

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for HIV/AIDS, Viral Hepatitis,
STD and TB Prevention
Division of Tuberculosis Elimination**



**Advisory Council for the Elimination of Tuberculosis
June 17-18, 2008
Atlanta, Georgia**

Record of the Proceedings

TABLE OF CONTENTS

	<u>Page</u>
Attachment 1: List of Participants	A1.1
Attachment 2: Acronyms Used In These Meeting Minutes	A2.1
Meeting Minutes.....	1
June 17, 2008	
Opening Session.....	1
NCHHSTP Director's Report.....	2
DTBE Director's Report.....	4
Overview of the Draft National Biosurveillance Strategy.....	6
Update by DGMQ.....	9
Overview of Travel Restrictions and Interventions to Prevent Communicable Diseases.....	10
Overview of the Philippine TBTI Program Review	12
Update by the NTCA/DTBE FY'10 Formula Workgroup	15
Update on Regional Training and Medical Consultation Center Activities	18
Overview of CCID Informatics Activities.....	22
Update on CDC's TB Surveillance Activities.....	24
Update on TBTC	25
Update on CDC's Public Health Law and TB Control Activities	28
June 18, 2008	
Update by the ACET TB in African Americans Workgroup	31
Update by the Foreign-Born Workgroup	35
Overview of the Office of Management and Budget Clearance Process	36
Overview of the Genetic Basis of Drug Resistance	38
Overview of the Impact of CCID Program Integration at Local and State Level	40
ACET Business Session	41
Public Comment Session.....	43
Closing Session	43

ATTACHMENT 1**List of Participants****ACET Members**

Dr. Michael Fleenor, Chair
 Dr. Jennifer Flood
 Mr. Shannon Jones
 Mr. Joseph Kinney
 Dr. Ana Lopez de Fede
 Dr. Masahiro Narita
 Ms. Sirlura Taylor

Acting Designated Federal Official

Dr. Kenneth Castro

Ex-Officio and Liaison Members

Dr. Naomi Aronson
 (Department of Defense)
 Dr. William Baine (Agency for Healthcare
 Research and Quality)
 Dr. Anita Barry (National Association of
 County and City Health Officials)
 Ms. Linda Danko
 (Department of Veterans Affairs)
 Dr. Edward Desmond (Association of
 Public Health Laboratories)
 Dr. Richard Ehrenberg (National Institute
 for Occupational Safety and Health)
 Dr. Joseph Goldenson
 (National (Commission on
 Correctional Health Care)
 Mr. Phillip Griffin (National Tuberculosis
 Controllers Association)
 Dr. Michael Leonard, Jr. (Infectious
 Disease Society of America)
 Dr. Edward Nardell (International Union
 Against Tuberculosis and Lung Disease)
 Ms. Susan Perez (Treatment Action Group)
 Dr. John Redd (Indian Health Service)
 Dr. Lee Reichman (American College of
 Chest Physicians)
 Mr. Daniel Reyna (U.S. Section,
 U.S.-Mexico Border Health Commission)
 Dr. Diana Schneider (Department of
 Homeland Security)

Dr. Lornel Tompkins
 (National Medical Association)
 Exec. Sec. Clemente Villalpando
 (Mexico Section, U.S.-Mexico Border
 Health Commission)
 Dr. Theresa Watkins-Bryant
 (Health Resources and
 Services Administration)

CDC Representatives

Dr. Kevin Fenton (NCHHSTP Director)
 Ms. Gail Burns-Grant
 Dr. Martin Cetron
 Dr. Terence Chorba
 Dr. Hazel Dean
 Ms. Heather Duncan
 Dr. Richard Goodman
 Ms. Natalie Greene (CDC Contractor)
 Dr. Kashef Ijaz
 Dr. John Jereb
 Dr. Dolly Katz
 Ms. Amara Khan
 Ms. Laura Leidel
 Dr. Phillip LoBue
 Ms. Lilia Manangan
 Ms. Tonya Martin
 Dr. Thomas Navin
 Dr. Drew Posey
 Mr. Daniel Ruggiero
 Ms. Margie Scott-Cseh
 Dr. Thomas Shinnick
 Dr. Vishnu-Priya Sneller
 Dr. Daniel Sosin
 Mr. Phillip Talboy
 Dr. Andrew Vernon
 Dr. Wanda Walton
 Ms. Pei-Chun Wan

**Guest Presenters and
Members of the Public**

Dr. Gisela Schechter (California Department
 of Health Services, Tuberculosis Control
 Branch)
 Mr. John Seggerson (Stop TB USA)

ATTACHMENT 2

Acronyms Used In These Meeting Minutes

AA	— African American
ACET	— Advisory Council for the Elimination of Tuberculosis
ACIP	— Advisory Committee on Immunization Practices
AFB	— Acid Fast Bacilli
APHL	— Association of Public Health Laboratories
ATS	— American Thoracic Society
BSC	— Board of Scientific Counselors
CCID	— Coordinating Center for Infectious Diseases
CDC	— Centers for Disease Control and Prevention
CXR _s	— Chest X-Rays
DFO	— Designated Federal Official
DGMQ	— Division of Global Migration and Quarantine
DHAP	— Division of HIV/AIDS Prevention
DHS	— Department of Homeland Security
DNB	— Do Not Board
DOT	— Directly Observed Therapy
DST	— Drug Susceptibility Testing
DTBE	— Division of Tuberculosis Elimination
EDN	— Electronic Disease Notification
FBPs	— Foreign-Born Populations/Persons
FBWG	— Foreign-Born Workgroup
FDA	— Food and Drug Administration
FIND	— Foundation for Innovative New Diagnostics
FSEB	— Field Services and Evaluation Branch
HBV	— Hepatitis B Virus
HCWs	— Healthcare Workers
HDW	— Health Disparities Workgroup
HHS	— Department of Health and Human Services
HL7	— Health Level 7
HRSA	— Health Resources and Services Administration
HSPD-21	— Homeland Security Presidential Directive
ICE	— U.S. Immigration and Customs Enforcement
ICRO	— Information Collection Review Office
ICRs	— Information Collection Requests
IDSA	— Infectious Disease Society of America
IGRAs	— Interferon Gamma Release Assays
IHS	— Indian Health Service
IMP	— Immigrant and Migrant Populations
INH	— Isoniazid
IT	— Information Technology
LOINC	— Logical Observation Identifier Names and Codes
LTBI	— Latent TB Infection

MDR-TB	—	Multi-Drug Resistant TB
MIRU	—	Mycobacterial Interspersed Repetitive Unit
MMWR	—	<i>Morbidity and Mortality Weekly Report</i>
<i>M.tb</i>	—	<i>Mycobacterium Tuberculosis</i>
NAATs	—	Nucleic Acid Amplification Tests
NCHHSTP	—	National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
NEDSS	—	National Electronic Disease Surveillance System
NIH	—	National Institutes of Health
NMA	—	National Medical Association
NTCA	—	National Tuberculosis Controllers Association
NTM	—	Non-Tuberculous Mycobacteria
OCSO	—	Office of the Chief Science Officer
PCR	—	Polymerase Chain Reaction
PCSI	—	Program Collaboration and Service Integration
PEPFAR	—	President's Emergency Plan for AIDS Relief
PHLIP	—	Public Health Laboratory Interoperability Project
PHLs	—	Public Health Laboratories
PRA	—	Paperwork Reduction Act
QFT	—	QuantIFERON
RTMCCs	—	Regional Training and Medical Consultation Centers
RVCT	—	Report Verified Case of TB
SAGE	—	Scientific Advisory Group of Experts
SLEC	—	St. Luke's Extension Clinic
Spoligotyping	—	Spacer Oligonucleotide Typing
TAG	—	Treatment Action Group
TBESC	—	TB Epidemiologic Studies Consortium
TBTC	—	TB Trials Consortium
TBTIs	—	TB Technical Instructions
TDF	—	Tropical Diseases Foundation
TIMS	—	Tuberculosis Information Management System
TSTs	—	Tuberculin Skin Tests
WHO	—	World Health Organization
XDR-TB	—	Extensively Drug-Resistant TB

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
National Center for HIV/AIDS, Viral Hepatitis,
STD and TB Prevention
Division of Tuberculosis Elimination**

**ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
June 17-18, 2008
Atlanta, Georgia**

Minutes of the Meeting

The Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (NCHHSTP) Division of Tuberculosis Elimination (DTBE) convened a meeting of the Advisory Council for the Elimination of Tuberculosis (ACET). The proceedings were held on June 17-18, 2008 in Building 8 of CDC's Corporate Square Offices, Conference Room A/B/C in Atlanta, Georgia.

Opening Session

Dr. Michael Fleenor, Chair of ACET, called the meeting to order at 8:32 a.m. on June 17, 2008. He welcomed the attendees to the proceedings and opened the floor for introductions. The list of participants is appended to the minutes as Attachment 1.

Dr. Kenneth Castro, Director of DTBE and Acting Designated Federal Official (DFO) of ACET, announced that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. He emphasized that ACET members should be mindful of potential conflicts of interest identified by the CDC Committee Management Office and recuse themselves from participating in discussions or voting on issues in which they have a real or perceived conflict.

Dr. Castro conveyed that Dr. Hazel Dean, Deputy Director of NCHHSTP, would begin serving as the permanent DFO for ACET at the next meeting.

Dr. Castro informed ACET that the terms of Drs. Jennifer Flood and Richard Fluck would expire after the current meeting. He presented certificates of appreciation to Dr. Flood and Dr. Fluck, *in absentia*, in recognition of their outstanding service and contributions to ACET and CDC.

NCHHSTP Director's Report

Dr. Kevin Fenton reported on CDC's ongoing activities at the agency, coordinating center, national center and division levels. At the agency level, Dr. Julie Gerberding, Director of CDC, recently announced a new strategic initiative that CDC is conducting with partners to make the United States one of the healthiest nations in the world.

To implement the new initiative, CDC, the Association of State and Territorial Health Officials, and the National Association of County and City Health Officials formed a "Healthiest Nation Alliance" to emphasize the critical need for the United States to change its fundamental strategic imperative and make more investments to protect health through health promotion, prevention of disease, injuries, disabilities, and preparedness for new threats.

The Healthiest Nation Initiative includes six key strategies. The "vision will be expanded" in collaboration with partners, organizations and other stakeholders at federal, state, local and private-sector levels to create a clear and compelling vision that motivates individuals and groups to support a true health system.

"Leaders will be empowered" by collaborating with current and new partners to assist in leading and aligning efforts and advancing a health protection agenda. "Persons will be energized" by creating excitement for the concept of health and health protection among individuals, communities and the general public. "Health will be enacted in all policies" by using structural interventions to integrate health protection into social policies and sectors at all levels.

"Health protection goals will be executed" to achieve greater health impact. Priorities outlined in CDC's health protection goals and goal action plans will be implemented in an efficient and timely manner to support this strategy. "Health will be evaluated" by defining and measuring health and health value for persons, families, communities, organizations, states and the nation.

CDC formed the "Healthiest Nation Coordination Council" with external partners to develop, coordinate and implement a cohesive and timely operational plan for accelerating the Healthiest Nation Initiative. CDC will identify a senior coordinator to lead the Coordination Council.

At the coordinating center level, the Coordinating Center for Infectious Diseases (CCID) Board of Scientific Counselors (BSC) convened a meeting in May 2008. The BSC Workgroup for NCHHSTP focused on Program Collaboration and Service Integration (PCSI) and made recommendations in three key areas: (1) investments to evaluate the effectiveness of PCSI; (2) operational research on PCSI; and (3) integrated health communications. NCHHSTP will report its progress on the recommendations at the next BSC meeting.

At the national center level, NCHHSTP is continuing to develop priorities for FY'08 to address its strategic imperatives of increasing PCSI, reducing health disparities and maximizing global synergies. NCHHSTP will conduct several activities to achieve its priorities. A PCSI white paper with research priorities will be published. A PCSI national mobilization plan has been developed and will be implemented from FY'08-FY'10.

The first integrated surveillance report will be published in August 2008 to provide guidance on the overlap and intersection among HIV, STDs, TB and viral hepatitis in the U.S. population. The report will include a section on African American (AA) men due to the high rates of infectious disease in this subpopulation and the need to develop more effective integrated intervention strategies for this group.

Dr. Fenton will continue his Director's site visits to rural states and U.S. territories to focus on the integration of HIV, STD, TB and viral hepatitis. A green paper will be published on using innovative models to reduce health disparities by tracking common social, economic and psychosocial determinants that play a significant role in HIV, STD, TB and viral hepatitis. NCHHSTP plans to integrate its social determinants research into program planning and implementation. Communications with external partners will be strengthened by developing new systems, such as a Director's blog and other web-based mechanisms.

Meta-leadership for prevention will be heightened with federal partners, particularly across HHS agencies. The *NCHHSTP 2020 Strategic Plan* will be completed and published by the fall of 2008. Opportunities for strategic partnerships for prevention will be identified. NCHHSTP recently published and posted the *PCSI Consultation Report* on its web site based on key outcomes from the PCSI meeting that was held in August 2007 with >100 CDC staff and external partners. The overarching aim of the consultation was for participants to provide NCHHSTP with guidance on its PCSI strategy over the next five years.

In terms of NCHHSTP's senior leadership, Dr. Hazel Dean was recently appointed as the new Deputy Director of NCHHSTP and Dr. Sal Butera was recently appointed as the Associate Director for Laboratory Sciences. Dr. Robert Janssen, former Director of the NCHHSTP Division of HIV/AIDS Prevention (DHAP), retired from CDC in May 2008.

Dr. Timothy Mastro, Deputy Director of DHAP, will retire from his position in the near future. Dr. Richard Wolitski and Ms. Janet Cleveland will rotate as acting DHAP Directors for six-month cycles. Dr. Fenton will form a search committee with both CDC staff and external colleagues to expedite permanently filling the DHAP Director and Deputy Director positions.

