gram-negative



bacteria. Investigators have prepared nine working standard preparations of bacteria and fungi clinically import in septicemia, to serve as calibrators for developing real-time PCR detection with increased sensitivity. Cp-PI committed to develop a bacterial concentration step that should also increase sensitivity of detection by PCR and to assemble a collection of representative blood samples from patients with various forms of endocarditis and normal subjects for eventual clinical trials.

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PROJECT TITLE: SMALL BUSINESS INNOVATION RESEARCH AND TECHNOLOGY  
TRANSFER RESEARCH PROGRAM (SBIR/STTR)

- **Agency:** NIH
- **Description:** SBIR/STTR program is an omnibus solicitation established under federal law that seeks to use small business to stimulate technological innovation, increase the participation of small business in federal R&D, and to increase private sector commercialization of technology development through Federal R&D. The annual set-aside for agencies with extramural research budgets over \$100M is 2.5%.
- **Results:** Ongoing. Examples of recent SBIR/STTR awards include: Mucin-degrading Microflora for Prophylactic Antibiotics, Quinoline-Based Inhibitors of Botulinum Neurotoxin A, Novel Inhibitors of Staphylococcal Biofilm Formation, Stable Cationic Bacteriochlorins for Antimicrobial Photodynamic Therapy, and Designed Antimalarial Agents Overcoming Chloroquine-Resistance.

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PROJECT TITLE: NIH CRISP DATABASE

- **Agency:** NIH
- **Description:** CRISP <<http://crisp.cit.nih.gov/>> (Computer Retrieval of Information on Scientific Projects) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The database, maintained by the Office of Extramural Research at the National Institutes of Health (NIH), includes projects funded by NIH, Substance Abuse and Mental Health Services Administration (SAMHSA), Health Resources and Services Administration (HRSA), Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Agency for Healthcare Research and Quality (AHRQ), and Office of the Assistant Secretary of Health (OASH). Users, including the public, can use the CRISP interface to search for scientific concepts, emerging trends and techniques, or identify specific projects and/or investigators.
- **Results:** Ongoing.

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PROJECT TITLE: PHARMACOLOGICAL APPROACHES TO COMBATING ANTIMICROBIAL  
RESISTANCE (R01) REQUEST FOR APPLICATIONS (RFA-AI-07-025)

- **Agency:** NIH

- **Description:** This solicitation invited Research Project Grant (R01) applications from institutions/organizations that propose to apply pharmacokinetic and pharmacodynamic principles to studies on the prevention of emergence of antimicrobial drug resistance. This initiative is also intended to stimulate and strengthen collaborations between antimicrobial pharmacologists and infectious disease researchers to provide a synergistic, integrated approach that will form the basis for future clinical management of antimicrobial drug resistance.
- **Results:** RFA was released in April 2007; awards to be made in 2008.

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PROJECT TITLE: INVESTIGATOR-INITIATED SMALL RESEARCH GRANT AWARD  
PROGRAM ANNOUNCEMENT (R03)

- **Agency:** NIH
- **Description:** The R03 award supports small research projects that can be carried out in a short period of time, with limited resources. This solicitation extends its use to unsolicited applications in addition to its use in individual Requests for Applications (RFA) and Program Announcements (PA). This is an important mechanism for attracting new investigators to a field of study and providing sufficient support to allow development of preliminary data that will enable successful long-term funding.
- **Results:** Program Announcement PA-06-180 was released on March 2, 2006 with expiration date May 2, 2009. Examples of awards made in FY2007 include: Antiretroviral Treatment Strategies with Optional Switching Times, Antibiotics Discovery from the Great Lakes, and Susceptibility of Mycobacterium tuberculosis Clinical Isolates to Moxifloxacin.

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PROJECT TITLE: CLINICAL TRIAL FOR COMMUNITY-ACQUIRED METHICILLIN-  
RESISTANT STAPHYLOCOCCUS AUREUS (CA-MRSA) INFECTIONS

- **Agency:** NIH
- **Description:** These studies are to define the effective outpatient treatment with skin and soft tissue infection in areas where prevalence of CA-MRSA is high. The efficacy of off-patent antimicrobials such as clindamycin and trimethoprim/sulfamethoxazole will be evaluated.
- **Results:** Two contracts were awarded in 2007, one to University of California San Francisco and one to Olive-View University of California Los Angeles.

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PROJECT TITLE: FOOD AND WATERBORNE DISEASES INTEGRATED RESEARCH  
NETWORK (FWDIRN)

- **Agency:** NIH
- **Description:** NIAID's FWDIRN network includes multidisciplinary research on all food and waterborne pathogens (bacteria, viruses, and protozoa), as well as toxins, to facilitate the development and evaluation of products to rapidly identify, prevent, and treat

food and waterborne diseases that threaten public health. The network includes Immunology (IRU), Microbiology (MRU), Zoonoses (ZRU) and Clinical (CRU) Research Units. The Network is supported by a Coordinating and Biostatistics Center. One of the MRUs will emphasize research aimed at developing and evaluating therapies for botulism.

- **Results:** Innovative projects that address this action item include: Retrospective study of the emergence of AR Salmonella enteritidis, and two additional studies focused on the emergence and transmission of AR zoonotic bacteria.

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PROJECT TITLE: NIAID INTRAMURAL LABORATORY OF CLINICAL INFECTIOUS DISEASES, TUBERCULOSIS RESEARCH SECTION

- **Agency:** NIH
- **Description:** The Tuberculosis Research Section is an integrated group of chemists, clinicians, and microbiologists dedicated to improving the chemotherapy of tuberculosis. Projects in the section include evaluation and validation of drug targets, understanding the mechanisms of resistance to specific drugs, and understanding the basic mechanisms of pathogenesis at a molecular level. Research is also focused on understanding how current TB drugs work using the most modern technologies and using this information to develop new and improved therapies and therapeutic approaches.
- **Results:** In 2007, section scientists and collaborators reported the first description of a series of phenomena unique to *M. tuberculosis* Beijing W strains that may help to explain their epidemic spread and increased likelihood of developing drug resistance. *J Bacteriol.* 2007 Apr;189(7):2583-9.

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PROJECT TITLE: THE CLINICAL MYCOLOGY SECTION CONDUCTS RESEARCH TO DETERMINE MOLECULAR MECHANISMS OF AZOLE RESISTANCE IN CLINICAL ISOLATES OF THE PATHOGENIC YEAST, CANDIDA GLABRATA.

- **Agency:** NIH
- **Description:** NIAID intramural Laboratory of Clinical Infectious Diseases, Clinical Mycology Section
- **Results:** In 2006, section scientists described a mechanism by which fluconazole resistance in *Candida glabrata* arises during therapy. In ten patients a single nucleotide mutation in the gene coding for the transcriptional regulator, CgPDR1, increased the transcription of two drug transporters and increased drug efflux so significantly that fluconazole susceptibility decreased at least four fold. Further study of this mechanism continues in 2008.

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PROJECT TITLE: NIAID INTRAMURAL LABORATORY OF HUMAN BACTERIAL PATHOGENESIS, PATHOGEN MOLECULAR GENETICS SECTION

- **Agency:** NIH
- **Description:** The Pathogen Molecular Genetics Section studies the pathogen-polymorphonuclear neutrophil interface at both the cell and molecular levels to provide information critical to our understanding, treatment, and control of human diseases caused by bacteria. The section's overarching goal is to develop and/or promote development of enhanced diagnostics and better prophylaxis and therapeutics for pathogens such as community-associated methicillin-resistant *S. aureus* (CA-MRSA).
- **Results:** In 2006-2007, section scientists reported that a bacterial toxin called PVL, epidemiologically linked to CA-MRSA outbreaks and the presumptive reason for its virulence, is not responsible for the increased incidence and severity of CA-MRSA disease. In 2008, section scientists reported that the USA300 group of CA-MRSA strains comprises nearly identical clones that have emerged from a single bacterial strain with extraordinary transmissibility. They also reported new details about the complex mechanisms MRSA uses to avoid destruction by neutrophils.

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PROJECT TITLE: NIAID INTRAMURAL LABORATORY OF HUMAN BACTERIAL PATHOGENESIS, PATHOGEN-HOST CELL BIOLOGY SECTION

- **Agency:** NIH
- **Description:** The Pathogen-Host Cell Biology Section studies the mechanisms of the formation of biofilms in chronic infections with staphylococci with a long-term objective to provide the scientific basis for the development of drugs interfering with these mechanisms. Such drugs would be useful in anti-staphylococcal therapy to both enable the immune system fight the infection and increase the efficiency of common antibiotics.
- **Results:** In 2007, the section reported the identification of novel cytolytic peptides as key virulence determinants for CA-MRSA. Section research indicates that phenol soluble modulins (PSM) peptides are major determinants of *S. aureus* virulence, and their increased production in CA-MRSA likely contributes to the enhanced virulence of CA- compared to HA-MRSA. These newly identified peptides encoded by the PSM gene cluster have a significant effect on the ability of CA-MRSA strains to cause disease in animal infection models.

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PROJECT TITLE: NIAID INTRAMURAL LABORATORY OF MALARIA AND VECTOR RESEARCH, MALARIA GENETICS SECTION

- **Agency:** NIH
- **Description:** Section research addresses malaria drug resistance, antigenic variation, and disease virulence. Discoveries in these areas will support the development and evaluation of new diagnostic tools, antimalarial strategies, and candidate molecules for vaccines. Strains of malaria that are resistant to chloroquine have become a major problem and section scientists are seeking the exact resistance mechanism to support searches for new antimalarial compounds that can reverse or circumvent it.

- **Results:** Research is ongoing to characterize molecules that determine chloroquine and quinine responses in Plasmodium parasites; dissect structure-function relationships of the P. falciparum chloroquine resistance transporter (CRT); and evaluate candidate genes in a chromosome locus recently shown to affect the quinine response of P. falciparum. In 2007, section scientists and collaborators reported that mutations in transmembrane domains 1, 4 and 9 of the P. falciparum CRT alter susceptibility to chloroquine, quinine and quinidine (Mol Microbiol 2007. 63:270-82).

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PROJECT TITLE: IMPACT OF DIET AND GUT MICROBIAL ECOLOGY ON FOODBORNE BACTERIAL PATHOGENS AND ANTIMICROBIAL RESISTANCE IN FARM ANIMALS.

- **Agency:** USDA
- **Description:** The project goal is to identify factors affecting persistence of antibiotic resistance genes and other genetic determinants among normal and pathogenic enteric bacteria.
- **Results:** We have found that low (sub-Mic) levels of the antimicrobial carbadox stimulate 100-fold increases in the in vitro transfer of natural resistance to the antibiotic tylosin.

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PROJECT TITLE: SURVEILLANCE OF ANTIBIOTIC RESISTANCE IN NORMAL ENTERIC BACTERIA

- **Agency:** USDA
- **Description:** The project goal is to determine tetracycline resistant genotypes, species identities, and resistance "baseline" levels of commensal bacteria in the swine intestinal tract. Current research aims to evaluate the transmissibility of resistance between *Megasphaera elsdenii* strains and other intestinal bacteria.
- **Results:** We found that *Megasphaera elsdenii* strains are multiply drug resistant. Further, strains contain hybrid (recombinant) tetracycline resistant genes. Thus *M. elsdenii* is a potential site for evolution of antibiotic resistance as well as for the persistence of resistance in the swine intestinal tract.

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PROJECT TITLE: TO ASSESS THE GENE VARIABILITY ASSOCIATED WITH RESISTANT VERSUS SUSCEPTIBLE STRAINS OF SALMONELLA, CAMPYLOBACTER, ENTEROCOCCI AND *E. COLI*

- **Agency:** USDA
- **Description:** A microarray chip has been developed that can screen for almost 800 resistance and virulence genes among the four bacterial species. Additional genes are being added for other bacteria. The microarray chip was also successfully tested on *Listeria*, another important food-borne pathogen.
- **Results:** Ongoing. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. A DNA microarray to detect 100 resistance genes was successfully

tested and has now been expanded to detect 775 resistance and virulence genes simultaneously.

