

**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
July 14-15, 2009
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
July 14, 2009	
Opening Session.....	1
NCHHSTP Director's Report	2
DTBE Director's Report.....	4
Update by the Division of Global Migration and Quarantine.....	6
Overview of TB and Substance Abuse in the United States	8
Update on Detection of TB Outbreak Aberrations.....	11
Update on the U.S. TB Elimination Plan	13
Update on the National Tuberculosis Indicators Project	15
ACET Workgroup Reports.....	17
Overview of the Mycobacteriology Laboratory Branch External Peer Review	23
July 15, 2009	
Update on TBTC	25
Update on TBESC Task Order 23	27
Update on TBESC.....	28
Update on TBESC Task Order 2	30
Overview of the Critical Path to TB Regimens Initiative	34
Update on the Role of Federal Agencies in Global TB Control and Research	37
Update on the National TB Archive	42
ACET Business Session	44
Public Comment Session	47
Closing Session	47

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

Dr. Michael Fleenor, Chair
 Dr. Iram Bakhtawar
 Dr. Christine Hahn
 Mr. Shannon Jones
 Mr. Joseph Kinney
 Dr. Ana Lopez-de Fede [via conference call]
 Dr. Barbara Seaworth

Designated Federal Official

Dr. Hazel Dean, NCHHSTP Deputy Director

Ex-Officio and Liaison Members

Dr. William Baine (Agency for Healthcare Research and Quality)
 Dr. Anita Barry (National Association of County and City Health Officials)
 Dr. Jane Carter (International Union Against Tuberculosis and Lung Disease)
 Dr. James Cheek (Indian Health Service)
 Dr. Edward Desmond (Association of Public Health Laboratories)
 Ms. Fran DuMelle (American Thoracic Society)
 Dr. Antonio Falcon (U.S. Section, U.S.-Mexico Border Health Commission)
 Mr. Phillip Griffin (National Tuberculosis Controllers Association)
 Mr. Warren Hewitt (Substance Abuse and Mental Health Administration)
 Dr. Michael Leonard, Jr. (Infectious Disease Society of America)
 Ms. Sue Perez (Treatment Action Group)
 Dr. Lee Reichman (American College of Chest Physicians)
 Dr. Gary Roselle (Department of Veterans Affairs)
 Mr. Dan Reyna (HHS Office of Global Health Affairs)
 Dr. Diana Schneider (Department of Homeland Security)
 Dr. Lornel Tompkins (National Medical Association)

Secretary Clemente Villalpando (Mexico Section, U.S.-Mexico Border Health Commission)
 Dr. Theresa Watkins-Bryant (Health Resources and Services Administration)
 Dr. David Weissman (National Institute for Occupational Safety and Health)

CDC Representatives

Dr. Kenneth Castro, DTBE Director
 Ms. Sandy Althomsons
 Dr. Jose Becerra
 Dr. Kevin Cain
 Dr. Terence Chorba
 Mr. Sha Juan Colbert
 Ms. Ann Cronin
 Ms. Beverly DeVoe
 Dr. Denise Garrett
 Dr. Jan Ghuens
 Dr. John Halpin
 Dr. John Jereb
 Dr. Dolly Katz
 Dr. Awal Khan
 Mr. Romel Lacson
 Ms. Ann Lanner
 Ms. Linda Leary
 Dr. Philip LoBue
 Ms. Suzanne Marks
 Ms. Tamara Miller
 Dr. Patrick Moonan
 Dr. Thomas Navin
 Dr. John Oeltmann
 Ms. Bonnie Plikaytis
 Dr. Drew Posey
 Dr. Mary Reichler
 Mr. Joseph Scavotto
 Ms. Angela Scott
 Ms. Margie Scott-Cseh
 Mr. Brian Sizemore
 Mr. Phillip Talboy
 Ms. Lisa Thombley
 Dr. Andrew Vernon
 Dr. Elsa Villarino
 Dr. Wanda Walton
 Ms. Pei-Chun Wan

Ms. Bethany Wexler
Ms. Jessie Wing
Ms. Kai Young

**Guest Presenters and
Members of the Public**

Dr. Damian Gessler (University of Arizona)
Dr. Jan Ghuens
(Bill and Melinda Gates Foundation)

Mr. James Kirkwood (Association of State
and Territorial Health Officials)
Ms. Carol Poszik (National Tuberculosis
Controllers Association)
Dr. Randall Reves (STOP TB USA)
Mr. John Seggerson (STOP TB USA)
Dr. Gary Simpson (Texas Tech University
Health Sciences Center)
Dr. Christine Sizemore (National Institute of
Allergy and Infectious Diseases)
Ms. Jamie White (Member of the Public)