Congress is currently considering a proposal to reauthorize the President's Emergency Plan for AIDS Relief (PEPFAR) for an additional five years. The proposed 10-year PEPFAR goals are to treat 2.5 million persons; prevent >12 million new HIV infections; and provide care to >12 million persons, including 5 million orphans and vulnerable children. The proposed legislation also will strengthen integration of TB, malaria and other prevention approaches in HIV prevention.

At a recent conference in Uganda, domestic leaders discussed the need to apply scientific and strategies lessons learned in PEPFAR to inform the HIV/TB portfolio in the United States. Efforts will be made to replicate innovations in PEPFAR countries domestically, such as community mobilization and engagement, leadership development, workforce capacity building, and new approaches to monitoring and evaluating the HIV epidemic.

NCHHSTP's FY'08 enacted budget is nearly \$1 billion and is relatively flat compared to previous years. Expenditures of the FY'08 NCHHSTP budget include 69% to domestic HIV prevention activities, 15% to STD prevention programs, 14% to TB prevention and control, and 2% to hepatitis prevention. The Global AIDS Program budget increased from ~\$1.1 billion in FY'07 to >\$1.4 billion in FY'08.

The breakdown of NCHHSTP's proposed FY'09 budget of ~\$1 billion for domestic activities is as follows: (1) \$691 million for HIV prevention (a decrease of ~\$713,000); (2) \$17.5 million for viral hepatitis prevention (a decrease of ~\$78,000); (3) \$151.7 million for STD prevention (a decrease of \$678,000); and (4) \$139.7 million to TB (a decrease of ~\$624,000). NCHHSTP is collaborating with colleagues in Congress and the CDC Washington Office to address decreased viability and feasibility of continuing prevention activities with budget cuts.

Dr. Fenton and the Indian Health Service (IHS) made a joint site visit to the Navajo and Tohono O'odham Nations and state and local public health programs in Arizona and New Mexico to explore PCSI activities in these jurisdictions and identify challenges in integrating local programs, particularly in rural parts of the Southwest. The agencies were impressed by creative strategies the programs have developed and implemented to reduce health disparities in Native persons.

NCHHSTP recently published its *FY'07 Annual Report* to highlight key accomplishments and provide information on its budget, priorities and performance indicators. The report is available on the NCHHSTP web site.

At the division level, DTBE data showed that the lowest TB incidence in U.S. history was reported in 2007. Key milestones were achieved in four TB Trials Consortium (TBTC) studies. DTBE completed ethnographic studies of TB in five immigrant ethnic groups. The DTBE Mycobacteriology Laboratory Branch and the Association of Public Health Laboratories (APHL) are jointly planning the "5th National Conference on Laboratory Aspects of Tuberculosis" in August 2008 in San Diego.

DTBE Director's Report

Dr. Castro covered the following areas in his update. The ACET BCG Workgroup initiated discussions with the CDC Advisory Committee on Immunization Practices (ACIP) to develop joint *Guidelines on the Role of BCG Vaccine in the Prevention and Control of TB in Healthcare Workers Traveling to High-Risk Areas*. The Assistant to the Director for Immunization Policy at CDC endorsed the ACET/ACIP collaboration. The updated draft ACET statement was shared with ACIP members and will also be presented during a face-to-face meeting later in June 2008.

DTBE convened a consultation in June 2008 with experts representing several organizations to discuss the use of nucleic acid amplification tests (NAATs) for the diagnosis of TB. The NAAT experts reached consensus in two key areas. All persons suspected to have pulmonary TB

should have a respiratory specimen tested by NAAT. A negative NAAT result plus two negative acid fast bacilli (AFB) smear results should be adequate for releasing persons from isolation.

The experts also reached consensus on several NAAT needs. Manufacturers should be encouraged to improve current tests by developing new NAATs to meet TB program needs. Regulatory approval of new NAATS should be streamlined and facilitated. A proficiency testing program should be implemented in laboratories. Research should be conducted to develop better sputum processing procedures, use NAATs in other body fluids and evaluate effective testing regimens. The experts also viewed rapid molecular drug susceptibility testing (DST) as an urgent public health and diagnostic need.

DTBE will publish the NAAT guidelines in the *Morbidity and Mortality Weekly Report (MMWR)*, but the publication will not be effective in reaching the target audience. As a result, DTBE will develop a communication and dissemination plan to ensure that the guidelines widely reach clinicians who are most likely to see patients with suspected TB and order NAATs. DTBE will ensure that the NAAT guidelines are consistent with those developed by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA).

The DTBE Field Services and Evaluation Branch (FSEB) is conducting a number of projects that compliment core activities. A mechanism was identified to continue funding the Cure TB Project to assure continuity of TB care among persons who cross the U.S.-Mexico Border. Funds were allocated to continue the development of the Electronic Disease Notification (EDN) System.

The EDN System was designed to improve the exchange of information among health departments regarding immigrants or refugees who received medical screening overseas and were classified as having non-infectious TB. FSEB will make efforts to publish B notification data reported to the EDN System in collaboration with the CDC Division of Global Migration and Quarantine (DGMQ).

TB program reviews for TB cooperative agreement grantees will be conducted in a number of jurisdictions. Language will be incorporated into program announcements to emphasize that grantees will be expected to assure outcomes of programmatic activities. Software is being developed for the National TB Indicators Project. FSEB provided technical assistance during a review of the New York City TB Program in April 2008 and an evaluation of implementation of the TB technical instructions in the Philippines in May-June 2008.

FSEB responded to requests for epidemiological assistance with TB transmission in a Rhode Island school and treatment and control of multidrug-resistant TB (MDR-TB) in the U.S. Pacific Islands. FSEB is continuing to plan the re-competition of the FY'10 TB cooperative agreement. The Cooperative Agreement Announcement Workgroup with DTBE staff and the Cooperative Agreement Formula and Laboratory Formula Workgroups with the National Tuberculosis Controllers Association (NTCA) were established to assist in this effort.

A number of TBTC studies are underway. Study 26 is a comparison between once-weekly isoniazid (INH)/rifapentine therapy for three months and daily INH for nine months. Enrollment of

>8,000 persons has been completed, but enrollment of children and HIV-infected persons is continuing. Study 27/28 is a pharmacokinetic study to examine draft time-to-positivity in liquid culture.

Study 28 is a substitution of moxifloxacin with INH during an initial two-month period. The study was completed and a manuscript has been drafted. Study 29 will be initiated in the summer of 2008 to examine daily rifapentine. Study 30 will be initiated in the fall of 2008 to examine linezolid for MDR-TB. A microbiology study is underway in Kampala. New collaborations were established with partners to conduct other TBTC projects funded by the National Institutes of Health (NIH). TBTC will be re-competed in FY'09.

DTBE will convene an expert consultation in August 2008 to focus on interferon gamma release assays (IGRAs) and inform updated guidelines for IGRA tests approved by the Food and Drug Administration (FDA). Several studies are underway to assess the use of IGRAs in contact investigations, Vietnamese immigrants, HIV-infected persons in Botswana, and U.S. Air Force entry screening facilities.

DTBE is implementing a number of health systems projects. An ethnographic study will be conducted on Karen Burmese immigrants in New York State. An evaluation of HIV/TB-related mortality was completed. Cost analyses on shorter TB regimens were initiated. The TB Epidemiologic Studies Consortium (TBESC) is planning to develop cost analyses for MDR-TB and extensively drug-resistant TB (XDR-TB). TBESC has nearly completed enrollment for a prospective study examining factors that influence completion of treatment for latent TB infection (LTBI).

TBESC will be re-competed in FY'11 with a reconfigured framework and a narrower and more focused approach to be more programmatically and operationally relevant. To support this effort, DTBE will develop a list of new research concepts, narrow the initial list to 6-8 concepts, develop four-page research proposals, and finalize the list with 2-4 proposals. Detailed research plans will be created and serve as the basis of selecting new focus areas for future research.

The Strategic Planning Workgroup for the TBESC re-competition has a membership of ~16 CDC scientists, domestic and international experts, and ACET representatives. All workgroup members must sign a non-disclosure agreement and would be ineligible for funding under the TBESC re-competition.

Overview of the Draft National Biosurveillance Strategy (NBS)

Dr. Daniel Sosin is the Director of the Biosurveillance Coordination Unit at CDC. He explained that Homeland Security Presidential Directive 21 (HSPD-21) calls for HHS to establish a national biosurveillance system for human health with international connectivity where appropriate. HSPD-21 specifically directs HHS to build a system predicated on capabilities at state, regional and community levels and to create a networked system that allows for two-way

information flow between and among federal, state and local public health authorities and clinical healthcare providers.

HSPD-21 defines “biosurveillance” as active data collection, analysis and interpretation of biosphere data related to disease activity and threats to human and animal health to achieve early warning, detection and situational awareness. “Epidemiologic surveillance” is defined as active data collection and analysis related to human health and disease in a population to obtain early warning, rapid characterization, and situational awareness of disease activity in the human population.

Dr. Gerberding published the following goals for the National Biosurveillance Strategy (NBS) in April 2008. A formal and regular process should be developed to make leaders and programs aware of the emergence, characteristics and integrated dynamics of acute health threats, events and crises. CDC should coordinate the definition of national biosurveillance for human health, identify data requirements, and explore strategies to analyze and fuse information to provide a common operating picture.

CDC drafted the NBS with three overarching goals based on Dr. Gerberding’s intent. State and local capacity will be strengthened for early warning, rapid characterization, and overall situation awareness of public health events of national concern. Multi-directional, near real-time and relevant information flows will be improved. The control of urgent health threats will be enhanced and based on integration of all relevant information.

CDC’s initial steps in drafting the NBS were to address four key issues related to information that users need; current capacity to detect and respond to acute health events; short-, mid- and long-term opportunities to enhance integrated activities; and strategies to implement and evolve the NBS over time.

After identifying the key issues, CDC formed the Biosurveillance Coordination Unit and four workgroups to advance the development of the draft NBS. Stakeholders on the workgroups include CDC’s executive leadership and surveillance experts; federal, state, local, tribal and territorial partners; and public and private national and international partners.

In May 2008, CDC established the National Biosurveillance Subcommittee and produced a draft of the NBS to define current and future capabilities. In October and December 2008, CDC will present the draft NBS to the Homeland Security Council and create an operational plan with an implementation strategy to design the next-generation biosurveillance system.

The scope of the NBS is to collect and integrate timely health-related information for public health action; focus on all hazards, including threats and exposures; conduct surveillance and investigations to validate and inform response actions; and control significant health events through early detection and characterization for intervention. The NBS will be designed to perform the following functions: recognize individual cases and clusters, validate signals, notify practitioners and communicate information for appropriate response actions, characterize events, and assure quality control and improvement.

CDC identified capabilities in several areas that are needed at this time to implement the NBS. Capacity is needed for pre-exposure, exposure, pre-diagnostic, diagnostic, pathogen detection and mortality surveillance. An assessment and models are needed to show the benefits of integration to various stakeholders and demonstrate the impact of data quality, standards and data-sharing methods. Strategies are needed to address the lower quality and validity of non-traditional sources; delays in the timeliness and coverage of traditional sources; and significant workforce shortages throughout the country.

The draft NBS report highlights six areas that are priorities for federal, state and local agencies at this time and need to be enhanced. One, “integrated interpretation and communication” should make better use of existing information; expand structured and unstructured sources; have the ability to query data to validate findings; provide rich, visual and comprehensible displays; and contain tools, methods and analyst capabilities.

Two, “global capability and connectivity” should use local capacity to detect and investigate threats; serve as a trusted partner to increase access to and awareness of relevant events; network field assignees; and address international system standards to improve effectiveness of sharing information.

Three, “workforce development” in both the public health and clinical communities should enhance human processing and judgments to query and validate data; take advantage of available hierarchical expertise; leverage the astuteness and participation of clinicians; and build cohesive professional networks.

Four, “electronic health information” should use National Healthcare Safety Network standards that support public health functions; facilitate automated analyses to support disease and outbreak detection; provide access to data to investigate signals or cues; give human feedback loops to validate findings and provide guidance; and promote electronic death registration.

Five, “laboratory innovation and exchange” should improve the timeliness and capacity of rapid assays and genetic and molecular characterization; strengthen data exchange standards and technology; enhance sharing of epidemiologic and laboratory results; and assure the availability of appropriate roles and capabilities across public health, clinical and research laboratories. Six, “unstructured data” should enhance informal notification and consultation channels and improve methods to aggregate and analyze electronic media.

CDC will take several actions over the next few months to finalize the draft NBS. Outreach efforts will be diversified within the National Biosurveillance Subcommittee, private-sector groups, global organizations and other stakeholders. Scenario-based focus groups will be held to formalize the needs of NBS users.

Innovative technologies for surveillance and communication will be explored more effectively. Relevant biosurveillance studies conducted in the past will be incorporated into the NBS. Legal and privacy considerations will be addressed in a robust manner. Enterprise architecture and health information technology experts will be engaged. Operational plans from key programs will be integrated. Performance measures and research priorities will be developed.

Dr. Sosin asked ACET to provide feedback in three areas to assist CDC in finalizing the draft NBS. The draft NBS should be reviewed to assure its reflection of ACET's interests and insights. The NBS should be widely distributed to engage and obtain endorsement from key stakeholders. Input should be provided on CDC's next steps and the role of ACET's interests in specific activities of the NBS.

Dr. William Baine, ACET's *ex-officio* member for the Agency for Healthcare Research and Quality, advised CDC to use the NBS to encourage a change in practice that would allow clinicians to perform gram stains, AFB smears and direct specimen examination by microscopy. He noted that this approach would play a significant role in improving clinical laboratories.