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PROJECT TITLE: PREVALENCE OF FOOD BORNE AND COMMENSAL PATHOGENS IN WILD BIRDS

- **Agency:** USDA
- **Description:** Fecal samples from approximately 175 wild birds were tested for the presence of *Campylobacter*, *E. coli*, *Enterococcus*, and *Salmonella*. Samples were negative for *Salmonella* but a few isolates of *Arcobacter* sp. were detected.
- **Results:** Completed-2007. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. From the study, 103 samples were positive for *Enterococcus*, 53 were positive for *Campylobacter*, 35 were positive for *E. coli*, and 19 were positive for *Arcobacter*. None of the samples contained *Salmonella*.

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PROJECT TITLE: ASSESS THE ABILITY TEMPERATURE HAS ON SURVIVAL OF RESISTANT VERSUS SENSITIVE BACTERIA.

- **Agency:** USDA
- **Description:** A pan-susceptible and multiple-resistant strains were compared for their ability to survive following challenge of poultry exposed to various room temperatures.
- **Results:** Ongoing. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: DETERMINE THE EFFECT OF ANTIMICROBIAL SELECTIVE PRESSURE ON THE RATE OF SPREAD OF *SALMONELLA TYPHIMURIUM* IN POULTRY

- **Agency:** USDA
- **Description:** *Salmonella* strains have arisen that are resistant to multiple antimicrobials including 3rd generation cephalosporins. The ability of those strains to be transmitted between hosts and under antimicrobial selective pressure is presently unknown.
- **Results:** Two *Salmonella* strains (one pan-susceptible and one resistant to 12 antimicrobials used in the NARMS program) were compared by a natural transmission study in chickens in the presence of MIC levels of chlortetracycline (tet). The percentage of positive cloacal swabs from birds exposed to the resistant strain indicated that more birds were positive when tet treatment was administered. Cloacal swabs from the susceptible strain exposed birds indicated that more birds were positive in the absence of tet treatment. The same results were observed for tissues at necropsy on D10. Results indicated that resistant strain did not transmit faster in the presence of tet, and suggested that use of tet had a protective effect on tissue colonization.

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PROJECT TITLE: TO PHENOTYPICALLY AND GENOTYPICALLY CHARACTERIZE  
SALMONELLA SEROTYPE NEWPORT IDENTIFIED FROM NARMS 2000 AND 2001  
COLLECTION OF ISOLATES

- **Agency:** USDA
- **Description:** To phenotypically and genotypically characterize Salmonella serotype Newport identified from NARMS 2000 and 2001 collection of isolates
- **Results:** Between 2000 and 2001, the animal arm of NARMS recovered a total of 241 Salmonella newport non-diagnostic (slaughter and on-farm) isolates. MDR S. newport isolates were recovered more frequently than pan-susceptible isolates and most of the MDR isolates were resistant to > nine antimicrobials. None of the Newport isolates contained Class 2, Class 3, or Class 4 integrons (int12, int13, or int14, respectively). However, Class I (int11) integrons were identified in most of the animal species regardless of whether they were MDR or pan-susceptible. Large and small plasmids were identified mainly in the MDR Newport isolates. By PFGE analysis, Newport appears to be heterogeneous among multiple animal species, but homogeneous in a particular species. These data can be used for comparison with isolates obtained from human outbreaks to determine if a particular animal species served as the source of infection.

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PROJECT TITLE: EVALUATE THE PREVALENCE AND ANTIMICROBIAL SUSCEPTIBILITY  
OF *E. COLI* ISOLATED FROM FRUITS AND VEGETABLES

- **Agency:** USDA
- **Description:** Although a number of studies have determined levels of resistant bacteria on meat items from grocery stores, few studies have been conducted on the prevalence of bacteria from fruits and vegetables. In collaboration with scientists from USDA-AMS, we evaluated the prevalence and antimicrobial susceptibility of generic *E. coli* isolated from fruits and vegetables collected from different regions of the US and determined that resistance to 17 different antimicrobials among these *E. coli* is low.
- **Results:** Completed-2004. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: ASSESS THE PREVALENCE OF *E. COLI* 0157:H7 IN DOWNER COWS

- **Agency:** USDA
- **Description:** This study assessed the prevalence of *E. coli* 0157:H7 in downer cows.
- **Results:** Data indicated that 4.9% of downer cows versus 1.5% of health cows harbor *E. coli* 0157:H7 in their colons. Not all isolates were clonal, resistance to antimicrobials was low and very little multiple resistance was observed. These data implicate downer cows as having a higher prevalence of *E. coli* 0157:H7 than healthy cows and may affect the use of downer cows as sources of meat.



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PROJECT TITLE: DETERMINE THE EFFECT OF THREE FEED-BASED ANTIMICROBIALS (APRAMYCIN, CARBADOX, AND TETRACYCLINE) ON THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE IN GENERIC *E. COLI*

- **Agency:** USDA
- **Description:** Study to determine the effect of three feed-based antimicrobials (apramycin, carbadox, and tetracycline) on the development of antimicrobial resistance in generic *E. coli*.
- **Results:** Resistance to tetracycline in *E. coli* varied widely by sample, group, and trial. However, a significant increase in the percentage of resistant isolates was observed in piglets fed antimicrobials when compared to controls. Resistance to apramycin also increased in piglets when compared to controls. However, upon removal of apramycin, resistance in *E. coli* declined. Resistance to carbadox remained unchanged after feeding carbadox when compared to controls. Piglets fed low doses of antimicrobials demonstrated improved growth when compared to controls. These data are useful for veterinarians, pharmaceutical manufacturers, and scientists as they devise ways to limit the development of resistance to antimicrobials while maintaining animal health.

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PROJECT TITLE: CHARACTERIZE ANTIMICROBIAL RESISTANCE, SPECIES, AND GENETIC DIVERSITY OF CAMPYLOBACTER ISOLATED FROM FEEDLOT CATTLE

- **Agency:** USDA
- **Description:** In collaboration with scientists from USDA-APHIS-VS-CEAH, antimicrobial resistance was examined in *Campylobacter* isolates from feedlot cattle as part of a NAHMS study. Results indicate that a majority of the isolates were susceptible to the antimicrobials that were tested and that there is significant genetic diversity among isolates. These data provided a significant overview of antibiotic resistance among *Campylobacter* from healthy beef cattle across the US. This work will be useful to beef producers, regulatory agencies and researchers in antimicrobial resistance.
- **Results:** Completed. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: STUDY THE ROLE OF TETRACYCLINE RESISTANCE IN CAMPYLOBACTER SPECIES.

- **Agency:** USDA
- **Description:** Tetracycline resistance appears to be common among bacteria particularly when multiple resistance is detected. Our goal is to study the presence of, and characterize, tetracycline resistant genes among *Campylobacter* species.
- **Results:** Ongoing. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA. Plasmids carrying genes that confer resistance to tetracycline and kanamycin in *Campylobacter* were identified and characterized. Two additional, novel

plasmids were also identified and sequenced. Jesse, T.W., L.G. Plttenger-Alley, and M.D. Englen. 2006. Sequence analysis of two cryptic plasmids from an agricultural isolate of *Campylobacter coli*. Plasmid. 55: 64-69.

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PROJECT TITLE: CHARACTERIZE ANTIMICROBIAL RESISTANCE AND SPECIES OF CAMPYLOBACTER ISOLATED FROM DAIRY CATTLE

- **Agency:** USDA
- **Description:** In collaboration with scientists from USDA-APHIS-VS-CEAH, antimicrobial resistance was examined in *Campylobacter* isolates from US dairy cattle as part of a NAHMS study.
- **Results:** Completed. Results indicate that a majority of the isolates were susceptible to the antimicrobials tested. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: TO INCREASE RECOVERY OF CAMPYLOBACTER FROM VARIOUS SOURCES

- **Agency:** USDA
- **Description:** Because of the fastidious nature of *Campylobacter*, recovery from meat or other sources is difficult. We developed enhanced methods for recovering *Campylobacter* from chicken carcass rinsates by employing a centrifugation step of the rinsate prior to enrichment in culture media. This resulted in a >50% increase in the recovery of *Campylobacter*. This is significant in that previous methods were leading to the isolation and under reporting of *Campylobacter* in samples. This work will be useful to scientists involved in *Campylobacter* research.
- **Results:** Completed. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: DETERMINE THE PREVALENCE AND LEVEL OF CAMPYLOBACTER IN PARENTS (BREEDERS) AND OFFSPRING (BROILERS) OF COMMERCIALY REARED PIGS

- **Agency:** USDA
- **Description:** Studies were conducted to determine the prevalence and level of *Campylobacter* in parents (breeders) and offspring (broilers) of commercially reared pigs. Prevalence of *Campylobacter* ranged from 42 to 100% positive in three broiler offspring flocks (90% of breeders were shedding).
- **Results:** Completed. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

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PROJECT TITLE: TO EVALUATE THE PREVALENCE AND ANTIMICROBIAL RESISTANCE OF ENTEROCOCCI ISOLATED FROM RETAIL FOOD ITEMS

- **Agency:** USDA
- **Description:** In a study of retail food (meat, vegetables, and fruit) collected from grocery stores in NE Georgia, enterococci were isolated, identified to species, and tested for antimicrobial susceptibility. Results indicated that although enterococci were prevalent among food items, resistance to antimicrobials used in human medicine was very low (linezolid, gentamicin, ciprofloxacin) or nonexistent (vancomycin). This was the first study analyzing enterococci isolated not only from meats, but fruits and vegetables as well. This work will be useful to scientists involved in Enterococcus research as well as regulatory agencies and the industry as they develop and implement mitigation strategies.
- **Results:** Results indicated that although enterococci were prevalent among food items, resistance to antimicrobials used in human medicine was very low (linezolid, gentamicin, ciprofloxacin) or nonexistent (vancomycin). This was the first study analyzing enterococci isolated not only from meats, but fruits and vegetables as well. This work will be useful to scientists involved in Enterococcus research as well as regulatory agencies and the industry as they develop and implement mitigation strategies.

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PROJECT TITLE: TO EVALUATE ANTIMICROBIAL RESISTANCE AND VIRULENCE OF ENTEROCOCCI ISOLATED FROM RETAIL FOOD ITEMS

- **Agency:** USDA
- **Description:** In a study of retail food (meat, vegetables, and fruit) collected from grocery stores in NE Georgia, enterococci were isolated, identified to species, and tested for antimicrobial susceptibility and presence of virulence determinants.
- **Results:** Results indicated positive statistical associations (significance level = 0.05) between several virulence genes and bacitracin resistance, erythromycin resistance, lincomycin resistance and tetracycline resistance. Negative correlations were observed among many of the virulence attributes and ciprofloxacin, erythromycin, flavomycin, gentamicin, kanamycin, and tylosin resistance.

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PROJECT TITLE: DETERMINE MOLECULAR GENETICS OF STREPTOGRAMIN RESISTANCE IN ENTEROCOCCI FROM ANIMALS.

- **Agency:** USDA
- **Description:** In this study, mechanisms of streptogramin resistance in enterococci from animals and the environment was investigated. From 2000-2004, enterococci were isolated from poultry carcass rinsates, fruits, vegetables, retail meats, and environmental rinsates or from swine and cattle fecal samples collected on-farm.
- **Results:** One Q/D resistance gene, vatD, which had not been found previously in enterococci from animals, was detected in three enterococcal isolates from the study. Two other Q/D resistance genes, vatB and vgaB, had never been previously reported in enterococci. To date, this is the first report of vatD from enterococci from animals in the U.S. and the first report of vatB and vgaB in enterococci.

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PROJECT TITLE: CHARACTERIZE ERYTHROMYCIN RESISTANCE IN ENTEROCOCCI ISOLATED FROM SWINE FARMS USING DIFFERENT REGIMENS OF TYLOSIN

- **Agency:** USDA
- **Description:** The effect of tylosin use on erythromycin resistant enterococci isolated from farms was investigated.
- **Results:** Results from the study suggested that although resistance was higher on a farm where tylosin was used as a growth promotant, a few resistant enterococci also persisted on a farm where no antimicrobials were being used. Isolates from farms were analyzed for antimicrobial resistance gene content as well as genetic determinants for dissemination of resistance. These data provide insight as to the development and persistence of resistance on-farm and will be useful to research and industry scientists as they develop and implement *Enterococcus* mitigation strategies.