ATTACHMENT 2

Acronyms Used In These Meeting Minutes

AA	— African American
ACET	— Advisory Council for the Elimination of Tuberculosis
AHRQ	— Agency for Healthcare Research and Quality
APHL	— Association of Public Health Laboratories
ARRA	— American Recovery and Reinvestment Act
ATS	— American Thoracic Society
CCID	— Coordinating Center for Infectious Diseases
CDC	— Centers for Disease Control and Prevention
CER	— Comparative Effectiveness Research
CLPH	— Centers for Law and the Public's Health
C-Path	— Critical Path Institute
CPI	— Critical Path Initiative
CPTR	— Critical Path to TB Drug Regimens
DGMQ	— Division of Global Migration and Quarantine
DHQP	— Division of Healthcare Quality Promotion
DoD	— Department of Defense
DOS	— U.S. Department of State
DOT	— Directly Observed Therapy
DTBE	— Division of Tuberculosis Elimination
EDN	— Electronic Disease Notification
FBP	— Foreign-Born Population/Person
FDA	— Food and Drug Administration
FTBTF	— Federal TB Task Force
GATB	— Global Alliance for TB Drug Development
H1N1	— Novel Influenza A Virus
HCP	— Healthcare Personnel
HHS	— Department of Health and Human Services
HIT	— Health Information Technology
HRSA	— Health Resources and Services Administration
IDSA	— Infectious Disease Society of America
IGRA	— Interferon Gamma Release Assay
INH	— Isoniazid
IoM	— Institute of Medicine
IOM	— International Organization for Migration
LLRs	— Log-Likelihood Ratios
LTBI	— Latent TB Infection
MDR-TB	— Multidrug-Resistant TB
MIRU	— Mycobacterial Interspersed Repetitive Unit
MLB	— Mycobacteriology Laboratory Branch
<i>MMWR</i>	— <i>Morbidity and Mortality Weekly Report</i>
<i>M.tb</i>	— <i>Mycobacterium Tuberculosis</i>
NCHHSTP	— National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

NIAID	—	National Institute of Allergy and Infectious Diseases
NMA	—	National Medical Association
NIAID	—	National Institute of Allergy and Infectious Diseases
NIH	—	National Institutes of Health
NTBA	—	National TB Archive
NTCA	—	National Tuberculosis Controllers Association
NTIP	—	National TB Indicators Project
NTM	—	Non-Tuberculous Mycobacteria
PDPs	—	Product Development Partnerships
PPD	—	Purified Protein Derivative
R&D	—	Research and Development
RVCT	—	Report Verified Case of TB
SAMHSA	—	Substance Abuse and Mental Health Services Administration
SDH	—	Social Determinants of Health
TBESC	—	TB Epidemiologic Studies Consortium
TB-GIMS	—	TB Genotyping Information Management System
TBTC	—	TB Trials Consortium
TBTIs	—	TB Technical Instructions
TEP	—	TB Elimination Plan
TST	—	Tuberculin Skin Test
USAID	—	U.S. Agency for International Development
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
July 14-15, 2009
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 July 14-15, 2009 in Building 8 of CDC's Corporate Square Offices, Conference Room A/B/C in Atlanta, Georgia.

Opening Session

Dr. Hazel Dean, Deputy Director of NCHHSTP and Designated Federal Official of ACET, called the meeting to order at 8:32 a.m. on July 14-15, 2009. She welcomed the attendees to the proceedings and particularly recognized the new and alternate *ex-officio* and liaison members.

Dr. Dean announced that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. She 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. Michael Fleenor, Chair of ACET, joined Dr. Dean in welcoming the attendees to the meeting and opened the floor for introductions. The list of participants is appended to the minutes as Attachment 1.

NCHHSTP Director's Report

Dr. Dean presented the update on behalf of Dr. Kevin Fenton, Director of NCHHSTP, who was unable to attend the meeting. Kathleen Sebelius, the new HHS Secretary, visited CDC and Agency for Toxic Substances and Disease Registry staff on May 5, 2009. William Corr was appointed as the Deputy Secretary of HHS.

The President committed to collaborating with Congress to pass comprehensive health reform in 2009. HHS assisted in coordinating a major White House Forum on Health Reform on March 5, 2009 as well as five Regional Health Forums across the country in March and April 2009. A priority initiative in the American Recovery and Reinvestment Act (ARRA) is to advance the development of a nationwide interoperable health information technology (HIT) infrastructure and accelerate the adoption of HIT. A critical component of this effort will be to ensure the private and security of patient information.

Comparative effectiveness research (CER) will be conducted to provide information on the relative strengths and weaknesses of different medical interventions. Under ARRA, \$300 million was allocated to the Agency for Healthcare Research and Quality (AHRQ), \$400 million was allocated to the Office of the Secretary, and \$400 million was allocated to the National Institutes of Health (NIH). CDC is engaged in discussions and the decision-making process related to CER, but CER funds are not expected to be allocated to CDC. However, CDC will use the existing Leader-to-Leader mechanism the HHS agencies previously established to engage AHRQ in discussions regarding the allocation of CER funds at both the CDC and NCHHSTP levels. ARRA requires all CER funds to be obligated by the end of FY2009.

The President signed an Executive Order on March 9, 2009 to lift the ban on federal funding for promising human embryonic stem cell research. The Executive Order directed NIH to draft guidelines that are both scientifically worthy and responsibly and ethically conducted.

Dr. Thomas Frieden was appointed as the new CDC Director and assumed his position in June 2009. Dr. Frieden was the Commissioner of the New York City Department of Health and Mental Hygiene and was employed by CDC for 12 years. He began his career at CDC as an Epidemic Intelligence Service Officer in 1990 and then led CDC's TB control program in India for five years. Dr. Frieden named Louis Salinas as CDC's acting Chief of Staff. Mr. Salinas previously served as Deputy Director of both the Division of Oral Health and Division of Adolescent and School Health.

