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## INVENTORY OF PROJECTS

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

## PROGRESS THROUGH 2008

## FOCUS AREA I: SURVEILLANCE

### ACTION ITEM #1

#### PROJECT TITLE: PUBLIC HEALTH SURVEILLANCE

- **Action Item(s):** #1
- **Project Type:** Ongoing
- **Agency:** CDC, 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, *Haemophilis 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.
- **2008 Update:** In 2008, CDC's Active Bacterial Core surveillance, part of the Emerging Infections Program Network, tracked MRSA as well as serious infections caused by resistant strains of groups A and B streptococcus, *H. Influenzae*, *N. meningitidis*, *S. pneumoniae*, and *Clostridium difficile*. Surveillance summaries are available at <http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm>. CDC's National Healthcare Safety Network (NHSN) published a report ([http://www.cdc.gov/nhsn/PDFs/AR\\_report2008.pdf](http://www.cdc.gov/nhsn/PDFs/AR_report2008.pdf)) to describe the frequency of selected antimicrobial resistance patterns among pathogens causing device-associated and procedure-associated healthcare-associated infections (HAIs). As many as 16% of all HAIs were associated with the following multidrug-resistant pathogens: methicillin-resistant *S. aureus* (8% of HAIs), vancomycin-resistant *Enterococcus faecium* (4%), carbapenem-resistant *P. aeruginosa* (2%), extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (1%), extended-spectrum cephalosporin-resistant *E. coli* (0.5%), and carbapenem-resistant *A. baumannii*, *K. pneumoniae*, *K. oxytoca*, and *E. coli* (0.5%). Continuing service activity providing testing and advice for treatment of resistant trichomoniasis. Collation of 2002-2008 data suggests successful treatment of > 80% of patient who had failed at least 2 rounds of standard therapy. In regards to *Trichomonas vaginalis*, over 100 testing kits were distributed to 84 clinics/physicians with patients who had failed standard therapy for trichomoniasis. In 2008 several new tests were cleared by FDA to enhance surveillance efforts of multi-drug resistance organisms. On September 24, 2008, FDA cleared a new nucleic acid amplification test (NAAT) for detection of Methicillin Resistant *Staphylococcus aureus* (MRSA) in patients with skin and soft tissue infection and on September 29, a similar NAAT for detection of MRSA in blood cultures of febrile patients. Also cleared in 2008, (December 19) was the first NAAT for the detection of *Clostridium difficile* toxin B in liquid or soft stool specimens from patients suspected of having *Clostridium difficile* – associated disease.

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**PROJECT TITLE: BURDEN OF DISEASE DUE TO ANTIMICROBIAL RESISTANT *NOCARDIA* SPECIES (2007-2009)**

- **Action item(s): #1**
- **Project Type:** New
- **Agency:** CDC
- **Description:** This is a collaborative project with 10 states to detect and monitor trends in emerging antimicrobial resistance among disease-causing *Nocardia* species. Sites collect and send to CDC *Nocardia* isolates for work-up and antimicrobial susceptibility testing. Clinical and epidemiologic data is collected and forwarded to CDC using a standard surveillance tool, including information on recent antimicrobial agent use and previous diagnostic cultures or susceptibility profiles for each patient from the catchment area. CDC will evaluate *Nocardia* data to estimate US burden of illness due to *Nocardia*, susceptible/resistant species, estimate cost per illness, and antimicrobial use patterns.
- **2008 Update:** CDC collected isolates and clinical data from the participating state health departments. 226 viable *Nocardia* isolates were collected from the states in 2008. Antimicrobial susceptibility panels were completed on all isolates.

**PROJECT TITLE: ISOLATION AND CHARACTERIZATION OF FLUOROQUINOLONE-RESISTANT BACTERIA FROM IMPORTED SHRIMP**

- **Action Item(s): #1**
- **Project Type:** New
- **Agency:** FDA
- **Description:** A collaborative research project with Centers for Veterinary Medicine (CVM/FDA) and Office of Regulatory Affairs (ORA/FDA) was initiated. Numerous fluoroquinolone-resistant, pathogenic bacteria such as *Vibrio* spp., *Salmonella* and *E. coli* have been isolated from imported shrimp purchased from retail stores. These isolates are currently being characterized at the molecular level by PCR, RFLP, PFGE, Southern hybridization and DNA sequencing. The molecular mechanism of fluoroquinolone-resistance in these food borne pathogens will also be investigated.
- **2008 Update:** Antibigrams of these bacteria indicate that many display resistance to multiple antimicrobials of public health significance.

**ACTION ITEM #2**

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

- **Action Item(s): #2**
- **Project Type:** Ongoing

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- **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, ten 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 baseline, and risk-based sampling programs.
- **2008 Update:** NARMS now includes all 50 states, providing national surveillance for antimicrobial resistance among select foodborne pathogens. *Campylobacter* sampling in the ten FoodNet states has been changed to allow for burden estimates and a plan is underway for further expanding to more sites. One site sends generic *E. coli* and three sites send *Enterococcus* sp isolated from outpatient stools to CDC NARMS for antimicrobial susceptibility testing. FDA, CDC, and USDA NARMS staff also met in Athens, GA, September 10-12, 2008 for a laboratory methods and strategic planning conference to discuss progress and future plans related to implementation of the recommendations put forward in the FDA Science Board Summary report. Additional funds and partnerships were sought to extend surveillance to include additional antimicrobial agents (beta-lactams and macrolides) and pathogens (clostridia and methicillin-resistant *Staphylococcus aureus* in retail foods). Developed a DNA microarray to identify and track 775 resistance and virulence genes in a variety of bacteria simultaneously. Resistance and virulence genes in *Campylobacter*, *Salmonella*, *E. coli*, *Enterococcus*, *Staphylococcus* (including MRSA), *Listeria* and *Clostridium* have been identified using the microarray. Analysis of bacteria collected on-farm with this technique has identified common genes in different species of bacteria co-cultured from the same animal.

#### **PROJECT TITLE: COORDINATION OF SURVEILLANCE EFFORTS**

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **Agency:** CDC, FDA
- **Description:** Coordinate surveillance activities.
- **2008 Update:** In 2007 the NARMS program was subjected to 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. Strategic planning and methods harmonization meetings were held in September 2007 and September 2008 focusing on progress and future plans to

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implement the Science Board recommendations where appropriate. These meetings have been and will continue to be held annually. As of the end of calendar year 2008, NARMS published two executive summaries of food animal, retail meat and human isolate susceptibility data collected by USDA, FDA-CVM and CDC, respectively, for calendar years 2003 and 2004. The three NARMS partner agencies began to explore business practices and electronic infrastructure that would facilitate efficient data sharing and presentation. NARMS does not currently screen for MRSA but has been working with partners at the University of Maryland to conduct a pilot study looking for MRSA in retail meats in the Washington, DC metro area. NARMS scientists from FDA, CDC, and USDA, were appointed in 2008 to serve on the steering committee of the newly established WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (WHO-AGISAR). The primary focus of AGISAR will be to exchange information and expertise in all matters relating to antimicrobial resistance surveillance programs globally.

**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**

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Data collection was completed in August 2008, and data cleaning was completed in April 2009. Data analysis and report writing are ongoing, with an expected date of completion of September 2009.

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

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** The purpose of this descriptive study is to provide detailed observational data on the diagnosis, treatment and management practices, outcomes, and costs of MDR and XDR TB patients in the United States. The study aims to collect data from

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multiple sites that are generalizable to the U.S. population of MDR and XDR TB cases. Inpatient, outpatient, laboratory, and public health clinic records will be abstracted from approximately 134 patients reported to the Centers for Disease Control and Prevention (CDC) for the study period of 2005-2007. Costs will be collected or estimated to calculate inpatient, outpatient, and total costs per patient.

- **2008 Update:** Project was awarded to three sites (the Departments of Health for California, Texas, and New York City) in November 2008. The study protocol and data collection instruments were drafted by June 2009 and are under CDC Institutional Review, after which the awarded sites will seek local IRB approval to begin data collection.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **Agency:** CDC, NIH, FDA, HRSA, USAID, DoD, DOHS, VA
- **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.
- **2008 Update:** The action plan was completed, cleared and submitted for publication in 2008.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.

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- **2008 Update:** Project has enrolled 79 patients at 9 consortium sites. Data cleaning and preliminary analyses are underway. Abstracts to be presented at the International Union Against TB and Lung Disease Annual Conference in December 2009.

#### **PROJECT TITLE: NATIONAL TUBERCULOSIS SURVEILLANCE SYSTEM (NTSS)**

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Data collection and analysis are conducted on a continuous basis. The proportion of patients with primary MDR TB decreased from 2.5% in 1993 to 1.0% in 2001. From 2001 to 2008, the most recent year for which data are available, the proportion has remained between 1.0% – 1.2% (all cases were culture positive with initial drug susceptibility testing performed). MDR TB differed by country of origin. In 2008, the percentage of U.S.-born persons with MDR was 0.6 %. The percentage of foreign-born persons with MDR was greater, at 1.2%. Of the total number of reported MDR TB cases, the proportion occurring in foreign-born persons increased from 25% in 1993 to 77% in 2008. The CDC annual TB surveillance report, Reported Tuberculosis in the United States, 2008, will provide 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/statistics/default.htm>.

#### **PROJECT TITLE: GONOCOCCAL ISOLATE SURVEILLANCE PROJECT (GISP)**

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **Agency:** CDC, DoD
- **Description:** Sentinel surveillance system for monitoring antimicrobial resistance of *Neisseria gonorrhoeae* in the US was 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 are

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published in an annual report, periodically in the MMWR, and other peer-reviewed journals. GISP annual reports from 1998-2007 can be found at <http://www.cdc.gov/std/gisp>. GISP data have 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. 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.

- **2008 Update:** In 2007, 27% of all GISP isolates were resistant to penicillin, tetracycline, ciprofloxacin, or some combination of those antibiotics. Prevalence of ciprofloxacin-resistant gonococcal isolates remains high at 14.8%. No isolates had decreased susceptibility to ceftriaxone. There is a steady increase in isolates that show decreased susceptibility to azithromycin. Similar trends continued in 2008. The DoD Global Emerging Infections Surveillance and Response System (DoD-GEIS) is currently trying to re-invigorate the military labs participating in GISP to include Tripler Army Medical Center Hawaii, the Navy lab in Peru as well the Army lab in Kenya.

**PROJECT TITLE: ENHANCEMENT OF INTERNATIONAL SURVEILLANCE FOR ANTIMICROBIAL RESISTANCE IN *NEISSERIA GONORRHOEAE* TO PREDICT POTENTIAL EMERGENCE OF CEPHALOSPORIN RESISTANCE IN THE UNITED STATES**

- **Action Item(s): #2**
- **Project Type:** New
- **Agency:** CDC
- **Description:** CDC/DSTDP will collaborate with WHO via financial and technical support to maintain its regional GC-resistance surveillance programs and to strengthen the laboratory/epidemiological capacity of countries, particularly in the Far East, to monitor the potential emergence of Ceph-resistant GC. The project will obtain early alerts of cephalosporin treatment failures detected in WHO member countries and establish a system for expedited sharing with CDC of information, research findings and gonococcal strains for laboratory studies. In addition, CDC with WHO will organize an international forum to share information on emerging problems of antimicrobial resistance in *N. gonorrhoeae* and formalize international approaches to respond to this significant public health problem. Domestically, to complement these international efforts, the project will expand susceptibility testing in Hawaii and build gonococcal culture and susceptibility testing capacity in Guam in order to provide a domestic "early warning system" for Ceph-resistant GC.
- **2008 Update:** Collaboration with WHO established and project planning initiated.

**PROJECT TITLE: FORMULATION OF A CEPHALOSPORIN-RESISTANT (CEPH-R) *NEISSERIA GONORRHOEAE* NATIONAL OUTBREAK RESPONSE PLAN**

- **Action Item(s): #2**
- **Project Type:** New



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- **Agency:** CDC
- **Description:** CDC/DSTDP will formulate a comprehensive national and state-level public health response plan to ensure the early detection of emerging cephalosporin-resistant *N. gonorrhoeae* cases and to prevent rapid spread of these strains through implementation of public health containment strategies in the United States. The project components include promoting awareness of clinicians of the threat of cephalosporin-resistant *N. gonorrhoeae* and to increase vigilance of cephalosporin treatment failures, development and pilot implementation of the outbreak response plan in a selective domestic sites and step-wise expansions to develop State-specific response plan.
- **2008 Update:** Project planning initiated.

#### **PROJECT TITLE: AZITHROMYCIN RESISTANCE IN SYPHILIS IN THE UNITED STATES**

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.
- **2008 Update:** At the end of 2008, CDC had received and tested a total of 494 samples from participating sites: 21% were positive for *T. pallidum*, of which 54% carried the 23S mutation. Notably, samples carrying the 23S mutation came from 9 of 11 sites. Preliminary analysis indicated that samples carrying the 23S mutation more likely came from men having sex with men than from heterosexual men or women.

#### **PROJECT TITLE: SURVEILLANCE FOR HIV DRUG RESISTANCE**

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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

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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.

- **2008 Update:** National surveillance for HIV drug resistance is ongoing. Currently (2008), eleven (11) surveillance areas (8 states, 2 cities, and 1 county) are funded to participate.

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

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **Agency:** CDC, WHO, 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.
- **2008 Update:** 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. A DBS protocol development update meeting was held by WHO in December 2008 and based on the recent publications at the time, the protocol was further modified. Discussions were held to identify urgently needed research and data. Based on the discussions, WHO, Uganda, and CDC ILB will collaborate and conduct a comprehensive study on DBS and the SDRL will conduct in-house assay validation using DBS. The DBS evaluation project is on going and the in-house assay validation using DBS is going to start in September.

**PROJECT TITLE: TRICHOMONAS VAGINALIS ANTIMICROBIAL SUSCEPTIBILITY IN THE UNITED STATES, STD SURVEILLANCE NETWORK (SSuN)**

- **Action Item(s): #2**
- **Project Type:** New
- **Agency:** CDC
- **Description:** This sentinel surveillance activity was designed to evaluate the prevalence of *T. vaginalis* susceptibility to 5-nitroimidazoles, the only class of antimicrobial agents currently recommended for treatment of trichomoniasis in the US. The activity is conducted as part of the STD Surveillance Network (SSuN), a multi-site sentinel surveillance system. The *T. vaginalis* susceptibility activity was initiated in 2009 and is projected to continue through 2010. STD clinics in 6 cities transmit clinical and demographic data and submit female vaginal *T. vaginalis* isolates to CDC for susceptibility testing. Isolates are tested for antimicrobial susceptibility to metronidazole

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and tinidazole. These data will be used to assess national and regional prevalence of drug resistance and evaluate the epidemiology of drug resistance at participating sites.

- **2008 Update:** Specimen and data collection are ongoing.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.
- **2008 Update:** As of August 2009, CDC has confirmed 9 VRSAs in the U.S.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.
- **2008 Update:** During 2008, microbiology, pharmacy and admission/discharge/transfer (ADT) data in the electronic HL7 Version 2.5 message format were received from pilot healthcare facilities. The validation of these data in the medications-associated module of the National Healthcare Safety Network continues. Expansion to additional hospitals has begun.

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

- **Action Item(s):** #2

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- **Project Type:** Ongoing
- **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. A convenience sample of isolates collected as part of this activity (approx. 1000/ year) are submitted to CDC for confirmation, typing and characterization.
- **2008 Update:** 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 2005-2007 were analyzed, population based incidence rates were calculated and annual summaries were completed (<http://www.cdc.gov/ncidod/dbmd/abcs/survreports.htm>). A preliminary analysis of trends in invasive disease between 2005 through 2007 were performed and demonstrate a 20% decrease in incidence among hospitalized patients, and a more modest decrease among other types of patients. A survey of 80% of participating facilities identified a variety of MRSA prevention programs in place. Analysis of 1984 isolates collected during 2005-2006 as part of the ABCs MRSA activity was completed, including PFGE typing, PCR for toxin genes, antimicrobial susceptibility testing. Ref: J Clin Microbiol. 2009 May;47(5):1344-51..

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Surveillance of healthcare associated infections and their antimicrobial resistance patterns.
- **2008 Update:** The first NHSN Antimicrobial Resistance Report was published in November, 2008 in infection control and hospital epidemiology. Analysis of trends includes incidence of MRSA central line bloodstream infection published in August in JAMA demonstrated an overall annual 8% decrease in the incidence of MRSA central-line associated bloodstream infections over the past decade. Development and implementation of a new module to monitor multi-drug resistant pathogens was developed, tested, and launched for use in 2009 for use by the CMS QIO network in a national MRSA prevention effort.

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

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- **Action Item(s): #2**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Held monthly conference calls with ACIP Pneumococcal Working Group to identify key areas of existing pneumococcal vaccine recommendations in need of updating; 2. Used ABCs data to evaluate the potential usefulness of new pneumococcal vaccines with varying activity against pneumococcal colonization vs. disease; 3. Estimated that since conjugate vaccine was introduced, over 210,000 cases of invasive disease and 14,000 deaths were prevented; 4. Determined that effects on hospitalized pneumonia are a key driver of the cost-effectiveness of conjugate vaccine and that, when such effects are incorporated, conjugate vaccine may be cost-saving; 5. Used ABCs data to evaluate different strategies for using pneumococcal polysaccharide vaccine among persons with underlying illnesses and determined that current vaccination policies are appropriate.

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

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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

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emergence of new resistant 19 A variants and that serotype switching has played an important role (1). The proportion of beta-lactam resistant strains within serotype 19A continues to increase, and this is due to continued preferential expansion of recently identified 19A strains (1, manuscript in preparation). We have also noted increases in antibiotic-nonsusceptible strains of additional serotypes not targeted by PCV7 and are completing MLST analysis of these strains. The newly discovered serotype 6C is of concern since it is not targeted by PCV7 and is increasing in resistance (2,3). We characterized (identification of resistance-conferring chromosomal alterations and MLST) current ABCs strains resistant to existing cephalosporins and found that ceftaroline (a new cephalosporin in development) was highly potent against these strains (4).

1. Moore MR et al. J. Infect. Dis. 2008. 197:1016-27.
2. Park IH et al. J. Infect. Dis. 2008. 198: 1818-22.
3. Carvalho Mda G et al. J. Clin. Microbiol. 2009. 47:554-9.
4. McGee L et al. Antimicrob. Agents Chemother. 2009. 552-6.

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

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** In 2008, approximately 3000 cases of invasive disease were identified through ABCs and serotyping and susceptibility testing of isolates is nearing completion. In addition, during 2008, multiple presentations of 2007 ABCs data were made at national and international meetings including CDC's Advisory Committee on Immunization Practices, ICAAC, ASM, IDSA, and the International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD).

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

- **Action Item(s): #2**
- **Project Type:** Ongoing
- **Agency:** CDC

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- **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 and to prospectively monitor for potential emergence of this phenotype among invasive GAS and GBS in the United States.
- **2008 Update:** We identified three different penicillin binding protein (PBP) gene mutations in invasive GBS isolates recovered during 1999-2005 that were putatively responsible for elevated MICs to beta lactam antibiotics. With one key *pbp2X* mutation, seen to occur within multiple invasive isolates, wild type MICs were restored after gene replacement with the wild type allele and after expression of the wild type allele in-trans on a multicopy plasmid (1). Interestingly, this mutation exactly corresponds to a well-characterized pneumococcal mutation that confers beta lactam resistance. Similar experiments are ongoing with a second nonconservative (Gly406 change to Asp) *pbp2X* mutation identified within multiple isolates and a potential resistance-conferring *pbp1A* allele. We red-flagged 32 invasive GBS and 6 GAS recovered during 2006-present using beta lactam MIC criteria and retested penicillin MICs. Of these 32, 2 were group D, and for 14 the penicillin retests showed MICs below the red flag levels. Sequencing is ongoing of the 3 key PBP genes from the 16 verified GBS strains and 3 new causative mutations have been putatively identified. Of 6 red-flagged GAS, 5 penicillin MIC repeats were below red flag level and 1 was not *S. pyogenes*.

1. Dahesh S. et al. 2008. Antimicrob Agents Chemother. 52:2915-8.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.

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- **2008 Update:** 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 and ended December 31, 2008. Patients are being followed for 30 months after enrollment. A total of 676 patients have been enrolled (386 stem cell and 290 lung transplants). There have been a total of 55 invasive fungal infections in 49 patients (29 IFIs in stem cell transplants; 26 in lung transplants). Antifungal susceptibility analysis is ongoing.

#### **PROJECT TITLE: MRSA DISEASE IN ALASKA**

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Isolates of MRSA from southwest Alaska are predominantly ST1 or USA400. This differs from the predominant strain in the rest of the US and in Anchorage which is ST8 or USA300. Ref. [Emerg Infect Dis.](#) 2008 Nov; 14(11): 1693-9.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **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 is 2-4 times higher than the general US population.
- **2008 Update:** Ongoing specimen collection and analysis. 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.

#### **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**



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- **Action Item(s): #2**
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** In the United States, two classes of antiviral drugs are approved by the Food and Drug Administration for managing influenza virus infections: neuraminidase inhibitors (oseltamivir and zanamivir) and adamantanes (amantadine and rimantidine). Extensive heterogeneity of influenza viruses necessitates resistance monitoring to be conducted on a basis of antigenic type (A or B) and subtype (H1N1, H3N2, and H5N1). The 2007 influenza season was marked by the global prevalence of H3N2 viruses resistant to adamantanes. In addition, adamantane-resistant viruses were also detected among H1N1 viruses and highly virulent avian H5N1 viruses. These events have highlighted the need for the close monitoring of virus susceptibility to the newer class of drugs, neuraminidase inhibitors. This project focuses on the improvement of pandemic preparedness and interpandemic control of influenza via 1) development of molecular tests for rapid, reliable and high throughput detection of viruses resistant to both classes of drugs; 2) enhancement of viruses sampling for antiviral susceptibility testing; and 3) enhancement of reporting and sharing of antiviral susceptibility data.
- **2008 Update:** The influenza season of 2008 was marked with the sudden and unprecedented emergence of oseltamivir resistance in seasonal influenza H1N1 viruses. It was first detected in the United States (U.S.), Australia, and Europe, particularly in countries where oseltamivir was not previously prescribed. All the H1N1 oseltamivir-resistant viruses shared a single genetic mutation (H274Y) in the neuraminidase that confers oseltamivir resistance. In response to this event, Influenza Division, CDC, developed and employed a pyrosequencing assay that allowed for the detection of H274Y mutants directly in clinical specimens thus facilitating the testing and reporting of the drug susceptibility data. In addition, a restriction fragment length polymorphism (RFLP) protocol was developed which also allowed the detection of H274Y mutants in original clinical respiratory specimens. Prevalence of oseltamivir resistance varied substantially, from 0% to 100%, among individual countries and states. Overall, 4,116 influenza A (n=2,844) and B (n=1,272) viruses collected in the U.S. (n=2,511) and abroad (n=1,605) were tested at CDC during FY 2008. Oseltamivir-resistance was detected in 12.8% of influenza H1N1 viruses collected in the U.S., which constitutes a substantial increase compared to the previous influenza season when the level of resistance was only 0.7%. No resistance to oseltamivir was identified among the 444 influenza H3N2 or 305 influenza B viruses collected in the U.S. during the FY 2008. All tested viruses were sensitive to zanamivir. The results of the drug susceptibility tests were posted on the CDC website (FluView) and updates on oseltamivir resistance in U.S. and abroad were also submitted to the WHO on a weekly basis. In addition, detailed phylogenetic analysis of the entire genome of H1N1 viruses was performed to elucidate molecular mechanisms underlying the unexpected fitness (wide transmissibility) of the oseltamivir resistant viruses. The fitness as well as unchanged virulence of oseltamivir resistant viruses was also established in epidemiological study conducted by CDC (Dharan, NJ et al, 2009). Continuous testing of H5N1 viruses revealed the presence of variants with reduced susceptibility to either oseltamivir and/or zanamivir. These results emphasized the need for detailed analysis of the detected variation on clinical efficacy of the available drugs. A

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series of new molecular methods to detect resistance in seasonal A and B as well as avian influenza viruses was developed at CDC and their protocols were shared with other virus surveillance laboratories and published in professional journals.