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PROJECT TITLE: CHARACTERIZE AMINOGLYCOSIDE RESISTANCE AMONG ENTEROCOCCI ISOLATED FROM POULTRY

- **Agency:** USDA
- **Description:** Aminoglycoside antimicrobials are of interest due to their use in both animals and humans.
- **Results:** In this study, resistance to aminoglycosides in enterococci from poultry samples was examined. High-level gentamicin, kanamycin, and streptomycin resistance was found in 23%, 41%, and 19% of the isolates, respectively. Of the ten aminoglycoside resistance genes examined, five were identified in the isolates using PCR. Seven resistant *E. faecalis* isolates were negative for all genes tested suggesting that additional resistance genes may exist. Phylogenetic analysis revealed that the isolates were genetically different with little clonality. Data from this study suggest that enterococci from poultry are diverse and contain potentially unidentified aminoglycoside resistance genes. This work will be useful to scientists involved in *Enterococcus* research as well as the industry as they develop and implement mitigation strategies.

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PROJECT TITLE: TO CHARACTERIZE 3RD GENERATION CEPHALOSPORIN RESISTANT SALMONELLA FROM ANIMAL SOURCES.

- **Agency:** USDA
- **Description:** We characterized the strains and resistance mechanisms of 3rd generation cephalosporin resistant *Salmonella* in the United states.
- **Results:** CMY-2 is the most common mechanism of B-lactam resistance in salmonellae in the US. This is in contrast to Europe where it is the Extended Spectrum Beta-Lactamase (ESBL). Isolates carrying the CMY-2 gene are significantly more likely to multiple drug resistant, and that certain *Salmonella* serotypes were more likely to carry the resistance. Third generation cephalosporins are important antimicrobials used to

treat severe infections in both humans and animals. The research resulted in a predictive diagnostic test for multiple drug resistant Salmonella. Turkeys, horses, cats and dogs are significantly more likely to have these isolates than cattle, swine, chicken and exotics. The multiple drug resistance identified was found to be encoded on a large transferable plasmid.

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PROJECT TITLE: TO STUDY THE ABILITY OF RESISTANT STRAINS TO HAVE A COMPETITIVE PERSISTENCE ADVANTAGE

- **Agency:** USDA
- **Description:** Recently, Salmonella strains have arisen that are resistant to multiple antimicrobials including 3rd generation cephalosporins. The ability of those strains to be transmitted between hosts and under antimicrobial selective pressure is presently unknown.
- **Results:** Two Salmonella strains (one pan-susceptible and one resistant to 12 antimicrobials used in the NARMS program) were compared by a natural transmission study in chickens in the presence of MIC levels of chlortetracycline (tet). The percentage of positive cloacal swabs from birds exposed to the resistant strain indicated that more birds were positive when tet treatment was administered. Conversely, cloacal swabs from the susceptible strain exposed birds indicated that more birds were positive in the absence of tet treatment. The same results were observed for tissues at necropsy on D10. These results indicated that resistant strain did not have an increased transmissibility in the presence of tet and suggested that use of tet had a protective effect on tissue colonization.

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PROJECT TITLE: ISOLATION AND CHARACTERIZATION OF METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) FROM RETAIL PORK.

- **Agency:** USDA
- **Description:** Retail pork products in the local Athens area are being collected and screened for MRSA. These isolates will be compared with human MRSA isolates donated by a local hospital to determine if the MRSA from swine and retail pork products are genetically related to those from humans. The isolates from the various sources will be subjected to antimicrobial susceptibility testing and the antimicrobial resistance genes identified by PCR. Virulence genes from the isolates will also be identified using PCR, multi-locus sequence typing (MLST), and multiple variable number of tandem repeat (MLVA) analysis. Genetic comparisons will be accomplished using PFGE analysis.

ACTION ITEM #68: CONDUCT FURTHER GOVERNMENT-WIDE ASSESSMENTS WITH EXTERNAL INPUT ON THE SCOPE AND COMPOSITION OF AR RESEARCH TO IDENTIFY RESEARCH OPPORTUNITIES.

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PROJECT TITLE: NOVEL ANTIMICROBIALS IN RESPIRATORY INFECTIONS

- **Agency:** NIH
- **Description:** On February 27-28, 2008, a meeting on novel antimicrobials for respiratory infections was sponsored by NIAID. The sessions addressed the scope of the problem of resistance, mechanisms of resistance, diagnostic assays, novel approaches, and recommendations for future research. Participants included investigators from academia and industry from the US, Europe and Japan.
- **Results:** An Executive Summary of the meeting will be posted on the NIAID website in 2008 ([www.niaid.nih.gov](http://www.niaid.nih.gov)).

ACTION ITEM #69: WORK WITH THE APPROPRIATE PEER REVIEW STRUCTURES TO ENSURE THAT THE REQUISITE EXPERTISE IS APPLIED TO THE REVIEW PROCESS TO FACILITATE FUNDING OF QUALITY AR RESEARCH.

- **Agency:** NIH
- **Description:** The Panel on Scientific Boundaries for Review has conducted a comprehensive examination of the organization and function of the review process that is carried out by the Center for Scientific Review (CSR) at NIH. The purpose of this evaluation is to position the CSR peer review system so that it fosters expanded research opportunities, as well as permits the review system to keep pace with the accelerating rate of change in the way that health-related research is performed. This examination is being carried out in two phases, with extensive involvement of the extramural research community.
- **Results:** The Infectious Diseases and Microbiology IRG review by the Expert Working Group was conducted from May – August 2001 and developed a proposed set of guidelines and shared interests for new study sections. NIH's CSR has established a new Study Section, Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR), within the new Infectious Diseases and Microbiology Integrated Review Group (IRG). It will review applications that are concerned with the identification of novel antimicrobial agents, including agents that could be used in bioterrorism, for the prevention and treatment of infectious diseases and the study of the evolution, mechanisms, and transmission of resistance.

NIH's CSR established a Study Section, Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR), within the new Infectious Diseases and Microbiology Integrated Review Group (IRG). It reviews application that are concerned with the identification of novel antimicrobial agents, including agents that could be used in bioterrorism, for the prevention and treatment of infectious diseases and the study of the evolution, mechanisms, and transmission of resistance. DDR held its first meeting in June of 2004, and has met regularly thereafter. In FY2007, over 200 applications were reviewed of which 43 were awarded.

ACTION ITEM #70: PROVIDE TO THE RESEARCH COMMUNITY GENOMICS AND OTHER POWERFUL TECHNOLOGIES TO IDENTIFY TARGETS IN CRITICAL AREAS FOR THE DEVELOPMENT OF NEW RAPID DIAGNOSTICS METHODOLOGIES, NOVEL THERAPEUTICS, AND INTERVENTIONS TO PREVENT THE EMERGENCE AND SPREAD OF RESISTANT PATHOGENS. EXAMPLES INCLUDE TOOLS SUCH AS MICROBIAL GENOME SEQUENCES, INFORMATION ON COMPARATIVE GENOMICS, DNA CHIP TECHNOLOGY, INFORMATICS, AND ASSISTANCE IN THE APPLICATION AND USE OF THESE TOOLS.

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PROJECT TITLE: MICROBE PROJECT INTERAGENCY WORKING GROUP

- **Agency:** NIH, USDA, FDA, EPA, FDA
- **Description:** NIAID staff is participating in the Microbe Project Interagency Working Group, which coordinates microbial genomics activities across Federal government agencies.
- **Results:** This working group continues to coordinate genomic activities across federal agencies, including those related to biodefense, and has also focused on issues related to genomic data release and usage, as well as on bioinformatics and microbial sequencing efforts.

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PROJECT TITLE: RESEARCH IN SUPPORT OF THE USE OF GENOMICS, PROTEOMICS AND OTHER POWERFUL TECHNOLOGIES TO IDENTIFY TARGETS IN CRITICAL AREAS FOR THE DEVELOPMENT OF NEW RAPID DIAGNOSTIC METHODOLOGIES, NOVEL THERAPEUTICS, AND INTERVENTIONS TO PREVENT THE EMERGENCE AND SPREAD OF RESISTANT PATHOGENS.

- **Agency:** FDA
- **Description:** Research in support of the use of genomics, proteomics and other powerful technologies to identify targets in critical areas for the development of new rapid diagnostic methodologies, novel therapeutics, and interventions to prevent the emergence and spread of resistant pathogens.
- **Results:** Established microarray group and CBER core program (for producing and reading oligonucleotide microarray chips). Initiated several research projects related to vaccine development, AR, pathogen identification and detection. Developed a rapid typing method for *Neisseria gonorrhoeae* applicable to non-cultured specimens and the identification of ciprofloxacin resistant strains. Also developing rapid DNA assays to detect all four species of human malaria parasites. And developing microarray technology for detecting drug resistance among mycobacteria.

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PROJECT TITLE: THE TUBERCULOSIS RESEARCH MATERIALS AND VACCINE TESTING CONTRACT (COLORADO STATE UNIVERSITY)

- **Agency:** NIH
- **Description:** The contract provides TB research reagents to qualified investigators throughout the world, enabling them to work with consistent, high quality microbiological, immunological and genomic reagents, prepared from contagious and technically demanding mycobacterial pathogens.
- **Results:** More than 150 new TB vaccine candidates had been evaluated under this contract, several of which have been or are going to be tested in human clinical trials with several others progressing through various stages of preclinical development. In addition, research reagents, including specialized post-genomic materials, continue to be provided to researchers worldwide and are being used for drug, vaccine and diagnostic development. Contract staff collaborates with the PFGRC for the production and dissemination of mycobacterial specific molecular reagents and with the NIH Tetramer Facility to provide mycobacterially relevant tetramers. This contract will soon provide optimized cloning vectors for the preparation of mycobacterial mutants with the ultimate goal of finding new drug, diagnostic and vaccine targets in TB.

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PROJECT TITLE: TUBERCULOSIS ANIMAL RESEARCH AND GENE EVALUATION TASK FORCE (TARGET, JOHNS HOPKINS UNIVERSITY)

- **Agency:** NIH
- **Description:** This contract provides a selection of animal models that collectively reproduce the most critical features of human tuberculosis, and provides services to evaluate *M. tuberculosis* and *M. tuberculosis mutants* in mice, guinea pigs, and hollow fibers to assess their virulence, capacity to induce, for example, acute, latent, or progressive tuberculosis, and ultimately to validate novel drugs, vaccine and diagnostic targets. This contract also provides transposon mutants either directly or through the he tuberculosis research materials and vaccine testing contract (Colorado State University)
- This contract continues to serve as a critical component in the process to validate putative therapeutic and preventive targets in TB in animal hosts.

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PROJECT TITLE: NIAID PATHOGEN FUNCTIONAL GENOMICS RESOURCE CENTER (PFGRC)

- **Agency:** NIH
- **Description:** The PFGRC was established in FY2001 to provide and distribute to the broader research community a wide range of genomic and related resources and technologies for the functional analysis of microbial pathogens and invertebrate vectors of infectious diseases. The PFGRC was expanded to provide the research community with the needed resources and reagents to conduct both basic and applied research on microorganisms responsible for emerging and re-emerging infectious diseases and those considered agents of bioterrorism and organisms considered agents of bioterrorism.
- **Results:** The number of organism-specific microarrays produced and distributed to the scientific community has increased to 30 in FY2007 and now includes arrays for viruses,



bacteria, fungi, and parasites. In addition, the PFGRC has developed 40 organism-specific protein expression clones since its inception.

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PROJECT TITLE: SEQUENCING OF WHOLE PATHOGEN GENOMES

- **Agency:** NIH
- **Description:** NIAID has made significant investment in large-scale projects to sequence the genomes of medically significant bacterial, fungal, and parasitic pathogens. In addition, NIAID collaborates with other funding agencies to sequence larger genomes of protozoan pathogens such as the organism that causes malaria. A listing of currently active pathogen genome sequencing projects is available at: <http://www.niaid.nih.gov/dmid/genomes/mscs/projects.htm>  
The availability of microbial and human DNA sequences will open up new opportunities and allow scientists to examine functional analysis of genes and proteins in whole genomes and cells, as well as the host immune response and an individuals' genetic susceptibility to pathogens.
- **Results:** In FY2007, NIAID supported approximately 40 large scale genome sequencing projects for additional strains of viruses, bacteria, fungi, parasites, and invertebrate vectors and new projects include additional strains of Actinomycetales, Burkholderia, E.coli 0157, Enterococcus, Lactobacillus, drug resistant - including XDR-*Mycobacterium tuberculosis* (Mtb) strains that were the source of a recent outbreak in HIV co-infected patients in South Africa and drug sensitive Mtb, *Neisseria meningitidis*, Salmonella, *Staphylococcus aureus*, *Plasmodium falciparum*, and Rotaviruses.