Dr. Frieden established the following key priorities for CDC: (1) strengthen epidemiology and surveillance; (2) improve effectiveness to support partners at state, local and city levels; and (3) provide leadership in the areas of health reform, community prevention to further reduce the burden from the leading preventable causes of illness and death, and global health.

According to the World Health Organization (WHO), >70 countries officially reported cases of novel influenza A (H1N1) infection. WHO's elevation of the pandemic alert level to Phase 6 on

June 11, 2009 reflected the spread rather than the severity of illness. Phase 6 indicated a global pandemic is underway. CDC's goals for the H1N1 response are to reduce the spread and severity of illness and provide information to help healthcare providers, public health officials and the public in addressing the challenges posed by this new public health threat. NCHHSTP accounted for 188 of 1,500 CDC staff members who responded to the pandemic.

A weekly influenza surveillance report showed that all states reported H1N1 cases. As of the week ending on July 4, 2009, nine states reported geographical widespread influenza activity, 12 states and Puerto Rico reported influenza activity, ten states and the District of Columbia reported local influenza activity, 18 states reported sporadic influenza activity, and one state did not report influenza activity.

Scientists in the Division of HIV/AIDS Prevention collaborated with colleagues to publish recommendations for protective behaviors relative to the novel H1N1 influenza virus for persons with HIV infection. The recommendations provided guidance on symptom recognition, treatment, self-protective measures, adherence to currently prescribed medication for HIV infection, and chemoprophylaxis for HIV-positive close contacts of persons with H1N1 infection. The guidance noted that HIV-positive persons do not appear to be at elevated risk for influenza infection, but might be susceptible to greater complications if infected. The recommendations were posted on the CDC web site at www.cdc.gov/h1n1flu/hiv_flu.htm.

The Senate Committee on Health, Education, Labor and Pensions released a draft health reform bill on June 9, 2009, but the mark-up has not been completed at this time. The committee proposed a \$10 billion prevention trust fund and listed new programs, but did not allocate funding to specific programs. The Senate Finance Committee has not yet publicly released its draft.

The House Ways and Means, Energy and Commerce, and Education and Labor Committees released a draft health reform bill on June 19, 2009 that will be revised later in the week and then marked-up. The three committees proposed \$15.2 billion over five years in prevention spending and allocated funding to specific programs. The majority of this funding would be dedicated to grants that support preventive services and state infrastructure development.

Both the Senate and House bills authorize activities by the U.S. Preventive Services Task Force and the Community Preventive Services Task Force with the House bill calling for annual funding of \$30 million for the Task Forces. Both the Senate and House bills proposed the creation of a National Prevention Strategy to guide research and grant-making. The Senate bill proposed the establishment of a "Prevention Council" with cabinet secretaries and other high-level officials across the Executive Branch to oversee strategy development.

The President's 2010 budget of approximately \$1 billion for NCHHSTP reflects approximately \$54 million above the FY2009 Omnibus. Of the approximately \$54 million increase, ~\$3 million would be targeted to pay increases and \$51 million would be targeted to pay increases. Of the proposed budget of approximately \$1 billion for NCHHSTP, approximately \$144 million would be allocated to TB, approximately \$745 million would be allocated to domestic HIV/AIDS, approximately \$18 million would be allocated to viral hepatitis, and approximately \$153 million

would be allocated to STDs. The proposed allocation of approximately \$745 million for domestic HIV/AIDS reflects an increase of approximately \$53 million above the FY2009 Omnibus to focus on high-risk populations.

NCHHSTP is continuing to develop its strategic plan with the following priorities: a core mission of preventing and controlling HIV, viral hepatitis, STDs and TB; program collaboration and service integration; health equity; global health protection and systems strengthening; partnerships; and workforce development and capacity building. NCHHSTP will solicit input on its strategic plan from ACET and other external partners later in the summer of 2009.

NCHHSTP and the Coordinating Center for Infectious Diseases co-hosted the “Corrections and Public Health Consultation: Expanding the Reach of Prevention” in March 2009. The consultation served as an opportunity for community partners and subject-matter experts from corrections, public health and academia to develop effective strategies to address health disparities and other issues related to TB, HIV/AIDS, viral hepatitis and STDs among the incarcerated population. A summary of the corrections consultation will be posted on the CDC website.

The summary report of the Social Determinants of Health (SDH) Consultation, convened by CDC with external partners in December 2008, was published in June 2009. The report, *Addressing Social Determinants of Health: Accelerating the Prevention and Control of HIV/AIDS, Viral Hepatitis, STD and TB*, suggests both long- and short-term priorities to achieve this goal. The report is available on CDC’s new SDH web page at www.cdc.gov/socialdeterminants with links to SDH resources both within and outside of CDC. CDC welcomes comments and suggestions to improve the effectiveness of the SDH website.

Dr. Kenneth Castro, Director of DTBE, emphasized the need for CDC to strengthen its partnership with AHRQ as funds are allocated to conduct CER projects. This collaboration would ensure that CDC has an influential role in the implementation of CER projects to advance the overall public health mission.