Dr. Baine also urged ACET to advocate, encourage and promote wider performance of acid-fast smears, in full compliance with CLIA, as a targeted screening test on unconcentrated sputum by clinical laboratories that perform gram-staining of sputum specimens, but refer processing for mycobacteriology, including microscopy on concentrated sputum, to reference laboratories.

Update by DGMQ

Dr. Drew Posey, of DGMQ, explained that DGMQ changed the medical screening requirements for immigrants and refugees from a sole focus on chest x-rays (CXRs) and sputum smears to a much more comprehensive system with sputum cultures, DST and treatment according to directly-observed therapy (DOT). The new TB technical instructions (TBTIs) are implemented in areas where the TB incidence is $\geq 20/100,000$ as defined by the World Health Organization (WHO).

DGMQ began implementing the new TBTIs in April 2007 with Burmese refugees who were screened in Thailand and scheduled for resettlement in the United States. As of June 13, 2008, populations from 14 countries on three continents were screened according to the new TBTIs. Based on 2006 data, the new TBTIs cover 28% of immigrants and 40%-50% of refugees. DGMQ is making efforts at this time to implement the new TBTIs in China, Egypt, the Dominican Republic, Ethiopia, Hong Kong, Iraq, Jordan, Kenya, Malaysia, Syria and Thailand.

Preliminary data show that implementation of the new TBTIs have made a significant impact in the United States, particularly for the arrival of immigrants from Mexico and the Philippines classified with B1 or B2 TB. DGMQ convened a panel of internal and external TB experts to evaluate implementation of the new TBTIs in the Philippines in May-June 2008.

The Saint Luke's Extension Clinic in the Philippines is the largest panel site in the world and began screening visa entrants with the new TBTIs in October 2007. Of 43,684 immigrant visa entrants screened in the clinic in FY'06, 47% were Class B TB arrivals. The goals of the Philippine program review were to thoroughly evaluate the TB program and inform DGMQ and DTBE of TBTI implementation activities. DGMQ found the assessment to be successful.

DOT continues to serve as the most significant challenge in implementing the new TBTIs. Most notably, some countries only use DOT for an initial two-month period. Some overseas National TB Programs use WHO regimens that are not as rigorous as the ATS/CDC/IDSA guidelines. Some countries have limited drug availability and lack opportunities for public-private collaborations. Due to these challenges, the development of overseas DOT sites stretches DGMQ resources and delays implementation.

DGMQ will continue to make site visits to promote implementation of the new TBTIs in several high-priority countries: Egypt, Jordan and Lebanon in the Middle East; Ethiopia and Kenya in Africa; and Nepal in Asia. DGMQ will reconvene the TBTI Workgroup to discuss findings from the Philippines program review and explore strategies to refine the TBTI indicators.

In addition to implementation of the new TBTIs, DGMQ is also focusing on the rollout of EDN. DGMQ has regulatory responsibility to provide information to receiving health departments on arriving immigrants and refugees who have a notifiable health condition. To fulfill its mandate, DGMQ is replacing the paper-based Immigrant and Migrant Populations (IMP) System with the EDN electronic system.

EDN is designed to provide health departments with access to data on Department of State forms that are recorded and scanned overseas. EDN will also serve as an electronic system for health departments to record and evaluate outcomes of domestic follow-up evaluations. DGMQ plans to rollout EDN to all states by June 30, 2008 and terminate data entry to the IMP System by the end of FY'08. DGMQ and states will collaborate to arrange for local health departments to become EDN users. By the end of 2008, DGMQ and DTBE will jointly convene a summit with key EDN users from each state to discuss the system and establish consensus on approaches to advance this effort.

ACET advised DGMQ to conduct a rigorous evaluation of the rollout of EDN to ensure that states and quarantine stations are properly trained to implement the system.

Overview of Travel Restrictions and Interventions to Prevent Communicable Diseases

Ms. Laura Leidel, of DGMQ, described the use of travel restrictions and interventions as tools to prevent the spread of communicable diseases of public health significance. The Department of Homeland Security (DHS) has developed and made two tools available to public health authorities.

The first tool is the "Do Not Board" (DNB) List. DHS places persons on the DNB List at CDC's request to restrict these individuals from boarding any flight departing from or arriving to the United States. The DNB List applies to all U.S. citizens and foreign nationals. DHS's criteria are designed to answer three key questions to determine whether an individual should be placed on the DNB List.

One, do public health officials reasonably believe the individual is contagious or likely to become contagious with a communicable disease that would constitute a public health threat to crew or passengers if the individual is permitted to board a commercial aircraft?

Two, is there reason to believe the individual would not comply with public health guidance or public health authorities would be unable to locate the individual? Is the individual unaware of the recommendation not to travel? Three, is there reason to believe that the individual would attempt to fly on a commercial aircraft?

The second tool is the "Lookout" List. This tool holds persons at ports of entry pending a review of their cases by quarantine public health officers, but placement on this list alone does not prevent travel. The Lookout List can supplement or be issued separately from the DNB List.

The following process has been established to place persons on the DNB or Lookout List. A local or state health department contacts the quarantine station. The quarantine station coordinates a conference call with DGMQ and state and local health departments to discuss DNB criteria and other key issues. Based on approval by the DGMQ Director, the CDC Emergency Operations sends the request to DHS for action.

Physicians at the Office of Health Affairs review the request to evaluate smear and culture results and treatment regimens. After the request receives final approval at this level, the quarantine station informs the state and local health department of actions that were taken. The state health department is responsible for keeping individuals informed of their status. CDC and state and local health departments regularly review each situation every 2-4 weeks to determine when an individual can be removed from the DNB List.

A number of issues are discussed during the initial conference call, such as criteria to add and remove persons from DNB and Lookout Lists; arrangements by local and state health authorities to address social needs and facilitate other aspects of the patient's care; international implications; and instructions for front-line personnel. The conference call is also used as an opportunity to make requests on behalf of the patient, such as the waiver of airline fees associated with changing the travel date and visa extensions.

Over the past year, DGMQ drafted a protocol with guiding principles and revised standard operating procedures for DNB and Lookout Lists. DTBE developed an algorithm to clear TB patients for air travel and obtained feedback from TB controllers to inform this effort. DGMQ is currently drafting guidance for state and local health departments that will be published in the *MMWR*. DGMQ has engaged the Department of State in these activities. All DNB cases to date had or were suspected of having suspected infectious TB, but DNB and Lookout requests can be made for other diseases as well.

DGMQ is continuing to address privacy protection issues related to DNB and Lookout Lists, such as the dilemma between law enforcement and healthcare standards. Moreover, the CDC Ethics Committee meets with DGMQ on a regular basis to evaluate cases and review the decision-making process of placing cases on DNB and Lookout Lists.

From May 2007-May 2008, 19 cases were removed from and 34 cases were added to the DNB List. The 15 active cases remained on the DNB List for a mean of 108 days. To implement a DNB action, 10 hours are required on average to add cases and 15 hours are required on average to remove cases. Of 34 active and inactive DNB cases, the United States, India, Vietnam and Mexico accounted for 18. Canada, Mexico, Guam and the U.S. Embassy in Guatemala requested six additions to the DNB List. From April 2007-April 2008, 100 flights required manifest requests from National Targeting Center contact investigations.

The ACET members made a number of comments and suggestions for CDC to consider in finalizing the draft DNB and Lookout guidance.

- DTBE should provide ACET with its algorithm to clear TB patients for air travel. This tool might assist domestic institutions on the ground in the control of patients with known or suspected MDR-TB.
- DGMQ should inform all quarantine stations of the need to coordinate with the Immigration and Customs Enforcement (ICE) Health Service Program when DNB cases are placed into ICE custody. This approach will assure the continuity of care for ICE detainees.
- DGMQ should distribute a “Dear Colleague” letter to inform states that DNB and Lookout guidance will be published in an upcoming *MMWR* article. DGMQ should also urge states and quarantine stations to improve coordination with and better inform local health departments of available travel restriction tools and interventions, particularly since patients with known or suspected TB will be identified at the local level. Communication from DGMQ at the federal level to health departments at both state and local levels will enhance the flow and consistency of information. DNB and Lookout procedures widely vary among quarantine stations at this time.

In preparation of the business session, Dr. Fleenor asked ACET to consider the possibility of formulating a resolution for CDC to expedite the review, clearance and dissemination of DGMQ’s DNB and Lookout List guidelines. Ms. Leidel confirmed that DTBE’s algorithm to clear TB patients for air travel would be distributed to ACET.

Overview of the Philippine TBTI Program Review

Dr. Gisela Schechter, of the California Department of Health Services Tuberculosis Control Branch, served on the evaluation team that assessed the implementation of the new TBTIs by the St. Luke’s Extension Clinic (SLEC) in the Philippines. The evaluation team made a site visit to SLEC on May 26-June 2, 2008 to achieve two key objectives that DGMQ established for the program review.

First, recommendations would be provided to SLEC for TB screening, diagnosis and treatment of persons who apply for immigration to the United States. Second, recommendations would be provided to DGMQ and DTBE to improve the effectiveness and practicality of implementing the 2007 TBTIs.

DGMQ commissioned the program review because 2007 data showed that foreign-born persons (FBPs) accounted for 58% of TB cases in the United States and 75% of TB cases in California. The Philippines accounted for the second highest number of foreign-born cases after Mexico and also accounted for more Class B TB waivers than any other country.

The major changes between the 1991 and 2007 TBTIs include the addition of AFB culture and DST; CXRs for persons ≥ 15 years of age; TST for persons 2-14 years of age; completion of the DOT regimen overseas according to ATS/CDC guidelines before pulmonary TB cases emigrate to the United States; and LTBI treatment for children < 5 years of age, HIV-positive persons and other high-risk contacts.

The evaluation team made several observations regarding the Philippines TB Program. SLEC is a nonprofit organization that has been providing medical examinations for the U.S. Consular Section in the Philippines since 1982. SLEC has radiology, laboratory, immunization, medical and psychiatric facilities onsite and also administers DOT short-course on the premises. SLEC began implementing the new TBTIs in October 2007.

Because SLEC provides services to 250-400 patients each day, digital photographs and passports are checked at each point of the screening process to avoid fraud. SLEC's medical fees of ~\$215 for adults ≥ 15 years of age and \$185 for children 0-14 years of age present financial burdens to applicants, particularly those who live outside of the metropolitan Manila area.

During the site visit, the evaluation team observed SLEC's screening, laboratory and treatment practices; interviewed key informants; and conducted extensive chart, radiology and data reviews. The evaluation team also assessed SLEC's radiology practices, sputum collection techniques, laboratory methods, TB treatment regimens and administration of DOT.

The evaluation team used CDC's checklist to review the placement and reading of tuberculin skin tests (TSTs) in children. SLEC's practices in all of these areas were found to be impeccable and professional, particularly the outstanding quality of radiology films and use of outside laboratories for quality assurance and control.

The evaluation team reached the following conclusions based on its review of SLEC data. From October 2007-March 2008, 21,173 pediatric and adult applicants were screened with the new TBTIs. Applicants 2-14 years of age accounted for 3,478 of 3,548 TSTs. Of TST reaction sizes in this population, 1,505 were < 5 mm, 845 were 5-9mm, and 1,128 were ≥ 10 mm. Abnormal findings suggested active TB in 16 cases with TST reaction sizes 5-9mm or ≥ 10 mm.

SLEC administered the remaining 70 TSTs to applicants < 2 years of age and ≥ 15 years of age as a result of contact investigations. Over the same six-month period, ~63% of 19,454 CXRs were normal, 9.41% suggested active TB, and 4.7% suggested inactive TB.

Of 27,425 applicants who were screened with the 1991 TBTIs from January-June 2007, 192 had diagnosed pulmonary TB. Of 21,173 applicants who were screened with the 2007 TBTIs

from October 2007-March 2008, 244 were diagnosed with pulmonary TB. The number of smear-negative/culture-positive cases increased from 0 with the 1991 TBIs to 142 with the 2007 TBIs.

The number of smear-negative/no culture cases decreased from 71 with the 1991 TBIs to 0 with the 2007 TBIs. The number of smear-positive/culture-negative cases decreased from 57 with the 1991 TBIs to 50 with the 2007 TBIs. SLEC data showed that 85%-95% of smear-positive/culture-negative cases grew non-tuberculous Mycobacteria (NTM) and played a significant role in TBIs.

Of 191 cases with DST outcomes from October 2007-March 2008, 76% were pan-susceptible; 9% were INH-resistant; 6% had MDR-TB; 2% were poly-resistant, but did not have MDR-TB; and 7% were mono-resistant, but not to INH or rifampin. Results are still pending in 29 cases that had DST outcomes. Of 244 cases that began TB treatment in the October 2007-March 2008 time period, 171 are still on treatment, 23 have been cured, 4 either defaulted or were transferred from SLEC, and 46 did not register for treatment.

The evaluation team identified a number of challenges during the SLEC site visit. Compliance with DOT requirements is difficult for applicants who live outside of the metropolitan Manila area. MDR-TB treatment presents a significant barrier because SLEC does not have drugs for these cases and refers patients to the Tropical Diseases Foundation (TDF). However, TDF does not provide SLEC with feedback or follow-up information on patients. The management of children with abnormal chest films is a challenge because SLEC does not perform gastric washings onsite. The prevalence of NTB is high and represents 10%-15% of all cultures.

The evaluation team made several recommendations to SLEC to fulfill objective 1 of its charge. To enhance the clinical management of patients, SLEC should not increase INH/rifampin doses to treat low-level TB resistance or initiate the WHO Category II regimen for patients who had extensive TB treatment in the past prior to receiving DST results. SLEC should hire a social worker to assist patients in navigating the complex TB treatment process.