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PROJECT TITLE: INFLUENZA GENOME SEQUENCING PROJECT

- **Agency:** NIH
- **Description:** This project was launched in 2004 and puts influenza sequence data rapidly into the public domain, enabling scientists to further study how influenza flu viruses evolve, spread, and cause disease and may ultimately lead to improved methods of treatment and prevention. This project is a collaborative effort among NIAID, NCBI/NLM, CDC, St. Jude Children's Research Hospital in Memphis and others, bringing together expertise in sequencing and bioinformatics, as well as expertise in human and avian influenza viruses to help NIAID prioritize, select and obtain strains.
- **Results:** As of February 2007, the entire genetic blueprints of more than 2,000 human and avian influenza viruses taken from samples around the world have been completed and the sequence data made available in a public database. See <http://www.niaid.nih.gov/dmid/genomes/mscs/default.htm#influenza> for details.

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PROJECT TITLE: NIAID PATHOGEN GENOMICS WEBSITE

- **Agency:** NIH
- **Description:** The NIAID genomics website serves as a focal point to disseminate to the scientific community current information about NIAID's microbial genomics research

program and related activities, including information on funding opportunities, policies, application procedures, priorities for large-scale genome sequencing projects, press releases, and currently funded large-scale genome sequencing projects.

- **Results:** Currently available to the scientific community:  
[www.niaid.nih.gov/dmid/genomes/](http://www.niaid.nih.gov/dmid/genomes/)

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PROJECT TITLE: NETWORK ON ANTIMICROBIAL RESISTANCE IN *STAPHYLOCOCCUS AUREUS* (NARSA) CONTRACT

- **Agency:** NIH
- **Description:** The network includes over two hundred domestic and international investigators made up of basic researchers, clinical laboratorians, epidemiologists, and infectious disease clinicians involved in staphylococcal and antimicrobial resistance research. NARSA supports electronic sharing of information and an annual conference of NIH funded researchers. The eighth annual NARSA meeting took place on March 5-6, 2007. The repository has over two hundred strains of *S. aureus* including the first three identified VRSA isolates noted above. Additional information is available through [www.narsa.net](http://www.narsa.net) and <http://www.niaid.nih.gov/dmid/antimicrob/>
- **Results:** In 2007, NIAID reissued a seven year contract, Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA), to Eurofins Medinet, Inc. in Herndon, VA.

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PROJECT TITLE: POPULATION GENETICS ANALYSIS PROGRAM: IMMUNITY TO VACCINES/INFECTIONS

- **Agency:** NIH
- **Description:** The goal of this program is to identify associations between specific immune response gene polymorphisms/genetic variations and susceptibility to infection or response to vaccination with a focus on one or more of NIAID Category A-C pathogens.
- **Results:** NIAID awarded 6 Centers in 2004 and studies include examining host response to immunization against smallpox, anthrax, typhoid fever, and cholera. In FY06, these centers focused on recruitment of the samples needed for genotyping and have begun genotyping assays. For example, more than 1100 smallpox vaccinated individuals and controls have been recruited and blood and PBMC samples obtained for whole genome association studies in FY07. In addition, one of the centers is using genome-wide linkage approaches to map, isolate, and validate human host genes that confer susceptibility to influenza infection. Approximately 100 individuals are being recruited using an Iceland genealogy database and in FY 2007 the Center has recruited more than 800 individuals and has almost finished genotyping the 800 samples received.

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PROJECT TITLE: PROGRAM PROJECT GRANT "STRUCTURAL ORGANIZATION AND PROTEOMICS OF TB"

- **Agency:** NIH
- **Description:** The goal of a global consortium, which involves over 70 laboratories in 12 countries, was to determine and analyze the structures of over 400 functionally relevant Mtb proteins. Originally developed under a Center Grant, which ended in early FY 2006, consortium activities, as well as more scientifically targeted, collaborative programs for specific drug targets in *Mycobacterium tuberculosis* are continues under a program project grant.
- **Results:** All data collated and produced by this consortium is publicly available through web-based databases: /www.webtb.org. Targeted studies mycobacterial proteins relevant for drug development are on-going under this grant.

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PROJECT TITLE: FOOD AND WATERBORNE DISEASES INTEGRATED RESEARCH NETWORK (FWDIRN)

- **Agency:** NIH
- **Results:** NIAID's FWDIRN network includes multidisciplinary research on all food and waterborne pathogens (bacteria, viruses, and protozoa), as well as toxins, to facilitate the development and evaluation of products to rapidly identify, prevent, and treat food and waterborne diseases that threaten public health. The network includes Immunology (IRU), Microbiology (MRU), Zoonoses (ZRU) and Clinical (CRU) Research Units. The Network is supported by a Coordinating and Biostatistics Center. One of the MRUs will emphasize research aimed at developing and evaluating therapies for botulism.
- **Description:** The network currently funds:
  - Research and development of improved diagnostics for enteric pathogens
  - Vaccine research on tularemia vaccine strain LVS, Shigella, and *S. typhi*
  - Therapeutics research for botulinum neurotoxin intoxication and for infections with Shiga-toxin producing *E. coli* (STEC)
  - Research on diagnostics for botulism
  - Clinical study to improve response to *S. typhi* vaccination
  - Research on the molecular evolution and transmission of antibiotic-resistance genes in enteric pathogens
  - Animal model development for botulinum neurotoxins, STEC-mediated HUS, Campylobacter-mediated enteritis, and Crohn's disease
  - Strain repository for STEC

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PROJECT TITLE: STRUCTURAL GENOMICS OF PATHOGENIC PROTOZOA

- **Agency:** NIH

- **Results:** NIAID has cofunded the Structural Genomics of Pathogenic Protozoa (<http://depts.washington.edu/sbpp/>) to provide the three dimensional structure of many proteins deduced from the genome information of the trypanosomatid and Plasmodium species. This will be valuable information for future drug and vaccine discovery design, as well as information for the discovery of new protein folds and function.
- **Description:** The overall goal of the project is to solve protein structures for diverse parasitic protozoa to aid in structure/function studies and drug design, emphasizing protein structures that can be exploited by differences with the human enzyme and sharing common features with those of parasitic protozoa.

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PROJECT TITLE: NIAID MICROBIAL SEQUENCING CENTERS

- **Agency:** NIH
- **Description:** The Microbial Genome Sequencing Centers address NIAID's need for sequencing of microorganism and invertebrate vectors of disease. The MGSCs provide rapid and cost efficient resources for production of high quality genome sequences of pathogens considered agents of bioterrorism (NIAID category A-C priority list), or causing emerging and re-emerging infectious diseases, their closely related organisms and clinical isolates and invertebrate vectors of disease.
- **Results:** These Centers have the capacity and are responding to scientific community and national and federal agencies' priorities for genome sequencing, filling in sequence gaps and therefore, providing genome sequencing data for multiple usages including understanding biology of microbe, forensic strain identification and identifying targets for drugs, vaccines and diagnostics. See <http://www.niaid.nih.gov/dmid/genomes/mgscs/default.htm>.

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PROJECT TITLE: BIOINFORMATICS RESOURCE CENTERS

- **Agency:** NIH
- **Description:** NIAID Bioinformatics Resource Centers are designed to develop, populate, and maintain comprehensive, relational databases to collect, store, display, annotate, query, analyze genomic, functional genomic, structural and related data for microorganisms responsible for emerging and re-emerging infectious diseases and for those considered agents of bioterrorism. The center will also develop and provide software tools.
- **Results:** Eight Centers were funded in FY04: <http://www.niaid.nih.gov/dmid/genomes/brc/default.htm>. In FY 2007, NIAID has continued to support these eight centers, each publicly accessible BRC web site has continued to be developed, the user interfaces have been improved and a variety of genomics data types have being integrated, including gene expression and proteomics information, host/pathogen interactions and signaling/metabolic pathways data. Visit <http://www.brc-central.org> for additional information. In FY2007 the National Microbial Pathogen Data Resource (NMPDR <http://www.nmpdr.org/>) BRC has made available

computational server that will provide the scientific community the annotation of bacterial genomes within 48 hours.

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PROJECT TITLE: BIODEFENSE PROTEOMICS RESEARCH CENTERS

- **Agency:** NIH
- **Description:** NIAID Proteomic Centers are intended to develop and enhance innovative proteomic technologies and methodologies and apply them to the understanding of the pathogen and/or host cell proteome for the discovery and identification of novel targets for the next generation of drugs, vaccines, diagnostics and immunotherapeutics against microorganisms considered agents of bioterrorism.
- **Results:** Seven Centers were funded in 2004: <http://www.niaid.nih.gov/dmid/genomes/prc/default.htm>. In FY 2007, an additional 5 SARS-CoV 3D protein structures were solved and additional project was initiated to solve the structures of two influenza polymerase proteins. Ninety-six percent of the coding genes for B. anthracis have been cloned and will be used to generate unique protein arrays.

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PROJECT TITLE: NOVEL, ALL NATURAL CITRUS-BASED ANTIMICROBIALS FOR COST EFFECTIVE SALMONELLA REDUCTION DURING ORGANIC POULTRY PROCESSING

- **Agency:** USDA
- **Description:** Research to determine the MIC for citrus oil fractions in model poultry skins systems, and the effectiveness and economics at 2 process interventions and evaluate antimicrobial activity
- **Results:** funded NRI, CSREES. Crandell, Univ. of Arkansas

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PROJECT TITLE: COMPARATIVE GENOMIC ANALYSIS OF *SALMONELLA* SEROTYPES.

- **Agency:** USDA
- **Description:** A multi serotype *Salmonella* whole genome microarray has been obtained for this study. To determine the genetic elements responsible for these variations, *Salmonella* serotypes are analyzed by comparative genomic hybridization (CGH).
- **Results:** Comparative genomic hybridizations have been completed on 20 bovine associated *Salmonella* serotype Newport isolates and on 11 poultry associated serotype Kentucky isolates. Data analysis is proceeding.

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PROJECT TITLE: COMPARATIVE GENOMIC ANALYSIS OF *CAMPYLOBACTER* SUBTYPES.

- **Agency:** USDA

- **Description:** To identify and trace *Campylobacter* isolates responsible for animal and human infections, a multi strain *Campylobacter* whole genome microarray has been obtained and is being used for comparative genomic hybridizations (CGH).

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PROJECT TITLE: COMPARATIVE GENOMIC ANALYSIS OF LISTERIA SUBTYPES.

- **Agency:** USDA
- **Description:** To identify and trace antimicrobial resistant *Listeria monocytogenes* from animals, food, and human sources, a *Listeria* whole genome microarray has been obtained and is being used for comparative genomic hybridizations (CGH).
- **Results:** Ongoing. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

ACTION ITEM #71: ENCOURAGE SHARING OF AR DATA BETWEEN INDUSTRY AND THE RESEARCH COMMUNITY, INCLUDING GENOMICS AND OTHER TECHNOLOGIES.

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PROJECT TITLE: COLLABORATION ON GENOMICS TECHNOLOGIES AND RESOURCES

- **Agency:** NIH, DoD
- **Description:** NIAID continued its agreement with the Defense Advanced Research Project Agency (DARPA) in support of genomics efforts targeted at pathogens of potential bioterrorist threat.
- **Results:** Through this collaboration with DARPA large-scale genome sequencing projects for *Brucella suis* and *Coxiella burnetii* have previously been completed. In 2006 sequencing of a multi-drug resistant strain of plague from Madagascar was completed (see reference: Ravel et al., 2007, PLoS ONE, Issue 3:e309). In addition, DARPA provides funds for the Poxvirus Bioinformatics Resource Center (<http://www.poxvirus.org>). This resource for the scientific community provides sequencing and functional comparisons of orthopox genes and the design and maintenance of a relational database to store, display, annotate, and query genome sequences, structural information, phenotypic data and bibliographic information. It also serves as a repository of well-documented viral strains.