DTBE Director’s Report

Dr. Kenneth Castro covered the following areas in his update. The CDC Procurement and Grants Office allowed DTBE to structure the FY2010 TB cooperative agreements as a competitive continuation cycle to enable state health departments to use unobligated year-end dollars. The funding opportunity announcement was posted on www.grants.gov on June 28, 2009 with an application deadline of August 28, 2009. The TB funding formula that was previously presented to ACET will be used in the FY2010 TB cooperative agreements.

DTBE will offer training to healthcare personnel (HCP) in state and local health departments, territories and Pacific Islands to accurately use the revised report verified case of TB (RVCT) form. Training will be targeted to HCP who collect data from patients, complete the RVCT form, enter data from the RVCT form into a data system, monitor the accuracy of TB program data

collection, and analyze data from the RVCT form. Most of the country was covered with the initial training and the 14 remaining states will receive training in September 2009. The RVCT self-study module will be available online at www2a.cdc.gov/TCEonline in late July 2009.

DTBE's other recent activities since the previous ACET meeting are highlighted as follows. Outbreak assistance was provided in response to requests from state and local health departments in Georgia and Florida in May-June 2009. The external review of the Mycobacteriology Laboratory Branch (MLB) will be held in August 2009 with Dr. Fleenor chairing the review panel. Provisional interferon gamma release assay (IGRA) guidelines were presented during the European Respiratory Society conference.

The DTBE web page was updated to be consistent with the formats of other CDC web pages. DTBE welcomes feedback and suggestions from ACET to improve the revised TB web page. The 9th Annual TB Education and Training Network and the 1st TB Program Evaluation Network Conference will be jointly held on July 28-30, 2009. The application review process for the TB Trials Consortium (TBTC) re-competition is underway.

DTBE supported CDC's H1N1 influenza response and will complete its TB-specific pandemic influenza operational plan by July 28, 2009. The Food and Drug Administration (FDA) Anti-Infective Advisory Committee held a meeting in June 2009 to discuss using FDA's regulatory authority to accelerate approval of promising new agents for treatment of multidrug-resistant TB (MDR-TB). The committee agreed to use sputum conversion within a period of three to six months as a surrogate marker of efficacy. DTBE will represent CDC during the Federal TB Task Force (FTBTF) meeting on August 26, 2009.

DTBE will target \$3 million in new funding to prevent future TB cases and implement elements of the Extensively Drug-Resistant TB (XDR-TB) Plan that was published in 2009 in the *Morbidity and Mortality Weekly Report (MMWR)*. Cure TB is scheduled to be the first of the DTBE-funded U.S.-Mexico binational projects that will be evaluated in August-September 2009. The National TB Indicators Project was launched in March 2009.

Dr. Castro provided additional details on DTBE's activities and future plans in response to ACET's specific questions and comments. DTBE intends to schedule a briefing with Dr. Frieden in the near future. The STOP TB Elimination Plan will be one of the key topics DTBE will discuss with Dr. Frieden.

Dr. Castro clarified that he welcomes the opportunity for DTBE staff to continue to participate in on-the-ground investigations, surveillance and other aspects of CDC's response to H1N1 influenza. However, he will not allow TB control efforts to cease while DTBE staff is involved in the H1N1 influenza response. In the event H1N1 influenza becomes more severe and causes significant mortality in the future, DTBE will retain its core functions of TB surveillance, laboratory support to diagnose TB cases, communications and contact investigations.

Dr. Castro raised the possibility of ACET formalizing a resolution regarding the need for TB programs to contribute to the H1N1 influenza response, while providing continuity for TB case management. During the June 2009 National Tuberculosis Controllers Association (NTCA)

meeting, he proposed administering seasonal influenza vaccine in TB clinics because many patients only receive care in these settings.

In response to Dr. Castro's request, Dr. Fleenor confirmed that he would identify a few ACET members to utilize their TB expertise to provide guidance to the CDC National Institute for Occupational Safety and Health during upcoming meetings on the appropriateness of respiratory protection for airborne transmission of H1N1 influenza with weak scientific evidence.

Several ACET members described actions that were taken to maintain TB control at state and local levels during the H1N1 influenza outbreak. The members also made two key suggestions for DTBE to consider in its future activities. In addition to scheduling a briefing with Dr. Frieden, DTBE also should meet with Mr. Salinas due to his long history as a TB public health advisor and extensive experience in TB control. DTBE should use the new Administration and the H1N1 influenza outbreak as opportunities to revisit the possibility of leveraging bioterrorism funds for TB.

Update by the Division of Global Migration and Quarantine (DGMQ)

Dr. Drew Posey, of the DGMQ Immigrant, Refugee and Migrant Health Branch, reported on DGMQ's ongoing activities related to the TB Technical Instructions (TBTIs), Electronic Disease Notification (EDN) system, and HIV Notice of Proposed Rule Making (NPRM). In terms of the TBTIs, all immigrants and refugees who apply for U.S. immigration are required to undergo TB screening. The 1991 TBTIs only relied on sputum smears, but the 2007 TBTIs require cultures, drug susceptibility testing (DST) on positive isolates, and directly observed therapy (DOT) for persons with TB in accordance with U.S. guidelines.

Since 2007, DGMQ has implemented the TBTIs in 24 countries. At this time, 45% of U.S.-bound immigrants and >50% of U.S.-bound refugees are screened with the new TBTIs. DGMQ is particularly pleased that China recently began implementing the TBTIs because this high-burden country is the third largest source of U.S.-bound immigrants. Other new countries where the TBTIs are being implemented include Ethiopia, Japan, Jordan, Kenya and Taiwan.