To strengthen laboratory practices, SLEC should send cultures with patients to facilitate second-line DST of MDR-TB treatment at TDF and continue to use outside laboratories for quality control. SLEC should implement the evaluation team's recommendations to improve internal infection control practices and enhance external collaborations, communications and linkages with TDF and the National TB Program in the Philippines.

The evaluation team made several recommendations to DGMQ to fulfill objective 2 of its charge. Additional DOT sites that meet the standard for TB treatment should be established to increase the number of patients who register for treatment following a diagnosis. Guidance should be provided for the management of applicants with culture-proven TB who elect not to be treated with DOT at SLEC or other accredited sites. DGMQ should partner with the U.S. Embassy in the Philippines to restrict persons who did not complete the rigorous DOT regimen at SLEC from reapplying for emigration to the United States for one year.

DGMQ should engage the TBTI Workgroup in changing the TST cutoff for triggering CXR results to ≥ 10 mm and creating a new protocol for treating LTBI contacts who are not < 5 years of age or HIV-positive. A new subcategory should be added to the TB indicators under the “smear-positive/culture-negative” category to capture a positive or negative response to NTM and provide guidance on the management of these cases.

Overall, the evaluation team found that the new TBTIs would play a significant role in reducing the number of new foreign-born TB cases immigrating to the United States. The evaluation team provided SLEC with its preliminary recommendations after the site visit and will distribute the revised draft report to SLEC for review and comment in the next two weeks. The evaluation team plans to submit its final draft report to DGMQ by the end of July 2008.

ACET asked DGMQ to consider two other suggestions in addition to the evaluation team’s guidance. First, DGMQ should ensure that ethical issues are addressed when implementing the LTBI treatment recommendations in developing countries.

Second, DGMQ should explore the possibility of providing community-based DOT as another method to increase the number of applicants who register for TB treatment in the Philippines. This strategy might reduce the need for temporary housing, minimize financial burdens or decrease other barriers to applicants registering for TB treatment at SLEC. Community-based DOT might also lead to low-paying jobs in communities.

Update by the NTCA/DTBE FY’10 Formula Workgroup

Dr. Kashef Ijaz, Chief of FSEB, and Mr. Phillip Griffin, ACET’s liaison representative to NTCA, reported on recent activities by the NTCA/DTBE FY’10 Formula Workgroup. The rationale for originally creating the TB redistribution formula was based on several major developments.

Federal funding for TB prevention and control activities was increased in 1992 with most of these dollars allocated to New York City, Los Angeles, San Diego, Houston, the District of Columbia and five other big cities based on the resurgence of TB and the emergence of MDR-TB. The epidemiology of TB in the United States has evolved over the past 15 years, but funding amounts have remained relatively static. TB cooperative agreement funds have decreased by 14% since 2001 due to inflation.

DTBE and its partners developed a model in the FY’05 TB cooperative agreement to redistribute funds that would more closely reflect the epidemiology of TB in United States. The formula resulted in redistributing 20% of funds annually through FY’07 based on a five-year average of selected factors. The funding amounts increased to 35% in FY’08.

The 35% redistribution was weighted based on data reported to CDC in 2001-2005 for specific occurrences of TB cases in various subpopulations. The formula variables along with weights included incident cases (40%), U.S.-born minorities., (15%), foreign-born persons (15%), Class

A, B1 or B2 TB (10%), HIV co-infection (5%), MDR-TB (5%), the substance abuse (5%), and homeless population (5%)..

In preparation of the re-competition of the TB cooperative agreement, DTBE and NTCA formed the "FY'10 Formula Workgroup" to achieve two key objectives. For objective 1, the workgroup is reviewing the current TB cooperative agreement redistribution formula, variables and weights and will make recommendations regarding additions, deletions or justifications to the variables; revisions and justifications needed for weights applied to the variables; and any drastic changes required for the entire formula. The workgroup will recommend measurable variables based on data previously reported to CDC through existing surveillance systems.

For the prevention and control component of the updated TB redistribution formula, the workgroup discussed the advantages and disadvantages of the existing formula variables. The workgroup proposed several new variables for possible inclusion in the updated formula: incarcerated at diagnosis, smear-positive pulmonary cases, confirmed cases not counted, diabetes co-morbidity, reactivated cases and immigration status. Because the last four proposed variables are not included in the current Report Verified Case of TB (RVCT) system and have no historical data at this time, the workgroup is considering the possibility of including them in 2015 rather than 2010 objectives to measure progress on these four variables.

The workgroup is currently discussing and analyzing application of various weights related to variables in six different scenarios. For example, a suggestion was made to combine U.S.-born minorities and FBPs and give the combined variable a different weight. The workgroup is questioning whether to continue using A, B1 and B2 classifications in the updated formula due to concerns about data validity.

For the new laboratory component, the workgroup formed a subgroup with laboratory directors, supervisors and technical managers from low, medium, and high incidence states and states with low, medium and high testing volumes. The subgroup is brainstorming ideas on the type of information to include in the new laboratory formula. No standardized data collection tools for laboratories have been developed to date and previous requests for this type of information have been difficult to understand.

The Association of Public Health Laboratories is closely collaborating with the subgroup to create a system to collect necessary data in a consistent and uniform manner to ensure that data are comparable among laboratories. A workshop with state laboratories will be convened during the 5th National Laboratory Conference on proper data collection techniques. Meeting minutes of the laboratory subgroup are available on the NTCA website.

For objective 2, the workgroup will reach consensus on a cohort of big cities and data elements to review the cohort and will also calculate numbers based on the data elements. The workgroup will recommend one of the following three outcomes for direct funding to big cities. One, direct TB cooperative agreement funding for a new group of ten 10 big cities based on data analyses.

Two, all future TB cooperative agreement funding should be allocated to states and then states should develop individual funding distribution formulas in collaboration with local partners at city, county and jurisdiction levels. Three, the status quo should be maintained and future direct TB cooperative agreement funding the current 10 big cities should continue. The workgroup's recommendation on direct funding to big cities will be presented to DTBE, NTCA and ACET.

The workgroup is currently discussing the advantages and disadvantages of the cohort of big cities. Tables 45 and 46 in the Annual TB Surveillance Project are being reviewed in this effort. Table 45 is being used to review incident cases, MDR-TB and TB/HIV co-morbidity surveillance data for the past three years to select the top 20 cities, while Table 46 is being used to review metropolitan statistical areas. The existing formula will be applied with weights, excluding B1 and B2 classifications, to the top 20 cities to compare and select the top 10 cities. The complete existing formula, excluding A, B1 and B2 classifications, will be compared to the current top 10 cities as well.

Overall, the workgroup reflects strong collaboration with NTCA and DTBE partners, including ACET, big cities, laboratories, and high, medium and low incidence states. The workgroup expects to achieve its objectives and meet its deadline of completing the review and submitting a draft report to the clearance process by October 2008.

To ensure transparency of the review process, NTCA has distributed "Dear Colleague" letters and regularly updates its website with the workgroup's meeting minutes; information on the workgroup members; a description of the purpose, goals and objectives of the workgroup; and the workgroup's background materials and timeline are also available on the website. The website also provides an opportunity for the public to provide input on the workgroup's process of updating the TB redistribution formula to the workgroup representatives.

ACET thanked the workgroup for addressing a politically sensitive and controversial issue. Several members urged CDC to use the workgroup's activities as a key opportunity to update and make the TB redistribution formula simpler, more efficient and equitable in terms of caseload. The ACET members made a number of suggestions for the workgroup to consider in its ongoing efforts to update the formula.

- The workgroup should consider revising the formula for funding to be allocated to states rather than big cities. This approach would be more cohesive and cooperative for TB control and also would avoid confusion and competition in certain jurisdictions.
- The workgroup should review other federal funding models in which states are required to allocate specific dollar amounts to certain local jurisdictions.
- The workgroup should take caution in recommending measurable variables based on data previously reported to CDC through existing surveillance systems. The workgroup should consider incorporating social, economic, psychosocial and cultural determinants of health into the updated formula. This approach would inform NCHHSTP's ongoing research in this area.
- The workgroup should update the TB redistribution formula to capture "program excellence" and TB best practices.

Dr. Fleenor thanked ACET for providing insightful comments and suggestions for the workgroup to consider. However, he noted that ACET would not provide formal guidance on the updated TB redistribution formula during the business session because the workgroup is currently attempting to reach consensus on the methods and overall process.

Update on Regional Training and Medical Consultation Center (RTMCC) Activities

Ms. Amera Khan, of DTBE, explained that DTBE funded four RTMCCs in 2005 in New Jersey, Florida, Texas and California. The RTMCCs are regionally located to cover all 50 states and the U.S. territories and are funded to (1) provide training and technical assistance to increase human resource development in TB programs; (2) develop and distribute TB educational materials; and (3) provide medical consultation to TB programs and medical providers.

The 2005 cooperative agreement requires the RTMCCs to spend 20% of time and resources on medical consultation and 80% on education and training, including 50% on training courses and technical assistance and 30% on educational product development. The RTMCCs must also adhere to annual training requirements of providing a minimum of 200 training hours per year to at least 500 participants. Of these training courses, a minimum of 30% must be offered offsite and six mini-fellowships must be offered to support individualized training experiences.

Each RTMCC met or exceeded the minimum training requirements in 2007. The four RTMCCs collectively provided 1,185 training hours, delivered training to 7,707 healthcare workers (HCWs), and offered 24 mini-fellowships. However, CDC is considering the possibility of changing the requirement for offsite training because webinars and other distance-based learning technologies accounted for the majority of training at non-RTMCC sites.

Needs assessments and guidance from RTMCC Advisory Committees and DTBE are used to identify training topics and determine the frequency of providing training. TB program staff is the primary target audience, but the RTMCCs also offer training to public and private HCWs and overseas panel physicians. The RTMCCs provide interactive training onsite or offsite that is led by facilitators, but distance-based webinars are offered as well.

Each RTMCC offers several core courses: the TB Program Managers Course, TST Train-the-Trainer Course, Contact Investigation and Interviewing Skills Course, and Case Management Course. Each RTMCC is asked to reserve at least two seats for overseas panel physicians to attend the Clinical Intensive and Clinical Update Course. In addition to the core courses, individual RTMCCs also offer training based on specific regional needs. The specialized courses have covered TB/HIV at the border, TB and corrections, TB cohort reviews, cultural awareness in TB control, and advanced TB courses for expert nurses and medical consultants.

The RTMCC webinars have become extremely popular over the past few years. On the one hand, webinars reach large audiences, are typically held for a short duration of 1-3 hours only, are ideal for information dissemination, and do not require participants to spend travel costs or miss time from work.

On the other hand, webinars do not provide interactive skill-building training and require a computer with high-speed Internet connection, speakers or a telephone line. These technologies are not available to all programs, particularly those in rural areas. DTBE has asked the four RTMCCs to collectively offer at least one national webinar on a common topic and archive each webinar on the Internet.

In 2008, the RTMCCs have or will offer webinars on genotyping, pediatric TB, factors related to non-adherence in recalcitrant patients, and best practices to ensure supportive social services for TB patients. The RTMCCs have developed educational products in print, electronic and video formats based on identified gaps and needs of both regional and national audiences. The educational products are offered free of charge when possible.

The RTMCCs recently developed several educational products, including the *Cultural Competency in TB Care Self-Assessment Guide*; *Drug-Resistant TB Clinicians' Survival Guide*; an interactive online pediatric TB course; and the "Impact of Poor Nutrition on TB Relapse" pocket card for clinicians. The RTMCCs also created an "All Products" web page for programs to easily locate all educational products in one source.

In terms of laboratory activities, CDC and the RTMCCs performed a needs assessment in June 2008 to identify laboratory training and education needs of TB program staff, clinicians and other non-laboratorians in the United States. The RTMCCs and CDC will analyze regional and national data collected by an online service. Dissemination of the needs assessment has resulted in 797 responses to date. Results of the assessment will be used to develop laboratory training courses and educational products, enhance communications between TB programs and laboratories, and improve TB management and care.

The RTMCCs are continuing to collaborate with training partners in other agencies that provide federally-funded training courses and educational materials for AIDS, STD/HIV prevention, addiction, and population affairs and family planning. The RTMCCs recently attended a meeting to increase the 4 Training Center collaborative on STD/HIV prevention and treatment and maximize the use of federal training resources. At the conclusion of the meeting, the 4 Training Center collaborative was expanded to formally include the RTMCCs and Viral Hepatitis Education Centers.

To support the NCHHSTP PCSI Initiative, a representative from each RTMCC will attend the PCSI meeting later in June 2008. Moreover, the RTMCCs will identify additional opportunities to integrate TB, HIV/AIDS, STDs and viral hepatitis training courses and educational products.

Mr. Daniel Ruggerio, of DTBE, described key outcomes of the RTMCC Strategic Planning Summit that was held in April 2008. Representatives of the four RTMCCs, CDC, NTCA, ACET, TB controllers and laboratories, and AIDS and STD/HIV prevention training centers attended the summit. The summit focused on administrative issues, training and education, and medical consultation.

The goal of the summit was to determine the future role of the RTMCCs in several areas. Changing needs for TB training and medical consultation should be identified and addressed.

Collaborations should be established with other organizations to enhance PCSI in delivering training and medical consultation. New education and training products should be developed. Research findings should be translated into operational practice. Assistance should be given to TB programs in building human resource capacity in state and local programs. Direct patient management or consultation should be provided.

Responses to the major topics discussed during the summit are summarized as follows. In terms of balancing resource allocations between training/education and medical consultation, CDC confirmed that consideration would be given to providing RTMCCs with more flexibility to allocate resources based on needs assessments.

In terms of justifying the cost of academic affiliations, the participants pointed out that these relationships have added value to the RTMCCs due to accessibility to experts and increased credibility. However, the participants noted that academic affiliations typically have tremendous overhead costs. CDC confirmed that consideration would be given to including caps in future cooperative agreements and exploring other strategies to reduce these costs.