In 2008, adamantane resistance continued to be high (99.8%) among the 525 influenza H3N2 viruses tested. Adamantane resistance among H1N1 viruses was detected at a lower level in the U.S. Of the 918 H1N1 viruses collected in the U.S., 98 (10.7%) were resistant to the adamantanes. However, adamantane-resistance remained high in some countries of Southeast Asia (e.g., China). None of the oseltamivir-resistant influenza H1N1 viruses collected in the U.S. during the 2008 season were resistant to adamantanes. Noteworthy, it was recognized that prevalence of adamantane resistance in avian H5N1 viruses varied significantly (~1% to 100%) among genetically distinct viral lineages circulating in different geographic regions.

Based on the virus surveillance data, in 2008 CDC continued to recommend the use of oseltamivir and zanamivir for the treatment and prevention of influenza while amantadine or rimantidine were not recommended.

**PROJECT TITLE: ENHANCED SURVEILLANCE OF ANTIMICROBIAL SUSCEPTIBILITY OF *NEISSERIA MENINGITIDIS* IN THE UNITED STATES AND CHARACTERIZATION OF EMERGING STRAINS WITH REDUCED SUSCEPTIBILITY TO ANTIMICROBIALS**

- **Action Item(s): #2**
- **Project Type:** New
- **Agency:** CDC
- **Description:** *Neisseria meningitidis* (Nm) is a leading cause of meningitis and severe sepsis in the U.S. and prompt treatment of patients and chemoprophylaxis of close contacts is vital to the management of meningococcal disease. Surveillance has recently detected new Nm strains with reduced susceptibility to commonly employed antimicrobials; spread of these strains or emergence of similar strains would require modifications to current recommendations for chemoprophylaxis and treatment, increased activities to conduct susceptibility testing and the possibility of both breakthrough cases (not prevented by prophylaxis) and suboptimal patient response to treatment. Increasing the population area covered by surveillance would enhance early detection of the emergence or spread of strains of Nm with reduced susceptibility to antimicrobials. Rapid detection and dissemination of susceptibility information is vital for effective surveillance.
- **2008 Update:** Funding from a previous ARWG grant allowed initiation of a surveillance program in 2007-2008. The Meningitis Laboratory receives all Nm isolates from the population-based Active Bacterial Core Surveillance (ABCs) covering 13% of the U.S. population and screens all incoming isolates for susceptibility to 6 antimicrobials by Etest. Isolates with resistant/non-susceptible MICs are confirmed by broth microdilution and the molecular mechanism of resistance is determined. That program made it possible for CDC to effectively and rapidly respond to and characterize the emergence of ciprofloxacin-resistant (cip-R) Nm in North America. In addition, the emergence of cip-R Nm in Minnesota and North Dakota changed chemoprophylaxis recommendations for

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that area. To date the surveillance program has detected cip-R, penicillin-resistant, and azithromycin non-susceptible isolates of Nm, the latter not previously seen in the U.S. To expand detection, which is critical for a condition with low incidence such as meningococcal disease, MeningNet, an enhanced surveillance system, was created in late 2008. MeningNet and ABCs together can provide surveillance for reduced susceptibility in Nm in 68% of the population.

**PROJECT TITLE: IMPROVING MEASUREMENT OF C. DIFFICILE-ASSOCIATED INFECTIONS (CDI)**

- **Action Item(s):** #2 and # 75
- **Project Type:** New
- **Agency:** CDC/ Prevention Epi Center CoAg
- **Description:** Multicenter Project (Harvard, Chicago, Ohio, Utah) evaluating the accuracy/efficiency of two emerging surveillance methods for CDI and comparing with traditional surveillance methods - 4 hospitals.
- **2008 Update:** 1) Extracted demographic data on patients admitted from 2000 through 2006 who had been given the diagnosis of CDI by ICD-9 discharge code or laboratory test 2) Conducted medical record review 3) Data collection complete and analyses is ongoing 4) One manuscript near completion 4 in progress 5) Participated in design and implementation of the Ohio program 6) Correlated antimicrobial use rates with C. difficile and other antimicrobial resistance 7) Data collection is complete and data analysis is being finalized.

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

- **Action Item(s):** #2
- **Project Type:** Ongoing
- **Agency:** DoD
- **Description:** Establish an overarching framework for facilitating the implementation, operation, and evaluation of activities in AR surveillance within DoD.
- **2008 Update:** In February 2007 DoD and 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. DOD-GEIS has also started projects at the Navy Marine Corps Public Health Center in

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Norfolk to use HL-7 data to monitor antimicrobial resistance in military facilities and is currently validating their electronic surveillance methodology. GEIS is also soliciting new proposals that specifically address MDR organisms, especially TB.

**PROJECT TITLE: EMERGING PATHOGENS INITIATIVE (EPI)**

- **Action Item(s):** #2, #6, and #24
- **Project Type:** Ongoing
- **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). Resistance data are being gathered in the EPI 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. 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. 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.
- **2008 Update:** Currently over 153 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 VHA Central Office and 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. 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.

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

- **Action Item(s):** #2, #6, and #24
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** VA is actively engaged in cooperative development of 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 final product.

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- **2008 Update:** 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. Design specification and pilot testing ongoing during 2008.

**PROJECT TITLE: PARTNERSHIP WITH CDC PREVENTION EPICENTERS—EVALUATING DATA SOURCES AND DETECTION**

- **Action Item(s):** #2 and #6
- **Project Type:** New
- **Agency:** VA
- **Description:** VHA is partnering with CDC Prevention Epicenters on several projects related to antimicrobial resistance.
- **2008 Update:** Funded Surveillance Prevention Epicenters/VA Collaboration to: i) Evaluate the use of electronic data sources to (e.g., Detect central-line associated bloodstream infections, detect MRSA outbreaks, evaluate impact of MRSA prevention programs by using clinical microbiology information to create incidence measures, demonstrate impact of current VA MRSA prevention activities using data from Veteran's Integrated Service Network [VISN]), and ii) Evaluate additional ways to detect HAIs (e.g., Surrogate inpatient surveillance measures for surgical site infections [SSI], Medicare claims to identify hospitals with high SSI rates, ICD9 codes for ascertaining device-days of use and related adverse events, Surveillance methods for *Clostridium difficile* infection, Measuring variability and appropriateness of antimicrobial utilization).

**ACTION ITEM #3**

**PROJECT TITLE: REFINING AND VALIDATING USE OF ADMINISTRATIVE CODING DATA TO ESTIMATE BURDEN OF MRSA**

- **Action Item(s):** #3
- **Project Type:** New
- **Agency:** CDC
- **Description:** The objective of this project is to develop and validate measures to determine the burden of overall *S. aureus* and MRSA infection using electronic administrative coding data. The project is being conducted via an inter-agency agreement with the Salt Lake City VA Medical Center and in collaboration with the University of Utah and Intermountain Healthcare Systems. Correlation between administrative coding data and clinical microbiology will be analyzed. Medical records will be reviewed on a subset of records, focusing primarily on those records in which there is discrepancy between administrative coding and microbiology data. Potential reasons for discordance will be explored. Results will be used to refine coding algorithms used to estimate MRSA burden nationally.

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- **2008 Update:** In 2008, administrative coding data and clinical microbiology records were analyzed for a total of 494,604 inpatients discharged between 2004 and 2007 and correlation between administrative coding data and microbiology culture data was analyzed on multiple levels - presence or absence of *S. aureus*, classification of infection type, and classification of *S. aureus* as methicillin-susceptible or methicillin-resistant given that *S. aureus* was present.

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

- **Action Item(s):** #3
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Manuscript on LC/MS/MS and water extraction methods published in March 2008 for the measurement of 54 human prescription pharmaceuticals. A second water method using SPE and LC/MS/MS is being developed, which focuses on antibiotics and steroids of both human and veterinary use. Work will begin on the fish tissue extraction method in early FY09. Future method development plans exist for a subset of pharmaceuticals in sediments (possible FY11).

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

- **Action Item(s):** #3
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Concluded: "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.

**PROJECT TITLE: ANTIMICROBIAL SUSCEPTIBILITY TESTING FOR *LISTERIA***

- **Action Item(s):** #3
- **Project Type:** Ongoing

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- **Agency:** USDA
- **Description:** Methodologies and standards for antimicrobial susceptibility testing of *Listeria* are being developed and implemented.
- **2008 Update:** A new *Listeria* broth microdilution plate was constructed and tested in 2007. Research determined the antimicrobial resistance of *L. monocytogenes* isolates detected in a poultry further processing facility. This large group of isolates is unique because they had been collected during one year in a commercial plant. Most of the *L. monocytogenes* isolates were susceptible to all antimicrobials. However, some were resistant to ceftriaxone, oxacillin, ciprofloxacin, clindamicin, tetracycline or some combination of these.

#### ACTION ITEM #4

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

- **Action Item(s):** #4
- **Project Type:** Ongoing
- **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.
- **2008 Update:** During 2008 antibiotic susceptibility testing of 907 invasive GAS isolates obtained from ABCs during 2006 was completed. Among these isolates, testing of all macrolide-resistant strains both for genetic determinants of resistance (*mef* and *erm*) and for inducible clindamycin resistance has also been completed. Results show that resistance to erythromycin has increased among ABCs sites from an average of approximately 8% during 2001 and 2003 to 11.8% in 2006. Tetracycline resistance among GAS isolates also increased from <1.0% to 14.9% during the same time periods. During 2007 and 2008 approximately 1800 GAS isolates were sent to CDC from the ABCs sites. Antibiotic susceptibility testing of these has recently been completed. 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: analyze antibiotic susceptibility testing results of ABCs 2007 and 2008 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.

**PROJECT TITLE: NATIONAL BURDEN OF ANTIMICROBIAL RESISTANT NEONATAL SEPSIS**

- **Action Item(s): #4**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** A full year of active surveillance for invasive neonatal sepsis was conducted in ABCs and in the NICHD neonatal network. In ABCs, in 2008, 175 neonatal sepsis cases were identified. Overall neonatal sepsis incidence was 0.75 cases /1000 live births; GBS was the leading cause (0.28/1000 live births). *E coli* sepsis was the leading cause after GBS (24% of cases). From 2006-8, the incidence of nonGBS sepsis was stable among term infants but increased among preterm from 2.10 to 2.48 cases/1000 live births; 83% of *E coli* infections among preterm were ampicillin resistant in 2008 compared to 56% among term infants. From 2005-8 there is still only 1 case of invasive early-onset MRSA infection detected in the ABCs neonatal sepsis catchment. The NICHD 2008 data are not finalized; from 2006-first 6 months of 2008 NICHD identified 381 early-onset sepsis cases; 108 were deemed contaminants and 273 were diagnosed with early onset sepsis or meningitis. GBS was the leading cause (38%) followed by *E. coli* (26%). Among the *E coli* cases, 96% were symptomatic, 91% were admitted to intensive care and 33% died. The NICHD data were presented at the 2009 Pediatric Academic Society Meetings. Both the ABCs and NICHD data were presented at a meeting in June 2009 to revise the US perinatal GBS disease prevention guidelines. These data were evaluated to determine whether unintended consequences of intrapartum prophylaxis for GBS prevention had reached a tipping point and all the guidelines partners agreed that IAP continues to cause benefit and that there are not yet evidence of an adverse impact on nonGBS sepsis. A preliminary estimate of the national burden of invasive neonatal sepsis suggests approximately 3100 cases occur annually in infants less than 72 hours of age. Further refinement and finalization of this estimate needs to occur in 2009.

**PROJECT TITLE: BURDEN OF ANTIMICROBIAL RESISTANT *STREPTOCOCCUS PNEUMONIAE***



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- **Action Item(s): #4**
- **Project Type:** New
- **Agency:** CDC
- **Description:** *Streptococcus pneumoniae*, or pneumococcus, is a common cause of otitis, meningitis, pneumonia, and blood stream infections. In the U.S., antibiotic resistance among pneumococcal strains increased during the 1990s, decreased during the first few years after 7-valent pneumococcal conjugate vaccine (PCV7) was introduced, and then began to increase again after non-PCV7 serotypes began to emerge. Multiple studies have attempted to estimate the national burden of individual pneumococcal syndromes (e.g., otitis cases, pneumonia hospitalizations) but there is not a single national estimate of disease burden or economic costs associated with pneumococcal disease, not to mention antibiotic resistant disease. Such estimates are critical for policy makers to assist them in prioritizing various options for public health interventions. This project aimed to estimate the total national burden of pneumococcal disease, including that portion associated with antibiotic resistance and the economic costs associated with those cases.
- **2008 Update:** In 2008, collaborators at the Harvard School of public health and CDC arrived at multiple estimates of the burden of antibiotic resistant pneumococcal disease. There are over 4.3 million episodes of pneumococcal disease in the U.S. each year. Of those, about 1.7 million are associated with penicillin resistance. Estimates of cases resistant to other agents are being finalized and are expected to be available this fall. After considering direct medical costs and costs associated with lost productivity, pneumococcal disease costs about \$8 billion annually. These findings have been accepted for presentation at the 2009 Annual Meeting of the Infectious Diseases Society of America and a manuscript outlining all of the findings associated with this project is in preparation.

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

- **Action Item(s): #4**
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Conduct population-based surveillance for antimicrobial resistance among *Candida* bloodstream infections in metropolitan Baltimore MD and Atlanta GA (limited by funding to two sites). Sites are collecting epidemiologic data and submitting *Candida* isolates to CDC for identification 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.
- **2008 Update:** 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 which data have been

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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.

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

- **Action Item(s): #4**
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Enhanced surveillance for non-Typhi *Salmonella* to investigate the impact of multi-drug resistance on clinical outcomes.
- **2008 Update:** All 10 participating sites completed 2 years of data/isolate collection. Participants submitted approximately 2600 isolates for susceptibility testing to NARMS lab at CDC as of the end of CY2008. Participants and CDC epidemiologists conducted teleconferences to finalize analysis scheme. The results of the interim analysis were presented at the 2008 FoodNet Vision Meeting held in Denver, CO.

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

- **Action Item(s): #4**
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** RDQMA is a 4 state university-based program partially supported by USDA. 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 research into specific issues such as Johne's Disease, salmonellosis, antimicrobial resistance and mastitis/milk quality.
- **2008 Update:** 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. In 2008, only 2 of 117 *Salmonella* isolates were resistant to any of the antimicrobials tested. Both isolates were identified as serotype Heidelberg and were

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resistant to kanamycin, streptomycin, sulfizoxale and tetracycline. Of the *E. coli* isolates tested, 91.2% were susceptible to all antimicrobials tested, 4.9% were resistant to a single drug, and 3.9% were resistant to multiple drugs. Of the *Campylobacter* species, 32.4% were susceptible to all while 67.6% showed resistance to a single drug, tetracycline. Among enterococcus, 84.8% were multi-drug resistant and 13.5% were resistant to a single drug.

#### **PROJECT TITLE: IMPLEMENTATION OF USDA VETNET**

- **Action Item(s): #4**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. VetNet has two functioning databases including the NARMS *Salmonella* and *Campylobacter* databases. The *Salmonella* database contains over 17,000 *Salmonella* isolates, while the *Campylobacter* database contains over 900 *Campylobacter* isolates. Over 2000 *Salmonella* isolates submitted to the animal arm of NARMS were submitted to VetNet in FY09. VetNet has been used by FSIS and CDC to assist in the investigation of several *Salmonella*-related foodborne outbreaks including those from fresh produce and meat. Both databases contain the PFGE Tagged Image File Format (TIFF) images, demographic information, and the antimicrobial resistance profiles assigned by NARMS. VetNet is a major component of the FSIS's risk-based sampling approach, and samples have been submitted to VetNet from FSIS's baseline studies. VetNet training on the methods have been conducted for investigators at the University College of Dublin, Ireland, and the Dept of Agriculture and Food Safety in Dublin so that they could pattern a PFGE system after VetNet.

#### **PROJECT TITLE: CHARACTERIZATION AND REPORTING OF ANTIMICROBIAL RESISTANCE AMONG ENTERIC BACTERIAL ISOLATES FROM SWINE ON FARMS**

- **Action Item(s): #4**
- **Project Type:** New
- **Agency:** USDA

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- **Description:** Collection of feces to be cultured for *Salmonella*, *Campylobacter*, *Enterococcus* and *E coli* as part of the USDA:APHIS National Animal Health Monitoring System study.
- **2008 Update:** Overall 7.2% of samples were positive for *Salmonella*. Resistance was most common for tetracycline, sulfisoxazole and streptomycin. For *Campylobacter*, 51.6 percent of samples were culture positive. Very few of the isolates were *Campylobacter jejuni*. Sixty nine percent of the samples were culture positive for *Enterococcus*, most commonly *E. hirae* or *E. faecalis*. Resistance was most common to lincomycin and tetracycline. Among the samples cultured for *E coli*, 94.9% were positive. Resistance was most common to tetracycline. Info sheets on the study results have been made available on the NAHMS website.

**PROJECT TITLE: CHARACTERIZATION AND REPORTING OF ANTIMICROBIAL RESISTANCE AMONG ENTERIC BACTERIAL ISOLATES FROM DAIRY COWS ON FARMS**

- **Action Item(s):** #4
- **Project Type:** New
- **Agency:** USDA
- **Description:** Collection of feces to be cultured for *Salmonella*, *Campylobacter*, *Enterococcus* and *E coli* as part of the USDA:APHIS National Animal Health Monitoring System study.
- **2008 Update:** Overall, 13.7 percent of samples were culture positive for *Salmonella* and 92.8% of the isolates were sensitive to all the antimicrobials tested in the panel. For *Campylobacter*, 33.7% of the samples were culture positive. For the *C. jejuni* isolates, 36.6% were susceptible to all antimicrobials in the panel and 61.2% were resistant to a single antimicrobial drug, almost always tetracycline.

**PROJECT TITLE: CHARACTERIZATION AND REPORTING OF ANTIMICROBIAL RESISTANCE AMONG ENTERIC BACTERIAL ISOLATES FROM BEEF COWS ON FARMS**

- **Action Item(s):** #4
- **Project Type:** New
- **Agency:** USDA
- **Description:** Collection of feces to be cultured for *Salmonella*, *Campylobacter*, *Enterococcus* and *E coli* as part of the USDA:APHIS National Animal Health Monitoring System study.
- **2008 Update:** Overall, 0.5% of samples were culture positive for *Salmonella* and all of these isolates were sensitive to all antimicrobials in the panel. For *Campylobacter jejuni*, 8.4% of samples were positive. Among the *C. jejuni* isolates 56.2% were sensitive to all antimicrobials in the panel and 38.9% were resistant only to tetracycline. Nearly 80% of the samples were positive for *Enterococcus* but these were most commonly *E. casseliflavus* and *E. hirae*.

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**PROJECT TITLE: CHARACTERIZATION OF ANTIMICROBIAL DRUG USE ON SWINE, DAIRY AND COW-CALF OPERATIONS**

- **Action Item(s): #4**
- **Project Type:** New
- **Agency:** USDA
- **Description:** As part of the National Animal Health Monitoring System data are collected from a representative sample of livestock operations in the U.S. During in-person interviews with the farm managers, data are collected on antimicrobial use as well as other management practices.
- **2008 Update:** Data have been collected on swine, dairy and cow-calf operations. Results for the swine and dairy operations have been published and posted to the website at <http://nahms.aphis.usda.gov/>.

**PROJECT TITLE: DETECTION AND CHARACTERIZATION OF EMERGING *CLOSTRIDIUM DIFFICILE* STRAINS**

- **Action Item(s): #4**
- **Project Type:** New
- **Agency:** CDC
- **Description:** *C. difficile* isolates associated with outbreaks, or from states or geographic regions that have not yet documented the presence of the NAP1 epidemic strain, will be typed and characterized to document the spread of the current epidemic strain. At the same time, we will request new *C. difficile* strains associated with clinical infection for characterization, and to ensure that we are able to recognize changing trends in the molecular epidemiology of *C. difficile*.
- **2008 Update:** The NAP1 *C. difficile* epidemic strain has been documented and confirmed in 40 US states. We have also documented the emergence of a new strain. Ref. Emerg Infect Dis. 2008 Jul;14(7):1039-45.

**PROJECT TITLE: CHARACTERIZE *C. DIFFICILE* STRAINS FROM COMMUNITY-ASSOCIATED INFECTIONS**

- **Action Item(s): #4**
- **Project Type:** New
- **Agency:** CDC
- **Description:** The epidemiology of *C. difficile* infection (CDI) appears to be changing, with emergence in the community and among persons without traditional risk factors for development of CDI. We sought to investigate the strains from confirmed community-associated CDI (CA-CDI) cases from two separate investigations. Chart review and patient interviews were performed to document CA-CDI cases, then stool specimens

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positive for *C. difficile* toxin were forwarded to CDC for culture. *C. difficile* isolates recovered were characterized by PFGE, characterization of the pathogenicity locus, PCR for binary toxin, and antimicrobial susceptibility testing.

- **2008 Update:** Organism recovery and isolate characterization is complete. Manuscript preparation is in progress.

**PROJECT TITLE: DEVELOPMENT OF MULTI-CENTER TRIAL TO DETERMINE PREVALENCE OF RESISTANT *T. VAGINALIS***

- **Action Item(s):** #4
- **Project Type:** New
- **Agency:** CDC
- **Description:** Point prevalence studies have suggested that up to 10% of *T. vaginalis* infections are resistant to treatment. However, the available data are not sufficient to warrant changes in treatment policy. DPD worked with DSTDP to develop a 6-site surveillance study to obtain a more accurate estimate for trichomoniasis AR in the US.
- **2008 Update:** Sample collection and testing began in 2009. Related publications:

Helms, D. J., D. J. Mosure, W. E. Secor, and K. A. Workowski. 2008. Management of *Trichomonas vaginalis* in women with suspected metronidazole hypersensitivity. *Am. J. Obstet. Gynecol.* 198:370.e1-7.

Kissinger, P., W. E. Secor, J. S. Leichter, R. A. Clark, N. Schmidt, E. Curtin, and D. H. Martin. 2008. Early repeated infections with *Trichomonas vaginalis* among HIV positive and negative women. *Clin. Infect. Dis.* 46:994-999.

**PROJECT TITLE: MOLECULAR AND IN-VITRO SURVEILLANCE FOR MONITORING ANTIMALARIAL DRUG RESISTANCE**

- **Action Item:** #4
- **Project Type:** New
- **Agency:** CDC
- **Description:** Establish an active surveillance program for early detection of resistance to newly used artemisinin based combination therapy (ACT) by using an in vitro drug susceptibility test and molecular characterization of gene targets involved in drug resistance in selected countries in Africa, Asia and South America. Conduct population based studies to detect changes in the drug resistant genotypes as new drug policies were implemented. Develop methods to understand the origin and spread of drug resistant genotypes in the population. Provide training to country partners in genotyping methodologies and in vitro drug susceptibility test.