Efforts are underway to implement the TBTIs in Chad, Ghana, Guatemala, India and Nigeria. DGMQ hopes to conduct a site visit in Russia in the summer of 2010 to explore the possibility of implementation in this country. ACET and NTCA will conduct an evaluation of the International Organization for Migration (IOM) program the week of August 10, 2009 in Nepal. This country is the site of the Bhutanese refugee resettlement and will account for >15,000 arrivals in FY2009.

Based on data collected in the first year the TBTIs were implemented in the Philippines and Vietnam, the addition of cultures yielded two to three times more applicants with TB. In both countries, ~1% of applicants were culture-positive. In terms of the resistance patterns of culture-positive applicants, 71% of 289 persons had pansusceptible TB in the Philippines and 47% of 86 persons had pansusceptible TB in Vietnam; 3% of 12 persons had MDR-TB in the Philippines and 5% of 10 persons had MDR-TB in Vietnam.

In terms of treatment outcomes of pulmonary TB cases, most applicants in both countries were undergoing treatment, completed treatment or were cured. In the Philippines, 14% of 73 applicants did not register for treatment at the panel physician site, while only 3% of five applicants did not register in Vietnam. The ACET/NTCA evaluation team made a critically important recommendation for CDC to add a second DOT site in the Philippines to increase the number of applicants with pulmonary TB who register for treatment. CDC added another DOT site at Perpetual Succour Hospital in the Philippines earlier in 2009. CDC's formal response to the evaluation team's recommendations for the Philippines TB program was distributed to ACET for review.

U.S. Department of State (DOS) forms are completed by overseas panel physicians and are being updated to incorporate changes in the 2007 TBTIs. Implementation of the updated DOS forms is targeted for October 1, 2009 in parallel to updates of the EDN system and the EDN-IOM electronic interface for refugee medical examinations.

The TBTI document is being updated to be consistent with the new DOS forms and allow for incorporation of changes based on recommendations made by the TBTI Workgroup and the evaluation team for the implementation of the TBTIs in the Philippines. Implementation of the updated TBTI document and the new DOS forms will be linked. The final draft of the updated document was reviewed by the TBTI Workgroup and is currently undergoing the CDC clearance process.

In terms of EDN, this electronic system allows information to be sent to receiving health departments on all refugees who arrive in the United States and all immigrants who arrive in the United States with a Class A or Class B TB condition. EDN also serves as a mechanism for health departments to enter results of post-arrival TB evaluations. DGMQ consolidated its EDN leadership with a medical director, program manager, data center manager and informatics project manager to address current problems in the system, particularly the significant eight-week backlog of ~15,000 records.

DGMQ is taking a number of actions to resolve the EDN backlog. Additional data entry staff will be hired to increase the number of personnel from 10 to 20. A night shift will be included within the next two to four weeks. An interim plan was proposed to be in effect until September 30, 2009. Records received electronically would be transmitted to states with or without scanning to reduce the burden on data entry staff and facilitate faster processing of records. EDN resources would be concentrated on new arrivals. EDN users have a deadline to submit comments on the proposed interim plan by July 20, 2009.

In terms of the HIV entry ban, the NPRM was published in the *Federal Register* on July 2, 2009 and proposed removing HIV from the list of inadmissible conditions. If the NPRM goes into effect, testing for HIV would no longer be required by panel physicians and civil surgeons and applicants with HIV infection would no longer require a waiver for entry into the United States. However, the waiver requirement would not apply to refugees. The rationale for the NPRM is three-fold. The risk to the public's health is not threatened by the entry of HIV-infected immigrants and refugees. The risk posed by HIV-infected persons is not based on nationality. HIV is not a new disease in the United States and accounts for >1 million cases in the country.

The 45-day public comment period for the NPRM will end in August 2009. CDC is obligated to review and respond to all public comments and has received >16,000 comments to date that primarily have been favorable. The regulations would become effective only after a Final Rule is issued. However, the Final Rule would not prohibit a standard of care for TB patients to be tested for HIV. CDC anticipates that the regulations would not become effective before October 1, 2009.

DGMQ is currently informing ACET, NTCA, the Association of Refugee Health Coordinators and other key non-U.S. government groups about the NPRM. DGMQ will develop guidance for panel physicians, civil surgeons and domestic refugee health programs if the proposed HIV regulations become effective.

On the one hand, some ACET members were pleased with the NPRM because the proposed HIV regulations would reduce the stigma and discrimination associated with HIV-positive immigrants and refugees. On the other hand, some ACET members expressed concern about the tremendous burden that would be placed on the public health system at state and local levels to resettle HIV-positive refugees in the United States with employment and health care.

ACET advised DGMQ to attempt to leverage resources to expand the TBTIs to include non-immigrant visa applicants, such as students and workers with H or L visas, as well as individuals who enter the United States under the Compact of Federal Free Association. These groups are not required to be screened for TB prior to U.S. entry.

Dr. Castro raised the possibility of ACET formalizing a resolution for CDC to strengthen local TB control programs overseas in all activities that are conducted overseas to improve screening procedures to reduce the importation of TB into the United States.