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PROJECT TITLE: REAGENT DEVELOPMENT

- **Agency:** FDA
- **Description:** Facilitation of research through reagent development for the scientific community: Pertussis, H. influenzae, TB, influenza and S. pneumoniae.
- **Results:** WHO, Aeras Global Tuberculosis Foundation CBER collaboration - standard reagents for pre-clinical testing of new TB vaccines. Influenza reagents for live and inactivated influenza vaccine including products of reassortant influenza viruses with high growth characteristics. Collaborative research with CDC and WHO supporting the

development of vaccines against influenza virus, including the H5NI strain. Ongoing research project to develop new pneumococcal reference serum.

ACTION ITEM #72: BRING NEW RESEARCHERS INTO THE FIELD, BY UTILIZING APPROPRIATE STRATEGIES SUCH AS TRAINING AND RESEARCH OPPORTUNITIES.

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PROJECT TITLE: RESEARCH SCHOLAR DEVELOPMENT AWARD (RSDA)(K22)

- **Agency:** NIH
- **Description:** The RSDA will provide support for postdoctoral fellows who are moving to assistant professor positions in an academic institution. The purpose of the RSDA is to ease the transition to an academic position by enabling the recipient to focus on the establishment of his/her research laboratory prior to submitting applications for grant support. This is intended to establish new young investigators in needed fields, including AR.
- **Results:** (PAR-07-347) released April 2, 2007; remains active.

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PROJECT TITLE: OTHER ONGOING TRAINING AND RESEARCH FELLOWSHIP AWARDS

- **Agency:** NIH
- **Description:** PA-06-512 Mentored Clinical Scientist Development Award (K08) PA-05-143 Mentored Patient Oriented Research Career Development Award (K23) PA-04-107 Mid-career Investigator Award in Patient Oriented Research (K24).
- **Results:** Important ongoing programs are fostering the development of young scientists and clinical investigators. Recent awards include: An In Vitro System to Study Antiviral Strategies Against Hepatitis C virus, Effect of Suppressive Therapy on Behavioral Determinants of HSV-2 Transmission, and Preventing the Establishment of Enfuvirtide-resistance in the Latent Reservoir.

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PROJECT TITLE: NIH EXPLORATORY/DEVELOPMENTAL RESEARCH GRANT AWARD (R21)

- **Agency:** NIH
- **Description:** This announcement redefines the National Institutes of Health (NIH) Exploratory/Developmental Research Grant Award (R21) mechanism, and extends its use as an investigator-initiated mechanism to a variety of Institutes and Centers (ICs) listed in the announcement. The R21 is intended to encourage exploratory and developmental research projects by providing support for the early and conceptual stages of these projects. This is an important mechanism for attracting new investigators to a field of study and providing sufficient support to allow development of preliminary data that will enable successful long-term funding.

- **Results:** Examples of recent R21 awards include: Novel Targets for Treatment of *Pseudomonas aeruginosa*, The NTHI Sap Transporter: A Mechanism of Antimicrobial Peptide Resistance, and Targets for Short-Course TB Therapy.

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PROJECT TITLE: INVESTIGATOR-INITIATED SMALL RESEARCH GRANT AWARD  
PROGRAM ANNOUNCEMENT (R03)

- **Agency:** NIH
- **Description:** The R03 award supports small research projects that can be carried out in a short period of time, with limited resources. This solicitation extends its use to unsolicited applications in addition to its use in individual Requests for Applications (RFA) and Program Announcements (PA). This is an important mechanism for attracting new investigators to a field of study and providing sufficient support to allow development of preliminary data that will enable successful long-term funding.
- **Results:** Program Announcement PA-06-180 was released on March 2, 2006; expiration date: May 2, 2009. Examples of awards made in FY2007 include: Antiretroviral Treatment Strategies with Optional Switching Times, Antibiotics Discovery from the Great Lakes, and Susceptibility of *Mycobacterium tuberculosis* Clinical Isolates to Moxifloxacin.

ACTION ITEM #73: ORGANIZE CONFERENCES THAT ADDRESS RESEARCH ISSUES RELATING TO AR.

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PROJECT TITLE: DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES PROGRAM  
STAFF SERVE AS EXTERNAL CONSULTANTS OR LIAISON TO A VARIETY OF NATIONAL  
AND INTERNATIONAL TB-RELATED GROUPS

- **Agency:** NIH
- **Description:** NIAID program staff members serve as external consultants or liaison to a variety of national and international TB-related groups. These collaborative activities inform NIAID's strategic directions for the TB Program to assure maximum utilization of NIAID resources. National groups include the Advisory Council for the Elimination of Tuberculosis (ACET), CDC's TB Clinical Trials Consortium and TB Epidemiologic Studies Consortium, and the Infectious Disease Society of America. International groups include the STOP TB Vaccine Partnership's Diagnostic, Vaccine, Drug Development and HIV/TB Working Groups, WHO's TDR, International Union against Tuberculosis and Lung Disease (IUATLD), the Global Alliance for TB Drug Development (GATB), and several European research consortia.
- **Results:** NIAID staff member serves as the Chair of the Scientific Advisory Committee to the Global Alliance for TB Drug Development. NIAID staff serve on WHO STOP-TB Partnership Working Groups for New Drugs and New Diagnostic tools to detect TB drug resistance. NIAID and CDC's Division of TB Elimination have signed a Memorandum of Understanding to coordinate and promote communications between these two agencies in the area of tuberculosis and TB/HIV co-infections.



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PROJECT TITLE: NOVEL ANTIMICROBIALS IN RESPIRATORY INFECTIONS

- **Agency:** NIH
- **Description:** On February 27-28, 2008, a meeting on novel antimicrobials in respiratory infections was sponsored by the Respiratory Diseases Branch. The sessions included the scope of the Problem, mechanisms of resistance, diagnostic assays, novel approaches, and a final session on recommendations for future research. Participants included investigators from academia and industry from the US, Europe and Japan.
- **Results:** An Executive Summary of the meeting will be posted on the NIAID website in the near future ([www.niaid.nih.gov](http://www.niaid.nih.gov)).

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PROJECT TITLE: AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES ANNUAL MEETING

- **Agency:** NIH
- **Description:** The issues concerning antiviral resistance and selection of mutation in genomes of hepatitis viruses B and C were discussed in two sessions organized jointly by NIAID and the American Association for the Study of Liver Diseases in November 2007.
- **Results:** NIAID and AASLD organized two joint sessions at the AASLD Annual Liver Meeting in November 2007 - (1) "Antiviral Therapy Against Hepatitis Viruses - Understanding and Managing Drug Resistance; (2) "HCV Plasticity: Escape and Resistance."

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PROJECT TITLE: UPDATE OF A PUBLIC HEALTH ACTION PLAN TO COMBAT ANTIMICROBIAL RESISTANCE

- **Agency:** All Task Force Member Agencies
- **Description:** The overarching goal of this December 2007 meeting was to gather expert input toward development of a new set of Action Items.
- **Results:** Information provided to Interagency Task Force, Action Plan in development.

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PROJECT TITLE: ANNUAL MEETING OF THE U.S.-JAPAN COOPERATIVE MEDICAL SCIENCES PROGRAM

- **Agency:** NIH
- **Description:** In January 2007, the U.S.-Japan Cooperative Medical Sciences Program Acute Respiratory Infections Panel held their annual meeting, which was focused on antimicrobial resistance. Presentations and discussions addressed the following areas: assessing the spread and impact of drug resistant bacteria in Japan and other Asian countries; assessing the use of pneumococcal vaccines and their impact; and assessing

the clinical significance of co-infections and identifying pathogenic mechanisms and new antimicrobial targets.

- **Results:** Ongoing. This, and an earlier TB specific meeting held in Zhengzhou, China have stimulated discussions about potential MDR-TB collaborations between US and Chinese scientists that may include clinical studies and basic science collaboration to improve specificity of existing diagnostic.

ACTION ITEM #74: EXPLORE THE NEED TO ENCOURAGE PRECLINICAL STUDIES ON THE TOXICOLOGY, PHARMACOKINETICS OF NOVEL THERAPEUTIC AGENTS FOR THE TREATMENT OF MULTIDRUG-RESISTANT PATHOGENS AND FACILITATE THE TRANSITION OF POTENTIAL PRODUCTS FROM PRECLINICAL TO CLINICAL STUDIES LEADING TO DEVELOPMENT BY INDUSTRY OF NOVEL THERAPEUTIC AGENTS.

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PROJECT TITLE: NIAID MDR/XDR TB RESEARCH AGENDA

- **Agency:** NIH
- **Description:** In early 2007, NIAID convened a special session of the National Advisory Allergy and Infectious Diseases Council to examine needs in tuberculosis research especially for extensively resistant forms and in HIV-infected people. Invited were TB experts from academia, industry, public-private partnerships, international research organizations, and the public.
- **Results:** In June 2007, NIAID published the MDR/XDR TB Research Agenda at: <http://www3.niaid.nih.gov/topics/tuberculosis/research/PDF/MDRXDRTBresearchAgenda06-06-07.pdf/>

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PROJECT TITLE: PHARMACOKINETICS AND PHARMACODYNAMICS ANIMAL MODEL CONTRACT

- **Agency:** NIH
- **Description:** This contract, awarded in June 2004, provides a resource to determine basic pharmacology and efficacy characteristics of new chemical entities in order to best evaluate candidate compounds as potential new drugs for tuberculosis and other infections. This contract will allow NIAID to provide critical support for investigator-initiated drug discovery, to stimulate private sector sponsorship of new drugs, to perform comparison (or confirmatory) studies from different sponsors, and to provide information for selection of antimicrobial drug candidates for design of clinical studies. This contract will serve as the central facility for evaluation of novel compounds for physical, pharmacokinetic, and pharmacodynamic properties.
- **Results:** Investigations of products from companies such as Sanofi-Aventis have led to renewed interest in research and development of rifapentine for tuberculosis. Pharmacokinetic evaluations of new drug combinations are planned to address regimens for treatment of drug resistant TB. Of note, data on new drug combination regimens from this preclinical research contract has informed and guided the development of new

protocols for clinical trials (TB Trials Consortium) coordinated by the CDC. Publications of improved drug combinations may serve as a model of regimens to shorten therapy, thereby reducing the potential of treatment interruptions leading to resistant TB.

**\*\* TOP PRIORITY \*\***

**ACTION ITEM #75: IN CONSULTATION WITH ACADEMIA AND THE PRIVATE SECTOR, IDENTIFY AND CONDUCT HUMAN CLINICAL STUDIES ADDRESSING AR ISSUES OF PUBLIC HEALTH SIGNIFICANCE THAT ARE UNLIKELY TO BE STUDIED IN THE PRIVATE SECTOR.**

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**PROJECT TITLE: DIVISION OF AIDS CLINICAL TRIALS**

- **Agency:** NIH, NIAID
- **Description:** Numerous trials underway that are monitoring for resistance: R. Chaisson, Johns Hopkins University, "Novel TB Prevention Regimens for HIV-Infected Adults" in South Africa. C. Whalen, Case Western Reserve, "Randomized, Phase II Study of Punctuated Antiretroviral Therapy for HIV Infected Patients with Active Pulmonary Tuberculosis and CD4 count > 350 cells/mm<sup>3</sup>."
- **Results:** Additional study started in 2005: (1) Sok Thim, Cambodian Health Committee: U01-AI-061736 "A Cambodian Clinical Research Network for HIV/TB" (CIPRA). This study is currently enrolling and will determine if early initiation of antiretroviral therapy impacts tuberculosis cure, survival, relapse and control of HIV in urban and rural settings. It is jointly sponsored by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) – ANRS 1295 CAMELIA. Expected total enrollment: 660. Positive cultures will be assessed for resistant TB. Additional study initiated in 2006: AIDS Clinical Trials Group study ACTG 5221 "A strategy study to determine the best time to begin ARV treatment in individuals who have HIV and TB with CD4<200 cells/mm<sup>3</sup>". TB cultures will be monitored for resistant TB and new diagnostic tests will be incorporated into the study to detect resistant TB early.