In terms of the potential for international involvement, the participants agreed that the RTMCCs are funded to address domestic TB needs. CDC emphasized that funds for domestic projects would not be used to support international activities because many domestic needs have not been met at this time. The participants conveyed that the RTMCCs would require additional funds and infrastructure if activities were expanded internationally in the future. The United States Agency for International Development was suggested as a potential source to support expansion of the RTMCCs internationally.

In terms of capacity building and regionalization, the participants emphasized the need for CDC to determine outcomes of Task Order 6, the implications of regionalizing the RTMCCs and laboratories, and the role of the RTMCCs in this effort. In terms of building TB nursing capacity, the participants raised the possibility of the RTMCCs offering mentoring programs and establishing nursing networks. The RTMCCs were advised to use nursing core competencies created by the National Tuberculosis Nursing Coalition to inform the development of course content targeted to nurses.

In terms of limited resources to meet education and training needs, the participants advised the RTMCCs to continue to provide webinars, utilize other distance-based training strategies, and offer mini-fellowships. However, the participants conveyed that a number of issues need further discussion, such as the development of webinars with a more collaborative process; potential strategies to collaborate in developing future TB educational products; standardized curricula and objectives for mini-fellowships; and target audiences for mini-fellowships.

In terms of laboratory training issues, CDC informed the participants that the RTMCCs would develop a laboratory training and education needs assessment for non-laboratorians. The participants emphasized the need for the RTMCCs to collaborate with the National Laboratory Training Network to deliver courses that would foster better communication between TB programs and laboratories.

In terms of translating new research findings into program practice, the participants advised the RTMCCs to (1) continue to participate in the TBESC Trip Workgroup; (2) collaborate with CDC and TB programs to determine new research findings that should be integrated in training and educational materials and develop approaches to effectively disseminate research information; and (3) identify other potential roles for the RTMCCs to facilitate the translation of research findings.

In terms of training panel physicians, the participants noted that the RTMCCs might be asked to train or develop educational resources for overseas panel physicians. The participants emphasized the need to determine whether training should be limited to panel physicians who attend RTMCC courses in the United States or if RTMCCs would be asked to assist in developing train-the-trainer courses internationally.

In terms of medical consultation, the participants agreed that TB control programs have ultimate responsibility for TB patient care and management. The participants noted that the RTMCCs should continue their efforts in implementing the medical consultation database. However, the participants pointed out that further discussion is needed to clearly define the limits of RTMCC medical consultations and the role and funding of the RTMCCs in direct patient management.

In terms of developing MDR-TB expertise, the participants agreed that RTMCCs and TB programs should be available for consultation of any drug-resistant case. However, the participants requested further discussion to determine the need for three potential strategies: (1) a formalized team approach for case management of drug-resistant cases; (2) follow-up from RTMCCs to providers to determine the status of patients; and (3) the expansion of current RTMCC MDR Network Case Conferences into a national effort.

Overall, the summit provided a forum to determine the future structure and priorities of the RTMCCs. The next steps to advance this effort include disseminating proceedings of the summit to the participants and convening meetings with DTBE senior staff and partners to identify strategies to best utilize outcomes from the summit to inform the future direction of the RTMCCs.

ACET commended the RTMCCs on conducting outstanding TB training activities. Several members made suggestions for CDC to consider in strengthening the RTMCCs in the future.

- CDC should explore the possibility of convening an expert consultation to advance the RTMCC project on factors related to non-adherence in recalcitrant TB patients. The consultation might lead to consensus to replace the word “recalcitrant” due to numerous issues that cause patients to be non-adherent to TB treatment.
- CDC should implement an innovative model in which 10% of funds would be diverted from the RTMCC budget. States would use these and matching funds to purchase RTMCC services. The cooperative agreement requires the RTMCCs to provide training to states, but regional training activities are generally prioritized. The proposed model would allow states to attend relevant RTMCC training activities outside of their regions. CDC should develop rigorous criteria to justify situations in which the model could be applied.

- CDC should take caution in opening training courses to states outside of their respective RTMCC regions. RTMCCs do not have sufficient funding and staff at this time to fully meet the training needs of states within their respective regions. RTMCC training courses are typically filled to capacity or have waiting lists of TB program staff.
- CDC should leverage resources and expertise from the Health Resources and Services Administration (HRSA) to strengthen its TB training activities. For example, HRSA's Area Health Education Centers are located throughout the country and HRSA regularly convenes meetings with large groups of providers who could benefit from TB training. RTMCC representatives could conduct training courses during these meetings.

Drs. Ijaz and Wanda Walton, of DTBE, informed ACET that human resource development funds included in the TB cooperative agreement can be used for states to attend training activities outside of their RTMCC regions. However, they clarified that the ultimate goal of CDC's TB training activities is for states to use training materials, technical assistance and other resources to build capacity to conduct training courses independent of the RTMCCs.

Overview of CCID Informatics Activities

Ms. Tonya Martin, Senior Advisor for Informatics at CDC, explained that the CCID Informatics Office was established to achieve four overarching goals. CCID programs will be strengthened through innovative applications of information science and information technology (IT). Informatics leadership will be provided. IT best practices will be promoted and implemented across CCID. Cross-functional collaboration will be facilitated between CCID and its partners.

The Informatics Office develops, conducts, manages and supports a variety of activities, including surveillance systems, data collection from field surveys, data standards, informatics support during public health emergencies, IT projects, portfolios and information, IT systems architecture, information protection, IT systems security, and Internet and Intranet support.

The Informatics Office is involved in a number of interoperability projects that focus on the use of data standards to facilitate the exchange of public health data. The Informatics Office is also positioning its systems to advance health information exchange through the development and use of standard health data language. Interoperability projects the Informatics Office is currently conducting are described below.

CDC and IHS collaborated to develop and pilot the "Map to Logical Observation Identifier Names and Codes (LOINC) Project" at five sites. Due to the success of the pilot, the project was subsequently expanded to ~75 IHS medical facilities. The goal of the project is to develop a semi-automated process to map local laboratory test files to LOINC at IHS medical facilities.

An automated mapping tool was designed for each facility to standardize $\geq 66\%$ of laboratory names to LOINC. Standardized laboratory names allowed IHS to more easily aggregate laboratory data for disease surveillance and clinical and administrative reporting efforts. The LOINC project resulted in a number of benefits to IHS, including its clinical data repository,

diabetic audit reporting, data warehousing, Government Performance Result Act reporting, interoperability with other information systems, and HIV Case Management System.

CDC created the “Public Health Laboratory Interoperability Project” (PHLIP) in FY’07 to achieve a number of key objectives. Bi-directional laboratory exchange would be facilitated among state public health laboratories (PHLs), CCID laboratories and local partners. Tests and test results would be harmonized and consistently represented with standard vocabularies. Detailed vocabulary implementation guidelines would be developed and disseminated to PHLs and their partners. A process would be established for electronic test ordering and result reporting. Data quality, accessibility and data sources for active surveillance would be improved.

Participants in the PHLIP pilot include six PHLs, CCID laboratories, APHL and the CDC National Center for Public Health Informatics. The PHLIP pilot is expected to accomplish a number of outcomes. A sustainable architecture for laboratory data exchange will be piloted between states and CDC and among states. Regional laboratory data exchange will be facilitated and test messages will be validated. Additional message partners beyond influenza will be identified. Message types will be expanded beyond the National Notifiable Diseases System.

To date, CDC and its partners have published an *Implementation Guide*, a *Mapping Workbook*, and *Encoding Guidelines* to report influenza results. A Community SharePoint Portal was launched with PHLIP artifacts. A protocol was developed, tested and deployed to production in four pilot states to send unsolicited result messages for influenza to the Health Level 7 (HL7) system version 2.3.1. CDC’s Public Health Information Network Messaging System was configured in the pilot PHLIP states. Collective knowledge and lessons learned were described in a primer that will be shared with states outside of the PHLIP pilot.

CDC is focusing on the “TB Case Notification Message” effort to make the transition from the Tuberculosis Information Management System (TIMS) to the National Electronic Disease Surveillance System (NEDSS). States will begin using the revised RVCT in January 2009 to report TB cases. The NEDSS HL7 TB Case Notification Message will be used as the reporting mechanism for the revised RVCT. TIMS will not be modified to include the revised RVCT.

Reporting areas will be allowed to select one of four options to report data with the RVCT: CDC’s NEDSS Base System, CDC’s new electronic RVCT software, commercial systems, or existing systems developed by states. The TB Case Notification Message includes both RVCT and *MMWR* reporting. A vocabulary and guides have been published for the current RVCT and will be updated for the revised RVCT.

CDC is also implementing a TB Message Validation Project to demonstrate its capacity in validating HL7 messages upon receipt. A Content Validation Reasoner Project was created with TB validation rules from TIMS for the current RVCT. The next steps in this effort will be to analyze error and alert data, develop a user interface to maintain rules, and report errors to sending programs.

Update on CDC's TB Surveillance Activities

Dr. Thomas Navin, Chief of the DTBE Surveillance, Epidemiology and Outbreak Investigations Branch, explained that TB is reportable in all states through clinic-based or laboratory-based reporting. Standardized report forms are electronically transmitted to CDC and DTBE believes the completeness of reporting is >90%.

TB surveillance reports submitted to CDC fall into one of three categories. Laboratory-confirmed cases account for 79% of reports. Clinically-defined cases account for 12% of reports as defined by positive TST results, abnormal CXR, symptoms consistent with TB and TB treatment. Provider diagnosis cases account for 9% of reports. CDC changed from aggregate data collection to case-based reporting in 1985.

The significant decline in 1993 of reported TB cases in the United States represents the public health success of expanded case-based reporting with the RVCT form. TB trends from 1993-2007 showed that the TB case rate decreased by 7.3% annually prior to 2007 and by 3.8% annually after 2007. Based on the current annual decline of 3.8%, 100 years would be needed to achieve the TB elimination goal of 1 case/1 million population. The TB elimination goal could be achieved by 2050 if the rate of decline was accelerated to 8.8% annually with new diagnostic tools, new and shorter treatment regimens, or an improved TB vaccine.

Data collected from 1993-2007 on the number and rate of TB cases among U.S.-born persons and FBPs showed a dramatic difference between the two groups. However, TB rates among FBPs in the United States are decreasing. Data collected from 1999-2000 showed the LTBI prevalence to be 1.8% among U.S.-born persons and 18.7% among FBPs. Of foreign-born TB cases in the United States, Mexico accounted for 25%, the Philippines accounted for 11%, Vietnam accounted for 8%, India accounted for 7%, and China accounted for 5%.

Data collected from 1993-2005 showed that the percentage of persons with MDR-TB decreased at a much higher rate than persons with INH resistance. Data collected from 1993-2006 showed a dramatic difference in primary MDR-TB between U.S.-born persons and FBPs. The percentage of cases among U.S.-born persons declined from ~2.5% in 1993 to <1% in 2006. The initial success in decreasing the percentage of MDR-TB cases in FBPs has been stable since 2000.

Data collected from 1993-2007 showed that an extremely small number of XDR-TB cases have been reported in the United States. U.S.-born persons accounted for 65% of XDR-TB cases from 1993-1999 and 25% of cases from 2000-2007. FBPs accounted for 9% of XDR-TB cases from 1993-1999 and 75% of cases from 2000-2007. HIV-positive persons accounted for 14% of XDR-TB cases from 1993-1999 and 10% of cases from 2000-2007. HIV-negative persons accounted for 14% of XDR-TB cases from 1993-1999 and 45% of cases from 2000-2007.

CDC has made significant investments to enhance MDR-/XDR-TB surveillance and awarded funds to four programs in California, New York City, Florida and Texas to pilot a study. The project includes expanded data collection to gather additional information on DST results,

treatment information and outcome data. Both counted and uncounted cases from January 2000 to June 30, 2007 are included in the study. Data collected for the study will be entered and analyzed during the summer of 2008.

DTBE created an outbreak surveillance system based on universal genotyping, geospatial clustering analysis, temporal analysis and sociodemographic factors. Techniques used in the TB genotyping program include spacer oligonucleotide typing (spoligotyping), mycobacterial interspersed repetitive units (MIRU), and restriction fragment length polymorphism. The CDC laboratory and two contract laboratories in California and Michigan perform spoligotyping plus MIRU as part of the National TB Genotyping Service. Since 2004, 25,659 isolates have been genotyped and matched with surveillance data.

The genotyping program had a tremendous public health impact during an outbreak of 30 TB cases in Indiana and nine TB cases in neighboring states in 2005. Interviews and record reviews did not establish epidemiologic links between cases in two counties in Indiana, but the genotyping program identified a clear association. The approach to cluster analysis used in the Indiana outbreak was refined and incorporated into the outbreak surveillance system. Dr. Navin presented a live demonstration of DTBE's refined genotyping algorithm.

DTBE will collaborate with TB controllers over the next few months to determine whether the refined genotyping approach will be useful in formatting data; identify other types of data of interest; and explore other strategies to collect, analyze and report data to assist TB controllers in allocating resources to detect and investigate potential TB outbreaks, aberrations or unusual clusters at the local level.

Dr. Flood's position was that the ability of the outbreak surveillance system to sort and display data would assist California and other states with overwhelming amounts of data to review in detecting unusual TB clusters. She advised DTBE to include pediatric TB cases in the refined genotyping algorithm, particularly children <5 years of age who might be more specific for recent transmission.

Dr. Lopez de Fede suggested that DTBE allocate resources and train TB programs on the use of the refined genotyping technology. She noted that this approach would make better use of limited resources because TB controllers would have the ability to detect and investigate cases at the local level.