Overview of TB and Substance Abuse in the United States

Dr. John Oeltmann, of DTBE, presented a study CDC conducted to report the prevalence of substance abuse among TB cases reported in the United States and examine the relationship between substance abuse and TB transmission. An overlooked and rather large tide pool of disease is among persons who abuse substances. For example, substance abuse is the third most significant risk factor for TB.

CDC's investigations from 2005-2008 showed that 10 of 13 TB outbreaks had populations with at least 50% of substance abusers. The risk for TB remains higher among certain demographic groups, including those who abuse substances. The ability of substance abuse to hinder TB control efforts is well documented in the literature, but no national summary has been developed to date to demonstrate the impact of substance abuse on TB control.

For purposes of the study, CDC defined "substance abuse" as self-reported excessive alcohol use or injection or non-injection use of illicit drugs during the year prior to TB diagnosis. All

incident TB cases ≥ 15 years of age reported to the National TB Surveillance System from 1997-2006 were included in the study. Prevalence was calculated based on injection drug use, non-injection drug use or excess alcohol use. A “substance abuse” composite variable was developed for any of these substances. Genotyping data were compiled from 2004-2005 to assess the relationship between substance abuse and county-level genotype clustering.

To evaluate a potential association with TB and increased transmission, CDC asked research questions to determine whether substance abuse was related to positive sputum-smear results at diagnosis, treatment failure or involvement in a county-level genotype cluster. The study was controlled for a number of confounders, including gender, HIV status, race, place of birth, homelessness and incarceration in a correctional facility. Due to the large sample size, a small p-value < 0.01 was selected.

Key results of the study are highlighted as follows. In the study period of 1997-2006, 153,268 TB cases met the inclusion criteria. The prevalence of substance abuse was 19% among all cases and 29% of U.S.-born cases; 35.3% among U.S.-born males and 16.9% among U.S.-born females; and 12.9% among foreign-born males and 1.5% among foreign-born females. Excess alcohol use was the most frequently reported substance in 23% of U.S.-born cases and 7% of foreign-born cases. Substance abuse was a more prevalent risk factor for TB than recent immigration, congregate settings, homelessness, HIV infection and high-risk occupation when U.S.-born and foreign-born cases were combined, but the burden was significantly higher in U.S.-born cases alone.

Of 105,688 cases, the odds ratios of an association between substance abuse and positive sputum-smear results at diagnosis were 1.2 for HIV-positive cases, 1.8 for HIV-negative cases, and 1.6 for cases with an unknown HIV status. Of 100,775 cases, the odds ratios of an association between substance abuse and treatment failure were 2.4 for females and 1.5 for males. Of 11,874 cases, the odds ratios of an association between substance abuse and involvement in a county-level genotype cluster were 2.3 for U.S.-born cases and 1.5 for foreign-born cases.

CDC reached a number of conclusions based on the study results. Of the entire study population, 1 in 5 patients reported substance abuse and 1 in 3 U.S.-born patients reported substance abuse. The prevalence of substance abuse in TB cases was greater than other established risk factors, such as recent immigration to the United States, residence in a congregate setting, homelessness, HIV infection or high-risk occupation. Patients who abuse substances were more likely to have sputum smear-positive disease, fail treatment and be involved in a genotype cluster representing recent TB transmission. Overall, the study showed that substance abuse was common and fueled TB transmission.

Potential explanations for the impact of substance abuse on TB include extended exposure to TB in drug use venues or other poorly ventilated and crowded settings, compromised immune systems of substance abusers, less access to routine care among substance abusers, and routine TB control measures that are ineffective for substance abusers. Substance abuse is related to four major barriers to TB control in the United States.

Substance abuse is associated with sputum smear-positive disease that delays care and prolongs infectiousness. Substance abusers often are unwilling or unable to recall the names of contacts. Contacts of patients with TB disease who abuse substances are more difficult to locate and less likely to be screened for TB disease and latent TB infection (LTBI). Contacts who abuse substances are less likely to initiate, adhere to and complete treatment. The NCHHSTP Drug Use Workgroup drafted guidelines for integrating HIV, hepatitis, STD and TB

services for persons using illicit drugs. The guidelines are based on a study that was published in the *Archives of Internal Medicine* in January 2009.

ACET thanked Dr. Oeltmann for presenting CDC's comprehensive study because many members have expressed a strong interest in addressing substance abuse in TB patients for quite some time. A number of ACET members made suggestions for the NCHHSTP Drug Use Workgroup to consider in its ongoing efforts to finalize the integrated guidelines for persons using illicit drugs.

- Caution should be taken against over-generalizing or making broad statements on substance abuse. For example, CDC's study does not clearly distinguish between "alcohol abuse" and "alcoholism" and also does not describe behaviors or various sociodemographic factors to define the "dependent" substance abuse population. The NCHHSTP Drug Use Workgroup should consider these issues while revising the draft guidelines.
- Best practices, lessons learned and field experiences should be compiled from San Francisco and other TB programs throughout the country that have taken advantage of the lengthy treatment period for TB to also treat substance abuse in their patient populations. These techniques should be rigorously evaluated to inform the development and implementation of CDC's guidelines.
- The NCHHSTP Drug Use Workgroup should obtain input from the ACET African American (AA) Workgroup in finalizing the guidelines because AAs had the highest prevalence of substance abuse than any other racial/ethnic group of TB patients in the CDC study.
- The drug use guidelines should include specific recommendations for "middle class" substance abusers as well as those with a high socioeconomic status.
- CDC should review non-traditional models of multidisciplinary clinics that include clinical care, psychiatry, substance abuse and a knowledgeable intermediary who would be available to interact with patients.