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**PROJECT TITLE: TUBERCULOSIS RESEARCH UNIT (TBRU)**

- **Agency:** NIH
- **Description:** The TBRU contract was recompleted in 2007 and awarded again to Case Western Reserve University. This contract will continue to develop surrogate markers of disease and human protective immunity and has now been redirected to focus more closely on preventive strategies for TB, to complement therapeutic approaches. Activities of the TBRU are coordinated with other major organizations involved in TB research, including the CDC, USAID, FDA, WHO, Aeras Global TB Vaccine Foundation and IUATLD. Study sites for the current TBRU are in Cape Town, South Africa and Kampala, Uganda.
- **Results:** Information about on-going TBRU supported studies can be found at: <http://www.tbresearchunit.org>.

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PROJECT TITLE: BACTERIOLOGY AND MYCOLOGY STUDY GROUP (BAMSG) AND BACTERIOLOGY AND MYCOLOGY BIOSTATISTICAL AND OPERATIONS UNIT (BAMBU)

- **Agency:** NIH
- **Description:** The BAMSG and BAMBU continue to support clinical trials against fungal and resistant bacterial infections. The BAMSG was awarded to the University of Alabama in 2001. A reserve fund to support orphan studies that cannot be funded through industrial sponsors is available through the BAMSG contract.
- **Results:** Active and Planned Protocols include: BAMSG 3-01 A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of AIDS-associated cryptococcal meningitis” (8 US sites, 5 Thai sites) Enrollment was completed in March 2007; BAMSG 4-01 Strategies to Reduce Transmission of Antimicrobial Resistant Bacteria in Intensive Care Units (STAR\*ICU Trial) (20 US sites) study completed; BAMSG 4-02 Randomized, Multi-Center, Comparative Trial of Short-Course Empiric Antibiotic Therapy versus Standard Antibiotic Therapy for Subjects with Pulmonary Infiltrates in the Intensive Care Unit (ICU) (12 US sites) Study terminated; and BAMSG 4-03 Derivation of a Clinical Prediction Rule for Bacterial Pulmonary Infection in Mechanically Ventilated Children (3 US sites)

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PROJECT TITLE: VACCINE AND TREATMENT EVALUATION UNITS (VTEUS)

- **Agency:** NIH
- **Description:** The VTEUs are a network of university research hospitals across the United States that conduct Phase I, II, and III clinical trials to test and evaluate vaccine and therapeutic candidates for infectious diseases. Through these sites, researchers can quickly carry out safety and efficacy studies of promising vaccines in children, adult, and specific high-risk populations. The results of these trials may have a profound effect on public health here and abroad. Through numerous studies at the VTEUs, researchers have tested and advanced vaccines for malaria, tuberculosis, pneumonia, cholera, and whooping cough. In the last 6 years alone, NIAID has supported more than 110 clinical trials through the VTEUs.
- **Results:** The VTEU is planning on sponsoring “Phase I Studies of the Safety and Immunogenicity of Primary and Secondary BCG Vaccination Delivered Intradermally, Orally, and by Combined Routes of Administration in Healthy and Previously Immunologically Naïve Volunteers.” Enrollment to begin in summer 2008.

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PROJECT TITLE: CLINICAL TRIALS AT MASAN NATIONAL TUBERCULOSIS HOSPITAL IN SOUTH KOREA

- **Agency:** NIH
- **Description:** NIAID intramural researchers are collaborating with colleagues at Masan National Tuberculosis Hospital in South Korea to study drug-resistant TB, new therapies, and markers of hypoxia in lung tissue. As part of a consortium of scientists jointly funded

by the Bill and Melinda Gates Foundation and the Wellcome trust under the Grand Challenges in Global Health Program, the researchers have also initiated a Phase II trial of metronidazole with an extensive investigation of surrogate drug efficacy endpoints in partnership with the Novartis Institute for Tropical Diseases in Singapore and scientists at the National University of Singapore.

- **Results:** A natural history clinical research protocol, initiated in 2006 at the Masan National Tuberculosis Hospital in South Korea, has enrolled several hundred volunteers in an effort to understand factors that contribute to MDR-TB. In addition, this patient cohort has allowed an examination of the occurrence of XDR (eXtensively Drug Resistant) disease in patients who have failed chemotherapy completely. In 2008, the scientists described risk factors and treatment outcomes among 26 XDR-TB patients enrolled in the study (Clin Infect Dis. 2008 Jan 1;46(1):42-9.). A study of metronidazole therapy for pulmonary tuberculosis was initiated in 2007; enrollment of volunteers continues.

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PROJECT TITLE: PREVENTION OF GROUP B STREPTOCOCCAL (GBS) DISEASE  
CONTRACT

- **Agency:** NIH
- **Description:** NIAID continues to support research on the prevention of GBS disease through a five year multidisciplinary contract awarded late in 2002 to the Channing Laboratory, Brigham and Women's Hospital. This collaborative multidisciplinary effort is focused on clinical studies in selected populations to further understand GBS infection and on studies of the host immune response.
- **Results:** Subject visits have been completed in a clinical trial to evaluate the impact of a GBS vaccine on GBS colonization. Laboratory assays will be completed in 2008 to provide data for statistical analyses to be incorporated into the final study report.

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PROJECT TITLE: CLINICAL TRIAL FOR COMMUNITY-ACQUIRED METHICILLIN-  
RESISTANT STAPHYLOCOCCUS AUREUS (CA-MRSA) INFECTIONS

- **Agency:** NIH
- **Description:** These studies are to define the optimal outpatient treatment with skin and soft tissue infection in areas where prevalence of CA-MRSA is high. The efficacy of off-patent antimicrobials such as clindamycin and trimethoprim/sulfamethoxazole will be evaluated.
- **Results:** Two contracts were awarded in 2007, one to University of California San Francisco and one to Olive-View University of California Los Angeles.

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PROJECT TITLE: VA RESEARCH UPDATE

- **Agency:** VA

- **Description:** Such topics as spread of resistance in nursing homes, the relationship of resistance to staffing levels, and work practices (organization) as they relate to antibiotic resistance are all part of VA investigators' portfolios and are topics unlikely to be studied in the private sector. VA investigators continue to have an extensive and expanding portfolio in antimicrobial resistance research.
- **Results:** Overall Medical Service research funding for projects associated with antimicrobial resistance increased 26% from FY 2005 to FY 2006, with both an increase in the number of funded projects and the number of sites receiving funding. For FY 2007 the budget for accepted research projects is a 29% increase over the monies spent on directed-antimicrobial research from FY 2006; the depth and breadth of funded projects remains varied. For FY 2008, funding remains stable with a continued medical service research portfolio of breadth and depth.

**\*\* TOP PRIORITY \*\***

ACTION ITEM #76: IDENTIFY, DEVELOP, TEST, AND EVALUATE NEW RAPID DIAGNOSTIC METHODS FOR HUMAN AND VETERINARY USES WITH PARTNERS, INCLUDING ACADEMIA AND THE PRIVATE SECTOR. SUCH METHODS SHOULD BE ACCURATE, AFFORDABLE, AND EASILY IMPLEMENTED IN ROUTINE CLINICAL SETTINGS.

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PROJECT TITLE: PARTNERSHIPS TO IMPROVE DIAGNOSIS AND TREATMENT OF SELECTED DRUG-RESISTANT HEALTHCARE-ASSOCIATED INFECTIONS

- **Agency:** NIH
- **Description:** This initiative was released in June 6 2006 with a receipt date of November 27, 2006 (RFA-AI-06-036). The purpose of the initiative is to support the development of rapid diagnosis capable of identifying specific bacterial strains and drug resistant phenotypes and treatment for the following healthcare-associated pathogens: Clostridium difficile, Pseudomonas, Acinetobacter, Klebsiella, Serratia, Proteus, Enterobacter and Stenotrophomonas.
- **Results:** Four awards were made in early spring and summer of 2007.

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PROJECT TITLE: FOOD AND WATERBORNE DISEASES INTEGRATED RESEARCH NETWORK (FWDIRN)

- **Agency:** NIH
- **Description:** NIAID's FWDIRN network includes multidisciplinary research on all food and waterborne pathogens (bacteria, viruses, and protozoa), as well as toxins, to facilitate the development and evaluation of products to rapidly identify, prevent, and treat food and waterborne diseases that threaten public health. The network includes Immunology (IRU), Microbiology (MRU), Zoonoses (ZRU) and Clinical (CRU) Research Units. The Network will be supported by a Coordinating and Biostatistics Center. One of

the MRUs will emphasize research aimed at developing and evaluating therapies for botulism.

- **Results:** Several projects utilizing different methodologies, i.e., RT-PCR, ELISA, antigen microarrays, and oligonucleotide microarrays are underway to develop rapid, sensitive clinical diagnostics. Targeted enteric pathogens include Salmonella, Shigella, Campylobacter, diarrheagenic Escherichia coli, Listeria, caliciviruses, hepatitis A, Francisella tularensis, Vibrio, and Clostridium difficile.

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PROJECT TITLE: FACTORS AFFECTING MICROBIAL ECOLOGY OF PATHOGEN COLONIZATION AND AR ACQUISITION

- **Agency:** USDA
- **Description:** An automated ribotyping system is being used at the USDA/ARS FFSRU to identify, characterize and monitor gut bacteria isolated by us and others; information obtained from this use is being maintained in the Gastrointestinal Microflora Ribotype Database (GMRD). Molecular typing methods (e.g. ribotyping, denaturing-gradient gel electrophoresis (DGGE), and DNA sequencing) are being used to distinguish bacterial strains inhabiting the gastrointestinal tract with even greater precision and to determine genetic alterations occurring within these bacteria. This database is being used by scientists worldwide to develop a more thorough understanding of the effects of sub-therapeutic antibiotic administration and other stressors on the ecology of the gut microflora.
- **Results:** Ongoing. Sheffield Food and Feed Safety Research Unit, ARS, College Station, TX.

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PROJECT TITLE: DEVELOP A MULTIPLEX PCR METHOD FOR IDENTIFYING THE MOST PREVALENT CLINICAL AND ANIMAL DERIVED SEROTYPES OF *SALMONELLA*.

- **Agency:** USDA
- **Description:** A new typing technique based on genomics is being developed that detects genes specific for *Salmonella* serotypes by multiplex PCR.
- **Results:** This assay can identify the top 31 serotypes isolated which represent 75% of all clinically isolated Salmonella. The technique has been adapted to a high-throughput platform by incorporation of capillary analysis of the multiplex PCR products, allowing the determination of up to 90 isolates in a day with very little hands on time. The technique requires little training, no specific anti-sera, and works in standard DNA sequencing instruments. Bacterial Epidemiology and Antimicrobial Resistance Research Unit, ARS, Athens, GA.

ACTION ITEM #77: ENCOURAGE BASIC AND CLINICAL RESEARCH IN SUPPORT OF THE DEVELOPMENT AND APPROPRIATE USE OF VACCINES IN HUMAN AND VETERINARY MEDICINE IN PARTNERSHIP WITH ACADEMIA AND THE PRIVATE SECTOR.

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PROJECT TITLE: DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL EFFECTIVENESS TRIAL OF THE 23-VALENT PNEUMOCOCCAL VACCINE

- **Agency:** DoD
- **Description:** *S. pneumoniae* is a leading cause of morbidity in the U.S., causing an estimated 500,000 cases of pneumonia, 3,000 cases of meningitis, 50,000 cases of bacteremia, and 7,000,000 cases of otitis media annually. Data from 1981 to 1991 suggest that *S. pneumoniae* causes approximately 12% of pneumonia hospitalizations in the military or 9.5 admissions per 100,000 person-years. A 23-valent pneumococcal vaccine is being used at one military basic training facility and at military training facilities. This vaccine provides coverage for 85 - 90% of the serotypes causing bacteremia in the general population, but its clinical benefit needs to be more fully characterized before the impact of its use on the emergence or spread of *S. pneumoniae* resistance can be determined.
- **Results:** Completed. Enrollment was completed in June 2003, with a total of 152,765 recruits enrolled. Low incidence of pneumonia cases among both vaccine and placebo groups was observed, and a protective effect was not seen. A five-year follow up period of monitoring electronic records for pneumonia in both vaccine and placebo groups has been completed. Analysis is nearing completion, and a manuscript is being prepared.