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- **2008 Update:** Training and capability to conduct *in vitro* drug susceptibility was established in Kenya, Tanzania and Peru. Sulphadoxine-pyrimethamine resistant genotypes declined in Peru five years after this drug use policy was changed to ACT. On the contrary, in Venezuela sulphadoxine-pyrimethamine resistant genotypes did not decline but reached fixation five years after the policy change. Copy number variation in the MDR-1 gene is associated with mefloquine resistance (one of the partner drug used in ACT in many countries). In Cambodia (where resistance to ACT is emerging), copy number variation in the *mdr-1* gene was found to have multiple genetic origins. The pyrimethamine resistant genetic marker *dhfr* in both East and West African parasite isolates were found to be related to Southeast Asian parasite isolates implying their spread from Southeast Asia to Africa. Attempts to identify new genetic markers to predict the resistance to ACT is in progress. Provided training to scientists from Tanzania, Peru, Brazil and Pakistan in *in vitro* drug susceptibility testing and genotyping of drug resistant mutations.

#### ACTION ITEM #5

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

- **Action Item(s):** #5 and #63
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** This project continues to support the development and implementation of comprehensive programs to reduce the incidence of MRSA infections in states and/or large regional networks. Continued work stems from an initial MRSA prevention project in collaboration with the Pittsburgh VA Medical Center.
- **2008 Update:** 2008 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. Data collection is ongoing and an additional interim analysis will occur in 2009. 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. CDC is providing in-kind support and assistance, including analysis of impact using electronic data submission through NHSN. Preliminary results of this multicenter study were presented at SHEA 2009, demonstrating significant reductions in both the incidence of MRSA and in methicillin-susceptibility among all *S. aureus* isolates. 3) Maryland Patient Safety Center Initiative continues a regional

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voluntary MRSA prevention program of >20 Maryland Hospitals that have implemented MRSA prevention initiatives using the “positive deviance” change model. CDC is providing in-kind support and assistance in analyzing electronically data submitted through NHSN as the outcome measurement tool.

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

- **Action Item(s):** #5
- **Project Type:** Ongoing
- **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.
- **2008 Update:** During 2008, an abstract was accepted to present at the 2009 Annual Meeting of the Infectious Diseases Society of America that will discuss changes in antimicrobial prescribing in ambulatory care and emergency department visits in the U.S. from 1997-2006 using NAMCS and NHAMCS data. Preliminary analyses revealed that while there has been a decrease in prescribing for upper respiratory infections in outpatient, primary care settings, there has been a concurrent increase in prescribing for these conditions in emergency department settings. In addition, a publication is in process that will describe findings from both NAMCS and NHAMCS and current trends in the prescribing of antimicrobial drugs in physician offices, hospital emergency rooms and outpatient facilities.

**PROJECT TITLE: DEVELOPING MEASUREMENT AND BENCHMARK STRATEGIES FOR ANTIMICROBIAL USE IN ACUTE CARE SETTINGS**

- **Action Item(s):** #5, #26, and #63
- **Project Type:** New
- **Agency:** CDC/ Prevention Epi Center CoAg
- **Description:** Multicenter project (Ohio, Utah, Washington) in which electronically extracted data are used to construct unit-specific measures of antimicrobial prescribing for the purpose of describing variability in use across units and facilities as a means for optimizing antimicrobial use.



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- **2008 Update:** 1) Antimicrobial use data have been compiled from 15 ICUs in four hospitals 2) Data have been validated by three separate methods 3) Data collected to date demonstrate substantial variation between months and between attending physician rotation periods within ICUs, without evident time trends in aggregate ICU antimicrobial use. 4) Currently comparing pharmacy charge data and electronic MAR data 4) Data collection for measuring use by antimicrobial days is complete-additional measures still being collected 5) Completed retrospective and prospective data collection and submitted data set for analysis 6) Completed prospective observation of antimicrobial administration 7) Currently completing manuscript on the project barriers 8) Two abstracts presented at national meetings.

**PROJECT TITLE: IMPROVING ANTIMICROBIAL USE IN ICUS**

- **Action Item(s):** #5, #26, and #63
- **Project Type:** New
- **Agency:** CDC/ Prevention Epi Center CoAg
- **Description:** Multicenter project (Ohio, Utah, Washington) Evaluate efficacy of a multidisciplinary antimicrobial stewardship program and evaluate computer expert system - 4 ICUs.
- **2008 Update:** 1) Completed retrospective and prospective data collection and submitted data set for analysis 2) Completed prospective observation of antimicrobial administration 3) Currently completing manuscript on the project barriers.

**PROJECT TITLE: COLLECTION AND CHARACTERIZATION OF *CLOSTRIDIUM DIFFICILE* FROM FOOD AND FOOD-PRODUCING ANIMALS**

- **Action Item(s):** #5
- **Project Type:** New
- **Agency:** CDC
- **Description:** The epidemiology of *C. difficile* infection (CDI) appears to be changing, with emergence in the community and among persons without traditional risk factors for development of CDI. At the same time, *C. difficile* is causing epidemic disease in food-producing animals. One potential link between these might be the food supply, and specifically retail meat products. We have previously collaborated with investigators in Canada and the United States to characterize *C. difficile* isolated from retail meats, and we are now working to develop an optimized method for detection and recovery of *C. difficile* from food products.
- **2008 Update:** Experts meeting convened at CDC in conjunction with FoodNet group, research gaps identified, and plan developed for study to define best recovery methods.

**PROJECT TITLE: ANTIBIOTIC RESISTANCE- SHIGELLA SURVEILLANCE PROJECT (PART OF BIDS- BORDER INFECTIOUS DISEASE SURVEILLANCE PROJECT)**

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- **Action Item(s): #5**
- **Project Type:** New
- **Agency:** CDC
- **Description:** Studies suggest that levels of antimicrobial resistance (AMR) for some pathogens may be higher in US states bordering Mexico, compared to national levels. In the US, shigellosis is among the most commonly reported enteric bacterial infections, with the highest incidence occurring in regions bordering Mexico. High levels of AMR have been observed in *Shigella* nationally, with 78% resistance to Ampicillin (AMP), 51% resistance to Trimethoprim-sulfamethoxazole (SXT) and 0% resistance to Ceftriaxone (CRO) and Ciprofloxacin (CIP) in 2004. To date no studies describe AMR in *Shigella* in the US-Mexico border region. Available isolates from all sporadic *Shigella* cases reported in San Diego County (SDC) beginning October 1, 2008 were submitted to the SDC Public Health Laboratory for serotype confirmation, antibiotic susceptibility testing (AST) by disc diffusion, and genetic characterization by pulsed field gel electrophoresis (PFGE). Cases were also administered a supplemental risk history questionnaire to further characterize risk factors such as travel history, antibiotic use, food consumption, severity of illness, management, and outcome.
- **2008 Update:** From October 1<sup>st</sup>, 2008 through December 31<sup>st</sup>, 2008, 36 sporadic *Shigella* cases have been reported to SDC; 29 (81%) were identified as *sonnei*, 6 (17%) *flexneri*, 1 (3%) *boydii*, and 0 (0%) *dysenteriae*. Of 25 *Shigella sonnei* isolates available for AST, all were resistant to SXT, 3 were resistant to AMP, and 0 were resistant to CRO and CIP. All of 6 *Shigella flexneri* isolates available for AST were resistant to AMP, 5 were resistant to SXT, 0 were resistant to CIP, and all were sensitive to CRO. PFGE typing has been completed for 31 isolates, although not yet compared to national databases. Supplemental epidemiologic risk data has been collected for 21 cases. Conclusions: Interim AST data suggest the patterns of resistance occurring along the US-Mexico border may differ from those seen nationally. These data suggest that differing selective pressures of the region may result in a unique AMR profile. Epidemiologic data will be reconciled with laboratory findings.

**PROJECT TITLE: ASSESSMENT OF ANTIMICROBIAL RESISTANCE AMONG CLINICAL CULTURES IN U.S. – MEXICO BORDER HOSPITALS (PART OF BIDS- BORDER INFECTIOUS DISEASE SURVEILLANCE PROJECT)**

- **Action Item(s): #5**
- **Project Type:** New
- **Agency:** CDC
- **Description:** Antimicrobial resistance (AR) and reduced efficacy of antibiotics is a growing problem globally associated with increased morbidity and costs. Antibiotic resistance data are lacking on the U.S. – Mexico border, while increased access to prescription antimicrobials in this region with high cross-border mobility and commerce may predispose to high rates of resistance in the region. To describe AR in the U.S. - Mexico border region, we obtained all bacterial cultures and antimicrobial sensitivities for

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the period January 2000 to December 2005 from 4 major hospitals on the border in CA, Arizona and Texas. We analyzed trend data for well recognized important pathogen-antibiotic combinations, methicillin-resistant *Staphylococcus aureus* (Sa), vancomycin-resistant enterococcus, penicillin-resistant *Streptococcus pneumoniae* (Sp), and sensitivities of *E. coli* to third generation cephalosporins, quinolones, and trimethoprim/sulfa.

- **2008 Update:** Data was cleaned, and analyzed and presented at the Border Epidemiology and Surveillance Annual Meeting in El Paso in December 2008. Forty-three percent of Sa cultures were resistant to methicillin overall with a significant trend of increasing resistance over time. Almost eighteen percent of enterococcus cultures overall were resistant to vancomycin, and 23% of Sp cultures overall were resistant to penicillin. Thirteen percent of *E. coli* cultures overall were resistant to quinolones with a significant increasing trend over time. Border hospital pooled proportions of resistant organisms were at the high end of the range of such proportions or higher than proportions in National Nosocomial Infectious Surveillance pooled data from 1998-2004. Conclusions: Resistance to common antibiotics appears to have increased between 2000-2005 in the US-Mexico border region, with increasing trend in resistance to antibiotics used to treat Staph aureus and *E. coli* most salient. Further studies and analysis of border antimicrobial resistance patterns are needed, as well as linkage with ongoing antimicrobial resistance prevention campaigns.

#### PROJECT TITLE: PRESCRIPTION DATABASES

- **Action Item(s):** #5
- **Project Type:** Ongoing
- **Agency:** DoD
- **Description:** Use of the prescription database (PDTS) is being piloted for gastrointestinal and respiratory outbreak detections.
- **2008 Update:** Ongoing. 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

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

- **Action Item(s):** #6
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** The Alaska Native Health System is an integrated population-based health delivery system serving 220 village-based clinics, 8 regional hospitals and a tertiary

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medical facility. In this system little is known antibiotic prescribing rates. We have developed a method to use electronic prescription and clinic visitation data to measure rates of antimicrobial prescriptions over time and compare with national trends.

- **2008 Update:** Prescription data for 3 Alaska regions have been analyzed. The overall visit-based prescribing rate of oral antimicrobials in <18 year-olds was lower than rates reported from similar ages in the general US population, but the decrease in prescribing rates seen in other regions of the US since the mid-1990's have not been seen in Alaska.

**PROJECT TITLE: NATIONAL COMPREHENSIVE ASSESSMENT OF AVAILABLE TB LABORATORY SERVICES TO FILL GAPS IN KNOWLEDGE ABOUT THE CAPABILITIES AND CAPACITIES OF JURISDICTIONAL LABORATORY NETWORKS TO PERFORM RAPID AND RELIABLE DRUG SUSCEPTIBILITY TESTING**

- **Action Item(s):** # 6
- **Project Type:** New
- **Agency:** CDC
- **Description:** DTBE/ MLB will collaborate with the APHL to develop a comprehensive laboratory services survey instrument. The survey will collect data on available services in each laboratory, including test methods and volumes, turnaround time, reporting processes, and integration with public health and TB Control programs. The survey will be developed for electronic dissemination and data collection via the MR Interview survey platform. In year one, APHL will compile a list of laboratories to be surveyed through multiple sources. Pilot testing will be conducted among a subset of public health and clinical laboratories after consultation with the ADS office of NCHHSTP regarding OMB limitations. Once data from the pilot are analyzed and the instrument is finalized, we will submit an application for OMB approval. Once OMB clearance is obtained, additional funds will be necessary to support conducting the survey and analyzing data in future years.
- **2008 Update:** Project planning initiated.

**ACTION ITEM #7**

**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**

- **Action Item(s):** #7
- **Project Type:** Ongoing
- **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 collaborated with experts in the development and testing of HEDIS measures to create measures of appropriate antimicrobial use in children and adults.

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Child 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. 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 originally 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.

- **2008 Update:** All four measures (two adult and two children) are currently being reported.

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

- **Action Item(s):** #7, #22, and #32
- **Project Type:** Ongoing
- **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. 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.
- **2008 Update:** 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, and FY 2008 the percent starting timely was 78.7%, 88.6%, 90.6%, and 96%, respectively. Additionally, for the measure of SIP10a (Correct Antibiotics ALL surgeries) comparing national numbers from fourth quarter FY 2006, FY 2007, and FY 2008, percent with correct antibiotics was 93.7%, 95.8%, and 97%, respectively. An additional Performance Measure of SIP3an (Prophylactic antibiotic discontinued timely) was introduced, and comparison of third and fourth quarters of FY 2007 to FY 2008 reveals results of 87% and 91%, respectively.

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

- **Action Item(s):** #7 and #22
- **Project Type:** Ongoing

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- **Agency:** VA
- **Description:** VHA Office of Quality and Performance has initiated quality measures for timing, diagnostics and treatment of community-acquired pneumonia.
- **2008 Update:** Data from VHA's Office of Quality and Performance reveal that for Performance Measures CAP 11 (Initial antibiotic started within 8 hours of presentation) comparing national numbers from 2005, 2006 and 2007, 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. For FY 2008, CAP11 and 12 transitioned to CAP23j (Initial antibiotic given within 6 hours of arrival) where this occurred 92% of the time (during the course of the year, this improved from 91% in first quarter to 95% in fourth quarter). CAP 14 (Appropriate initial antibiotic for immunocompromised, non-ICU admission) was 69.7%, 82.2%, 89%, and 92%, respectively for FY 2005, 2006, 2007, and 2008. 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. During FY 2008 the measure was transitioned to CAP18 (Blood cultures performed in Emergency Department prior to first antibiotic dosing) where the performance was 97%. During FY 2008, a new measure of CAP13 (Appropriate initial antibiotic for immunocompromised, ICU admission) was added for baseline measurement.

**PROJECT TITLE: TRANSFORMATIONAL MEASURES FOR VHA-INFECTIION RATE REDUCTION**

- **Action Item(s):** #7 and #22
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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.

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

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- **Action Item(s): #7**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. 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

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

- **Action Item(s): #8**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. Our laboratory is the only laboratory within CDC which has been accredited by College of American Pathologists (CAP) and one of only 6 laboratories in the world that has been accredited by WHO ResNet as a specialized drug resistance laboratory (SDRL). Any data we provide to PEPFAR countries have been generated by certified technologists or scientists and the assays we use have been validated in our lab based on CAP standards. We routinely participate in CAP, WHO and AccuTest PT programs for our assays. For the past two years, we have provided genotyping and analytic services for the surveillance of transmitted HIV DR in recently-HIV-infected populations in Tanzania, Malawi, Kenya, China and Botswana. The results indicate that transmitted HIV DR in recently-infected populations are low, less than 5%. Results from two of the surveys, Tanzania and Malawi, have been published in peer-reviewed scientific journal (*Antiviral Therapy*, 2008). A manuscript describing the transmitted HIV DR results from China has been submitted to a peer-reviewed journal for review and manuscripts are currently in preparation describing results from Botswana and Kenya. In 2008, we also expanded HIV drug resistance surveillance to include HIV-infected patients on ARV treatment. The pilot projects for monitoring patients on ART were implemented in

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2 sites in Nigeria and 3 sites in Malawi. Analyses on baseline samples from Nigeria indicated that patients infected with CRF06-cpx viruses from harbored high proportion of MDR and 6 patients with primary DR. These results suggest treatment outcomes from these patients should be closely monitored.

**PROJECT TITLE: DEVELOPMENT OF STANDARDIZED HIV DR TRAINING PACKAGE AND PILOT OF THE TRAINING IN AFRICA**

- **Action Item(s): #8**
- **Project Type:** New
- **Agency:** CDC
- **Description:** In order to generate quality-assured genotyping data and to make sustainability of HIV DR genotyping a reality in resource-limited countries, in collaboration with WHO ResNet and acting as a member of the ResNet laboratory group, the International Laboratory Branch (ILB) has been closely working with WHO in 2008 to develop a standardized HIV DR training package.
- **2008 Update:** In 2008, a framework for a standardized HIV DR laboratory training package was established in collaboration with WHO ResNet group. The training package was developed according to the 12 essential of quality management systems of CLSI. Thirteen modules were developed and a pilot training session was conducted in April 2009. Thirty-four trainees from 13 African countries attended the training. Current plan is to develop additional modules and to plan a 2<sup>nd</sup> training.

**PROJECT TITLE: PERTINENT TRAINING**

- **Action Item(s): #8**
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Continue to ensure validity of antimicrobial susceptibility information derived from NARMS.
- **2008 Update:** NARMS laboratories continue to participate 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 developed two secondary antimicrobial testing plates for Salmonella and *E. coli*; a fluoroquinolone panel and extended-spectrum cephalosporin panel, which are now in use in all three NARMS laboratories.

**ACTION ITEM #10**

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



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- **Action Item(s):** #10
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. In 2008, the surveillance of transmitted HIV DR in recently HIV-infected populations has been expanded to Botswana and China.

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

- **Action Item(s):** #10
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Results remain the same as for 2007. 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,

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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.

**PROJECT TITLE: PRESERVING EFFECTIVE TB TREATMENT STUDY (PETTS)**

- **Action Item(s):** #10
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Prospective, multinational cohort study of MDR TB treatment to determine the extent to which the "Green Light Committee" mechanism prevents acquired resistance to 2nd-line drugs. The Green Light Committee is an international committee of experts on MDR TB that enables TB control programs to purchase quality-assured 2nd-line anti-TB drugs at substantially reduced costs through WHO and the Global Drug Facility's pooled procurement program. To receive Green Light Committee approval, programs must demonstrate their readiness to manage MDR TB in accordance to published WHO guidelines.
- **2008 Update:** Enrollment was completed in June 2008 with a total of 1,785 patients entered into the database. From these patients, approximately 4,710 culture isolates of *M. tuberculosis* were received at CDC's mycobacteriology laboratory, including 1617 baseline isolates and 3,093 follow-up isolates. Baseline drug susceptibility test results to date indicate resistance to 2nd-line drugs in 10% to 20% (depending on which drug) of MDR TB patients at the start of treatment with ~5% having extensively drug resistant (XDR) TB with a broad range across countries. Follow-up will continue until 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.

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

- **Action Item(s):** #10
- **Project Type:** Ongoing
- **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

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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

- **2008 Update:** 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.

#### **PROJECT TITLE: DEVICES CONTAINING ANTIMICROBIALS GUIDANCE**

- **Action Item(s):** #10
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Draft guidance published in July 2007 with comments due by October 2007. Comments received and reviewed with final guidance to issue soon.

#### **ACTION ITEM #13**

#### **PROJECT TITLE: MONITORING DRUG RESISTANCE IN LYMPHATIC FILARIASIS ELIMINATION PROGRAMS**

- **Action Item(s):** #13
- **Project Type:** New
- **Agency:** CDC
- **Description:** Annual mass treatment with antifilarial drugs (albendazole plus either ivermectin or diethylcarbamazine) is the cornerstone of the global program to eliminate lymphatic filariasis (LF). Although the primary goal of the program is to interrupt transmission of LF, additional benefits also are expected because of the known anthelmintic properties of these drugs. Substantial reductions in the prevalence of intestinal helminth infections are associated with mass treatment for LF. Though encouraging, the results also raise questions about the intensity of selection for albendazole resistance. Genes for resistance to benzimidazoles are known to occur at a low frequency in all nematodes studied to date. Monitoring for drug resistance has not been done as part of the LF elimination program. We are monitoring the development of albendazole resistance in the context of the LF elimination efforts in Haiti.

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- **2008 Update:** Samples were collected pre- and post-MDA from 4 sites. These samples are being analyzed by colleagues at McGill University with pyrosequencing techniques to detect changes in the frequency of alleles for benzimidazole resistance.

#### ACTION ITEM #15

#### PROJECT TITLE: SENTINEL SURVEILLANCE FOR HUMAN AFRICAN TRYPANOSOMIASIS TREATMENT FAILURE AND DRUG RESISTANCE

- **Action Item(s):** #15
- **Project Type:** New
- **Agency:** CDC
- **Description:** A sentinel surveillance network (HATSENTINEL) has operated since 2002 to monitor geographical and temporal trends in efficacy of treatment for human African trypanosomiasis, identify risk factors for treatment failure, and perform limited drug susceptibility testing. During 2008, the network operated at 8 sites in 5 countries (Angola, Democratic Republic of Congo, Sudan, Tanzania, and Uganda).
- **2008 Update:** Despite high rates (61-98%) of melarsoprol treatment failure documented in parts of Angola and Democratic Republic of Congo, eflornithine remains fully effective at all sentinel sites treating *Trypanosoma brucei gambiense* infection. Melarsoprol efficacy remains high for treatment of *T. b. rhodesiense*. Drug susceptibility data are being collected for specimens from areas of melarsoprol-refractory *T. b. gambiense* in central Democratic Republic of Congo.

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

- **Action Item(s):** #15
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. Reports of susceptibility test results and summary statements are being provided to primary care facilities, 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

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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. This project is a core part of the Navy Health Research Center funding by GEIS.

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

- **Action Item(s):** #15
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. This project is a core part of the Navy Health Research Center funding by GEIS.

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

- **Action Item(s):** #15
- **Project Type:** Ongoing
- **Agency:** DoD

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- **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, which is the mobile genetic element that mediates the methicillin resistance.
- **2008 Update:** 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. This is a core project funded yearly by GEIS at BAMC.

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

- **Action Item(s):** #15
- **Project Type:** Ongoing
- **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 the Naval Medical Research Center.
- **2008 Update:** 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. SOPs and quality control procedures have been established and data exchange has been initiated. The goal is to have regular reports generated by this project and disseminated to the military health system. This system will expand to other MDROs in the future. GEIS is also funding an in theater study

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at a combat support hospital to try to identify the common source of Acinetobacter infections.

**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)**

- **Action Item(s):** #15
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. 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. Electronic methodologies are currently being validated with laboratory result data.

**ACTION ITEM #17**

**PROJECT TITLE: FDA SCIENCE BOARD REVIEW OF THE NARMS PROGRAM**

- **Action Item(s):** #17
- **Project Type:** Ongoing
- **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.

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- **2008 Update:** 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. Strategic planning and methods harmonization meetings were held September 17-18, 2007 and September 10-12, 2008 focusing on progress and plans to continue implementing the Science Board recommendations where appropriate. Sampling strategies have since focused on alternate approaches to food animal slaughter surveillance and extension of retail monitoring to capture additional pathogens of interest such as *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus*. Data reporting and harmonization goals have been furthered by publication of executive summaries of NARMS food animal, retail meat and human isolate data for CY2004 and 2005, and resources have been sought to improve business practices and electronic infrastructure to better share and present combined NARMS data. Plans for joint NARMS projects/publications were developed in CY2008. The three NARMS agencies have engaged in international activities such as participating in AGISAR (the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance), the Codex Alimentarius ad hoc Task Force on Antimicrobial Resistance as well as expanding support for international capacity building in surveillance of antimicrobial resistance in foodborne pathogens through WHO.