Dr. Castro followed-up on one of ACET's suggestions by proposing that CDC engage in an interagency effort with federal partners to collectively address confounding problems in TB patients. For example, CDC's partnership should include the Substance Abuse and Mental Health Services Administration (SAMHSA) for TB patients who need rehabilitation services, Health Resources and Services Administration (HRSA) for TB patients who are homeless, and correctional health agencies for TB patients who will be released from correctional facilities.

Dr. Castro further explained that CDC-funded TB programs could make referrals to SAMHSA-funded rehabilitation centers or HRSA-funded homeless centers for TB patients who need these services. He also noted that the effectiveness of administering DOT in methadone clinics was well documented in the literature during the resurgence of TB.

Update on Detection of TB Outbreak Aberrations

Dr. Thomas Navin, of DTBE, reported that CDC's TB Genotyping Information Management System (TB-GIMS) is a single web location where isolate submission is requested, genotyping results are posted and analysis occurs. With the exception of paperwork to submit isolates, TB control staff will not be required to enter any additional data. Genotyping and surveillance data will be automatically updated and placed in a single web location. Beta testing of TB GIMS is underway and the final version of the system will be released in January 2010 in parallel to the transition of CDC's surveillance data set to real-time data.

CDC's aberration detection developmental activities include risk factor summaries, measures of space and time aberrations, aberration detection alerts and revised epidemiologic curve representations. Maps will be produced at national, state and county levels to detect clusters of TB genotypes. Log-likelihood ratios (LLRs) also will be developed to measure the difference between the observed and expected geospatial concentration. LLRs are weighted by case count and also are log transformed. LLRs are widely studied in statistical analyses and used by the SaTScan system.

LLRs in recent TB outbreaks CDC investigated throughout the country were quite high and ranged from 7-33.6. CDC also evaluated the 14 highest LLR clusters ranging from 20-59 that represented significant problems for TB controllers. Based on previous evaluations by experts, the threshold for LLRs of concern is ~6. High LLRs can be used to identify clusters of major public health importance.

LLRs are effective in determining whether a cluster has become or has been a problem, but are ineffective in determining whether a cluster still is a problem. CDC has developed two approaches to determine if a cluster still is a problem. First, cumulative six-month LLR is used to measure LLRs in successive six-month time windows. Second, cumulative sum analysis is performed to examine the time between cases to detect when cases occur more frequently than expected. CDC will use cumulative LLRs, current six-month LLRs and risk factors to send alerts of the current overall status of TB outbreak aberrations to TB controllers.

The TB Epidemiologic Studies Consortium (TBESC) is funding Task Order 26 to evaluate the sensitivity and specificity of LLRs in detecting outbreaks at lower cutoff values. The study is being conducted in Georgia, Maryland, Massachusetts and Texas. CDC's next steps in its activities to detect TB outbreak aberrations include the development of phase 2 of TB GIMS with

more interactive maps and additional functions. Surge capacity to respond to outbreaks was increased with the addition of Drs. Juliana Grant and Adam Langer to the DTBE Outbreak Investigations Team.

Task Order 26 will be conducted over the next two years and will produce the most solid data set to date on distinguishing between clusters of public health significance and non-significant clusters. CDC will use data from Task Order 26 to refine the current alert system. CDC will offer training on contact, cluster and outbreak investigation modules. Mycobacterial interspersed repetitive unit (MIRU) 2 typing of isolates will increase discrimination in detecting clusters of importance.

Dr. Navin concluded his update by asking an ACET member to participate on DTBE's Advisory Group to assist in developing consensus-based data sharing guidelines, policies and safeguards for use by TB controllers. He also requested ACET's input on whether patient confidentiality could still be protected if state data on TB outbreak aberrations were publicly shared more broadly at the national level. States could then endorse or opt-out of the data sharing guidelines.

ACET made a number of comments and suggestions in response to Dr. Navin's request for input.

- CDC should ensure that the TB aberration detection alert system is beneficial to users of the system in actually detecting aberrations earlier.
- CDC should structure the data sharing agreements to make TB outbreak aberration data available to local and county health departments.
- CDC's RVCT training should offer clear guidance to HCP on incorporating zip codes into the TB aberration detection alert system for TB patients who are homeless. For example, zip codes of homeless shelters or clinics where homeless TB patients received treatment could be entered into the system. This approach would provide TB controllers with better capacity to group homeless persons in a potential outbreak.
- CDC should ensure that its existing data sharing guidelines for states to share data on reportable diseases are consistent with the new data sharing guidelines for TB controllers.
- CDC should closely monitor any adverse impacts of reductions in state laboratory staff on monthly shipments of cultures to state laboratories for genotyping.