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PROJECT TITLE: VACCINE RESEARCH

- **Agency:** FDA
- **Description:** Research in support of the development and appropriate use of vaccines in humans to: 1) prevent viral infections, i.e. influenza, RSV; 2) prevent common bacterial infections i.e. *S. pneumoniae*, non-typable *Haemophilus influenzae*, group B streptococcus, *N. gonorrhoeae*, *N. meningitidis*. 3) Prevent bacterial infections caused by potential bioterror agents including *Bacillus anthracis* and *Yersinia pestis*.
- **Results:** Fifteen ongoing research projects support development of vaccines for the organisms listed 1) Completed study of protective levels of antibody against neonatal type 1a and 3 group B streptococcal infection (funded through interagency agreement with NICHD) *Bacillus anthracis* and *Yersinia pestis*. 2) Ongoing research regarding correlates of protection against other common types of group B streptococcus. 3) Investigating correlates of protection against infection with *Streptococcus pneumoniae*. 4) *N. gonorrhoeae*. Studying immunogenicity and pathogenicity of associated proteins, funded through the FDA Office of Women's Health. 5) Ongoing regulatory review, research support and guidance for both current vaccines and those vaccines under IND, including vaccines against avian influenza.

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PROJECT TITLE: VACCINE RESEARCH - PNEUMOCOCCAL CONJUGATE VACCINE

- **Agency:** FDA



- **Description:** Identify mechanisms for establishing efficacy of additional pneumococcal conjugate vaccines with additional serotypes. Participated in multiple WHO Workshops held to discuss serologic correlates of protection. Also, provide regulatory review, conduct research and provide guidance to support licensure of additional pneumococcal vaccines (various products under IND). New research project to develop pneumococcal reference sera.
- **Results:** Research regarding serologic assessment of response to vaccines ongoing. Also, provide regulatory review, conduct research and provide guidance to support licensure of additional pneumococcal vaccines (various products under IND). CBER scientists have worked with the WHO to derive a set of immunological response endpoints or measures to evaluate possible new higher valent pneumococcal conjugate vaccines.

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PROJECT TITLE: VACCINE DEVELOPMENT - TB

- **Agency:** FDA
- **Description:** Research in support of the development of vaccines to prevent colonization, infection, and transmission of tuberculosis
- **Results:** Current projects investigate the following vaccine candidates in mouse model of tuberculosis: combination DNA vaccines, multigene DNA constructs, attenuated live vaccines and subunit vaccines. These vaccines are also being tested using prime-boost strategies and post-exposure models. ([Kamath AT, et.al., Vaccine 2005; 23\(29\):3753-3761](#)). Collaborations include the Albert Einstein College of Medicine, the NIH, and the Aeras Global TB Foundation. Also, with support from the NIAID. LMDCI scientists are developing in vitro assays for assessing the potency of TB vaccines. Over 25 peer-reviewed papers published since 2004.

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PROJECT TITLE: DRUG THERAPY

- **Agency:** FDA
- **Description:** Research: novel targets for drug therapy (to avoid resistance).
- **Results:** Two ongoing projects that examine the mechanisms of development of HIV drug resistance.

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PROJECT TITLE: BACTERIAL RESPIRATORY PATHOGEN RESEARCH UNIT (BRPRU)

- **Agency:** NIH
- **Description:** This project supports bacterial pre-clinical and clinical studies for the diagnosis, prevention, and management of selected human bacterial respiratory pathogens. The contractor is currently pursuing clinical studies to evaluate vaccines for non-typeable Haemophilus influenzae organisms using a human challenge model, as well as vaccines against Group B Streptococci in a phase I trial. Additional studies include the development of candidate vaccines against Pseudomonas and Moraxella.

- **Results:** A sub study to examine the emergence of antibiotic-resistant respiratory pathogens in otitis prone children was started in 2006.

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PROJECT TITLE: THE TUBERCULOSIS RESEARCH MATERIALS AND VACCINE TESTING CONTRACT (COLORADO STATE UNIVERSITY)

- **Agency:** NIH
- **Description:** The contract provides exploratory and preclinical evaluation of promising new TB vaccine candidates in state of the art animal models and as such continues to provide critical resources for the interface between fundamental and applied science.
- **Results:** More than 150 new TB vaccine candidates had been evaluated under this contract, several of which have been or are going to be tested in human clinical trials with several others progressing through various stages of preclinical development.

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PROJECT TITLE: PHASE I AND II MALARIA VACCINE TRIAL IN MALI

- **Agency:** NIH
- **Description:** NIAID, in collaboration with Walter Reed Army Institute of Research (WRAIR), GlaxoSmithKline Biologicals, U.S. Agency for International Development (USAID), the University of Maryland School of Medicine Center for Vaccine Development (Md/CVD), and the University of Bamako, Mali, completed two Phase I trials in Mali of novel candidate vaccines that target the blood-stage of malaria parasites.
- **Results:** Under the initiative International Collaborations in Infectious Disease Research, NIAID, in collaboration with Walter Reed Army Institute of Research (WRAIR), GlaxoSmithKline Biologicals, U.S. Agency for International Development (USAID), the University of Maryland School of Medicine Center for Vaccine Development (Md/CVD), and the University of Bamako, Mali. The same group of investigators and collaborators have completed Phase I and Phase II trials in children of a different candidate malaria vaccine also targeting the blood-stage of falciparum malaria parasites.

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PROJECT TITLE: PHASE I MALARIA VACCINE TRIALS IN USA

- **Agency:** NIH
- **Description:** Phase I Malaria vaccine trials in USA
- **Results:** NIAID has undertaken two Phase I dosage-escalation trials of two novel candidate malaria vaccines at the Baylor College of Medicine, Vanderbilt University, and Stanford University. Enrollment is ongoing in the Vanderbilt and Stanford trials, and data from the Baylor trial are being analyzed.

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PROJECT TITLE: FOOD AND WATERBORNE DISEASES INTEGRATED RESEARCH NETWORK (FWDIRN)

- **Agency:** NIH
- **Description:** NIAID's FWDIRN network includes multidisciplinary research on all food and waterborne pathogens (bacteria, viruses, and protozoa), as well as toxins, to facilitate the development and evaluation of products to rapidly identify, prevent, and treat food and waterborne diseases that threaten public health. The network includes Immunology (IRU), Microbiology (MRU), Zoonoses (ZRU) and Clinical (CRU) Research Units. The Network is supported by a Coordinating and Biostatistics Center. One of the MRUs will emphasize research aimed at developing and evaluating therapies for botulism.
- **Results:** Planned clinical activities within the FWDIRN include: "Cell-mediated immunity studies from Salmonella typhi vaccine trials", "Sensitivity of TLR4 polymorphisms to Shigella LPS," "Immunogenicity of tularemia live vaccine strain in humans," "Prime-boost study of the immunogenicity of Vi polysaccharide typhoid vaccine after priming by oral Vi+ S. typhi strain," and evaluating the intestinal microbiome prior to and after dosing with an antibiotic, Ciprofloxacin.

ACTION ITEM #78: ENCOURAGE BASIC AND CLINICAL RESEARCH IN SUPPORT OF NOVEL APPROACHES TO PREVENTING OR TREATING INFECTIONS WITH RESISTANT ORGANISMS THAT OCCUR IN HUMANS AND ANIMALS BY PARTNERING WITH ACADEMIA AND THE PRIVATE SECTOR.

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PROJECT TITLE: TB TRIALS CONSORTIUM (TBTC)

- **Agency:** CDC
- **Description:** The TBTC is an investigator-driven collaboration involving TB control programs, academic medical researchers, and CDC whose mission is to conduct programmatically relevant clinical research on TB control and prevention. TBTC designs and executes clinical trials of TB treatment and prevention at sites on 4 continents. Trials are designed both to increase the effectiveness of current regimens and to identify new agents. Collaboration with the commercial sector is common. TBTC trials have identified new regimens, clarified risk factors for development of drug resistance, and assessed regimens used to treat drug resistant TB. Growing collaborations exist with the commercial sector, the not-for-profit private sector (GATB, MSF, TAG) and the public sector (FDA, NIAID).
- **Results:** TBTC is presently in its 10th year of existence as a formal consortium, and its 12th year of trials. Eight major studies and numerous substudies have been undertaken. More information and a list of publications are available at: <http://www.cdc.gov/nchstp/tb/tbtc/default.htm>. TBTC studies have identified factors favoring development of rifamycin resistance, and are assessing the efficacy of an intermittent regimen for treatment of INH-resistant TB. TBTC will soon begin a pilot study of the treatment of XDR/MDR TB. TBTC is also working with FDA, the TB Alliance, and others to develop improved biomarkers for TB trials and to facilitate the regulatory process around new TB drug development. It has recently undergone extensive peer review.

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PROJECT TITLE: RANDOMIZED CLINICAL TRIAL EVALUATING EFFICACY OF GENTAMICIN/AZITHROMYCIN AND GEMIFLOXACIN/AZITHROMYCIN COMBINATION THERAPIES AS A SALVAGE REGIMEN FOR UNCOMPLICATED UROGENITAL GONORRHEA.

- **Agency:** CDC/NIH
- **Description:** A randomized clinical trial to determine the efficacy of each of two combination antimicrobial regimens for the treatment of uncomplicated gonococcal infection (Regimen A = gentamicin plus azithromycin, Regimen B = gemifloxacin plus azithromycin). For each regimen, 250 patients with cervical or urethral gonorrhea will be enrolled in participating STD clinics in 3 geographically diverse areas. Efficacy of each regimen will be assessed as the proportion of enrollees with a positive gonococcal culture at enrollment who are negative by culture at 12-18 days after treatment.
- **Results:** Protocol has been developed and is under final review by the Sexually Transmitted Infection Clinical Trials Group.

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PROJECT TITLE: HIV RESISTANCE NETWORK (HIVRESNET, INTERNATIONAL LABORATORY BRANCH, DIVISION OF GLOBAL AIDS, NCHHSTP).

- **Agency:** WHO, CDC, Academic institutions
- **Description:** HIVResNet have developed a global strategy for HIV drug resistance prevention, surveillance and monitoring. The strategy aims to build evidence on the scale of HIV drug resistance and equip and prepare countries with knowledge, skills and systems to respond should HIV drug resistance epidemics emerge.
- **Results:** HIVResNet has developed laboratory guidelines on HIV drug resistance using dried blood spot samples. In the process of developing laboratory networks at different levels to meet the need of HIV drug resistance surveillance and monitoring around the world.

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PROJECT TITLE: TUBERCULOSIS ANTIMICROBIAL ACQUISITION AND COORDINATING FACILITY (TAACF)

- **Agency:** NIH
- **Description:** This contract was established to acquire compounds for screening against virulent Mtb, maintain a computerized chemical database of compound structures, coordinate and distribute compounds for evaluation in vitro and in an animal model, and report data to suppliers. The TAACF has contacted over 3,500 chemists throughout the world seeking candidate anti-TB compounds.
- **Results:** Over 87, 235 compounds have been received from academic and private sector investigators, principally in the United States and Europe, with growing involvement of scientists from Africa, Asia, Australia, South America, and other geographic sites. Data generated have led to discoveries of new chemical classes of drugs active against M.

tuberculosis, advanced and supported research grants in this area, and identified FDA approved drugs with in vitro inhibition of TB. The TAACF recently refocused its efforts following a review panel of academic and industry experts in anti-infective drug discovery and development. TAACF now provides rapid turnaround of data collection to support suppliers with dedicated programs for the discovery of new anti-tubercular agents and who can commit to providing sufficient compounds for advanced testing in vivo. The facility website is <http://www.taacf.org/> where data and publications from this activity are posted.

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PROJECT TITLE: SUBMISSION OF COMPOUNDS FOR IN VITRO EVALUATION

- **Agency:** NIH
- **Description:** Staff has selected for evaluation more than 10,000 compounds, based on their chemical structure, from the National Cancer Institute (NCI) chemical repository of over 500,000 compounds. Of these compounds, many have shown initial in vitro activity against a wild-type strain, and some have promising in vitro activity against isoniazid (INH)-resistant strains. A large part of this effort is conducted under an interagency agreement with the Health Resources and Services Administration at the National Hansen's Disease Programs Center.
- **Results:** Efficacy evaluations in animal models of TB are being conducted on selected compounds. Novel chemical classes have been identified with in vitro activity against wild-type and drug-resistant strains. Follow-up of compound is continuing.