Update on TBTC

Dr. Andrew Vernon, Chief of the DTBE Clinical and Health Systems Research Branch, reported that the 2007 review of TBTC included an internal review of the scientific agenda by the TBTC Core Science Group; an external review of the scientific agenda; and a peer review of the TBTC Intramural Research Program as required by CDC's peer review policy. The external and peer review panels included national and international experts from a diverse and respected group of academic institutions, federal agencies, nonprofit organizations and commercial entities.

Of 27 TBTC sites in 2007, 23 were located in North America and four were located in Brazil, Spain, Uganda and South Africa. The review panel was asked to evaluate TBTC in the areas of its strengths and limitations, contributions to the global effort to improve TB treatment, and research that needs to be conducted. The Core Science Group suggested three philosophic underpinnings to guide the review: 1). TBTC should maintain its focus on areas of strength; 2). TBTC should retain its close linkages to TB public health programs; and 3). TBTC should sustain and build its partnerships and collaborations.

The review panel provided general advice on the future direction of TBTC. Collaborations should be increased with laboratory scientists, AIDS clinical trials groups and other TB trials groups to gather more data on biomarkers and HIV/TB co-morbidity. The possibility of periodically convening a TBTC-sponsored global forum for TB trials should be explored. Collaborations with NIH should be strengthened to address funding problems. TBTC peer reviews should be held on a regular basis.

The review panel identified the two highest priorities for TBTC. For LTBI, enrollment of Study 26 should be completed. For active TB, efforts should be continued in linked Phase II and III trials to develop treatment-shortening regimens. The review panel provided guidance on other potential TBTC trials. Caution should be taken in conducting MDR-TB trials, but involvement in HIV/TB co-morbidity trials should be continued. Pediatric TB trials should be conducted only after new regimens have been evaluated in adults. Diagnostic trials should be conducted only in conjunction with a planned randomized trial. The Intramural Research Program Review panel agreed with the key findings of the External Agenda Review panel and strongly recommended continued support for TBTC.

TBTC has taken a number of actions in response to recommendations from the 2007 review. Enrollment in Study 26 focusing on LTBI was completed. Follow-up and sub-studies are underway to enroll a larger number of HIV-positive patients and young children. Study 28 focusing on active TB was completed. Microbiology findings from this study were extensively reviewed and reanalyzed.

Study 29 will be initiated in the summer of 2008 as a Phase II trial focusing on a higher dose of daily rifapentine. Results of the trial could form the basis of a treatment-shortening regimen for active TB. Based on outcomes from the Phase II trial, TBTC could be poised for the design and implementation of a Phase III trial.

CDC allocated new funds for TBTC to conduct Study 30 focusing on a regimen of once-daily linezolid in MDR-TB patients. The study will be initiated in the fall of 2008 in Durban. In 2008, TBTC will participate in antiretroviral rifapentine interaction studies focusing on HIV/TB co-morbidity. TBTC plans to collaborate with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group on pediatric TB studies focusing on pharmacokinetics and tolerability of rifapentine.

TBTC has been selective in conducting two key diagnostic studies: biomarker research on time-to-detection in liquid culture and a microbiology supplemental study in Uganda. TBTC has

substantially increased its collaborations with a number of external groups. The re-competition of TBTC will be peer reviewed. TBTC hopes to address its funding problems.

In addition to responding to the recommendations of the 2007 peer review, TBTC leadership met with the Scientific Advisory Group of Experts (SAGE) in March 2008. The presentations covered TBTC's major accomplishments from 1995-2007, including ongoing studies and collaborations, influential trials, reestablishment of the clinical research infrastructure for TB in the United States, restoration of CDC's leading role in TB clinical research, creation of a new model for research partnerships between the public health system and academic medical centers, and training of a new generation of TB researchers in the United States.

TBTC also described its accomplishments in leveraging CDC support to attract funding from other groups to further the TBTC agenda and establishing semi-annual TBTC meetings as major venues for TB trials worldwide. At the time of the SAGE meeting, a total of 11,524 persons had been enrolled in major TBTC studies and sub-studies.

TBTC informed SAGE of a number of key points. The median cost per patient enrolled in TBTC studies was ~\$6,000; investigators in other trials groups found TBTC costs to be quite low. TBTC is exploring approaches to better estimate, assess and compare costs.

TBTC will demonstrate the non-inferiority of a three-month/once-weekly LTBI treatment regimen by 2010 if Study 26 is successful. TBTC will demonstrate the efficacy of a three-month TB treatment regimen by mid-2013 if Studies 29 and 31 are successful. If both sets of studies are successful, TBTC estimates that tens of millions of dollars could be saved domestically by a combination of shorter treatment durations for both active TB and LTBI.

TBTC highlighted changes to its sites. The composition of TBTC has evolved to reflect scientific needs and funding realities. Several sites outside of North America were added and a number of sites within North American were closed due to budgetary pressures and quality issues. New workgroups and partnerships have been formed; including the Community Research Advisory Group, Drug Induced Liver Injury Network, Microbiology Workgroup, MDR Workgroup, AIDS trials groups, and the Joint U.S. Partnership Implementing TB Elimination Research with the National Institute of Allergy and Infectious Diseases.

TBTC emphasized that its unmet needs include standardized laboratory processes, stable funding indexed to inflation and adequate support to investigators. TBTC will be re-competed in 2009 and its reconfiguration will be driven by public health and scientific needs, availability of patients and funding.

Fiscal attrition was a major concern at the time of the 2008 SAGE meeting. From 2005-2008, two TBTC sites were closed, funding was reduced at three sites, and eight sites were decreased to a "closeout" mode. During the meeting, TBTC presented a graph to illustrate funding disparities between TBTC and other infectious disease research programs for HIV/AIDS, AIDS clinical research and anthrax.

TBTC informed SAGE that in addition to executing trials, its charge also includes developing science and determining important trials to conduct. DTBE noted that current resources would need to be increased by ~50% to support additional costs of the 2009-2019 re-competition.

These costs including increased business at overseas sites, more regulatory and registration costs for clinical trials, management of experimental active drugs and placebos, centralized and standardized laboratory activities, oversight of laboratories conducting clinical trials, expanded clinical site monitoring and data management activities, increased travel and shipping costs, and increased investigator support in light of local cost pressures.

Dr. Vernon shared his vision for the “new” TBTC in the 2009-2019 re-competition. Domestic and high-burden sites will be combined. Capacity will be strengthened for TBTC to enroll ~1,000 patients in treatment trials each year. New international partner sites will be established with leading external partners and new relationships with CDC field research sites. Quantitative microbiology and animal modeling studies will be incorporated into TBTC in a complementary fashion. International experts will be formally engaged.

He proposed a step-wise process to achieve the new vision for TBTC in 2009-2019. In 2009, ~13 domestic TBTC sites would be decreased to a closeout mode; ~3-4 new international partner sites would be added through contract mechanisms; trials would be conducted at ~1-2 CDC field research sites; and ~1-3 expert positions would be funded.

In 2010, 8-12 domestic TBTC sites would be closed; enrollment would be launched at international sites; collaboration with the Tuberculosis Research Unit on microbiology studies would be continued in a more robust manner; and current collaborations on murine studies would be strengthened and formalized. In 2011-2019, TBTC trials would be continued and collaborations would be expanded.

Overall, external reviewers provided DTBE with an excellent assessment of TBTC. TBTC has made outstanding progress since the 2007 external review. Current fiscal realities emphasize the critical need to either increase funding support or decrease activity and slow progress.

Dr. Fleenor confirmed that ACET would formulate guidance on the need for additional resources and partners to TBTC at a later time.

Update on CDC’s Public Health Law and TB Control Activities

Dr. Richard Goodman, of the CDC Public Health Law Program, explained that the overarching aim of CDC’s TB legal preparedness activities is to improve understanding of the status and sufficiency of state laws for TB control and prevention among practitioners and other groups in the setting of progressively emergent drug-resistant TB. CDC and the Centers for Law and the Public’s Health are conducting research and developing resources for TB legal preparedness in five major areas.

Activity 1. Express laws for TB control within selected states and local jurisdictions were reviewed and characterized. The goal of this activity was to examine, organize and characterize legislative, regulatory or judicial case laws in 24 states and New York City that expressly relate to the control of TB, MDR-TB or XDR-TB through state or local health departments, other governmental actors and private-sector partners. The review focused on express TB control laws and excluded general communicable disease laws.

Findings of the review will be used to inform the development of a model act on state and local TB control and a practice-directed handbook; prepare and nationally disseminate a full report on patterns, gaps and options for strengthening and harmonizing TB control laws; and serve as a resource for ACET to review its 1993 recommendations and consider future reviews or guidance.

A survey template was developed to organize TB control laws in six categories: (1) prevention of TB cases, including general preventive measures; (2) identification of TB cases, including measures to confirm cases through screening, examination and reporting; (3) management of TB cases, including measures to manage confirmed cases through investigation, treatment and other specific tools; (4) safeguarding of rights, including measures to protect the rights of patients through due process, confidentiality, anti-discrimination and religious exemptions; (5) special populations, including TB control measures and laws targeting specific groups; and (6) additional TB provisions that are not otherwise covered in the other five categories.

Key findings from the review are summarized as follows. Most jurisdictions have express laws addressing the prevention, identification and management of TB cases and due process. A minority of jurisdictions has express laws related to selected safeguards for patients with TB, such as privacy and confidentiality, religious exemption and anti-discrimination. A minority of jurisdictions has express laws addressing inter-jurisdictional issues in TB control. Of the 25 selected jurisdictions:

- 84% have laws that appear to authorize regulation and establishment of TB control plans by various government levels;
- 94% have laws that address identification of cases;
- 100% have laws that authorize TB screening;
- 88% have laws that authorize use of diagnostic examination and testing to determine TB;
- 96% have laws that establish reporting requirements;
- 96% have laws that authorize health officials to prescribe appropriate treatments for TB patients;
- 80% have laws that permit isolation;
- 68% have laws that permit emergency detention;
- 44% have laws that permit quarantine;
- 80% have laws with other restrictions;
- 68% have laws encompassing rights to due process;
- 44% have privacy and confidentiality laws; and
- 36% have religious exemption laws; and

- 8% have anti-discrimination laws.

A number of limitations were identified during the review. The findings only represent 24 states and one jurisdiction. The review excludes general communicable disease laws and does not characterize the adequacy of the overall legal framework for TB control in states. Findings regarding laws that protect the rights of TB patients may be limited because those protections are likely provided in many state general communicable disease statutes of public health powers or administrative procedure acts.

Activity 2. Officials were convened from relevant sectors to perform a scenario of TB control laws in Kansas and Florida in May 2008. The scenario was designed to assess participants' understanding of the sufficiency of TB control laws and identify potential gaps in legal authority that might inform the development of the TB control model act. The methodology and scenario-based assessment tool can be made available for other states and jurisdictions to use.

The scenario illustrated issues included in legal authorities applicable to (1) screening persons potentially exposed to TB in settings where institutions are uncooperative with public health officials; (2) ordering persons into home isolation in situations of non-voluntary compliance; (3) preventing infectious non-U.S. citizens from leaving the country by commercial airline flights; (4) considering due process for infectious non-U.S. citizens; (5) governing concurrent jurisdiction over infectious persons in international airports and other settings; and (6) identifying government agencies with responsibility for transporting infectious persons from settings, such as from airports to hospitals, and covering associated costs.

Activity 3. Selected tribal laws for TB control will be identified, reviewed and characterized to inform the development of the TB control model act. Data sources for this activity include the National Tribal Justice Resource Center; Tribal Court Clearinghouse of the Tribal Law and Policy Institute; HHS Office of the General Counsel; and tribes with existing TB control laws, such as the Mississippi Band of Choctaw Tribe, White Mountain Apache Tribe, Oglala Sioux Tribe, Navajo Nation, and Poarch Band of Creek Indians.

Activity 4. A model act on state and local TB control will be developed based on information from the review of state laws and the scenario-based assessment. The model act will serve as a tool for state and local public health officials, policymakers, legislators and other groups to use in reviewing and potentially strengthening laws for preventing and controlling TB in their individual jurisdictions.

The Centers for Law and the Public's Health have completed a number of activities and will perform additional tasks to develop the model act. The study of state TB laws and the draft *TB Control Law Handbook* were completed in May 2008 and shared with CDC. An initial blueprint of the model act was prepared and disseminated to subject matter experts and partners for preliminary review in June 2008.

A presentation was made during the NTCA meeting in June 2008 regarding the suite of TB law activities. A breakout session was also held during the NTCA meeting for participants to review and provide feedback on the model act blueprint. The blueprint will be finalized in August 2008

based on input submitted by experts. The initial draft of the model act will be completed in October 2008. The model act will be substantially revised in November 2008 based on feedback submitted by experts. The model act will be finalized in December 2008.

Activity 5. A *TB Control Law Handbook* will be created to improve understanding of and competency in applying these laws. The target audiences of the handbook will include public health practitioners who are active in TB control at local, state and tribal levels as well as their legal counsel. The handbook will focus on pertinent local, state and tribal laws and essential information on federal and international laws, such as the International Health Regulations. The handbook will be available in print and electronic formats and an instructional PowerPoint presentation will be created for education and training purposes.

The handbook will be structured with six major sections: the principles of public health practice for TB control; a general legal framework for disease control; communicable disease control law; TB control law; legal controversies in TB control law; and TB control law in practice. The first section would be primarily targeted to attorneys.

The ACET members suggested a number of next steps to revise and finalize the TB legal preparedness activities and products.