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

- **Action Item(s):** #17
- **Project Type:** Ongoing
- **Agency:** CDC, FDA, USDA
- **Description:** An integrated summary of human, animal, and retail meat NARMS data for annual publication.
- **2008 Update:** Center for Veterinary Medicine (CVM) released the CY 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 CY 2004 Executive Summary of NARMS data became 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; the report was released in December, 2007. As of the end of CY 2008, NARMS published two executive summaries of food animal, retail meat and human isolate susceptibility data collected by USDA, FDA-CVM and CDC, respectively, for calendar years 2003 and 2004. The three NARMS partner agencies began to explore business practices and electronic infrastructure that would facilitate efficient data sharing and presentation in a more timely fashion, and sought additional resources and partnerships to further these goals. Center for Veterinary Medicine (CVM) released the CY 2004 executive report on CVM's Website July 2008. The fifth annual NARMS Retail Meat Annual Report was released in October 2008 and provides 2006 data on the



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prevalence of antimicrobial resistant foodborne pathogens and commensal bacteria among retail meat and poultry samples, comprising results from nearly 4,800 samples.

**PROJECT TITLE: ANTIMICROBIAL RESISTANT BACTERIA IN FEED INGREDIENTS**

- **Action Item(s):** #17
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Assess the prevalence of antimicrobial resistant bacteria in feed ingredients, primarily rendered product. This work is being done in conjunction with FDA field personnel. Results will be coordinated with NARMS.
- **2008 Update:** 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**

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

- **Action Item(s):** #18
- **Project Type:** Ongoing
- **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.
- **2008 Update:** In CY2008, three states sent isolates of enterococci and one state submitted generic *E. coli* to the NARMS CDC lab collected from stool of healthy volunteers or outpatients who report no hospitalization. Interviews were conducted to determine specific environmental, medical, and food exposures previous to the culture. The three NARMS agencies explored comparability and reporting options for food animal, retail meat, and human *Enterococcus* and generic *E. coli* isolates.

**PROJECT TITLE: ANTIMICROBIAL RESISTANT BACTERIA IN SENTINEL HUMAN POPULATIONS**

- **Action Item(s):** #18
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Evaluate abattoir workers for carriage of antimicrobial resistant bacterial pathogens.

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- **2008 Update:** 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 has concluded and data analysis is complete. CVM scientists continue to partner 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

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

- **Action Item(s):** #19
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. Thus far, four articles have been published in a direct response to this research.

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

- **Action Item(s):** #19
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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

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human fecal contamination; and (2) ascertaining which chemicals are present in finished drinking water.

**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**

- **Action Item(s):** #19
- **Project Type:** Ongoing
- **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. This project is being conducted in two phases. In Phase I (2007), source and finished water from nine drinking water treatment plants (DWTPs) were analyzed for 83 different chemicals. In Phase II (2009-2010), both the number of DWTPs (20-30) and the number of analytes (~200) will be increased.
- **2008 Update:** 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.

**PROJECT TITLE: MONITORING FOR RESISTANCE TO KASUGAMYCIN IN APPLE ORCHARDS PRIOR TO AND AFTER THE APPLICATION OF KASUGAMYCIN TO CONTROL FIRE BLIGHT**

- **Action Item(s):** #19
- **Project Type:** New
- **Agency:** EPA
- **Description:** Project intended to examine bacterial resistance to kasugamycin in the blossom, leaf surface, and soil bacterial communities. In addition, it will identify any kasugamycin-resistant (KmR) bacterial isolates and determine the occurrence of KmR genes in these environmental isolates.
- **2008 Update:** Planning for the study occurred in 2008 and research was initiated in Spring 2009. Data are expected to be submitted to the Agency in the Winter/Spring of 2010.

**PROJECT TITLE: HYDROLYTIC TRANSFORMATION OF EMERGING CONTAMINANTS**

- **Action Item(s):** #19

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- **Project Type:** New
- **Agency:** EPA
- **Description:** This project plans to assess the fate of emerging contaminants, with emphasis on pharmaceutically-active chemicals and their chemical transformations, at environmentally relevant conditions. The target list of chemicals to be studied includes antibiotics such as amoxicillin, azithromycin, clarithromycin, erythromycin, lincomycin, penicillin, and tylosin, which have the potential to undergo chemical transformation in the environment. The effect of environmental variables, which could include pH, temperature, dissolved metals, natural organic matter, and presence of solid media (sediments and soils) on the chemical transformation of such chemicals will be evaluated.
- **2008 Update:** Ongoing. Study scheduled to begin FY 2011.

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

- **Action Item(s):** #19
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Pilot study to determine the contribution waterways play in movement of bacteria originating from animal production facilities in particular.
- **2008 Update:** Sulfonamide antibacterial agents have been found in effluent from wastewater treatment plants and waterways worldwide. Sulfamethazine (used in veterinary medicine) and sulfamethoxazole (used in human medicine) are two sulfonamides of particular interest because of their extensive use. Immunoassays for sulfamethazine and sulfamethoxazole worked well in the analyses of wastewater from swine-rearing facilities and municipal wastewater treatment plants. The immunoassay results were confirmed by liquid chromatography-mass spectrometry-based analyses. New methods have been developed to look at levels of chemicals and bacteria in wastewater, lagoon pits, and wetlands. These methods and research may point to potential mediation.

**FOCUS AREA II: PREVENTION AND CONTROL**

**ACTION ITEM #21**

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

- **Action Item(s):** #21
- **Project Type:** Ongoing

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- **Agency:** AHRQ
- **Description:** 1. 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.
- **2008 Update:** 1. To identify factors that influence community practitioners to prescribe antibiotics and examine how they differ from the recommendations of the Centers for Disease Control and Prevention (CDC) guideline for treatment of ARI, 101 community practitioners were asked to estimate how likely they would be to prescribe antibiotics in each of 20 hypothetical cases of ARI. Practitioners were compared with eight faculty physicians who evaluated the cases following the CDC guidelines rather than their own judgments. Practitioners prescribed antibiotics in 44.5% of cases, over twice the percentage treated by the faculty panel using the CDC guidelines (20%). Practitioners were most strongly influenced by duration of illness, particularly when accompanied by fever or productive cough (Wigton RS et al. J Gen Intern Med 2008;23:1615-20). 2. A prospective, chart-review study was conducted among residents of 16 nursing homes in three states with 2 signs and symptoms of pneumonia during the 2004–2005 influenza season. Mid and high certified nursing assistant (CNA) hours per resident per day were significantly associated with better pneumococcal and influenza vaccination rates. More than 1.2 licensed nurse hours per resident per day was significantly associated with appropriate hospitalization and guideline-recommended antibiotics. A >70% nurse turnover was inversely related to timely physician notification and appropriate hospitalization (Hutt E et al. J Gerontol A Biol Sci Med Sci 2008;63:1105-11).

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

- **Action Item(s):** #21
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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

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feedback, the project will assess the effects of intervention on quality, resource use, and clinician adoption of the technology.

**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**

- **Action Item(s):** #21
- **Project Type:** Ongoing
- **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. 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.
- **2008 Update:** To identify the prevalence of and risk factors for fluoroquinolone-resistant *Escherichia coli* (FQREC) colonization among hospitalized patients annual fecal surveillance studies were conducted in two large medical centers within an academic health system. Of the 774 subjects, 89 (11.5%) were colonized with FQREC. The association between prior FQ use and FQREC colonization varied significantly by study year, suggesting that the clinical epidemiology of resistant organisms may change over time (Lautenbach E et al. *Infect Control Hosp Epidemiol* 2009;30:18-24).

**PROJECT TITLE: HIV DRUG RESISTANCE AND CLINICAL EPIDEMIOLOGY**

- **Action Item(s):** #21
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** DHAP's Epidemiology Branch conducts a number of activities to assess the clinical relevance of HIV resistance. The Epidemiology 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.
- **2008 Update:** To summarize the data thus far:
  - Among the nearly 1,000 children enrolled in LEGACY, clinicians have ordered the following (and results available): 930 genotype tests from among 543

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participants (1.71 test per participant); 329 phenotype tests from among 230 participants (1.43 test per participant); and 85 virtual phenotype tests from among 68 participants (1.25 test per participant).

- In HOPS, which has observed over 8,000 patients in an open cohort since 1997, clinicians have ordered the following (and results available): 4,130 genotype tests from among 2,194 patients (1.88 tests per patient) and 1,633 phenotype tests from among 893 patients (1.83 tests per patient).
- In the SUN study which enrolled 700 patients in a closed cohort starting in March 2004, clinicians have ordered the following (and results available): 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).
- Multiple guidelines recommend widespread use of antiretroviral resistance testing in the management of HIV-infected patients. Although intellectually compelling, these recommendations are based predominately on equivocal studies of its effect on short-term improvement suppressing HIV replication. It is unlikely that in the current environment, randomized controlled trials could be conducted to assess the benefit of antiretroviral resistance testing. Our research indicates that use of both genotypic and phenotypic antiretroviral resistance testing is significantly associated with improved survival even after accounting for other factors known to affect survival and for potential confounding due to differential intensity or quality of care. Early disparities in the use of antiretroviral resistance testing observed when the technology became commercially available (i.e., less testing among non-Hispanic black and Hispanics, less testing among publicly insured patients) appear to have improved or resolved. Testing of patients prior to initiation of antiretroviral therapy has increased substantially following release of guidance recommending this practice. Initiating suppressive antiretroviral therapy at higher CD4 cell counts does not appear to increase the prevalence of clinically relevant resistance mutations when virologic failure develops.

#### **PROJECT TITLE: APPROPRIATE USE OF ANTIMICROBIALS**

- **Action Item(s):** #21, #22, and #30
- **Project Type:** Ongoing
- **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

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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.

- **2008 Update:** 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 #24

##### PROJECT TITLE: INPATIENT EVALUATION CENTER (IPEC)

- **Action Item(s):** #24, #63, and #64
- **Project Type:** Ongoing
- **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.
- **2008 Update:** IPEC program initiated nationwide during FY 2006 with results demonstrating a significant decrease in ventilator-associated pneumonias and central catheter related bloodstream infections nationwide since implementation of the program. Pilot testing for expansion of the IPEC process into non-ICU acute inpatient care was initiated. The IPEC intranet website provides numerous resources regarding evidence-based practices and implementation strategies for the reduction of healthcare-associated events, including infections with antimicrobial-resistant organisms, for frontline healthcare personnel. Initial discussions on expansion to the Community Living Center (nursing home/long term care) component of VHA care also begun.

#### ACTION ITEM #25

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

- **Action Item(s):** #25
- **Project Type:** Ongoing
- **Agency:** CDC, FDA



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- **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 the general public, primarily focusing on parents of young children, and healthcare providers. 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. The first annual Get Smart About Antibiotics Week (GSW) was launched during the week of October 6<sup>th</sup> through 10<sup>th</sup>, 2008. GSW Goals included recruiting new partners and reinvigorating existing partners' interest in the campaign. By creating a newsworthy activity, this goal would lead to expanding the reach of key messages by generating media interest regarding the judicious use of antibiotics. The observation week would be the basis for forming new partnerships and re-engaging past partners to collaborate on a particular project, thereby potentially revitalizing the year-round campaign.
- **2008 Update:** To estimate GSW's reach, data was collected by totaling the number of subscribers to publications that advertised GSW messages. The total number of healthcare providers who were estimated to be exposed to GSW messages was 510,000 and the number of parents of young children estimated to be exposed was 3.8 million. Healthcare providers were primarily exposed to GSW messages through advertisements in professional publications and websites. Parents of young children were primarily exposed through parent newsletters and by the video PSA that played in 2,900 pediatric and obstetrician/gynecology waiting rooms. It was anticipated that a total of 500,000 healthcare providers would be exposed to GSW messages through publications and websites. Because there was an estimated 510,000 healthcare providers exposed to GSW messages, the target was exceeded. The target of 1.5 million parents with young children exposed to GSW messages was also exceeded. To gauge the level of online media coverage, staff members used search engines like Google and Yahoo to search websites using the key terms "get smart week" and "get smart campaign" during the month of October. A total of 145 unique websites were found that contained GSW messages or advertised GSW. Eight miscellaneous websites sent out their own press releases about GSW. Staff members expected only 75 unique websites to reference GSW. This target was exceeded.

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

- **Action Item(s):** #25
- **Project Type:** Ongoing
- **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 customers on appropriate antibiotic use.

**2008 Update:** In 2008, the Get Smart Team conducted a survey of local pharmacists about new trends in retail pharmacies. This information was used to recruit retail pharmacy partners and develop pharmacy content for the Get Smart website and Get

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Smart About Antibiotics Week. The primary audience for Get Smart About Antibiotics Week 2009 is pharmacists. Get Smart has developed a print ad and podcast to be distributed through partners such as the American Pharmacists Association and the National Alliance of State Pharmacy Associations. Get Smart staff worked in collaboration with the Infectious Diseases Society of America (IDSA) to respond, through letters and press releases, to pharmacies that offer free and low-cost antibiotics. This outreach led to opportunities to work with retail pharmacies to educate consumers about appropriate antibiotic use. CDC is currently inviting these retailers to CDC for a meeting to take place on October, 1, 2009.

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

- **Action Item(s): #25**
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Conduct a public health education campaign to promote appropriate antimicrobial use with the veterinary and agricultural settings as a national health priority, involving many partners.
- **2008 Update:** Completed. 7 funded state-based campaigns completed state-based projects addressing appropriate antimicrobial use in veterinary and agricultural settings. This work resulted in 10 peer-reviewed publications, 11 oral/poster presentations, 3 behavioral surveys, and printed materials that were distributed to thousands of veterinarians and food animal producers. Two state partners, Michigan and Minnesota, are developing modules for an online AR veterinary curriculum.

**ACTION ITEM #26**

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

- **Action Item(s): #26**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** To determine whether publicly reporting hospital scores on antibiotic timing in pneumonia (percentage of patients with pneumonia receiving antibiotics within 4 hours) has led to unintended adverse consequences for patients retrospective analyses of 13,042 emergency department (ED) visits by adult patients with respiratory symptoms in the National Hospital Ambulatory Medical Care Survey, 2001-2005, were carried out.

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Public reporting of hospital antibiotic timing scores has not led to increased pneumonia diagnosis, antibiotic use, or a change in patient prioritization (Friedberg MW et al. Am J Managed Care 2009;15:137-44). Linder JA. Editorial commentary: antibiotics for treatment of acute respiratory tract infections: decreasing benefit, increasing risk, and the irrelevance of antimicrobial resistance. Clin Infect Dis 2008;47:744-6.

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

- **Action Item(s):** #26
- **Project Type:** Ongoing
- **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).
- **2008 Update:** 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 2008 activities included: 1) Finalizing IPA with ID pharmacist to help develop campaign 2) Hosted experts meeting in April to get input on the campaign 3) Conducted focused interviews with experts around the country to get input on how best to structure the campaign.

#### **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**

- **Action Item(s):** #26
- **Project Type:** Ongoing
- **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

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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.

- **2008 Update:** In FY08, 14 local programs were funded through CDC's Epidemiology and Laboratory Capacity mechanism. 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 of the programs. In addition, the funded programs assisted with the planning and promotion of Get Smart Week within their states and local communities.

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

- **Action Item(s):** #26
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** Developing and promoting four appropriate antibiotic use curricula for medical professionals:
  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 family practice and pediatric residents for diagnosing otitis media.
  - 3/4. Two Continuing Education courses for MDs, PAs, and NPs
- **2008 Update:** 1) Medical school curriculum, ongoing: The curriculum is intended to be distributed nationally in FY2010. CDC is working in collaboration with Wake Forest University to complete the curriculum. 2) 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 acute otitis media; available at: <http://pedsed.pitt.edu/>. 3) CDC funded the Colorado Get Smart campaign to develop and promote an online video-based continuing education course for acute respiratory infections; available at: <http://www.getsmartcolorado.com/08course.htm>. 4) CDC has also funded the New Jersey Department of Health and Senior Services to develop a web-based continuing education course, which will highlight primary care provider communication techniques, to be available FY2009/2010.

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

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- **Action Item(s):** #26
- **Project Type:** Ongoing
- **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 to shift the focus of Get Smart's messages to include patient safety and healthcare quality promotion.
- **2008 Update:** Get Smart staff began conducting formative research to be able to develop, test and implement new messages that highlight quality promotion and patient safety (e.g. adverse drug events). Get Smart staff will work with the Oak Ridge Institute for Science and Education, which has been awarded a contract through an interagency agreement to develop materials and conduct formative research. In-depth-interviews with physicians were conducted in FY09 and focus groups with the general public are scheduled to be conducted in FY09. New materials should be available in early FY2010. CDC's Division of Healthcare Quality Promotion is a partner in this effort.

**PROJECT TITLE: GET SMART: KNOW WHEN ANTIBIOTICS WORK ON THE FARM: DEVELOPMENT OF A VETERINARY CURRICULUM AND COLLABORATIONS PROMOTING APPROPRIATE ANTIBIOTIC USE IN VETERINARY MEDICINE**

- **Action Item(s):** #26
- **Project Type:** New
- **Agency:** CDC
- **Description:** An antimicrobial resistance curriculum is being developed in partnership with two of our Get Smart on the Farm state partners, Michigan and Minnesota. When completed, the Antimicrobial Resistance Learning Site (AMRLS) will house an online curriculum for veterinary students. The AMRLS utilizes multiple digital media to innovatively deliver modular, fact-based and peer-reviewed scientific information regarding AR.
- **2008 Update:** 5 new modules were developed for the AMRLS. Additionally, the veterinary curriculum produced 4 peer-reviewed publications and 4 oral/poster presentations in 2008.

**PROJECT TITLE: NATIONAL METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS EDUCATION INITIATIVE**

- **Action Item:** #26 and #43
- **Project Type:** New
- **Agency:** CDC

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- **Description:** Recent increases in methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections in the community have resulted in millions of outpatient medical visits each year and intense demand for accurate MRSA information from the public, clinicians, and legislators. In response this Initiative provides both the public and clinicians with credible resources about MRSA skin infection recognition, prevention, clinical management and treatment. It targets both the general public – with specific outreach to at-risk groups including African Americans and people involved with caring for children (e.g., moms, parents, school personnel) – and first-line clinicians in emergency medicine, family practice, and pediatrics.
- **2008 Update:** Within the first months, team members developed a communications plan. The planning and initial research phase consisted of developing a research protocol for focus groups and concept testing with target audiences, obtaining IRB approval, developing campaign concepts and content, conducting focus groups and interviews with target audiences, and assessing baseline knowledge among 5,000 individuals who revealed that only 25% knew the signs and symptoms for MRSA skin infections. With the first research phase complete, the team developed and tested a comprehensive set of education materials that addressed Spanish translation and other audience requests including child care centers, and athletic community for both the general public and clinicians. Materials were posted to newly developed CDC Initiative Web pages prior to launch, and were printed and delivered to CDC Info and the Public Health Foundation. The team developed a media relations and communications strategy that employed traditional media methods (e.g., news media coverage, print advertisements, radio public service announcements, web features, professional association newsletters, press releases) as well as electronic methods (e.g., Mom blog networks, online communities, listservs, Web sites), engaging both internal and external partners. The initiative launched on September 9 and active collaboration occurred with more than 25 partners following the launch to ensure information is reaching target audiences.

**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**

- **Action Item(s):** #26
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Office of Quality and Performance measures began implementation in FY 2005 and continue through FY 2008 with plans for additional measures in FY 2009. See Action Item #7 for more details.

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

- **Action Item(s):** #26

*Last revised: December 29, 2009*

- **Project Type:** Ongoing
- **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.
- **2008 Update:** IPEC program initiated nationwide during FY 2006 with results demonstrating a significant decrease in ventilator-associated pneumonias and central catheter related bloodstream infections nationwide since implementation of the program. Pilot testing for expansion of the IPEC process into non-ICU acute inpatient care was initiated. The IPEC intranet website provides numerous resources regarding evidence-based practices and implementation strategies for the reduction of healthcare-associated events, including infections with antimicrobial-resistant organisms, for frontline healthcare personnel.

#### **PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE**

- **Action Item(s):** #26, #43, #44, #63, and #64
- **Project Type:** Ongoing
- **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).
- **2008 Update:** 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. All acute care units in all VA medical centers nationally implemented initiative by December 31, 2007. All VHA community living centers (long term care/nursing home care) nationally implemented the initiative by December 31, 2008. National healthcare-associated MRSA infection rates in the ICU setting decreased by about 50% during the first year, while healthcare-associated MRSA infections in the non-ICU setting decreased by about 30%. The prevention initiative was expanded to include VHA's Community Living Centers (nursing home care) during 2008, with full coverage completed by Dec 31, 2008. Dr. Rajiv Jain, Project for the National VHA MRSA Prevention Initiative awarded the 2008 Citizen Services-Service to America Medal from the Partnership for Public Service.

#### ACTION ITEM #30

##### PROJECT TITLE: NATIONAL MRSA SUMMIT AND MRSA IMPLEMENTATION TASK FORCE

- **Action Item(s):** #30
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. Additional working groups for mental health and ambulatory care have been chartered. Task Force has continued providing guidance for the prevention initiative. Most planning for a second MRSA Summit (which was held in February 2009) was done during 2008.

#### ACTION ITEM #32

##### PROJECT TITLE: COMMUNITY-ACQUIRED PNEUMONIA TREATMENT

- **Action Item(s):** #32
- **Project Type:** Ongoing
- **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.
- **2008 Update:** During FY 2006 these measures have been introduced and are being refined. Ongoing FY 2008. See action item #7 for more detail.

##### PROJECT TITLE: IMMUNIZATIONS-HEDIS

- **Action Item(s):** #32
- **Project Type:** New
- **Agency:** VA



Last revised: December 29, 2009

- **Description:** VHA Office of Quality and Performance has adopted measures of pneumococcal vaccination and influenza vaccination since introduction of national performance measures for VHA.
- **2008 Update:** Rates of immunization in VHA-served population meets or exceeds other national comparative measures. In FY 2008, achieved 94% immunization for those for whom pneumococcal vaccination was indicated and achieved 84% immunization for those over age 65 for whom influenza vaccination was indicated, and 69% for those age 50-64 for whom influenza vaccination was indicated. Ongoing into 2009.

#### ACTION ITEM #38

##### PROJECT TITLE: LONG TERM CARE INFECTION SURVEILLANCE

- **Action Item(s):** #38
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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; publication of article in Am J Infect Control 2008 Apr;36(3):173-179. 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. A second conference is planned for 2009.

#### ACTION ITEM #39

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

- **Action Item(s):** #39
- **Project Type:** Ongoing
- **Agency:** AHRQ, CDC

Last revised: December 29, 2009

- **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.
- **2008 Update:** Indiana University has developed and implemented a novel approach to reduce MRSA in Intensive Care Units (ICUs) in hospital systems in Indianapolis. Focusing on improved surveillance, hand hygiene, and contact isolation, participants in this Accelerating Change and Transformation in Organizations and Networks (ACTION) project have documented an average 60% reduction in MRSA infections in intervention units in comparison with a 20% reduction in control units. Other hospitals in the Indianapolis area and elsewhere are adopting this approach.