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PROJECT TITLE: HIGH-THROUGHPUT SCREENING CONTRACT WITH SOUTHERN RESEARCH INSTITUTE

- **Agency:** NIH
- **Description:** This contract provides a high throughput screening capability to develop and implement biochemical, target-specific Mtb drug screening assays and to develop and implement Mtb metabolic stage-specific drug screening assays.
- **Results:** Selected molecular targets are being screened against large chemical libraries to identify new candidate antibiotics as potential additions to the combined regimen for treatment of tuberculosis, particularly to combat multidrug resistant strains. Assays have been developed and run for specific biochemical targets of active and persistent TB: inhA, DHFR, isocitrate lyase, pantothenate C, malate synthase, and Mtb growth inhibition. A diverse publicly available library of 100,000 compounds have recently completed screening against virulent m. tuberculosis. Data will be posted to the website for use by the research community.

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PROJECT TITLE: BACTERIAL RESPIRATORY PATHOGEN RESEARCH UNIT (BRPRU)

- **Agency:** NIH

- **Description:** This project supports bacterial pre-clinical and clinical studies for the diagnosis, prevention, and management of selected human bacterial respiratory pathogens. DMID is partnering with Emergent Europe Limited to conduct a phase I clinical trial for Group B Streptococci at the University of Iowa.
- **Results:** A sub study to examine the emergence of antibiotic-resistant respiratory pathogens in otitis prone children was started in 2006.

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PROJECT TITLE: FOOD AND WATERBORNE DISEASES INTEGRATED RESEARCH NETWORK (FWDIRN)

- **Agency:** NIH
- **Description:** NIAID's FWDIRN network includes multidisciplinary research on all food and waterborne pathogens (bacteria, viruses, and protozoa), as well as toxins, to facilitate the development and evaluation of products to rapidly identify, prevent, and treat food and waterborne diseases that threaten public health. The network includes Immunology (IRU), Microbiology (MRU), Zoonoses (ZRU) and Clinical (CRU) Research Units. The Network will be supported by a Coordinating and Biostatistics Center. One of the MRUs will emphasize research aimed at developing and evaluating therapies for botulism.
- **Results:** Basic research to support novel prevention and/or treatment of infections include projects that focus on: i) the development of small animal models that mimic human disease caused by Campylobacter and the life-threatening sequelae to infection by Shiga toxin-producing Escherichia coli, the hemolytic uremic syndrome (HUS); ii) comparison of the efficacy and potential side-effects of several antibiotics in the treatment of Shiga toxin-producing Escherichia coli; and iii) evaluation of the intestinal microbiome prior to and after dosing with an antibiotic, Ciprofloxacin.

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PROJECT TITLE: PHARMACOKINETICS AND PHARMACODYNAMICS OF ANTIMICROBIALS IN ANIMAL MODELS

- **Agency:** NIH
- **Description:** This contract, awarded in 2004, provides a resource to determine basic pharmacology and efficacy characteristics of new chemical entities in order to best evaluate candidate compounds as potential new drugs for tuberculosis and other infections. This contract will allow NIAID to provide critical support for investigator-initiated drug discovery, to stimulate private sector sponsorship of new drugs, to perform comparison (or confirmatory) studies from different sponsors, and to provide information for selection of antimicrobial drug candidates for design of clinical studies. This contract will serve as the central facility for evaluation of novel compounds for physical, pharmacokinetic, and pharmacodynamic properties.
- **Results:** Data on new drug combination regimens from this preclinical research contract has informed and guided the development of new protocols for clinical trials (TB Trials Consortium) coordinated by the CDC. Publications of improved drug combinations may serve as a model of regimens to shorten therapy, thereby reducing the potential of

treatment interruptions leading to resistant TB. In addition, this contract contributed to the successful IND application for PA 824 from the Global Alliance for TB Drug Development. PA 824 is a new drug candidate active against multiply resistant M. tuberculosis.

#### FOCUS AREA IV: PRODUCT DEVELOPMENT

**\*\* TOP PRIORITY \*\***

ACTION ITEM #80: IDENTIFY WAYS (E.G., FINANCIAL AND/OR OTHER INCENTIVES OR INVESTMENTS) TO PROMOTE THE DEVELOPMENT AND/OR APPROPRIATE USE OF PRIORITY AR PRODUCTS, SUCH AS NOVEL COMPOUNDS AND APPROACHES, FOR HUMAN AND VETERINARY MEDICINE FOR WHICH MARKET INCENTIVES ARE INADEQUATE.

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#### PROJECT TITLE: EVOLUTION OF HIV DRUG RESISTANCE MUTATIONS IN ANIMAL MODELS

- **Agency:** CDC
- **Description:** The DHAP Laboratory Branch focuses on the development of improved diagnostics for HIV drug resistance surveillance, laboratory investigations on the clinical implications of drug resistant HIV, and studies in monkey models of drug resistance emergence and evolution during chemoprophylaxis and microbicide interventions. Studies also address the development of improved diagnostics for HIV drug resistance surveillance.
- **Results:** HIVResNet has developed laboratory guidelines on HIV drug resistance using dried blood spot samples.

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#### PROJECT TITLE: COLLABORATIONS TO FACILITATE VACCINE DEVELOPMENT

- **Agency:** FDA
- **Description:** Collaborations to facilitate vaccine development.
- **Results:** Participated in and supported international efforts to develop improved vaccines and drugs to prevent multi-drug resistant TB. For example, scientists from the LMDCI have participated in a project (funded by the Biotechnology Engagement Program) that is focused on developing a new class of drugs against TB. This research is being conducted in collaboration with Russian scientists and chemists from the Southern Research Institute and investigators at the Albert Einstein College of Medicine, the Aeras Global Tuberculosis Foundation, and NIH in evaluating the safety and effectiveness of new TB vaccines.

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#### PROJECT TITLE: SUPPORT PARTNERSHIPS TO PROMOTE DEVELOPMENT OF PRIORITY AR PRODUCTS

- **Agency:** NIH
- **Description:** NIAID brings together leading scientists to share capabilities and expertise in new drug discovery
- **Results:** NIAID, Eli Lilly and Company, the Infectious Disease Research Institute, and others have begun a not-for-profit partnership announced in June 2007 to promote discovery of new TB drugs especially for resistant cases ([www3.niaid.nih.gov/topics/tuberculosis/Research/lilly.htm/](http://www3.niaid.nih.gov/topics/tuberculosis/Research/lilly.htm/)).

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PROJECT TITLE: INCLUSION OF MANY ASPECTS OF AR AS BIODEFENCE

- **Agency:** NIH
- **Description:** Study of the spread of antibiotic resistance, mechanisms of resistance and development of strategies to recover use of existing antibiotics
- **Results:** Example of recent award include: Microbiotix Inc. "Bacterial DNA helicases: Targets for novel antibiotics."

ACTION ITEM #82: CONTINUE ONGOING APPROACHES THAT STREAMLINE THE REGULATORY PROCESS, INCLUDING CLINICAL TRIALS AND ENHANCED PRE-CLINICAL STUDIES (E.G., USE OF PHARMACOKINETICS AND PHARMACODYNAMICS DATA) TO HELP BRING AR PRODUCTS (INCLUDING DRUGS, VACCINES, DIAGNOSTICS AND DEVICES) TO MARKET AS EFFICIENTLY AND AS RAPIDLY AS POSSIBLE, WHILE STILL ASSURING THEIR SAFETY AND EFFICACY.

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PROJECT TITLE: MENINGITIS VACCINE PROJECT (MVP)

- **Agency:** FDA
- **Description:** MVP is a combined WHO Program for Appropriate Technology in Health (PATH) project to develop affordable meningococcal conjugate vaccines for Africa.
- **Results:** CBER-PATH Cooperative Research and Development (CRADA) resulted in development of novel efficient conjugation technology and tech transfer to Serum Institute of India. Vaccine currently in phase 2-3 trials in Africa. Additional CBER research supporting immunologic assays to evaluate vaccine efficacy. This consortium of public, private, and non-profit organizations, and a philanthropic organization (the Gate Foundation) will develop a vaccine that is critically needed in Africa.

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PROJECT TITLE: REGULATORY REQUIREMENTS – INDUSTRY AND SCIENTIFIC COMMUNITY

- **Agency:** FDA
- **Description:** Clarify FDA regulatory requirements to both industry and the scientific community.



- **Results:** 1) Presented regulatory requirements for tests used in AR initiatives to the Professional IVD Roundtable twice yearly. Discussed obstacles/issues that might exist in technology transfer; 2) CDRH assisted device manufacturers in the most efficient way to get an alternative method for detecting vancomycin resistance in *S. aureus* to market; 3) preliminary stages of submission for AST devices to promote a faster more efficient means of presenting data for a 510(k) review process; 4) 4/10/06 FDA published guidance document to ensure the safe & effective use of in vitro diagnostics for detecting novel influenza A; 5) 2/3/06 FDA cleared new assay submitted by CDC for the detecting human infection with H5 Avian Flu virus; 6) other approvals: 10/18/06 MASTALEX-MRSA rapid test for confirming Methicillin Resistant Staph aureus; 12/12/06, Smart GBS Dx System rapid DNA test for detecting Group B strep in pregnant women; 2/14/07 ImmunoCard STAT EHEC rapid test for detecting Shiga toxins 1 & 2 produced by *E.coli* in stool to aid in the diagnosis of diseases caused by enterohemorrhagic *E.coli* (EHEC).

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PROJECT TITLE: HIV DRUG RESISTANCE GENOTYPE ASSAY GUIDANCE

- **Agency:** FDA
- **Description:** Revised guidance on HIV Drug Resistance Genotype Assays. Significantly reduces the extent of studies required for clearance.
- **Results:** Published now.

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PROJECT TITLE: TB MEETING WITH EMEA

- **Agency:** FDA
- **Description:** A working group with representatives from FDA and EMEA met to discuss strategies for developing drugs for TB, a disease in for which resistance is a significant problem.
- **Results:** Meeting was held in early Spring 2008.

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PROJECT TITLE: GUIDANCE TO INDUSTRY: USE OF NONINFERIORITY STUDIES TO SUPPORT APPROVAL

- **Agency:** FDA
- **Description:** This guidance made recommendations on the appropriate use of noninferiority studies to approve antimicrobial drugs, with an emphasis on acute bacterial sinusitis, acute otitis media, and acute bacterial exacerbations of chronic bronchitis, indications for which overuse of antibiotics is common.
- **Results:** Draft guidance published 10/12/2007.

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PROJECT TITLE: GUIDANCE TO INDUSTRY: ACUTE BACTERIAL SINUSITIS - DEVELOPING ANTIMICROBIAL DRUGS FOR TREATMENT

- **Agency:** FDA
- **Description:** This document provided guidance on the development of drugs for ABS, a less serious, self-limited infection. Emphasis was placed on the importance of conducting meaningful clinical trials that adequately support approval. Overuse of antibiotics in infections such as these leads to the development of resistance.
- **Results:** Draft guidance published 10/29/2007.

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PROJECT TITLE: GUIDANCE TO INDUSTRY: ACUTE BACTERIAL OTITIS MEDIA -  
DEVELOPING ANTIMICROBIAL DRUGS FOR TREATMENT

- **Agency:** FDA
- **Description:** This document provided guidance on the development of drugs for acute bacterial otitis media, a less serious, self-limited infection. Emphasis was placed on the importance of conducting meaningful clinical trials that adequately support approval. Overuse of antibiotics in infections such as these leads to the development of resistance.
- **Results:** Draft guidance published 1/17/2008.

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PROJECT TITLE: GUIDANCE TO INDUSTRY: MALARIA - DEVELOPING DRUG AND  
NONVACCINE BIOLOGICS FOR TREATMENT AND PREVENTION

- **Agency:** FDA
- **Description:** This document provided guidance for the development of drugs for malaria, a disease for which the development of resistance is a major concern.
- **Results:** Draft guidance published 6/2007.

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PROJECT TITLE: ADVISORY COMMITTEE MEETING: DEVELOPING THERAPIES FOR THE  
TREATMENT AND/OR PREVENTION OF DISEASE CAUSED BY SHIGA TOXIN-  
PRODUCING BACTERIA.

- **Agency:** FDA
- **Description:** Meeting to discuss challenging clinical development issues for a bacterial disease that occurs in sporadic outbreaks and is particularly difficult to study.
- **Results:** Meeting held on 4/12/2007.