- The CDC Ethics Committee should review the TB legal preparedness activities to ensure that ethical issues are considered in the development of these products.
- ACET should make a formal request for CDC to define a “model facility” to administer compulsory TB treatment when needed.
- ACET should make a formal statement to urge states and local jurisdictions to apply the scenario-based assessment tool before taking drastic measures in developing and enforcing new TB control laws. States could use the CDC-tested tool to strategically and methodically ask local legislators to make significant changes to existing TB control laws.
- The background section of the handbook should provide guidance on the critical need to apply solid public health practices to individuals upfront before enforcement of TB control laws is necessary.
- The model act should address additional gaps, such as problems with TB patients in ICE custody and inter-jurisdictional issues, particularly in border states.

With no further discussion or business brought before ACET, Dr. Fleenor recessed the meeting at 5:35 p.m. on June 17, 2008.

Update by the ACET TB in African Americans Workgroup (AAWG)

Dr. Fleenor reconvened the ACET meeting at 8:34 a.m. on June 18, 2008 and yielded the floor to the first presenter.

Mr. Shannon Jones III is an ACET member and chair of the AAWG. He reported that ACET charged AAWG with developing a strategic plan of action and formulating recommendations regarding the disproportionate burden of TB among AAs in the United States. AAWG was formed in July 2007 with multidisciplinary experts representing programs, research, social services, communications and evaluation.

During the November 2007 ACET meeting, AAWG presented its recommendations on TB in AAs in the areas of research, protocols and guidelines, and community awareness and outreach. ACET unanimously approved and CDC adopted AAWG's recommendations. Mr. Jones reminded ACET of AAWG's recommendations in the three focus areas.

In its "research" recommendations, AAWG advised CDC to conduct studies on (1) the impact of educational attainment on health literacy and the TB health disparity in AAs and (2) epidemiological impacts of poverty, employment, segregation, unstable housing and other socioeconomic factors on the TB health disparity in AAs.

In its "protocols and guidelines" recommendations, AAWG advised CDC to take the following actions. Culturally appropriate and appealing fact sheets, CDC's TB screening, diagnostic and treatment algorithms for TB and LTBI, and other materials should be disseminated to the medical community. A TB toolkit should be developed for AA providers and other groups that serve the AA community.

The toolkit should include (1) posters for waiting rooms and other targeted settings similar to those developed by Chicago, Georgia and South Carolina under TBESC Task Order 11; (2) fact sheets that describe the impact of TB on project areas; and (3) templates and other products to educate, mobilize and raise awareness in communities. The toolkit should be widely distributed, particularly in AA communities with high TB rates.

In its "community awareness and outreach" recommendations, AAWG advised CDC to take the following actions. Councils or advisory boards should be established in areas with the highest TB rates among AAs, particularly in Southeastern states. Members of these groups should reflect all sectors of the community. Culturally appropriate standards of care and other products for the medical community should be created to inform providers of the critical need to treat AAs with TB.

Television and radio media campaigns should be launched to raise public awareness of the TB/HIV disparity in AAs. The "asthma bus" and other best practices from other disease programs should be replicated for TB in AAs and implemented in communities. Celebrities and respected leaders should be recruited for media campaigns to deliver messages about TB in AAs.

Ms. Gail Burns-Grant, of DTBE, provided DTBE's formal response to the recommendations on the TB health disparity in AAs. DTBE established several Division-wide priorities during a retreat in February 2008: interrupt transmission of *Mycobacterium tuberculosis* (M.tb); reduce TB in FBPs and racial/ethnic populations; mitigate and reduce the impact of MDR-/XDR-TB; and reduce HIV-associated TB.

Since 2002, DTBE has conducted a number of activities and allocated funds to address the TB health disparity in AAs. A consultation and summit were convened for federal partners, AA leaders, community organizations and other representatives from various sectors to commit to concrete action steps to address TB in AAs. Demonstration projects in Chicago, Georgia and South Carolina were implemented and evaluated to intensify efforts to reduce TB in AAs.

A research study focusing on overcoming barriers to LTBI treatment adherence in the Southeast led to the development and dissemination of a successful intervention. The University of South Carolina was funded to conduct and disseminate a three-site evaluation across demonstration projects. National indicators were developed and included in the TB cooperative agreement to provide additional funding to project areas with ≥ 50 TB cases in U.S.-born AAs and areas with a high burden of TB/HIV co-infection.

Collaborations between DTBE and project areas are ongoing to achieve previous goals and objectives that were established to address TB in AAs. Opportunities were maximized with Historically Black Colleges and Universities by providing student internships and investing in future public health leaders. The use of carryover dollars was authorized and TB cooperative agreement funds were redirected to support programmatic efforts to address TB in AAs. DTBE's activities to promote and enhance PCSI initiatives are ongoing.

DTBE staff in all seven branches recently submitted a funding proposal to establish a new cross-Division Health Disparities Workgroup (HDW) with a multidisciplinary team representing fiscal issues, research, programs, surveillance, evaluation and communications. The mission of HDW would be to collaborate with partners to eliminate disease disparities in populations affected by TB. The concept for HDW was not funded, but resources might be available at the end of FY'08 to support this effort.

In response to ACET's "research" recommendations, DTBE will inventory former and current research initiatives to determine gaps. Resources will be identified and findings from DTBE research projects will be utilized to establish a research agenda for TB, TB/HIV co-morbidity and other diseases. The research agenda will be designed with planning, development, evaluation and implementation components. Best practices for translating research into practice will be identified and implemented.

In response to ACET's "protocol and guidelines" recommendations, DTBE will collaborate with the RTMCCs to inventory current TB diagnostic and treatment policies and guidelines and evaluate whether these protocols are appropriate for the target audience. Opportunities and gaps in this focus area will be identified.

Focus groups and other forums will be convened to determine best practices for closing gaps and leverage resources that will lead to desired outcomes among public and private medical providers who serve the AA community. Activities and interventions will be implemented and evaluated to close gaps in this focus area, such as sponsoring video conferencing rounds and including TB in AAs in medical school curricula.

In response to ACET's "community awareness and outreach" recommendations, DTBE will collaborate with partners to inventory current activities and products. Pilot testing and other methods will be utilized to strengthen existing products and media campaigns. DTBE's current community awareness and outreach products targeted to TB in AAs include the "Stop TB in the AA Community" electronic mailing list and website; the *TB Challenge Newsletter*; fact sheets and posters; and a toolkit with a DVD and agenda templates. Best practices will be utilized to partner with the community, celebrities and other influential leaders in the AA community and also to evaluate the impact of these products.

To advance ACET's TB in AAs recommendations, DTBE will improve communication and coordination to enhance the flow of information across divisions and with partners. Activities will be prioritized in a strategic planning process to achieve DTBE's national objectives, develop an action plan with timelines for the recommendations, and report on HDW's progress.

HDW, DTBE senior management and external partners will be involved in implementing activities to ensure priorities are coordinated. Evaluations will be conducted on a regular basis to measure progress in achieving HDW's goals and objectives. DTBE will remain engaged to address the AA community and its history of disenfranchisement in terms of health, education and distribution of wealth.

ACET commended DTBE on developing an action plan to respond to the recommendations on TB in the AA community. The members made a number of suggestions and comments for DTBE to consider in advancing this effort.

- Congress has encouraged a group of non-governmental organizations to develop a National HIV Strategy. DTBE should partner with this group to advance the TB in the AA agenda, particularly to address HIV/TB co-morbidity.
- DTBE should encourage states to use genotyping data to answer questions related to the TB health disparity in the AA community.
- DTBE should link geospatial analyses to its genotyping tool to develop a strong epidemiologic profile to determine the geographic distribution of TB in the AA population, identify and characterize growing clusters, and detect "hot spots" of transmission. This approach would be beneficial in targeting interventions to AA communities.
- Epidemiologic data on death disparities that show higher case fatality ratios in AAs ≥ 45 years of age should be widely distributed to increase advocacy and leverage resources for TB in AAs.
- DTBE should explore the possibility of establishing a booth at the upcoming National Medical Association (NMA) meeting to present its DVD on TB in the AA community.
- DTBE should link its activities on TB in AAs to the new TB web page on the web site of HRSA's Health Disparities Collaborative Initiative.
- DTBE should revise the national indicator of "project areas with ≥ 50 TB cases in U.S.-born AAs" in the TB cooperative agreement. Most areas of the country would ignore this language and would not receive funding under this objective because many states have < 50 TB cases in their entire populations.
- DTBE should ensure that its activities on TB in AAs are targeted to correctional institutions to educate practitioners on recognizing TB. Persons in correctional settings

who are symptomatic or have abnormal chest x-rays are often missed and are not immediately diagnosed, isolated and treated for TB.

- DTBE should partner with Results International and use ACET's liaison representative to the Treatment Action Group (TAG) to strengthen advocacy for TB in the AA community.

Dr. Fleenor confirmed that DTBE's progress in responding to the recommendations on TB in the AA community would be placed on ACET's future agendas on an ongoing basis. These updates would include a report by Dr. Castro during the next ACET meeting regarding his presentation to NMA.

Update by the Foreign-Born Workgroup (FBWG)

Dr. Dolly Katz, of DTBE, reported on FBWG's activities since the previous ACET meeting. FBWG is currently addressing a major issue in its ongoing efforts to update CDC's 1998 "Recommendations for Prevention and Control of Tuberculosis Among FBPs." Both TST and IGRAs are approved for all testing indications, including contact investigations, evaluation of recent immigrants who had BCG vaccination, and TB screening of HCWs and other groups undergoing serial evaluation.

FBWG is attempting to determine whether recommendations for testing of FBPs should be changed to provide stronger support for IGRAs as first-line screening tools when efforts are made to identify TB infection in FBPs. On the one hand, FBWG agreed on three key issues to include in the updated guidelines. BCG status should not affect decisions to treat TST-positive persons who otherwise would meet criteria for determining TB infection. IGRAs are more specific than TST. Neither TST nor IGRAs should be used to rule-out active disease in persons with symptoms or x-ray findings that are consistent with TB.

On the other hand, FBWG identified two key questions that need further discussion and input from ACET. First, what is an appropriate level of support the updated guidelines should give on using IGRAs in FBPs? Current CDC guidelines state that TST and IGRAs can be used interchangeably depending on local circumstances and decisions. Second, should the updated guidelines state that IGRAs for FBPs are better than TST and should be considered as first-line testing mechanisms for ruling-out TB infection in FBPs?

The ACET members made a number of comments to assist FBWG in answering the two key questions Dr. Katz posed.

- IGRAs are the best tests for HCWs and FBPs because TST has traditionally over-treated and over-diagnosed TB infection in these groups. However, no data have been gathered to date on long-term follow-up with IGRAs.
- IGRAs are more specific and better than TST, but issues related to implementation of IGRAs have not been addressed to date. Most notably, IGRAs are not available at this time in many cities and counties and funding is not adequate at the local level to pay for

IGRAs. Although the evidence-based foreign-born guidelines will address the science of IGRAs, implementation issues and other barriers must be considered as well.

- FBWG should not attempt to determine whether IGRAs for FBPs are better than TST. With this approach, the updated foreign-born guidelines would be inconsistent with the current QuantiFERON (QFT) statement.
- DTBE should prioritize research to determine the ability of IGRAs to predict progression to disease as well as their capacity to address pediatric contacts and HIV infection in terms of QFT use. Existing data on IGRAs are not sufficiently definitive at this time to inform the updated foreign-born guidelines. ACET should strongly support the use of IGRAs, but recommend collection of additional data at the local level.
- FBWG should review outcomes from DTBE's upcoming expert consultation to answer the two key questions.

Overview of the Office of Management and Budget (OMB) Clearance Process

Dr. Navin explained that Institutional Review Boards conduct OMB reviews of scientific studies to assure ethical appropriateness of the research, protection of human subjects, and minimal burden on the public in data collection in accordance with the Paperwork Reduction Act (PRA). OMB reviews were recently conducted for four DTBE research projects: surveillance of adverse events associated with LTBI treatment, the revised RVCT, TBESC studies, and Aggregate Reports for TB Program Evaluation. OMB either approved or exempted all four of the research projects.

DTBE presented a compelling case to exempt TBESC studies from OMB review when TBESC was originally established. DTBE highlighted its role as a technical advisor to TBESC, the role of external investigators and contractors in conducting research, and ownership of data by TBESC rather than CDC. However, the CDC Procurement and Grant Office determined that three TBESC studies would be subject to the PRA in 2008 based on a new interpretation of existing CDC policy. HHS subsequently clarified in writing that current and future TBESC studies would be exempt from OMB review in perpetuity.

CDC's new interpretation of existing policy has led to an enormous increase in the burden for DTBE to comply with PRA regulations. The need for scientists to respond to this requirement has paralyzed CDC's ability to conduct core activities and disseminate research findings in a timely manner.

Dr. Terence Chorba, Associate Director for Science of NCHHSTP, reported that the PRA was established in 1995 to regulate the collection, storage and use of information collected from the public by the U.S. government. Systematic data collection efforts involving ≥ 10 persons are subject to the PRA.

HHS makes PRA requests on behalf of staff in each of its agencies and offices. The OMB review or clearance process is independent of human subjects research and determinations. CDC has been in a remedial mode over the past two years for being too permissive with the

PRA and is now being closely watched for violations. Most notably, CDC's Office of the Chief Science Officer (OCSO) recently informed NCHHSTP of its non-compliance with the PRA in at least five projects. Consequences of PRA violations would affect both CDC and the individual project.

Dr. Vishnu-Priya Sneller, OMB Coordinator for NCHHSTP, explained that the PRA requires OMB to review data collection to improve the quality and practical utility of information required by the federal government and reduce the paperwork burden on the public. The PRA covers data collections outlined in current regulations and published as final rules; those contained in proposed rules and published for public comment; and those used to meet other needs, such as general statistical purposes.

OMB's interest in program evaluations and studies is based on an authorizing statute; development of a program mission or strategic plan; and program administration, management and evaluation. OMB clearance is required when the federal government collects or sponsors the collection of data from ≥ 10 persons using a standardized data collection instrument or format. OMB clearance covers both research and non-research activities regardless of the format or method, such as hard copies, electronic materials, telephone surveys, focus groups or one-on-one interviews.