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

- **Action Item(s):** #39
- **Project Type:** Ongoing
- **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.
- **2008 Update:** See descriptions below for projects titled: 1) randomized evaluation of decolonization vs. universal clearance to eliminate methicillin resistant *Staphylococcus aureus* (reduce mrsa trial) and reducing nosocomial infections with chlorhexidine cleansing of icu patients

**PROJECT TITLE: REDUCING NOSOCOMIAL INFECTIONS WITH CHLORHEXIDINE CLEANSING OF ICU PATIENTS**

- **Action Item(s):** #39 and #75
- **Project Type:** New
- **Agency:** CDC/ Prevention Epi Center CoAg
- **Description:** Cleansing patients with chlorhexidine to reduce rates of CVC BSIs and lower risk of acquiring antimicrobial resistant pathogens, including MRSA and VRE.
- **2008 Update:** 1) Completed data analysis and presented data on chlorhexidine bathing study at SHEA 2008 national meeting 2) Examined the incidence of nosocomial bloodstream infections due to CA-MRSA strains 3) Published two review articles and prepared two editorials (one in press and one in preparation) on CA-MRSA 4) Preparing manuscripts for our studies of CA-MRSA in critically ill and HIV-infected individuals and additionally, we now are examining CA-MRSA among individuals with prior healthcare exposures.

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**PROJECT TITLE: RANDOMIZED EVALUATION OF DECOLONIZATION VS. UNIVERSAL CLEARANCE TO ELIMINATE METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS (REDUCE MRSA TRIAL)**

- **Action Item(s):** #39
- **Project Type:** New
- **Agency:** CDC/ Prevention Epi Center CoAg
- **Project :** Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin Resistant Staphylococcus Aureus (REDUCE MRSA Trial)
- **Description:** A Cluster Randomized Trial of Hospitals to Assess Impact of Targeted Versus Universal Strategies to Reduce Methicillin-Resistant Staphylococcus aureus in Intensive Care Units. Conducted in partnership with Hospital Corporation of America. 60 hospitals will be randomized to one of three separate approaches to MRSA control. The study aims are as follows: 1) Compare the effectiveness of three strategies for the prevention of MRSA+ clinical cultures in intensive care units: a) screening followed by isolation of MRSA+ patients, b) screening followed by decolonization of MRSA+ patients, c) universal decolonization without screening. The study will assess both decolonization vs. no decolonization, and selective vs. universal decolonization. 2) To assess the impact of the two decolonization strategies on bloodstream and urinary tract infections due to MRSA, as well as all pathogens 3) to assess the impact that targeted or universal decolonization regimens have on antimicrobial resistance to topical decolonizing agents 4) To determine the intervention costs of each arm.
- **2008 Update:** 1) Protocol IRB approved, funding secured, and recruitment has begun. 2) Initiation of Study planned September 2009.

**PROJECT TITLE: CDC EXPERTS MEETING ON STAPHYLOCOCCAL DECOLONIZATION**

- **Action Item(s):** #39
- **Project Type:** New
- **Agency:** CDC
- **Description:** in August 2008, CDC held an experts meeting for approximately 30 National and International Experts on Staphylococcal disease to discuss the role of decolonization in community and healthcare settings.
- **2008 Update:** The meeting was held in August 2008. Expert input was provided on a number of important topics. Experts felt that decolonization although it has shown promise in a number of settings its widespread implementation is not yet supported by the available data. Potential settings where decolonization may be reasonable in settings where rates of Staphylococcal infection continue to be above National averages despite use of standard infection control recommendations include perioperative for patients undergoing cardiac or orthopedic surgery (with implants) and potentially in some outbreak settings. A summary of the meeting is currently being produced. The meeting provided important input to CDC and has helped to solidify research needs in this area.

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**PROJECT TITLE: EVALUATING THE EFFECTIVENESS OF THE RECENT IL STATE LAW REQUIRING ALL HOSPITALS TO IMPLEMENT SPECIFIC MRSA INFECTION PREVENTION MEASURES**

- **Action Item(s):** #39
- **Project Type:** New
- **Agency:** CDC
- **Description:** Determine whether a legislative mandate to implement active surveillance testing for MRSA is associated with (1) a decreased prevalence of MRSA colonization among patient receiving care in an ICU, or (2) a decreased prevalence of MRSA bloodstream infection (BSIs) by an annual cross-sectional survey for colonized or infected patients over a three-year time period.
- **2008 Update:** Initiation of a regional program involving >90% of Chicago area hospitals includes systematic periodic evaluation of all intensive care unit patients for carriage or infection with MRSA. Isolates have been processed by partner laboratories in Chicago, with 100% compliance in surveillance cultures at participating sites.

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

- **Action Item(s):** #39
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** MRSA laboratory data collected nationwide from VA medical facilities to identify antibiotic resistance patterns.
- **2008 Update:** 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 VHA National MRSA Prevention Initiative at the annual meeting of the Association of Professionals in Infection Control and Epidemiology for June 2008; with follow-up invited presentation scheduled for June 2009. Work continues through the MRSA Prevention Initiative.

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

- **Action Item(s):** #39 and #63
- **Project Type:** Ongoing

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- **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.
- **2008 Update:** 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. Publication: Infect Control Hosp Epidemiol 2008;29:702-708.

**PROJECT TITLE: PARTNERSHIP WITH CDC PREVENTION EPICENTERS—DEVELOPING INTERVENTIONS, EVALUATING EFFECTIVENESS OF INTERVENTIONS**

- **Action Item(s):** #39
- **Project Type:** New
- **Agency:** VA
- **Description:** VHA is partnering with CDC Prevention Epicenters on several projects related to antimicrobial resistance.
- **2008 Update:** Funded Prevention Epicenters/VA Collaboration regarding developing interventions and evaluating effectiveness of interventions. These include MRSA focused prevention efforts such as cleansing of patients with chlorhexidine cloths, reducing transmission of MRSA and VRE (e.g., using electronic alerts to flag high risk patients, collection of nasal swab (PCR), Toyota Production System-based quality improvement program large VA multi-site study, evaluating effectiveness of screening and decolonization for MRSA control automated standing orders for routine ICU MRSA surveillance cultures, and the impact on ICU and total hospital MRSA bacteremia), Urinary Tract Infections prevention (Implementing an intervention to electronically identify and flag patients for whom urinary catheters may no longer be needed), and evaluating impact of *Clostridium difficile* infections (CDI) prevention strategies.

**PROJECT TITLE: POSITIVE DEVIANCE**

- **Action Item(s):** #39 and #63
- **Project Type:** New
- **Agency:** VA
- **Description:** Use of Positive Deviance model to assist with national MRSA Prevention Initiative. VA has partnered with the Plexus Institute, an organization which has espoused the Positive Deviance Model for cultural change, on a number of projects related to MRSA.

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- **2008 Update:** 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-Cochran, J Lloyd, J Jernigan on the first abstract and J Jacob, R Muder, C Cunighham, E McCray, C Squier, C Mehta, R Jain, R Sinkowitz-Cochran, J Lloyd and J Jernigan on the second abstract. VA MRSA experience highlighted on the Plexus Institute website; an MRSA blog is available on the Plexus Institute website also. Ongoing.

#### ACTION ITEM #43

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

- **Action Item(s):** #43
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. Remains active with annual publication of materials and user guide for field facilities across the nation.

#### ACTION ITEM #44

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

- **Action Item(s):** #44
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** 2-3 minute "infomercials" covering issues relating to influenza, PPD's and bloodborne pathogens
- **2008 Update:** Completed. Airing of infomercials ongoing.

##### **PROJECT TITLE: NATIONAL CENTER FOR HEALTH PROMOTION MONTHLY TOPICS**

- **Action Item(s):** #44

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- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** Some of the monthly topics address specific diseases and some address specific infectious diseases preventive measures.
- **2008 Update:** 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.

**PROJECT TITLE: PLANNED LONG TERM CARE CONFERENCE IN SEPTEMBER 2006**

- **Action Item(s):** #44
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** Issues of antibiotic resistance discussed.
- **2008 Update:** Completed January 2008. Conference provided for administrators, front line nursing personnel, infection control professionals for all VHA Community Living Centers (nursing home care/long term care) nationwide. A second conference is planned for Summer 2009 where infection prevention and control issues regarding antimicrobial resistant organisms such as MRSA will be discussed.

**ACTION ITEM #45**

**PROJECT TITLE: INNOVATIVE FS PROGRAM FOR LOW LITERACY FOOD HANDLERS**

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Using enhanced and distance education programs
- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (University of Connecticut). See CSREES website.

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

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Focused on consumers with use of collected data, databases

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- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (University of Missouri). See CSREES website.

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

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Will also assess impact of training
- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (Cornell University). See CSREES website.

**PROJECT TITLE: RISK ANALYSIS BASED FOOD DEFENSE CERTIFICATION PROGRAM**

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** For professional and academic programs
- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (University of Maryland). See CSREES website.

**PROJECT TITLE: FOOD SAFETY TRAINING PROGRAMS FOR ETHNIC VENDORS**

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Evaluate programs and implement changes, particularly for Asian and Mexican foods
- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (University of Florida). See CSREES website.

**PROJECT TITLE: FIGHT BAC!® CAMPAIGN**

- **Action Item:** #45
- **Project Type:** Ongoing
- **Agency:** CDC, FDA, USDA



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- **Description:** This national program emphasizes the four basic safe handling behaviors: Clean, Separate, Cook, and Chill.
- **2008 Update:** 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. Ongoing research funded by CSREES, National Integrated Food Safety Initiative (University of Georgia)-see CSREES website.

**PROJECT TITLE: USDA/FSIS SAFE FOOD HANDLING OUTREACH INITIATIVES**

- **Action Item(s):** #45
- **Project Type:** Ongoing
- **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, and 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 handling. The FSIS podcast and videocast series, "Food Safety at Home", began in April 2008 and is available on the FSIS website in English and Spanish.
- **2008 Update:** Ongoing.

**PROJECT TITLE: BE FOOD SAFE INITIATIVE**

- **Action Item(s):** #45
- **Project Type:** New
- **Agency:** USDA
- **Description:** Launched in September 2006, this nationwide food safety educational campaign gives educators the tools to inform consumers about foodborne illness and raises awareness of the dangers associated with improper handling and undercooking of food. The toolkit includes: print media including a brochure, ads, an activity book and posters, broadcast media including public service announcements for radio and TV, and an extensive graphics library.
- **2008 Update:** Ongoing.

**PROJECT TITLE: "ASK KAREN" A WEB-BASED COMMUNICATION TOOL**

- **Action Item(s):** #45
- **Project Type:** New
- **Activity in 2008:** yes

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- **Agency:** USDA
- **Description:** This “virtual representative” debuted in 2004 and is available 24/7. “Ask Karen” responds, from an extensive database of food safety information, to inquiries from the public about the safe handling, preparation, and storage of meat, poultry, and egg products.
- **2008 Update:** Ongoing.

**PROJECT TITLE: SEPTEMBER IS NATIONAL FOOD SAFETY EDUCATION MONTH**

- **Action Item(s):** #45
- **Project Type:** New
- **Agency:** USDA
- **Description:** Provides educational materials as a resource for educators at the state, local and federal level.
- **2008 Update:** Distributed a DVD developed by USDA, FDA and the Partnership for Food Safety Education for use in current year’s food safety educational efforts.

**ACTION ITEM #47**

**PROJECT TITLE: ANNUAL INFLUENZA/PNEUMOCOCCAL VACCINE TOOLKIT**

- **Action Item(s):** #47
- **Project Type:** Ongoing
- **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
- **2008 Update:** 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, 2007-2008 season, and 2008-2009 season. Planning for the toolkit for the 2009-2010 season toolkit is underway.

**PROJECT TITLE: ANNUAL INFLUENZA VACCINATION DIRECTIVE**

- **Action Item(s):** #47
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** Provide to the field facilities central direction for the consistent use of influenza vaccination and treatment strategies nationwide within VHA.

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- **2008 Update:** 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 2008-2009 influenza season.

**PROJECT TITLE: PNEUMOCOCCAL AND INFLUENZA VACCINATION AS PERFORMANCE MEASURES**

- **Action Item(s): #47**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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 and achieved 97% for CAP2j (Inpatients with diagnosis of pneumonia screened for previous pneumococcal vaccination or received vaccination by time of discharge). See Action Item #7 for additional details.

**ACTION ITEM #48**

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

- **Action Item(s): #48**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. Several licensed vaccines. Continued vaccine supply essential to maintaining the near elimination of resistant *H. influenzae* disease in the U.S.

**PROJECT TITLE: PNEUMOCOCCAL VACCINE**

- **Action Item(s): #48**
- **Project Type:** Ongoing

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- **Agency:** FDA
- **Description:** Monitoring of polysaccharide and polysaccharide conjugate vaccines, including regulator inspections of the production facilities, review and conduct of Lot Release studies, and review of amendments to the current biologic License Application.
- **2008 Update:** Ongoing. One licensed polysaccharide primarily for use in the elderly and one licensed seven valent 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. Continued vaccine supply essential for continued prevention of pneumococcal disease.

#### **PROJECT TITLE: INFLUENZA VACCINE**

- **Action Item(s):** #48
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Six seasonal influenza vaccines are currently licensed and distributed in the U.S. These vaccines include Medimmune (FluMist®), Sanofi (Fluzone®), Novartis (Fluvirin®), ID Biomedical (FlulavalO), GSK (Fluarix®), and CSL Ltd (Afluria). At the February 2008 ACIP meeting, there was discussion and vote to expand the pediatric recommendation to include children 6 months through 18 years of age. September 2008 Vaccine and Related Products Advisory Committee meeting considered use of MDCK Cells for Manufacture of Live Attenuated Influenza Virus Vaccines. The VRPAC supported initiation of phase 1 clinical studies for LAIV manufactured in MDCK cells and provided recommendations for additional pre-clinical studies.

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

- **Action Item(s):** #48
- **Project Type:** Ongoing
- **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

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recommendations for these immunizations for Nursing Home Care Units within VHA system.

- **2008 Update:** 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. For FY 2008, Performance Measurement monitors of p1 (persons at increased risk for pneumococcal vaccine have received vaccination) was 94%, while measurement p22h (persons between ages of 50-64 have received influenza vaccination) was 69% and p25h (persons greater than age 65 and/or at increased risk for influenza have received influenza vaccination) was 84%.

#### ACTION ITEM #49

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

- **Action Item(s): #49**
- **Project Type:** Ongoing
- **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 affects on public health, reduces the health of swine, and whether antibiotic growth promoters mediate their effects by alteration of the intestinal bacterial microflora.
- **2008 Update:** Ongoing. Funded by CSREES, National Research Initiative (University of Minnesota). See CSREES website.

#### **PROJECT TITLE: METAGENOMICS OF ANTIBIOTIC RESISTANCE**

- **Action Item(s): #49**
- **Project Type:** New
- **Agency:** USDA
- **Description:** Using metagenomics (and culture) approaches to evaluate the effects of feeding subtherapeutic (growth promoting) and therapeutic antibiotics on swine intestinal microbiota. The goal is to identify changes in microbial composition associated with performance enhancement. Once we identify how growth promotants work, then alternatives to antibiotics can be found that give the same effects. We are also looking at the changes in antibiotic resistance gene contents in swine exposed to one or more antibiotics in parallel. Finally, we will test whether or not growth promoting antibiotics still work in swine and use metagenomics to detect changes in intestinal microbiota to marketed probiotics

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- **2008 Update:** In FY 2008 we tested an important hypothesis - that antibiotic sensitive commensal bacteria could block sow-to-piglet transmission of antibiotic resistant bacteria of the same species, thereby reducing the incidence of antibiotic resistance in the piglets. At ten days after weaning, only antibiotic sensitive *M. elsdenii* strains were recovered from the dosed piglets. At 25 and 39 days after weaning, however, multiply antibiotic resistant *M. elsdenii* strains from the mother sow colonized and eventually predominated in the dosed piglets. Control piglets (not dosed) were colonized with antibiotic resistant sow strains earlier. One explanation for these results is that *Megasphaera elsdenii* strains colonizing swine exhibit specificity for the host swine genotype. Thus exogenous dosed strains cannot prevent sow-to-piglet transmission. If this is more broadly true for intestinal commensal bacteria, then probiotic applications requiring colonization of animal or human by dosing non-specific probiotic bacteria are unlikely to be uniformly successful.

#### ACTION ITEM #50

##### PROJECT TITLE: DISSEMINATION OF CEPHALOSPORIN RESISTANCE GENES

- **Action Item(s):** #50
- **Project Type:** Ongoing
- **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 cm<sub>y</sub>-2 resistance in commensal *e.coli* populations
- **2008 Update:** Ongoing. Funded by CSREES, National Research Initiative (Washington State University). See CSREES website.

#### ACTION ITEM #52

##### PROJECT TITLE: RAPID METHODS DEVELOPMENT

- **Action Item(s):** #52
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Validated culture methods for foodborne pathogens in animal feeds.
- **2008 Update:** 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 continued to collaborate with USDA-Agricultural Marketing Service to determine DNA fingerprint patterns and antimicrobial susceptibilities

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among Salmonella and *E. coli* isolates recovered from produce obtained from the microbiological data program plan.

#### ACTION ITEM #53

##### PROJECT TITLE: NARMS RETAIL FOOD

- **Action Item(s):** #53
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Monitor prevalence of antimicrobial resistant zoonotic pathogens and commensal organisms among foods of animal origin.
- **2008 Update:** NARMS retail was initiated in 2002, as of 2008, 9 FoodNet sites plus Pennsylvania are participating. The 2006 NARMS retail meat annual report was published in 2008 and can be found at <http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/ucm164662.htm>. FDA just published the 2007 Retail Meat Annual Report and is currently involved in publishing the 2008 annual report.

#### ACTION ITEM #55

##### PROJECT TITLE: ANIMAL PRODUCTION STUDIES

- **Action Item(s):** #55
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Determine dynamics of resistance development in naïve animal populations exposed to antimicrobial agents.
- **2008 Update:** Completed animal studies focusing on the development and persistence of bacteria resistance after exposure to specific antimicrobials. 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).

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

- **Action Item(s):** #55
- **Project Type:** Ongoing
- **Agency:** USDA

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- **Description:** Research to test the ability of *Salmonella* to survive in oysters and to track the source of *Salmonella* in surface waters.
- **2008 Update:** Ongoing. Funded by CSREES, National Research Initiative (University of Arizona). See CSREES website.

#### ACTION ITEM #58

##### PROJECT TITLE: RISK ASSESSMENT

- **Action Item(s):** #58
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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 continues 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.

##### PROJECT TITLE: ORDER PROHIBITING THE EXTRA-LABEL USE OF CEPHALOSPORIN ANTIMICROBIAL DRUGS IN FOOD-PRODUCING ANIMALS

- **Action Item(s):** #58
- **Project Type:** New
- **Agency:** FDA
- **Description:** Order prohibiting the extra-label use of cephalosporin antimicrobial drugs in food-producing animals.
- **2008 Update:** FDA issued an order prohibiting the extra-label use of cephalosporin drugs July 3, 2008. The order is based on evidence that extra-label use of these drugs in food-producing animals will likely cause an adverse event in humans and, as such, presents a risk to the public health. CVM received many substantive comments on the Order. Many comments felt that the scope of the Order was too broad and/or was not adequately justified. The Order was revoked on November 26, 2008, so that CVM could fully



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consider the comments. CVM has completed its analysis of comments and expects to publish a revised Order in 2010.

#### ACTION ITEM #59

##### **PROJECT TITLE: AR USE BY VETERINARIANS**

- **Action Item(s):** #59
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Develop a Web-based decision support system for use by veterinarians to select and use antimicrobial agents appropriately.
- **2008 Update:** Provided funding for development of Veterinary Antimicrobial Decision Support (VADS) System; 5 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. VADS can be found at: <http://vads.vetmed.vt.edu/Mission.cfm>.

#### ACTION ITEM #62

##### **PROJECT TITLE: ANTIMICROBIAL RESISTANCE TASK FORCE**

- **Action Item(s):** #62
- **Project Type:** Ongoing
- **Agency:** ARHQ, CDC, DoD, VA, EPA, FDA, NIH, USDA
- **Description:** Annual Progress Report and Public Meeting.
- **2008 Update:** 2001 - 2008, annual progress reports issued consisting of inventory of projects that address Action Plan items. Held eighth annual public meeting June 25, 2008, Bethesda, MD. Task Force worked on reviewing information from December 2007, consultants meeting to discuss issues relating to revising the Action Plan. Task Force worked to revise the action plan.

##### **PROJECT TITLE: ANTIMICROBIAL RESISTANCE TASK FORCE ACTION PLAN UPDATE**

- **Action Item(s):** #62
- **Project Type:** Ongoing
- **Agency:** ARHQ, CDC, DoD, VA, EPA, FDA, NIH, USDA
- **Description:** The Task Force is currently working on Revising and Updating The Action Plan to Combat Antimicrobial Resistance.

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- **2008 Update:** On December 12 and 13, 2007, the Interagency Task Force on Antimicrobial Resistance, held a consultants meeting in Atlanta, Georgia to obtain input 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. Following the meeting the Task Force reviewed input and worked to revise the Action Plan.

**PROJECT TITLE: CDC/KINDRED HOSPITALS *Clostridium DIFFICILE* INFECTION QUALITY IMPROVEMENT COLLABORATIVE**

- **Action Item(s):** #62
- **Project Type:** New
- **Agency:** CDC
- **Description:** Long-term acute care (LTAC) hospitals care for medically complex patients requiring intensive care for prolonged periods of time. These patients are frequently exposed to multiple antimicrobials before and during their LTAC hospital stay and are at high risk for infections with multi-drug resistant organisms and *C. difficile*. The long-term goal of this project is to reduce CDI rates in Kindred LTAC hospitals by optimizing existing CDI prevention measures. The initial step will be to establish standardized surveillance for CDI in 7 volunteering Kindred LTAC hospitals and evaluate existing CDI control measures. This information will be used to identify appropriate prevention and control measures for each facility.
- **2008 Update:** Protocol and plan for surveillance was developed and initiated in 7 LTAC hospitals.

**ACTION ITEM #63**

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

- **Action Item(s):** #63
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** The Prevention of Infection caused by Methicillin or Oxacillin resistant Staphylococcus aureus or PRIMO study. A 2 x 2 phase iii open-label clinical trial of therapy for patients with recurrent methicillin resistant staphylococcus aureus infections:

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topical nasal and body decolonization of household members versus standard of care, and environmental decontamination versus standard of care.

- **2008 Update:** Enrollment continued through 2008 and is ongoing. As of July 30, 2009, enrollment was completed (goal of 350 participants successfully reached). Follow-up phase will continue through July 2010.

#### ACTION ITEM #64

#### **PROJECT TITLE: INFLUENZA AND PNEUMOCOCCAL VACCINATIONS AS PERFORMANCE MEASURES**

- **Action Item(s):** #64
- **Project Type:** Ongoing
- **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.
- **2008 Update:** For Federal Fiscal Year 2006, VHA introduced timing of antibiotics for community-acquired pneumonia for inpatients and is pursuing measures for appropriate antibiotic choices, along with existing vaccination performance measures. See Action items # 7, 32, 47 and 48 above for specific results. Ongoing.

#### ACTION ITEM #65

#### **PROJECT TITLE: QUALITY ASSURANCE PROGRAMS**

- **Action Item(s):** #65
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. See Action items #7, 32, 47 and 48 above for results.

#### **PROJECT TITLE: NATIONAL MRSA PREVENTION INITIATIVE—BETA TEST SITES**

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- **Action Item(s):** #65
- **Project Type:** Ongoing
- **Agency:** VA
- **Description:** For the National MRSA Prevention Initiative (noted above), 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.
- **2008 Update:** 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

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** CDC
- **Description:** PCR methodologies are used to assist ongoing lab-based surveillance of invasive pneumococcal disease (IPD) 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).
- **2008 Update:** 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 serotype 19A disease among rural Alaska Native children. Recent identification of a multidrug-resistant sequence type 320 isolate is of concern since it has emerged as the second most common clonal group in the rest of the U.S.

##### **PROJECT TITLE: EPIDEMIOLOGY OF CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE IN A HEALTHCARE SETTING**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** CDC

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- **Description:** A cooperative agreement with Mount Sinai Hospital with sub-contract to New York University to study the transmission dynamics of carbapenemase-producing enterobacteriaceae in acute care hospitals.
- **2008 Update:** 1) Data collection began at both sites and is on-schedule 2) Supplemental funds were provided out of division budget to extend laboratory testing.

**PROJECT TITLE: PREVALENCE OF COLONIZATION AND INCIDENCE OF INFECTION WITH COMMUNITY-ASSOCIATED METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* IN A LARGE URBAN HIV OUTPATIENT CLINIC**

- **Action Item(s): #67**
- **Project Type:** New
- **Agency:** CDC, VA
- **Description:** Skin and soft tissue infections with community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) are an increasing problem among people living with HIV/AIDS. Fundamental aspects of the epidemiology of this condition, in particular asymptomatic carriage rates and risks for clinical disease, remain unknown. We are conducting a prospective cohort study at the Atlanta Veterans Affairs Medical Center (VAMC) to evaluate CA-MRSA carriage rates and risks for carriage and clinical disease. Approximately 700 patients (a maximum of 1100 patients) at the VAMC HIV Clinic will be recruited to provide nasal and groin swabs for *S. aureus* culture at a baseline visit and at two subsequent visits 6 and 12 months. At the baseline visit, participants will complete a questionnaire to collect data about possible risk factors associated with CA-MRSA carriage and clinical disease, and clinical and demographic risk-related data will also be collected. All *S. aureus* isolates will be characterized by antimicrobial susceptibility, pulsed-field gel electrophoresis, and detection of toxin genes. Participants who develop clinical disease will complete an additional questionnaire to further characterize their course of illness and response to treatment.
- **2008 Update:** 600 patients were enrolled, data was abstracted, and specimens were collected at baseline, 6 months and 12 months and processed. Preliminary analysis suggested that the prevalence of MRSA colonization is high in this cohort of HIV-infected adults compared with the general population. Addition of groin culture enhanced recovery over nasal swabs alone, and specifically enhanced detection of some MRSA strains. Prevalence of MRSA colonization at either site at baseline was 13%. Including groin swabs increased detection of MRSA colonization by 20%.

**PROJECT TITLE: PREVALENCE AND RISK FACTORS FOR COMMUNITY-ASSOCIATED MRSA PNEUMONIA**

- **Action Item(s): #67**
- **Project Type:** New
- **Agency:** CDC
- **Description:** Study performed by the CDC-funded EMERGENCY ID Net to assess the prevalence of and risk factors for CA-MRSA pneumonia. Patients presenting to 12

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network emergency departments and subsequently admitted to the hospital with *S. aureus* community-acquired pneumonia were enrolled and clinical, epidemiologic, and microbiologic data were collected. Isolates were characterized at CDC.

- **2008 Update:** Database was cleaned and finalized and data analysis initiated.

**PROJECT TITLE: PREVALENCE OF COMMUNITY-ASSOCIATED MRSA INFECTION AMONG EMERGENCY DEPARTMENT PATIENTS WITH SKIN INFECTIONS, AND FACTORS ASSOCIATED WITH HOSPITAL ADMISSION AND ISOLATION DECISIONS**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** CDC
- **Description:** Study performed by the CDC-funded EMERGENCY ID Net to assess the prevalence of CA-MRSA among emergency department patients with skin infections and to evaluate factors associated with hospital admission and isolation decisions.
- **2008 Update:** 643 patients were enrolled and data collection was completed. Isolates were characterized at CDC. Data entry completed and database cleaning initiated.

**PROJECT TITLE: LABORATORY-BASED STUDIES ON THE MOLECULAR MECHANISMS RESPONSIBLE FOR CEPHALOSPORIN RESISTANCE IN *NEISSERIA GONORRHOEAE***

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** CDC
- **Description:** CDC/DSTDP will determine the *Neisseria gonorrhoeae* strain populations most likely to give rise to biological variants resistant to cephalosporin, and the rapidity with which they may emerge. To do this it is important to understand the genetic basis for such resistance and the biochemical mechanisms through which it is mediated. Studies on the prevalence of the penA mosaic allele in domestic gonococcal isolates will be conducted together with studies on the ability of any newly discovered gene variants that contribute to cephalosporin resistance to be transferred to additional strains of *N.gonorrhoeae* by DNA-mediated transformation. It is not clear whether or not known mutations in the TEM beta-lactamase gene that expand the substrate spectrum of the enzyme will confer significant levels of resistance in *N. gonorrhoeae*. It will also be important to determine if there exists a possibility for novel mutations in the *bla* gene that will confer cephalosporin resistance on beta-lactamase-producing *N. gonorrhoeae* and the frequency with which this can occur. The impact of known mutations introduced into the *bla* gene harbored by *N. gonorrhoeae* and by direct selection of cephalosporin resistance in PPNG strains with subsequent genetic analysis of the *bla* gene will be investigated.
- **2008 Update:** Project planning initiated.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. The Republic of Georgia lab is scheduled to be operational in 2010.

**PROJECT TITLE: DNA MICROARRAY PROFILING OF ANTIBIOTIC RESISTANCE GENES**

- **Action Item(s):** #67
  - **Project Type:** Ongoing
  - **Agency:** FDA
  - **Description:** Develop DNA microarray techniques and DNA chips for characterizing antibiotic resistance genes for multiple bacterial pathogens.
- 2008 Update:** 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. The DNA sequences were completed during 2008, and gene identification and labeling should be finished in FY 2009.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** FDA

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- **Description:** Isolate and characterize antimicrobial resistant bacteria from aquaculture and aquaculture products.
- **2008 Update:** Sixty-three tetracycline-resistant *E coli* strains were isolated from the intestinal contents of 407 farm-raised catfish. PCR protocols were designed to amplify the various tetracycline resistant genes (*tet*) from the template DNA and *tetB* was determined to be the predominant gene. Sequence analysis of identified integrons demonstrated different gene cassettes conferring resistance to aminoglycosides and potentiated sulfonamides.

**PROJECT TITLE: DEVELOPMENT OF MICROARRAY CHIP FOR THE DETECTION OF ANTIBIOTIC RESISTANCE MARKERS**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** FDA
- **Description:** Develop a microarray chip for rapid characterization of antimicrobial resistance genes present among foodborne bacteria.
- **2008 Update:** The Tn 1546 transposon regions from seventeen vancomycin-resistant *Enterococcus faecium* isolates of human clinical origin were analyzed by PCR fragment length polymorphism, PFGE and sequence analysis. Several isolates were shown to have new arrangements of Tn 1546 structural genes. Research is currently underway to determine potential associations of gene arrangements with decreased susceptibility of antimicrobials of human health significance.

**PROJECT TITLE: MOLECULAR CHARACTERIZATION OF SALMONELLA AND VIBRIO spp. ISOLATED FROM SEAFOOD**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** FDA
- **Description:** Characterize antimicrobial resistance Salmonella recovered from imported seafood.
- **2008 Update:** Fifty multiple antibiotic resistant strains of Salmonella spp. were isolated from imported seafood. Multidrug resistance was observed among several serovars including *S. Newport*, *S. Typhimurium* and *S. Lansing*. Resistance was associated with the presence of integrons containing gene cassettes conferring resistance to aminoglycosides and potentiated sulfonamides.

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

- **Action Item(s):** #67



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- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The 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%.
- **2008 Update:** In 2008, NIH funded more than 1,800 research grants to small business, including a number that focused on antimicrobial resistance mechanisms and the development of novel vaccines, diagnostics and antimicrobial drugs for resistant pathogens. Examples of 2008 SBIR/STTR awards include: (1) Oral Prodrugs of Carbacephem Antibiotics Active Against Antibiotic-Resistant Bacteria, (2) Detection of Antibiotic Resistance Genes in Bacterial Agents of Hospital-Acquired Infections and (3) Rapid Affordable TB Drug Susceptibility Testing.

**PROJECT TITLE: RESEARCH, CONDITION, AND DISEASE CATEGORIZATION (RCDC) SYSTEM**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** NIH
- **Description:** Recently, NIH has implemented a new computerized reporting process called Research, Condition, and Disease Categorization (RCDC), which all NIH institutes must now use to categorize and report funding in 215 research, condition, and disease categories, including antimicrobial resistance. The NIH RePORTER <<http://projectreporter.nih.gov/reporter.cfm>> (Research Portfolio Online Reporting Tool) is a new web query tool within the RCDC system that allows the public to drill deeper into each RCDC category. RePORTER provides links to abstracts and other project-level data such as histories and start/end dates. It also features links to publications and patents associated with the research. The RCDC System can be accessed at the following link: <http://www.report.nih.gov/rcdc/categories/>.
- **2008 Update:** Ongoing.

**PROJECT TITLE: INVESTIGATOR-INITIATED RESEARCH GRANTS (R01)**

- **Action item(s):** #67
- **Project Type:** New
- **Agency:** NIH
- **Description:** The Research Project Grant (R01) is the oldest and most frequently utilized NIH grant mechanism. The R01 provides support for health-related research and

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development based on the mission of the NIH. R01s can be investigator-initiated or can be in response to a program announcement or request for application. R01 awards comprise the the largest overall NIH program, both in terms of number of awards and budget amount.

- **2008 Update:** In 2008 NIH/NIAID awarded hundreds of R01 projects focused on antimicrobial resistance mechanisms and the early development of vaccines, diagnostics and antimicrobial drugs for a broad range of resistant pathogens. Example of investigator-initiated R01 grants awarded in 2008 include: (1) *Candida glabrata* Pdr1: Master Regulator of Azole Resistance, (2) Design and mechanistic studies of mimics of antimicrobial peptides and (3) Design of New Antimicrobials.

**PROJECT TITLE: NIAID PRODUCT DEVELOPMENT PUBLIC/PRIVATE PARTNERSHIPS (RFA AI-06-033)**

- **Action item(s):** #67
- **Project Type:** New
- **Agency:** NIH
- **Description:** This Request for Applications calls attention to the vital role played by Public-Private Partnerships (PDPPP's) in developing new products directed against the neglected tropical diseases.
- **2008 Update:** Under this RFA, 4 new awards (U01) were made in 2007, two of which focus on antimalarial drug discovery and development, one of which focuses on new drug development for leishmaniasis, and one of which focuses on diseases caused by trypanosomes. Support for these awards continued in 2008.

**COOPERATIVE RESEARCH PARTNERSHIPS FOR BIODEFENSE**

- **Action Item(s):** #67
- **Project Type:** ongoing
- **Agency:** NIH
- **Description:** The purpose of this cooperative agreement program is to support discovery/design and development of vaccines, therapeutics, adjuvants and diagnostics for NIAID Category A, B and C priority pathogens and toxins. NIAID issues this RFA annually. Importantly, resistant pathogens are considered NIAID Category C pathogens and are therefore eligible for study under this initiative.
- **2008 Update:** In 2008, NIAID supported several awards with relevance to Antimicrobial Resistance, including: (1) Chemotherapeutics Against Multi-Drug Resistant Tuberculosis, (2) Response therapies for MDR-TB, and (3) Integrated Antimicrobial Drug Discovery Scheme for Multidrug Resistant Bacteria.

**PROJECT TITLE: INVESTIGATOR-INITIATED SMALL RESEARCH GRANT AWARDS (R03)**

- **Action Item(s):** #67 and #72

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- **Project Type:** Ongoing
- **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 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.
- **2008 Update:** Examples of awards made in FY2008 include: (1) Understanding a Mechanism of Antibiotic Resistance by Phosphorylation: Fosfomycin, (2) Biosynthesis of HSAF, an antifungal natural product with a novel mode of action and (3) Etiology, Epidemiology and Clinical Outcomes of Health Care Associated Pneumonia.

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

- **Action Item(s):** #67, #70, #76, #77, and #78
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Clinical activities within the FWDIRN in 2008 included: cell-mediated immunity studies from *Salmonella typhi* vaccine trials; 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; phase I Study of the Safety and Immunogenicity of Recombinant *Staphylococcal* Enterotoxin B Vaccine (STEBVax) in Healthy Adults; evaluating the intestinal microbiome prior to and after dosing with an antibiotic, Ciprofloxacin; comparison of the efficacy and potential side-effects of several antibiotics in the treatment of Shiga toxin-producing *Escherichia coli*; and 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).

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** NIH

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- **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.
- **2008 Update:** In 2008, section scientists reported on their determination of the mode of action of the candidate TB drug, PA-824. They found that PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular generation of nitric oxide (NO) and other reactive nitrogen species, which is the major cause of the anaerobic activity of these compounds. The scientists observed that NO generation during PA-824 metabolism is greatest when oxygen levels are low. This observation suggests how PA-824 may work against non-dividing *M.tb*. Science. 2008 Nov 28;322(5906):1392-5.

**PROJECT TITLE: NIAID INTRAMURAL LABORATORY OF CLINICAL INFECTIOUS DISEASES, CLINICAL MYCOLOGY SECTION**

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The Clinical Mycology Section conducts research to determine molecular mechanisms of azole resistance in clinical isolates of the pathogenic yeast, *Candida glabrata*.
- **2008 Update:** 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.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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

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development of enhanced diagnostics and better prophylaxis and therapeutics for pathogens such as community-associated methicillin-resistant *S. aureus* (CA-MRSA).

- **2008 Update:** In 2008, section scientists continued to study the pathogenic role of a bacterial toxin called PVL, epidemiologically linked to CA-MRSA outbreaks and the presumptive reason for its virulence (J Infect Dis 2008. 198:1166-1170; PLoS ONE 2008.3:e3198). Also in 2008, section scientists reported results of a collaborative study showing that the USA300 group of CA-MRSA strains comprises nearly identical clones that have emerged from a single bacterial strain with extraordinary transmissibility (Proc Natl Acad Sci U S A. 2008 Jan 29;105(4):1327-32). They also reported new details about the complex mechanisms MRSA uses to avoid destruction by neutrophils.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** In 2008, section scientists compared the phylogeny and virulence of USA300 with that of closely related MRSA clones, discovering that the sublineage from which USA300 evolved is characterized by a phenotype of high virulence that is clearly distinct from other MRSA strains.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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

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genes in a chromosome locus recently shown to affect the quinine response of *P. falciparum*. In 2008, section scientists reported on genome-wide compensatory changes accompanying chloroquine induced mutations in the CRT gene. Investigation of the genes involved is continuing (PLoS One. 2008 Jun 25;3(6):e2484).

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Demonstrated a collateral effect of a growth performance antibiotic widely used in the US, the quinolone antibiotic, carbadox. Sub-inhibitory carbadox concentrations in bacterial cultures induce both prophage-like Gene Transfer Agents carrying antimicrobial resistance genes and traditional prophages. Impact: This research provides important data on the use of sub-inhibitory concentrations of carbadox and its role in antimicrobial resistance induction. This study has also generated new knowledge about phage induction and may be useful for future interventions. 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.

**PROJECT TITLE: SURVEILLANCE OF ANTIBIOTIC RESISTANCE IN NORMAL ENTERIC BACTERIA**

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** This was the first report of tetracycline gene class recombination. Studies showed that established *M. elsdenii* strains from swine that were never exposed to antimicrobials are multiply drug resistant, and that resistance genes can be transferred inter-strain at very high frequency. By genome sequencing, work demonstrated that resistance mobile elements in one *M. elsdenii* strain are identical to those in *C. jejuni*. Impact: These findings provide new knowledge implicating swine commensal bacteria not only as reservoirs of antimicrobial resistance for pathogens such as *Campylobacter*, but also as sites for the evolution of antimicrobial resistance. This research provides new directions for research in the role of commensals and antimicrobial resistance. We found

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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.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing. *Salmonella* species resistant to multiple antibiotics frequently harbor plasmids or other mobile genetic elements that carry the resistance genes that can be spread to non-resistant bacteria. The DNA sequence of an 84.5-kb MR plasmid, pU302L, from *S. Typhimurium* U302, revealed 12 antibiotic resistance genes and 6 genes involved in mercury resistance, as well as regions suggestive of multiple gene rearrangement events occurring during the evolution of the plasmid. Moreover, the DNA sequence of 4 small plasmids conferring antibiotic resistance in *Salmonella* strains were compared and were shown to be closely related to plasmids from *E. coli* and other pathogens that cause gastrointestinal illness. Impact: This sequence information was used to design probes for a microarray chip for typing and characterizing multi-resistance genes/plasmids. A DNA microarray to detect 100 resistance genes was successfully tested and has now been expanded to detect 775 resistance and virulence genes simultaneously.

**PROJECT TITLE: ASSESS THE EFFECTS OF TEMPERATURE ON THE SURVIVAL OF RESISTANT VERSUS SENSITIVE BACTERIA**

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** A pan-susceptible and multiple-resistant strains were compared for their ability to survive following challenge of poultry exposed to various temperatures.
- **2008 Update:** Research has been conducted to look at the effect of temperature on various bacteria not only in animals, but also in culturing methods.

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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***

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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*.
- **2008 Update:** Scientists determined the capability of a poultry feed additive, known as flavophospholipol, to inhibit the spread of genetic information from one *E. coli* to another in living poultry. The studies used chicks inoculated with *E. coli*, and established that the additive did not prevent the bacteria from sharing genetic information. Impact: Although flavophospholipol demonstrated no useful biochemical actions, the work is important because it provides scientific data on feed additive interactions with poultry microorganisms. Ongoing work may be successful in identifying practical means to inhibit bacterial conjugation in animals and reduce the threat posed by the antibiotic resistance phenomenon. 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.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Completed. Results indicate that a majority of the isolates were susceptible to the antimicrobials tested. Reporting of the results is ongoing in a variety of formats.

**PROJECT TITLE: TO INCREASE RECOVERY OF *CAMPYLOBACTER* FROM VARIOUS SOURCES**



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- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Because of the fastidious nature of *Campylobacter*, recovery from meat and other sources is difficult. We developed an enhanced method 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 under-reporting of *Campylobacter* in samples. This work will be useful to scientists involved in *Campylobacter* research.
- **2008 Update:** Ongoing- Continual research on various *Campylobacter* sp. methods.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** In this study, mechanisms of streptogramin resistance in enterococci from animals and the environment were investigated. From 2000-2004, enterococci were isolated from poultry carcass rinsates, fruits, vegetables, retail meats, environmental rinsates, and from swine and cattle fecal samples collected on farms.
- **2008 Update:** 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. Ongoing in conjunction with NARMS.

**PROJECT TITLE: CHARACTERIZE AMINOGLYCOSIDE RESISTANCE AMONG ENTEROCOCCI ISOLATED FROM POULTRY**

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** Aminoglycoside antimicrobials are of interest due to their use in both animals and humans.
- **2008 Update:** 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

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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. Ongoing in conjunction with NARMS.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** We characterized the strains and resistance mechanisms of 3rd generation cephalosporin resistant *Salmonella* in the United States.
- **2008 Update:** Ongoing in conjunction with NARMS. 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.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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

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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. Ongoing as studies are being designed.

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

- **Action Item(s):** #67
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Ongoing.

**PROJECT TITLE: INTERACTION BETWEEN PROTOZOA AND RESISTANCE BACTERIA AND ITS EFFECT ON ANTIMICROBIAL RESISTANCE**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** USDA
- **Description:** Protozoa in the environment are known to consume pathogenic bacteria and are believed to contribute to their survival and distribution. Understanding this relationship requires a method to locate and identify such protozoa. ARS scientists labeled a strain of disease-causing *E. coli* bacteria with a green fluorescent protein to identify and sort protozoa that ingest these bacteria. Application of this method to environmental samples should allow us to identify disease harboring protozoa and may aid in on-farm foodborne pathogen control. Research in FY 2008 is continuing in a broader scope to better understand the role of protozoa, pathogenic bacteria, and potentially antimicrobial resistance. For example, ARS scientists observed a rapid consumption of *E. coli* O157:H7 by protozoa in wastewater from dairy lagoons. These protozoa were characterized using 18S rRNA sequencing. An understanding of the biological and environmental factors responsible for the survival of *E. coli* O157:H7 will help in developing on-farm pathogen control strategies, and may help in the understanding of resistance persistence and transfer.

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- **2008 Update:** *Salmonella* spp. have a 44 gene integron structure, designated *Salmonella* Genomic Island 1 (SGI1) that are multi-drug resistant. Research showed that SGI1 also promotes a hypervirulent phenotype of *Salmonella* residing in protozoa of the bovine rumen. Furthermore, studies showed that *Salmonella* can acquire antibiotic resistance from co-existing bacteria in rumen protozoa. Elevated pathogenicity and acquisition of antibiotic resistance by multi-resistant *Salmonella*, such as DT104, are significant since DT104 is associated with increased cattle mortality and human morbidity. Impact: This research provides new knowledge about the potential interaction between antimicrobial resistance and virulence in *Salmonella* in cattle. These findings also begin to elucidate the role of protozoa in the increased pathogenicity of *Salmonella* and their potential role in antimicrobial resistance transference. Interventions focused on eliminating rumen protozoa may have an effect on *Salmonella* prevalence, virulence, and antimicrobial resistance.

**PROJECT TITLE: EVALUATION OF THE HYPOTHESIS THAT *MYCOPLASMA HOMINIS* INFECTION OF TRICHOMONADS CONTRIBUTES TO CLINICALLY RESISTANT TRICHOMONIASIS**

- **Action Item(s):** #67
- **Project Type:** New
- **Agency:** CDC
- **Description:** A 2006 publication (Xiao, et al., *Parasitol. Res.* 100:123-130) suggested that when *T. vaginalis* parasites are infected by *M. hominis*, resistance to metronidazole and other nitroimidazole drugs is increased. If true, this information provides both a potential marker and mechanism for combating antimicrobial resistant trichomoniasis.
- **2008 Update:** We did not find any evidence for increased prevalence of *M. hominis* in trichomonas isolates demonstrating clinical and/or in drug vitro resistance.

**ACTION ITEM #68**

**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**

- **Action Item(s):** #68
- **Project Type:** New
- **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

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- **2008 Update:** NIAID staff engage with the following national groups: the US Federal TB task Force; the Advisory Council for the Elimination of Tuberculosis (ACET); CDC's TB Clinical Trials Consortium and TB Epidemiologic Studies Consortium; the Infectious Disease Society of America and the American Thoracic Society. In addition, NIAID program staff are involved with these international groups: the STOP TB Vaccine Partnership's Diagnostic, Vaccine, Drug Development and HIV/TB Working Groups; WHO/TDR; the International Union against Tuberculosis and Lung Disease (IUATLD); the Global Alliance for TB Drug Development (GATB); the External Scientific Advisory Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds; the WHO Malaria Vaccine Advisory Committee; Aeras Global TB Vaccine Foundation; the Foundation for Innovative new Diagnostics; Lilly TB Drug Discovery Initiative; the Bill and Melinda Gates Foundation; the US-Indo Vaccine Action Program; and several European research consortia.

#### **PROJECT TITLE: NIAID MDR/XDR TB RESEARCH AGENDA**

- **Action Item(s):** #68
- **Project Type:** New
- **Agency:** NIH
- **Description:** In early 2007, NIAID convened a special session of the National Allergy and Infectious Diseases Advisory 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.
- **2008 Update:** In June 2007, NIAID published the MDR/XDR TB Research Agenda at: [http://www3.niaid.nih.gov/topics/tuberculosis/Research/PDF/MDRXDRTBResearchAgenda060607\\_tagged.pdf](http://www3.niaid.nih.gov/topics/tuberculosis/Research/PDF/MDRXDRTBResearchAgenda060607_tagged.pdf).