The OMB Office of Information and Regulatory Affairs performs three basic functions: (1) oversee and coordinate regulatory policy and information collected by the federal government; (2) coordinate statistical policies, budgets, standards, long-range plans and international activities; and (3) develop and oversee government-wide information policy and IT policy. A regular OMB review can require up to three years for clearance and an emergency OMB review can be completed in six months.

The data collection statute covers any action by a federal agency involved in obtaining voluntary or mandatory information resulting in a benefit. These actions include questions asked by contractors or grantees that are sponsored by the agency and surveys to assess program performance.

OCSO formed a workgroup in 2007 to create a framework, system, standards and guidelines for CDC to become more compliant with the PRA and respond to HHS. The OCSO Information Collection Review Office (ICRO) processes documents for OMB reviews and HHS certifications. Of all CDC operating units in 2007, NCHHSTP had the second highest number of information collection requests (ICRs) processed under the PRA.

Actors in the ICR process at CDC include the investigator, National Center PRA contact and oversight official, IRCO administrative staff and manager, and Office of Scientific Regulatory Service Director. After approval at the final level within CDC, the package of ICRs is submitted to HHS for certification and OMB for technical review and final approval.

HHS certifies ICRs to avoid unnecessary duplication, reduce the data collection burden on small entities, and assure the use of plain, coherent, unambiguous and understandable language to respondents. The HHS certification process informs respondents of data called for under the

law and ensures that implementation will be consistent and compatible with current reporting, record-keeping and data retention practices. HHS must also make the following certifications. The ICRs were developed by an office that planned and allocated resources for the efficient and effective management and use of the information to be collected. The agency used effective and efficient statistical methods if applicable. The agency made appropriate use of IT.

OMB submits an "Information Request Budget" to Congress each year with a total of the public burden from data collections, costs to the government by each agency, a description of the agency's performance in complying with the PRA, and agency violations. Agency scientists must write a justification to each violation of the PRA.

Since August 2007, NCHHSTP has followed the same framework as OCSO and integrated the OMB PRA process at the level of the Associate Director for Science. OMB determinations were added to determination checklists for all Division and Branch Science Officers to reduce delays in preparing and processing supporting statements within NCHHSTP. NCHHSTP will establish an ad hoc committee to standardize forms and resolve conflicts regarding determinations.

Dr. Fleenor confirmed that ACET would make decisions on providing formal guidance on the PRA during the business session. The ACET members made several comments in preparation of the discussion.

- CDC should compile and provide ACET with a list of unintended consequences of the PRA. ACET could use the list as the basis for providing formal guidance on the need to exempt TB research projects from the PRA. ACET's input would be extremely timely in light of OMB's reauthorization of the PRA in 2010.
- ACET should ask CDC to provide compelling evidence or strong data that support or justify the need, benefit and value of the PRA for TB research projects.
- ACET should take leadership in coordinating efforts with other organizations to achieve broad support in recommending significant changes to or complete abolishment of the PRA.
- ACET should formally recommend that CDC commission a study in which an academic institution or external organization would attempt to determine the effectiveness of the PRA.

Overview of the Genetic Basis of Drug Resistance

Dr. Thomas Shinnick, of the DTBE Mycobacteriology Laboratory Branch, explained that *M.tb* can become drug-resistant by the acquisition of mutations blocking the activity of a drug. For example, mutations in the *rpoB* gene prevent binding of rifampin and make cells resistant to the drug. *M.tb* can also become drug-resistant by the acquisition of mutations that block activation of a prodrug. For example, mutations in the *katG* gene prevent the activation of INH from the prodrug to active form. *M.tb* can acquire an activity that destroys the drug as well.

Many genes, targets, gene products and mutations within individual targets have been identified in *M.tb* that can produce resistance to certain drugs, including rifampin, INH, streptomycin, ethambutol, ciprofloxacin, and pyrazinamide. For example, 96% of drug-resistant mutations in rifampin are in the *rpoB* gene. In INH, 50%-66% of drug-resistant mutations are in the *katG* gene, 10%-15% are in the *inhA* gene, 10% are in the *kasA* gene, and 15%-20% are in unknown genes.

In pyrazinamide, 95% of drug-resistant mutations are in the *pncA* gene. The *rrs* gene accounts for 85%-100% of drug-resistant mutations in amikacin, >95% in high-level kanamycin, and 10%-90% in capreomycin. Molecular detection of drug resistance is problematic for streptomycin, ethambutol, fluoroquinolones and low-level kanamycin because 30%-80% of drug-resistant mutations have not been identified in any known gene.

A variety of laboratory methods can be used to detect genes and mutations, including DNA sequencing, electrophoretic detection methods, heteroduplex analyses and hybridization assays, such as molecular beacons, microarrays and membrane hybridization assays. Polymerase chain reaction (PCR) oligonucleotide hybridization assays detect *M.tb* DNA and mutations associated with INH or rifampin resistance. These tests can be directly performed from AFB smear-positive sputum specimens.

Membrane-based assays are closest to application at this time. The GenoType® MTBDRplus Assay and the INNO-LiPA Rif.TB tests are commercially available and widely used in Europe and other parts of the world. The MTBDRplus assay uses DNA extraction, PCR amplification to obtain a target of interest, hybridization and evaluation.

The Foundation for Innovative New Diagnostics (FIND) conducted two large trials in Africa to evaluate the MTBDRplus assay for clinical use under field conditions. The assay was performed on 536 consecutive AFB-positive sputum specimens and 100 AFB-negative specimens as a control group. The performance of the MTBDRplus assay in detecting INH and rifampin resistance and MDR-TB was compared to specimens that were cultured in liquid media and conventional DST.

The FIND study showed that 97% of specimens with the MTBDRplus assay had interpretable results within 1-2 days. The sensitivity, specificity, and positive and negative predictive values of the MTBDRplus assay in detecting rifampin and INH resistance and MDR-TB were outstanding and ranged from 94%-100%. The MTBDRplus assay produced accurate results for 14 of 15 AFB-negative/culture-positive sputum specimens.

The FIND study found the overall performance of the MTBDRplus assay to be superior to conventional culture and DST with respect to speed, accuracy, interpretable results and throughput. The FIND study demonstrated that the cost of the test might be less than culture and DST. The FIND study also showed that the test could substantially reduce the need for culture and DST when screening for MDR-TB and might be easier to establish than culture.

WHO convened an expert committee meeting in March 2008 to consider the use of line-probe assays for MDR-TB. After reviewing data from the FIND study, meta-analyses and other

research, the expert committee concluded that sufficient generalizable evidence exists to justify a recommendation on the use of line-probe assays for rapid screening of MDR-TB in country-specific settings. During a recent meeting convened by CDC, an APHL expert committee reached a similar conclusion and stated that line-probe assays have sufficient performance to recommend routine use in settings with high drug resistance.

Overall, DST results must be available as soon as possible to guide treatment choices. The development of molecular tests for rifampin resistance and other testing algorithms might accelerate the decision-making process. Clinicians need data to interpret results, particularly data on performance parameters of a test and the potential impact of resistance prevalence on predictive value and other variables. However, laboratory tests do not replace clinical judgment.

Dr. Shinnick emphasized that a formal recommendation from ACET advising CDC not to wait for FDA-approved drug-resistant assays could accelerate the use of these tests. He pointed out that analyte-specific reagent tests are well validated with strong performance characteristics. Florida, New York and California laboratories are currently using these tests. After funding is identified, analyte-specific reagent tests could be rapidly incorporated into regional laboratories.

Overview of the Impact of CCID Program Integration at Local and State Levels

Dr. Fleenor announced that he attended the BSC meeting in May 2008 as the representative for ACET. The BSC workgroup for NCHHSTP focused on PCSI, including the impact of integration at local and state levels. The workgroup had reservations about launching full-scale integration at local and state levels and agreed to review integration models, evidence or lessons learned from local or state health departments to inform CDC's decision-making process.

Dr. Fleenor reported that the BSC was asked to review and provide input on a list of the top 10 priorities CCID has proposed for collaborative focus areas in 2009 and thereafter. He explained that the BSC could revise or replace existing priorities, but could not add new activities beyond the proposed top 10 list. CCID's proposed top 10 priorities were distributed to ACET for review and comment.

Dr. Fleenor made several remarks to guide ACET's discussion. ACET should particularly focus on priority 2: "improve the health of populations disproportionately affected by HIV/AIDS, viral hepatitis, STDs and TB and ultimately to help eliminate health disparities." ACET should decide whether priority 3, "eliminate hepatitis B virus (HBV) transmission in the United States," should be revised as a health disparities goal and not serve as a standalone priority. ACET should determine whether to recommend replacing one of the priorities with a new activity to focus on drug resistance.

Several ACET members noted that TB was mentioned in only one of the 10 priorities. Other members were surprised that antibiotic-resistant organisms were not included and the elimination of HBV transmission was captured as a standalone priority. The members pointed

out that the incidence of TB, syphilis, gonorrhea and chlamydia is greater than HBV. The ACET members made a number of suggestions on CCID's proposed top 10 priorities.

- The “elimination of HBV transmission” in priority 3 should be incorporated into a revised version of priority 1 to “implement existing and new vaccines to reduce disease both domestically and globally.”
- “Drug resistance” should serve as the new priority 3 with MDR-/XDR-TB, nosocomial infections and *Staphylococcus* as specific goals.
- The language in priority 4 should be modified to “a social-ecological approach” to infectious diseases.
- MDR-TB should be mentioned in a revised version of priority 9: “including tropical diseases and multidrug-resistant diseases, such as MDR-TB.”
- TB should be mentioned in priority 10 along with pneumonia as another “severe respiratory disease” that significantly contributes to “worldwide deaths.”

ACET Business Session

Dr. Fleenor entertained a motion for ACET to approve the previous meeting minutes. A motion was properly placed on the floor and seconded by Dr. Flood and Mr. Kinney, respectively, for ACET to accept the previous minutes. ACET **unanimously approved** the March 26-27, 2008 Draft Meeting Minutes with no changes or further discussion.

Dr. Fleenor led ACET in a review of future agenda items that were raised over the course of the meeting and during the business session.

- Update on the public health law and TB control initiative, including ethical considerations of implementing compulsory hospitalization.
- Report on key outcomes from the expert consultation on IGRAs.
- Ongoing updates on DTBE's progress in responding to the recommendations on TB in the AA community.
- Overview of the epidemiological profile of TB in AAs based on specific risk factors, such as age, gender, urban versus rural distribution, educational status, occupation, alcohol and substance abuse, and incarceration.
- Discussion and formal resolution by ACET to improve TB diagnostics. ACET's guidance should encourage a change in practice to allow clinical laboratories that process respiratory specimens to perform AFB smears. The recommendation should include laboratories that do not perform mycobacteriology testing.
- Ongoing reports from DTBE regarding TB diagnostics, advocacy and other important efforts by influential groups, such as WHO, the TB Alliance and Stop TB USA.
- Update on the TB redistribution formula.
- Overview by Dr. Naomi Aronson on TB activities conducted by the Department of Defense.
- Update by the BCG Workgroup.

- Update by the ACET workgroup that was charged with reviewing and providing input on existing guidelines related to the removal of drug-resistant patients from isolation.

Dr. Fleenor led ACET in a review of three business items that would require formal votes.

Issue 1: CCID's Proposed Top 10 Priorities

A motion was properly placed on the floor and seconded by Mr. Jones and Dr. Flood, respectively, for ACET to adopt the following changes to CCID's proposed top 10 priorities.

- Priority 3 of "eliminating HBV transmission" should be combined with priority 1. The new priority 3 should be to "prevent and control antimicrobial resistance."
- Priority 4 should be revised to "expand disease prevention and control strategies through social and ecologic approaches to infectious diseases."
- DTBE should incorporate TB goals into priorities 9 and 10.

ACET **unanimously approved** the motion with no further discussion. The final version of CCID's top 10 priorities would be distributed to ACET.

Issue 2: PRA

A motion was properly placed on the floor and seconded by Dr. Narita and Mr. Jones, respectively, for ACET to adopt language regarding the PRA. Dr. Narita and Mr. Jones agreed to accept amendments to the motion as outlined below.

"ACET expressed concern about risks associated with delays in the OMB clearance process, thereby impeding the ability of CDC to implement core public health activities, surveillance, timely investigations and research. Be it resolved that ACET recommends that the CDC Director solicit and coordinate responses from Division Directors to inform the HHS Secretary and other policymakers of the unintended consequences of the PRA."

ACET **unanimously approved** the amended motion with no further discussion.

Issue 3: Rapid Drug-Resistant Assays

A motion was properly placed on the floor and seconded by Drs. Flood and Narita, respectively, for ACET to adopt the following language regarding rapid drug-resistant assays.

"Be it resolved that ACET recommends that CDC fund and expedite implementation of currently available rapid drug-resistant assays in qualified public health laboratories representing Centers of Excellence to quickly identify MDR-TB, reduce transmission and prevent further acquired drug resistance, such that by the end of 2008, CDC-funded laboratories are able to provide this assay for federal, state and local agency use.

ACET **unanimously approved** the motion with no further discussion.

Public Comment Session

Dr. Fleenor opened the floor for public comments; no participants responded.

Closing Session

The next ACET meeting would be held on December 8-9, 2008. With no further discussion or business brought before ACET, Dr. Fleenor adjourned the meeting at 2:15 p.m. on June 18, 2008.

I hereby certify that to the best of my knowledge, the foregoing Minutes of the proceedings are accurate and complete.

Date

Michael E. Fleenor, M.D., M.P.H.
Chair, Advisory Committee for the
Elimination of Tuberculosis