#### **ACTION ITEM #69**

#### **PROJECT TITLE: COMPREHENSIVE EXAMINATION OF THE ORGANIZATION AND FUNCTION OF THE NIH REVIEW PROCESS**

- **Action Item(s):** #69
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The Infectious Diseases and Microbiology IRG review by the Expert Working Group was conducted from May – August 2001 and resulted in the development of a proposed set of guidelines and shared interests for new study sections.
- **2008 Update:** NIH's CSR established the Drug Discovery and Mechanisms of Antimicrobial Resistance (DDR) Study Section within the new Infectious Diseases and Microbiology Integrated Review Group (IRG). It reviews applications concerned with the

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identification of novel antimicrobial agents, including agents that could be used in bioterrorism, with the prevention and treatment of infectious diseases; and with 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 FY2008, 245 applications were reviewed, of which 41 were awarded.

#### ACTION ITEM #70

##### **PROJECT TITLE: COMPARATIVE HYBRIDIZATION OF *C. DIFFICILE* STRAINS FROM HUMAN AND ANIMAL HOST ORIGINS**

- **Action Item(s):** #70
- **Project Type:** New
- **Agency:** CDC, NIH
- **Description:** NIH awarded development grants to Cornell University for creation of a *C. difficile*-specific microarray based on the two sequenced *C. difficile* genomes that are publicly available, and for the development of a *C. difficile* diagnostic array. CDC collaborated in development and testing of the microarrays by providing *C. difficile* strains of human and animal origin for genomic comparison, and by providing isolates of other *Clostridium* species for testing specificity of the diagnostic array.
- **2008 Update:** Two microarrays were developed, one for investigation of *C. difficile* genomics and one for *C. difficile* diagnosis. Ref. J Bacteriol. 2009 Jun;191(12):3881-91. Epub 2009 Apr 17.

##### **PROJECT TITLE: MICROBE PROJECT INTERAGENCY WORKING GROUP**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH, USDA, FDA, EPA, FDA
- **Description:** The Microbe Project Interagency Working Group coordinates microbial genomics activities across Federal government agencies.
- **2008 Update:** 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.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing

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- **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.
- **2008 Update:** This contract has significantly contributed to the selection of clinical vaccine candidates, several of which have recently entered human clinical trials and others of which are at various stages of preclinical development. In addition, research reagents from BSL3-grown mycobacteria, 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 Pathogen Functional Genomic Resource Center (PFGRC) for the production and dissemination of mycobacterial specific molecular reagents, with the NIH Tetramer Facility to provide mycobacterially relevant tetramers and with the Biodefense and Emerging Infections Research Resources Repository (BEI Resources) to broaden availability of research resources.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** This contract provides a selection of animal models that collectively reproduce the most critical features of human tuberculosis, as well as services to evaluate *M. tuberculosis* and *M. tuberculosis* mutants in mice, guinea pigs, and hollow fibers. These models make it possible to assess mutant strains for virulence and the capacity to induce acute, latent, or progressive tuberculosis. Ultimately, they will facilitate the validation of novel drugs, vaccine and diagnostic targets. This contract also provides transposon mutants either directly or through the tuberculosis research materials and vaccine testing contract (Colorado State University).
- **2008 Update:** This contract continues to serve as a critical component in the process to validate putative therapeutic and preventive targets in TB in animal hosts. In addition, the contract continues to develop new models that probe the progression of natural infection and identify biochemical pathways that are most suitable for pharmaceutical intervention.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH

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- **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.
- **2008 Update:** The number of organism-specific microarrays produced and distributed to the scientific community has increased to 33 in FY2008 and now includes arrays for viruses, bacteria, fungi, and parasites. The PFGRC has also developed the method and pipeline for generating organism-specific protein expression clones and has increased the throughput of the platform in 2008. Complete protein expression clone sets are now available for the following pathogens: *Bacillus anthracis*, *Francisella tularensis*, *Helicobacter pylori*, Human SARS coronavirus, *Mycobacterium tuberculosis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Vibrio cholera* and *Yersinia pestis*. In addition, a clone set for *Rickettsia prowazekii* was generated in collaboration with one of NIAID's Regional Centers of Excellence. Additional custom clone sets, which are made available upon request, have now been generated for more than 40 organisms, including human and avian influenza virus clone sets.

#### PROJECT TITLE: SEQUENCING OF WHOLE PATHOGEN GENOMES

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** NIAID has made significant investments 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.
- **2008 Update:** In FY2008, NIAID supported large scale genome sequencing projects for approximately 40 different pathogens. New projects include additional strains of Influenza, Coronaviruses, Brucella (109 strains), E. coli (52 strains), West Nile Viruses (300 strains), *Neisseria gonorrhoeae* (14 strains), Group A Streptococcus (81 strains), *Staphylococcus aureus* (57 strains), and filarial worms (3).

#### PROJECT TITLE: INFLUENZA GENOME SEQUENCING PROJECT

- **Action Item(s):** #70
- **Project Type:** Ongoing



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- **Agency:** NIH
- **Description:** This project puts influenza sequence data rapidly into the public domain, enabling scientists to further study how influenza viruses evolve, spread, and cause disease. 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.
- **2008 Update:** As of June 15, 2009, 3717 human and avian isolates have been completely sequenced and made available through GenBank. See <http://www.niaid.nih.gov/dmid/genomes/mscs/default.htm#influenza> for details.

#### PROJECT TITLE: NIAID PATHOGEN GENOMICS WEBSITE

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Currently available to the scientific community: <http://www3.niaid.nih.gov/topics/pathogenGenomics/>.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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 sharing of information, bacterial strains and reagents, as well as an annual conference of NIH funded researchers. The 10<sup>th</sup> Annual NARSA Investigator's Meeting was held on March 9 - 10, 2008 in Reston, Virginia. The repository has over two hundred strains of *S. aureus* including the first three identified VRSA isolates. Additional information is available at [www.narsa.net](http://www.narsa.net) and <http://www.niaid.nih.gov/dmid/antimicrob/>
- **2008 Update:** In 2007, NIAID reissued a seven year contract, Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA), to Eurofins Medinet, Inc. in Herndon,

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VA. NARSA currently supports 425 registered users: 228 from academia, 128 from industry, and 69 from government or other sectors. The repository houses 425 strains to date.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The goal of this program is to identify associations between specific immune response gene polymorphisms/genetic variations or polymorphisms in immune response genes and susceptibility to infection or response to vaccination with a focus on one or more of NIAID Category A-C pathogens and influenza.
- **2008 Update:** Ongoing.

**PROJECT TITLE: PROGRAM PROJECT GRANT “STRUCTURAL ORGANIZATION AND PROTEOMICS OF TB”**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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* continue under a program project grant.
- **2008 Update:** All data collated and produced by this consortium is publicly available online at [www.webtb.org](http://www.webtb.org). Targeted studies of mycobacterial proteins relevant for drug development are ongoing under this grant.

**PROJECT TITLE: STRUCTURAL GENOMICS OF PATHOGENIC PROTOZOA**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The Structural Genomics of Pathogenic Protozoa project (<http://depts.washington.edu/sgpp/>) includes studies to derive the three dimensional structure of proteins deduced from the trypanosomatid and Plasmodium genomes. This

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will be valuable information for future drug and vaccine discovery design, as well as for the discovery of new protein fold structures.

- **2008 Update:** 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 differ significantly from the human enzyme while remaining conserved among parasitic protozoa. These studies are ongoing.

#### **PROJECT TITLE: NIAID MICROBIAL SEQUENCING CENTERS**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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, including those considered agents of bioterrorism (NIAID category A-C priority list) and those responsible for emerging and re-emerging infectious diseases. Also eligible for sequencing at these centers are clinical isolates, non-pathogenic relatives of pathogenic organisms, and invertebrate vectors of disease.
- **2008 Update:** These Centers are responding to the sequencing priorities of the scientific community and federal agencies. Filling in these sequence gaps facilitates basic understanding of microbes, forensic strain identification, and identification of targets for drugs, vaccines and diagnostics. See <http://www.niaid.nih.gov/dmid/genomes/mscs/default.htm>.

#### **PROJECT TITLE: BIOINFORMATICS RESOURCE CENTERS**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** NIAID Bioinformatics Resource Centers are designed to develop, populate, and maintain comprehensive, relational databases to collect, store, display, annotate, query, and 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.
- **2008 Update:** Eight Centers were funded in FY04: <http://www.niaid.nih.gov/dmid/genomes/brc/default.htm>. In 2008, NIAID continued to support these centers. Ongoing activities include: development of publicly accessible BRC websites, improvement of public interfaces, and integration of a variety of genomic data types, including gene expression, proteomics, host/pathogen interactions, and signaling/metabolic pathways data. Visit <http://www.brc-central.org> for additional

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information. In FY2008, the National Microbial Pathogen Data Resource BRC (NMPDR <http://www.nmpdr.org/>) made available a computational server, RAST, which provides the scientific community with automated annotation of their bacterial genomes within 48 hours of submission to NMPDR.

#### **PROJECT TITLE: BIODEFENSE PROTEOMICS RESEARCH CENTERS**

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Seven Centers were funded in 2004: <http://www.niaid.nih.gov/dmid/genomes/prc/default.htm>. In FY 2008 an additional 2 SARS-CoV 3D protein structures were solved. As of FY2007 more than 7900 potential new pathogen targets and more than 11,700 potential host targets had been identified. During FY2008, more than 10,900 new potential pathogen targets and over 700 new potential host proteins were identified. In FY2009 24 protein interactions related to *Salmonella* pathogenesis were identified and several hundred human-pathogen interactions were identified for *Bacillus anthracis*, *Francisella tularensis*, *Yersinia pestis* and *Vaccinia* virus.

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

- **Action Item(s):** #70 and #78
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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. The facility website is <http://www.taacf.org/> where data and publications from this activity are posted.

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

- **Action Item(s):** #70 and #78
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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.

**PROJECT TITLE: NIAID RESOURCES FOR RESEARCHERS**

- **Action Item:** #70, #78, and #80
- **Project Type:** New
- **Agency:** NIH
- **Description:** NIAID provides a comprehensive set of services to facilitate efforts to develop the next generation of vaccines, diagnostics, and therapeutics. These services make needed expertise as well as standardized, high-quality research materials and state-of-the art technologies available to eligible investigators worldwide. Provision of these pre-clinical and clinical services to drug development entities should stimulate the development of novel antimicrobial products by offsetting the risks inherent in antimicrobial development.
- **2008 Update:** Descriptions and links to these services can be found at: <http://www3.niaid.nih.gov/LabsAndResources/resources/>.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **Agency:** USDA

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- **Description:** Research to determine the in vitro activity (i.e., MICs) of citrus oil fractions for *Salmonella* spp., and to measure the effectiveness and economics of implementing this novel treatment in 2 process interventions.
- **2008 Update:** Ongoing research. Funded by CSREES, National Research Initiative (University of Arkansas). See CSREES website.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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).
- **2008 Update:** Research has revealed that bacterial stress in *Salmonella* induces mutations resulting in resistance to 5 different antibiotics. Studies were performed to evaluate the genetic expression patterns of a multiple antibiotic resistant isolate of *Salmonella enterica* derived during antibiotic exposure from a wild type strain. Many important genetic systems were modified in the mutant isolate compared to its parent strain. These included porins, lipopolysaccharides, efflux pumps, and global regulatory mechanisms. Impact: Elucidation of these genetic mechanisms that may contribute to antibiotic resistance will allow researchers to design and test better treatments, as well as determine alternative drugs or adjuvants, such as the efflux pump inhibitory chemicals. 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.

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

- **Action Item(s):** #70
- **Project Type:** Ongoing
- **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).
- **2008 Update:** Ongoing. Genomic analysis has been done on several outbreak strains of *Campylobacter* spp and compared with animal samples. This has been in done with collaboration with Departments of Health and Agriculture. Additional analytic methods are being developed.

#### **PROJECT TITLE: COMPARATIVE GENOMIC ANALYSIS OF LISTERIA SUBTYPES**

- **Action Item(s):** #70

Last revised: December 29, 2009

- **Project Type:** Ongoing
- **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).
- **2008 Update:** Ongoing. Comparative genomic analysis has been done on *Listeria* subtypes from foodborne outbreaks (animal, food, and human). Publication has occurred and this data has been transferred to requesting agencies.

#### ACTION ITEM #71

#### PROJECT TITLE: COLLABORATION ON GENOMICS TECHNOLOGIES AND RESOURCES

- **Action Item(s):** #71
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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.

#### PROJECT TITLE: REAGENT DEVELOPMENT

- **Action Item(s):** #71
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Facilitation of research through reagent development for the scientific community: Pertussis, *H. influenzae*, TB, influenza and *S. pneumoniae*.
- **2008 Update:** 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

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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

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

- **Action Item(s):** #72
- **Project Type:** Ongoing
- **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.
- **2008 Update:** PAR 09-068 was released in December 2008 (see: <http://grants.nih.gov/grants/guide/pa-files/PAR-09-068.html>).

##### **PROJECT TITLE: OTHER ONGOING TRAINING AND RESEARCH FELLOWSHIP AWARDS**

- **Action Item(s):** #72
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** NIAID continues to support young scientists and clinical investigators through National Research Service Awards and various types of career development awards, including: Mentored Research Scientist Award (K01), Independent Scientist Award (K02), Mentored Clinical Scientist Development Award (K08), Mentored Patient Oriented Research Career Development Award (K23), Mid-career Investigator Award in Patient Oriented Research (K24) and NIH Pathway to Independence Award (K99).
- **2008 Update:** Examples of projects awarded in 2008 include: (1) Epidemiology of resistant bacteria in acute-care and long-term care facilities, (2) Social Networks and the Spread of Influenza and other Nosocomial Infections and (3) A longitudinal Study of CA-MRSA Nasal Colonization in College Sports Participants.

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

- **Action Item(s):** #72
- **Project Type:** Ongoing



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- **Agency:** NIH
- **Description:** 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.
- **2008 Update:** In 2008 NIH awarded a number of R21 projects focused on antimicrobial resistance mechanisms and the early development of vaccines, diagnostics and antimicrobial drugs for a broad range of resistant pathogens. Examples of R21 projects awarded in 2008 include: (1) Impact of Fluoroquinolone resistance on *Pseudomonas* virulence and patient outcome, (2) Impact of ARV Chemoprophylaxis on Emergence and Spread of HIV Drug Resistance and (3) High throughput screening for anti-fungal drugs that inhibit mRNA polyadenylation.

#### ACTION ITEM #73

#### PROJECT TITLE: NIH SUPPORT FOR CONFERENCES AND SCIENTIFIC MEETINGS

- **Action Item(s):** #73
- **Project Type:** New
- **Agency:** NIH
- **Description:** The purpose of the NIH Research Conference Grant Program (R13 and U13) is to support high quality conferences/scientific meetings that are relevant to the scientific mission of the NIH and to the public health. A conference/scientific meeting is defined as a gathering, symposium, seminar, scientific meeting, workshop or any other organized, formal meeting where persons assemble to coordinate, exchange, and disseminate information or to explore or clarify a defined subject, problem, or area of knowledge.
- **2008 Update:** The following conference grants enabling scientific meetings on topics of relevance to antimicrobial resistance were awarded in 2008: (1) Pathogenesis and Control of Emerging Infections and Drug Resistant Organisms, (2) Computer-Aided Drug Design and (3) International conference on Gram-Positive Pathogens.

#### PROJECT TITLE: ANTIBIOTIC RESISTANCE CONFERENCE

- **Action Item(s):** #73
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** USDA-CSREES and Ohio State University co-sponsored the conference on "Food Safety and Public Health Frontier: Minimizing Antibiotic Resistance Transmission through the Food Chain", which brought together experts from academia, industry and federal agencies to provide a balanced and scientific review on antibiotic resistance.

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Over 20 senior experts shared their most up-to-date discoveries and vision on antibiotic management through oral presentations, and over 80 attendees participated in the ensuing open discussion. A conference report detailing recommendations for future research on antibiotic resistance is under development.

- **2008 Update:** Ongoing research. Funded by CSREES, National Integrated Food Safety Initiative (Ohio State University). See CSREES website.

#### ACTION ITEM #74

#### **PROJECT TITLE: PHARMACOLOGICAL APPROACHES TO COMBATING ANTIMICROBIAL RESISTANCE (R01) TARGETED INITIATIVE (RFA-AI-07-025)**

- **Action Item:** # 74 and #67
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** This solicitation invited Research Project Grant (R01) applications from institutions/organizations proposing 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.
- **2008 Update:** Examples of awards made under this RFA include: (1) PK-PD of combination antituberculosis therapy for suppression of drug-resistance, (2) Resistance Suppression for *Pseudomonas aeruginosa* using Novel Combination Therapy Modeling and (3) Pharmacologic Approaches to Combating Resistance to Antimalarial Compounds.

#### **PROJECT TITLE: PHARMACOKINETICS AND PHARMACODYNAMICS ANIMAL MODEL CONTRACT**

- **Action Item(s):** #74 and #70
- **Project Type:** Ongoing
- **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.

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- **2008 Update:** 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.

#### ACTION ITEM #75

#### PROJECT TITLE: INVESTIGATION OF FLUOROQUINOLONE RESTRICTION FOR CONTROL OF CLOSTRIDIUM DIFFICILE IN A HOSPITAL SETTING

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** CDC
- **Description:** The emergence of the NAP1 epidemic strain of *C. difficile* appears to have been driven largely by fluoroquinolone overuse in healthcare settings. We investigated an outbreak in a healthcare setting that implemented a complete ban on all fluoroquinolone antibiotics in an attempt to control and outbreak in their hospital caused by the NAP1 strain. All *C. difficile* toxin-positive stools from the time period before, during and after the outbreak were cultured for *C. difficile*, and isolates from each time period were characterized by PFGE, characterization of the pathogenicity locus, PCR for binary toxin, and antimicrobial susceptibility testing.
- **2008 Update:** Organism recovery and isolate characterization completed. Patients infected with the NAP1 epidemic strain were more likely to have received a fluoroquinolone than those patients infected with other strains. Ref: Infect Control Hosp Epidemiol. 2009 Mar;30(3):264-72.

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

- **Action Item(s):** #75
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** Numerous trials are underway related to prevention and treatment of HIV-TB co-infected patients as well as monitoring for TB 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>." Sok Thim, "A Cambodian Clinical Research Network for HIV/TB" (CIPRA). AIDS Clinical Trials Group (ACTG) 5221 "A strategy study of

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immediate versus deferred initiation of ART for AIDS disease-free survival in HIV-infected persons treated for TB with CD4<250 cells/mm<sup>3</sup>".

- **2008 Update:** These studies will help inform standard of care for optimizing treatment of HIV-TB co-infected individuals.

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

- **Action Item(s):** #75
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The TBRU contract was recompeted in 2007 and awarded again to Case Western Reserve University. Development of surrogate markers of disease and human protective immunity will continue. In addition, activities under this contract will now 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.
- **2008 Update:** Information about ongoing TBRU supported studies can be found at: <http://www.tbresearchunit.org>.

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

- **Action Item(s):** #75
- **Project Type:** Completed
- **Agency:** NIH
- **Description:** The BAMSG and BAMBU 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.
- **2008 Update:** All studies have been completed. The results of the BAMSG study can be found in the following publication: Pappas PG et. al, Clinical Infectious Diseases 2009; 48:1775–83.

**PROJECT TITLE: VACCINE AND TREATMENT EVALUATION UNITS (VTEUS)**

- **Action Item(s):** #75
- **Project Type:** Ongoing
- **Agency:** NIH

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- **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.
- **2008 Update:** “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” was initiated in 2008. Enrollment is underway.

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

- **Action Item(s): #75**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** A natural history clinical research protocol, initiated in 2006 at the Masan National Tuberculosis Hospital in South Korea, has enrolled more than 700 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 trial of metronidazole therapy for pulmonary tuberculosis initiated in 2007 has enrolled nearly 30 volunteers. IRB and US and Korean FDA approvals have been received for a new protocol “A Phase 2a, Randomized, Two Arm, Open-label, Clinical Trial of the Efficacy of Linezolid Combined with Antituberculous Therapy in Subjects with Extensively Drug-Resistant (XDR) Pulmonary Tuberculosis.”

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

- **Action Item(s): #75**

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- **Project Type:** Ongoing
- **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.
- **2008 Update** A clinical trial to evaluate the impact of a GBS vaccine on GBS colonization has been completed and the final study report is under development.

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

- **Action Item(s):** #75
- **Project Type:** Ongoing
- **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 4 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.
- **2008 Update:** Protocol has been reviewed and approved by NIH Office of Clinical Research Affairs and Office of Regulatory Affairs, and is under review by the CDC and site institutional review boards.

**PROJECT TITLE: EMERGENCE OF HEPATITIS B VIRUS MUTANTS IN HIV AND HBV CO-INFECTED WOMEN TREATED WITH LAMUVIDINE**

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** CDC, Ministry of Public Health, Thailand
- **Description:** Between 2005 and 2007, 217 HIV-infected women received GPOvir, containing zidovudine, 3TC and nevirapine (NVP), for 48 weeks to evaluate the impact of previous NVP exposure on clinical and virologic responses. From these patients, the prevalence and emergence of HBV mutations are being evaluated.
- **2008 Update:** Baseline serologies completed.

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**PROJECT TITLE: CHARACTERIZATION OF CHANGES IN THE HBV GENOME CARRIED BY PATIENTS WITH CHRONIC HEPATITIS B AND RECIPIENTS OF ORTHOTOPIC LIVER TRANSPLANTATIONS**

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** CDC, University of Michigan Medical Center
- **Description:** Serum samples collected serially from patients enrolled in the NIH HBV Orthotopic Liver Transplantation Study (n=50) and from hepatitis B patients receiving antiviral treatment at the Liver Clinic, University of Michigan (n=50) are characterized to determine if they carry HBV with drug-resistant mutations in the reverse transcriptase region of the HBV polymerase. They are then sent to CDC for whole-genome characterization of HBV including that of HBV quasispecies constituents, and for studies into changes in antibody affinity and secretion of HBsAg.
- **2008 Update:** Baseline sequencing completed.

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

- **Action Item(s):** #75
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Two contracts were awarded in 2007: one to University of California San Francisco entitled "Randomized, Double-Blind Trial of Clindamycin, Trimethoprim-Sulfamethoxazole, or Placebo for Uncomplicated Skin and Soft Tissue Infections Caused by Community-Associated Methicillin-Resistant *Staphylococcus aureus*" and one to Olive View University of California Los Angeles entitled "Strategies using Off-Patent antibiotics for Methicillin-Resistant *Staphylococcus aureus*" ("STOP MRSA") – a multi-center, randomized, double-blind clinical trial. Enrollment for these studies began in 2008.

**PROJECT TITLE: A LONGITUDINAL STUDY OF CHLOROQUINE AS MONOTHERAPY OR IN COMBINATION WITH ARTESUNATE, AZITHROMYCIN OR ATOVAQUONE-PROGUANIL TO TREAT MALARIA IN CHILDREN IN BLANTYRE**

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** NIH

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- **Description:** NIAID is supporting a longitudinal study of chloroquine as monotherapy or in combination with artesunate, azithromycin or atovaquone-proguanil to treat malaria in children in Blantyre, Malawi. These studies are needed to identify the pharmacokinetic and pharmacodynamic properties of drug combinations that will deter resistance and prolong the useful therapeutic life of the next generation of antimalarial drug combinations.
- **2008 Update:** The trial is ongoing; results expected in 2009.

**PROJECT TITLE: PHASE I CLINICAL TRIAL UNIT FOR THERAPEUTICS AGAINST INFECTIOUS DISEASES (REQUEST FOR PROPOSALS RFP-NIH-NIAID-DMID-08-06)**

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** NIH
- **Description:** The purpose of this program is to provide a dedicated resource to assess the safety of investigational therapeutic products for a variety of infectious diseases. Using this resource, investigators may submit proposals for Phase I clinical trials to their scientific Program Officers.  
<http://www3.niaid.nih.gov/LabsAndResources/resources/dmid/phasetherap/>
- **2008 Update:** The solicitation for this program was issued in 2007. In 2008, contracts were awarded to DynPort Vaccine Company (with a clinical site at the Quintiles Phase I Unit in Overland Park, Kansas) or Clinical Research Management (with clinical sites at Johns Hopkins University in Baltimore and Case Western Reserve University in Cleveland, Ohio). The process of selecting clinical projects to be conducted at the study sites from the research community also began in 2008, and resulted in the launch of a Phase Ib study evaluating a promising new anti-TB drug, SQ109 in 2009.

**PROJECT TITLE: TARGETED CLINICAL TRIALS TO REDUCE THE RISK OF ANIMICROBIAL RESISTANCE**

- **Action Item(s):** #75
- **Project Type:** New
- **Agency:** NIH
- **Description:** This Broad Agency Announcement (BAA-NIAID-DMID-NIHAI2008025) targets infectious diseases where improved treatment strategies could reduce the risk of antimicrobial resistance and preserve the effectiveness of existing antimicrobials. A central goal of this solicitation is to target disease areas experiencing the greatest antimicrobial selective pressure, and within these areas, develop strategies that test the safety and effectiveness of different therapeutic approaches/regimens that reduce the probability of the emergence of drug resistance by minimizing unnecessary drug exposure.



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- **2008 Update:** The solicitation for proposals under this BAA was released in April of 2008. Contracts will be awarded in 2009.

**PROJECT TITLE: AIDS CLINICAL TRIALS GROUP**

- **Action item(s): #75**
- **Project type:** ongoing
- **Agency:** NIH
- **Description:** The ACTG was initially established in 1987 to broaden the scope of the AIDS research effort of the National Institute of Allergy and Infectious Diseases (NIAID). The ACTG established and supports the largest Network of expert clinical and translational investigators and therapeutic clinical trials units in the world, including sites in resource-limited countries. These investigators and units serve as the major resource for HIV/AIDS research, treatment, care, and training/education in their communities.
- **2008 Update:** Numerous clinical trials testing novel therapeutics and novel combination therapies, as well as their relationship to the emergence of resistant HIV strains, are ongoing. For more information, visit [www.aactg.org/](http://www.aactg.org/).

**PROJECT TITLE: VA RESEARCH UPDATE**

- **Action Item(s): #75**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** 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 remained stable with a continued medical service research portfolio of breadth and depth. Proposed funding for FY 2009 also remains stable with a diverse portfolio of projects.

**ACTION ITEM #76**

**PROJECT TITLE: DETECTION AND EPIDEMIOLOGY OF CARBAPENEMASE-PRODUCING GRAM-NEGATIVE BACTERIA**

- **Action Item(s): #76**

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- **Project Type:** New
- **Agency:** CDC
- **Description:** Carbapenemase-producing gram-negative bacilli harbor a mobile broad-spectrum  $\beta$ -lactamase, which constitute a serious treatment and infection control concern. Studies were conducted at CDC to (1) evaluate current susceptibility testing methods for detection of carbapenemase-mediated resistance, (2) develop and evaluate novel methods for detection of carbapenemase-mediated resistance, and (3) describe the molecular epidemiology of the resistant isolates to understand mechanisms of transmission and to develop prevention strategies.
- **2008 Update:** (A) A study was conducted to evaluate commonly used antimicrobial susceptibility testing methods for detection of carbapenemase-mediated resistance. Many methods failed to detect resistance and strategies to overcome these limitations were recommended. These results were published in a clinical microbiology journal. (B) A multicenter evaluation of a phenotypic assay for detection of carbapenemase-mediated resistance was performed. This study was designed for placement of the phenotypic test in an international susceptibility testing guideline. (C) Studies were initiated to examine the molecular epidemiology of carbapenemase-producing Enterobacteriaceae.

**PROJECT TITLE: DETECTION AND EPIDEMIOLOGY OF EMERGING ANTIMICROBIAL RESISTANCE IN STAPHYLOCOCCUS AUREUS**

- **Action Item:** #76
- **Project Type:** New
- **Agency:** CDC
- **Description:** To improve detection and prevention of emerging antimicrobial resistance in *S. aureus*, studies were conducted to (1) evaluate commonly used methods for detecting antimicrobial resistance, (2) develop and evaluate novel methods for detection of resistance, and (3) describe the molecular epidemiology of resistant isolates to develop effective prevention strategies.
- **2008 Update:** (A) A study was conducted to evaluate commonly used susceptibility testing methods for detection of vancomycin intermediate *S. aureus*. (B) Studies were initiated to validate a disk diffusion test to detect resistance to mupirocin, an antimicrobial agent used for nasal MRSA decolonization of patients. (C) A plasmid associated with transfer of vancomycin resistance between *Enterococcus* and *S. aureus* was identified and a surveillance study was conducted to identify the prevalence and geographic distribution of *Enterococcus* with these plasmids. This information will be used to predict and prevent vancomycin resistance in *S. aureus*. (D) Surveillance isolates of USA300, the epidemic strain of MRSA which commonly causes community MRSA infection in the U.S. were examined for the presence of new or emerging antimicrobial resistance. An epidemiological study was conducted to describe isolates and patients infected with these isolates.

**PROJECT TITLE: COMPARISON OF METHODS FOR STRAIN TYPING OF (METHICILLIN-RESISTANT) STAPHYLOCOCCUS AUREUS**

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- **Action Item(s): #76**
- **Project Type:** New
- **Agency:** CDC
- **Description:** PFGE, the method used routinely at CDC to type isolates from healthcare-associated infections, has significant limitations. Sequence-based typing methods, including *spa* typing and the T500 PCR-mass spectroscopy assay, will be evaluated for utility in investigating outbreaks and staphylococcal evolution, and for cost, ease of use, and reproducibility. Goals are to determine concordance of results obtained with different methods, and to establish a plan for transitioning MRSA strain typing to the most robust and reliable method.
- **2008 Update:** Project planned, timeline established, earliest testing in progress.

**PROJECT TITLE: EVALUATION OF THE SPECTRACELL INSTRUMENT FOR STRAIN TYPING OF HEALTHCARE-ASSOCIATED PATHOGENS, MRSA AND *ACINETOBACTER BAUMANNII***

- **Action Item(s): #76**
- **Project Type:** New
- **Agency:** CDC
- **Description:** PFGE, the method used at CDC to type MRSA strains, has limitations for the strain typing of certain organisms, and is time-intensive and expensive to perform. The recently developed SpectraCell instrument uses RAMAN spectroscopy to directly assay intact bacterial cells, requiring approx. 1 min per isolate. Goals are to determine concordance of results obtained with different methods, and to establish a plan for transitioning strain typing to the most robust and reliable method.
- **2008 Update:** Project planned, timeline established, MRSA testing started.

**PROJECT TITLE: ANTIMICROBIAL SUSCEPTIBILITY TESTING (AST) PRACTICES IN SIX STATES: RESULTS OF THE NATIONAL LABORATORY SYSTEM (NLS) ASSESSMENT**

- **Action Item(s): #76**
- **Project Type:** New
- **Agency:** CDC
- **Description:** In collaboration with CDC, six states performed an initial assessment of AST practices. This effort was a part of the NLS cooperative agreement (CoAg) initiative to integrate clinical laboratories into public health testing. The CoAg partners, Wisconsin, Nebraska and Montana led the effort. Montana worked in collaboration with other states in the Northern Plains Consortium (North Dakota, South Dakota, and Wyoming). All laboratories performing AST in each state were asked to participate; the response rate was 76.5% (231/302). The assessment included information on demographics, methods used, practices, training, and knowledge of CLSI recommendations for AST practices.

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Subsequently, the states conducted targeted training and offered resources for ongoing AST consultation.

- **2008 Update:** The descriptive results reflected the demographics of the region: the majority of the participant laboratories were from non-profit hospitals having fewer than 200 beds, although other lab- types were represented. The mean annual testing volume was 2528; median was 898. Only 62% of respondents obtained CLSI guidelines annually. Of nine practice- based questions, only 47.2% of the laboratories answered more than half of the questions correctly. The participants cited the need for more training and consultation with state public health laboratories. As a result of this assessment, other NLS initiative activities, and the recognized need for stronger and ongoing interaction between clinical laboratories and public health laboratories, the states involved have established networks to provide ongoing collaboration and consultation on AST. Using the results of this assessment, the participating states have conducted targeted training based upon the needs of laboratories within their state or network. A follow-up post-intervention assessment is being conducted this year (2009), with plans to compare the results.

#### **PROJECT TITLE: NEW DIAGNOSTICS FOR HIV DRUG RESISTANCE SCREENING**

- **Action Item(s):** #76
- **Project Type:** New
- **Agency:** CDC
- **Description:** The CDC DHAP Laboratory continues to develop and assess methods with improved sensitivity and cost-efficiency for testing drug resistance markers in HIV. One goal is that these methods eventually could be used to augment national HIV drug resistance surveillance to better estimate transmitted drug-resistant HIV.
- **2008 Update:** A seminal Laboratory Branch paper on the prevalence and clinical impact of transmitted drug resistance at low levels was published in 2008 (Johnson et al., PLoS Medicine). As a result, as of 2008, two international public health laboratories (in London and Tokyo) have adopted the sensitive resistance tests, and other sites in Thailand and Africa have expressed an interest in acquiring the method. Development and evaluation of new tests for other mutations and subtypes continues.

#### **PROJECT TITLE: PARTNERSHIPS TO IMPROVE DIAGNOSIS AND TREATMENT OF SELECTED DRUG-RESISTANT HEALTHCARE-ASSOCIATED INFECTIONS (RFA-AI-06-036)**

- **Action Item(s):** #76
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** The purpose of the initiative is to support the development of rapid diagnostics capable of identifying specific bacterial strains and drug resistant phenotypes and treatment for the following healthcare-associated pathogens: *Clostridium difficile*,

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*Pseudomonas*, *Acinetobacter*, *Klebsiella*, *Serratia*, *Proteus*, *Enterobacter* and *Stenotrophomonas*. Four cooperative agreements (U01) were awarded in 2007.

- **2008 Update:** In 2008, NIAID continued to support the following projects: (1) Tailoring Novel Therapeutics for Emerging Drug-Resistant *C. Difficile* Colitis, (2) Sensor Technology for Rapid Microbial Identification and Susceptibility Testing, (3) Resequencing microarray for rapid detection & antimicrobial resistance profiling and (4) Development of an antimicrobial peptide therapeutic for *Pseudomonas* infections.

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

- **Action Item(s):** #76
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** An automated ribotyping system is being used at ARS 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.
- **2008 Update:** Ongoing. The database continues to be updated.

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

- **Action Item(s):** #76
- **Project Type:** Ongoing
- **Agency:** USDA
- **Description:** A new typing technique based on genomics is being developed that detects genes specific for *Salmonella* serotypes by multiplex PCR.
- **2008 Update:** 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. This method continues to be modified and validated.

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#### PROJECT TITLE: VACCINE RESEARCH

- **Action Item(s):** #77 and #81
- **Project Type:** Ongoing
- **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*.
- **2008 Update:** Fifteen ongoing research projects support development of vaccines for the organisms listed.

#### PROJECT TITLE: STAPHYLOCOCCAL VACCINE GROUP

- **Action Item(s):** #77 and #81
- **Project Type:** New
- **Agency:** FDA
- **Description:** Conduct research and provide guidance for the evaluation of multiple proposed vaccine candidates to advance the public health effort to develop effective vaccines to prevent staphylococcal disease.
- **2008 Update:** Research program initiated involving several investigators with expertise in Gram-positive bacterial genetics, animal modeling of infectious diseases, protein chemistry, and assay design and development. Under this program investigators will generate purified, recombinant forms of *S. aureus* vaccine candidates, as well as develop immunoassays to investigate vaccine-induced immune responses.

#### PROJECT TITLE: VACCINE RESEARCH - PNEUMOCOCCAL CONJUGATE VACCINE

- **Action Item(s):** #77 and #81
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Conduct research and provide guidance to support licensure of additional pneumococcal vaccines (various products under IND). Collaborative research project to develop pneumococcal reference sera. Provide expertise and guidance to facilitate development and licensure of new pneumococcal vaccines.
- **2008 Update:** Research regarding serologic assessment of response to vaccines ongoing. Collection and testing of serum for new reference completed resulting in 15,333 lyophilized 6 ml vials. Protocol for collaborative study to bridge new reference to existing reference under development.

**PROJECT TITLE: VACCINE DEVELOPMENT - TB**

- **Action Item(s):** #77, #80, and #81
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Conduct research in support of the development of vaccines to prevent colonization, infection, and transmission of tuberculosis. Provide expertise and guidance to facilitate development and licensure of TB vaccines.
- **2008 Update:** Current projects investigate the following vaccine candidates in mouse model of tuberculosis: novel recombinant BCG vaccines, 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. Collaborations include the Albert Einstein College of Medicine and the University of Maryland. Participated in meetings and workshops to address clinical trial design and development plans (Geneva, Tanzania).

**PROJECT TITLE: MENINGITIS VACCINE PROJECT (MVP)**

- **Action Item(s):** #77, #80, and #82
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** MVP is a combined WHO Program for Appropriate Technology in Health (PATH) project to develop affordable meningococcal conjugate vaccines for Africa.
- **2008 Update:** CBER-PATH Cooperative Research and Development (CRADA) resulted in development of novel efficient conjugation technology and technology 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 Gates Foundation) will develop a vaccine that is critically needed in Africa.

**PROJECT TITLE: DRUG THERAPY**

- **Action Item(s):** #77
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Research: novel targets for drug therapy (to avoid resistance).
- **2008 Update:** Two ongoing projects that examine the mechanisms of development of HIV drug resistance.

**PROJECT TITLE: FACILITATION OF MALARIA VACCINE DEVELOPMENT**

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- **Action Item(s):** #77, #80, #81 and #82
- **Project Type:** New
- **Agency:** FDA
- **Description:** Conduct research in support of the development of vaccines to prevent malaria. Provide expertise and guidance to facilitate development and licensure of malaria vaccines.
- **2008 Update:** Research resulted in: development of a novel TB-malaria co-infection model, and identified potential bio-markers of cerebral malaria. Participated in an NIAID/Malaria Vaccine Initiative meeting on human challenge models. Participation in the EC/EMVI/WHO EURHAVAC Workshop "Safety Harmonisation in Pre-Licensure Clinical Trials" Brussels October 2008.

#### **PROJECT TITLE: BACTERIAL RESPIRATORY PATHOGEN RESEARCH UNIT (BRPRU)**

- **Action Item(s):** #77
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** This project supports bacterial pre-clinical and clinical studies for the diagnosis, prevention, and management of selected human bacterial respiratory pathogens.
- **2008 Update:** 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*.

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

- **Action Item(s):** #77
- **Project Type:** Ongoing
- **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.
- **2008 Update:** This contract has significantly contributed to the selection of clinical vaccine candidates, several of which have recently entered human clinical trials and others of which are in various stages of preclinical development. In addition, research reagents from BSL3-grown mycobacteria, 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 Pathogen Functional



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Genomic Resource Center (PFGRC) for the production and dissemination of mycobacterial specific molecular reagents, with the NIH Tetramer Facility to provide mycobacterially relevant tetramers and with the Biodefense and Emerging Infections Research Resources Repository (BEI Resources) to broaden availability of research resources.

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

- **Action Item(s): #77**
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Final analysis of the trials will be completed in 2009.

**PROJECT TITLE: PHASE I MALARIA VACCINE TRIALS IN USA**

- **Action Item(s): #77**
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** Phase I Malaria vaccine trials in USA
- **2008 Update:** 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.

**ACTION ITEM #78**

**PROJECT TITLE: TB TRIALS CONSORTIUM (TBTC)**

- **Action Item(s): #78 and #75**
- **Project Type:** Ongoing
- **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

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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).

- **2008 Update:** Study 30 - In 2008, in collaboration with investigators at the University of KwaZulu Natal in Durban, South Africa, we developed a protocol, manual of operations and case report forms for TBTC Study 30 (A phase I/II pilot study for evaluation of low-dose, once-daily linezolid plus optimized background therapy (OBT) versus placebo plus OBT for the treatment of multi-drug resistant tuberculosis). We submitted an investigational new drug (IND) application to use linezolid in the treatment of resistant tuberculosis and received approval from the U.S. Food and Drug Administration (FDA). The protocol was also approved by CDC and local IRBs. Linezolid was donated by Pfizer Pharmaceuticals and a blinded placebo was created by Bilcare Pharmaceutical Services. The South African Medicines Control Council, a regulatory body similar to the U.S. FDA, required eight months to review and approve this protocol. This delayed the commencement of enrollment well into 2009. This study has now begun enrolling. It will include the evaluation of the potential development of resistance to tuberculosis during treatment and whether the mycobacterial isolate's baseline sensitivity to linezolid, as measured by the minimum inhibitory concentration, impacts the effectiveness of linezolid.

#### PROJECT TITLE: SUBMISSION OF COMPOUNDS FOR IN VITRO EVALUATION

- **Action Item(s):** #78
- **Project Type:** Ongoing
- **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 Mtb 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.
- **2008 Update:** 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.

#### FOCUS AREA IV: PRODUCT DEVELOPMENT

##### ACTION ITEM #80

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

- **Action Item(s):** #80

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- **Project Type:** Ongoing
- **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.
- **2008 Update:** We have successfully generated and characterized SIV/HIV chimeric viruses that are resistant to the HIV reverse transcriptase inhibitors FTC and TDF (combined=Truvada). We are currently evaluating in macaques if the effectiveness of chemoprophylaxis and microbicide interventions may be compromised by drug-resistant viruses. We are also continuing to monitor for drug resistance in macaques infected during pre-exposure prophylaxis with Truvada as a measure of drug resistance risk for human trial failures.

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

- **Action Item(s):** #80
- **Project Type:** Ongoing
- **Agency:** NIH
- **Description:** NIAID brings together leading scientists to share capabilities and expertise in new drug discovery.
- **2008 Update:** 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/)).

ACTION ITEM #81

**PROJECT TITLE: EVALUATION OF RESOURCE-LIMITED COUNTRY-FRIENDLY SAMPLE COLLECTION**

- **Action Item(s):** #81
- **Project Type:** New
- **Agency:** CDC
- **Description:** To meet the needs of HIV DR surveillance and monitoring, the HIV DR laboratory in the International Laboratory Branch (ILB) has focused on evaluating sample collection devices that can be utilized in resource-limited countries. The laboratory developed a broadly sensitive in-house genotyping assay using dried blood spots (DBS).

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- **2008 Update:** By applying this assay, the laboratory has assisted 5 PEPFAR countries to conduct HIV DR surveys. Survey results ensured policy maker and physicians that the scaling up of antiretroviral therapy in countries under PEPFAR has not caused the widely-spread development of HIV DR, as had been feared. By utilizing DBS for resistance testing, this method not only made HIV DR surveillance a reality in PEPFAR countries, it also reduced the cost by almost 50%.

#### ACTION ITEM #82

#### PROJECT TITLE: CHALLENGES IN EVALUATION AND LICENSING OF NEW PNEUMOCOCCAL VACCINES- WHO SPONSORED WORKSHOP

- **Action Item(s):** #82
- **Project Type:** New
- **Agency:** FDA
- **Description:** Develop consensus regarding standardized approaches for evaluation and licensure of new pneumococcal vaccines with added serotype coverage.
- **2008 Update:** 2008 meeting in Ottawa and subsequent workshop in London UK with WHO and EMEA representatives to develop standards for immunologic evaluation of new pneumococcal vaccines. Updates to the WHO recommendations published at <http://www.who.int/biologicals/meetings/areas/vaccines/pneumococcal/en/index.html>. Meeting report prepared for publication in Vaccine.

#### PROJECT TITLE: REGULATORY REQUIREMENTS – INDUSTRY AND SCIENTIFIC COMMUNITY

- **Action Item(s):** #82
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Clarify FDA regulatory requirements to both industry and the scientific community.
- **2008 Update:** 1) Presented regulatory requirements for AR tests at the Professional and IVD Industry Roundtable meetings 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 eSubmission 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

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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).

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

- **Action Item(s):** #82
- **Project Type:** Ongoing
- **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.
- **2008 Update:** Draft guidance published 1/17/2008.

**PROJECT TITLE: PANDEMIC INFLUENZA VACCINE**

- **Action Item(s):** #82
- **Project Type:** Ongoing
- **Agency:** FDA
- **Description:** Regulatory and research activities to support development, licensure and rapid widespread availability of vaccines for pandemic influenza.
- **2008 Update:** Multiple INDs under review for vaccines against potential pandemic influenza virus strains H5N1, H7N3, and H9N2. December 2008: CBER co-chaired and participated in a Public Workshop "Adjuvants and Adjuvanted Preventative and Therapeutic Vaccines for Infectious Disease Indications. September 2008: CBER - sponsored meeting "Rapid Methods for Detecting Mycoplasma Contamination in the Manufacture of Vaccines, Including Pandemic Influenza Vaccines and other Biological Products. Vaccines and Related Products Advisory Committee meeting in February 2009 to address pediatric clinical development of novel Pandemic Vaccines. February 2008 Vaccines and Related Biological Products Advisory Committee Pandemic and Pre-Pandemic Clinical Development Issues

**PROJECT TITLE: GUIDANCE TO INDUSTRY- UPDATING LABELING FOR SUSCEPTIBILITY TEST INFORMATION IN SYSTEMIC ANTIBACTERIAL DRUG PRODUCTS AND ANTIMICROBIAL SUSCEPTIBILITY TESTING DEVICES**

- **Action Item(s):** #82
- **Project Type:** New
- **Agency:** FDA

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- **Description:** This document provides guidance to industry on how to periodically update susceptibility test interpretive criteria, susceptibility test methods, and quality control parameters in drug product labeling. Drug labeling that is updated in this regard is critical in encouraging appropriate use of antibacterial drug products.
- **2008 Update:** Draft guidance published in June 2008.

**PROJECT TITLE: ACUTE BACTERIAL EXACERBATIONS OF CHRONIC BRONCHITIS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE: DEVELOPING ANTIMICROBIAL DRUGS FOR TREATMENT**

- **Action Item(s):** #82
- **Project Type:** New
- **Agency:** FDA
- **Description:** This document provides guidance to industry on the development of drugs for the treatment of ABECB. Special emphasis is placed on clinical trial design. In particular, the need for informative trials that adequately differentiate the effect of the test drug vs. placebo. Such information will allow for one to weigh the benefits of therapies for this condition against the risks.
- **2008 Update:** Published in draft in August 2008.

**PROJECT TITLE: ADVISORY COMMITTEE TO DISCUSS THE CLINICAL TRIAL DESIGN FOR DEVELOPING DRUGS FOR SKIN AND SKIN STRUCTURE INFECTIONS**

- **Action Item(s):** #82
- **Project Type:** New
- **Agency:** FDA
- **Description:** This meeting focused on clinical trial designs for the development of drugs for skin infections.
- **2008 Update:** Meeting was held in November 2008.