Dr. Navin provided additional details in response to ACET's comments and suggestions. Each state will designate an administrator to make decisions on individuals who can have access to TB outbreak aberration data. County health departments will have access to line-listed data, but will not have rights to edit surveillance data. CDC created a FedEx account for health departments to easily and rapidly ship cultures to laboratories for genotyping. The Michigan laboratory is returning 90% of genotyping results to health departments within two weeks.

Update on the U.S. TB Elimination Plan (TEP)

Dr. Randall Reves, of the Denver Public Health Department, provided an update on the TEP on behalf of STOP TB USA. The TB control community failed to meet the TB elimination goals. ACET's 1989 goal to eliminate TB by 2010 based on a definition of 1 case/1 million population will not be achieved. The Institute of Medicine's (IoM) 2000 goal to eliminate TB by 2035 with the development and implementation of new prevention tools and the expansion of LTBI treatment is unlikely. Based on a 3.8% reduction in TB cases per year since 2003, CDC has projected that TB elimination could be achieved in 2104 in the general U.S. population. Because non-Hispanic whites account for only 17% of TB cases in the United States at this time, CDC's projections also show that minorities would exclusively account for all TB cases in 50 years.

Mr. Van Simsiman is a member of the Filipino community who attended a recent community consultation on TB. He commented that TB elimination in 100 years would be meaningless to him. He emphasized that establishing progressive interim goals at ten-year periods would be more operationally realistic. During the consultation, Mr. Simsiman asked about actions that need to be taken to ensure funding and support for TB elimination efforts continue. He also inquired about the persons and entities that would be held accountable for measuring progress in performance and ultimate achievement of the TEP goals.

The TEP Writing Committee does not believe a new plan is needed because the key guidance remains valid. However, the IoM's recommendations to meet all of the TEP goals have not been implemented to date. The IoM goals of maintaining TB control despite the decline in the number of cases and increasing U.S. involvement in global TB control have been achieved based on a continual decline in TB cases since 1993 and increased funding for TB.

The IoM goal of accelerating the decline in the number of TB cases by increasing targeted testing and treatment of LTBI has not been achieved because LTBI treatment is limited to public health departments, a few prisons and refugee clinics. Private practitioners who are treating patients with risk factors for TB are not identifying, testing and providing treatment to these patients. CDC data showed increasing prevalence in LTBI among the foreign-born population (FBP) in 1999-2000.

The IoM goals of developing new diagnostics, treatment and prevention tools as well as mobilizing and sustaining public support have not been fully achieved. Research in these areas was expanded, but implementation of new tools has been limited at federal, state and local levels. Moreover, success in mobilizing support has been modest at best.

On an individual level, the TB control community failed a woman 19 years of age from Nepal who attended school in Colorado and died from TB. Stigma and perceptions regarding TB from different parts of the world inhibit solid actions on TB elimination. TB prevention is an essential component of TB elimination, but has become less of a priority. Due to resource constraints in state and local TB programs, efforts are limited to treating TB cases and conducting contact investigations.

The TB control community recognizes the critical need to take more aggressive actions in TB elimination. TB case detection and curative treatment are still necessary, but mobilization for TB prevention and elimination is essential. Outrage over the growing health disparity in which TB will be an exclusive disease among minorities in 50 years should be shared with communities. Time is being wasted on learning to use poor second-line drugs. Communities should be reminded that local and state TB programs are the only mechanisms to stop the development and spread of XDR-TB in the United States. The benefits of TB elimination by 2035 also should be widely publicized to communities, such as 253,000 fewer active TB cases, 15,200 fewer TB-associated deaths, and ~\$1.3 billion in cost-savings from TB treatment.

The TEP Writing Committee completed the first draft of the plan in October 2008 with funding and support from NTCA and the American Thoracic Society (ATS) for conference calls, writer/editor expertise and graphics. The draft plan was revised based on external input from DTBE, the Department of Homeland Security, state and local health departments, and academic institutions. The Executive Summary of the TEP was posted on the NTCA website in June 2009 for a 30-day open comment period. The next steps in the TEP will be to develop advocacy documents, create communication tools to engage community members, and post other sections on the website, particularly the U.S.-born, foreign-born and low incidence chapters.

Dr. Reves concluded his update by asking ACET to provide him with comments on the TEP Executive Summary at rreves@dhha.org. He also requested ACET's review and formal endorsement after the entire TEP is updated as well as recommendations on ensuring the plan is implemented.

ACET commended STOP TB USA and the TEP Writing Committee for updating the plan with a voluntary and grassroots effort. Several ACET members made suggestions for the Writing Committee to consider in broadly disseminating and implementing the TEP.

- Successful models in reaching specific populations for other diseases should be used to ensure implementation of the TEP. For example, churches, beauty salons and barber shops served as extremely effective partners with CDC to reach the AA community regarding breast and prostate cancers.
- The National Medical Association (NMA) should be used to educate and engage AA physicians in the TEP. For example, an NMA member could serve as a reviewer of the TEP.
- The Writing Committee should incorporate recommendations into the TEP from CDC's previous consultations on TB in the AA community.
- CDC should take more aggressive actions in holding grantees accountable for targeting federal cooperative agreement funds to AAs and other minority groups that are disproportionately impacted by TB in the United States.
- The TEP should be provided to HRSA-funded Clinicians Networks and Community Health Centers for wider distribution during conferences of these grantees. Providers in these HRSA-funded settings serve homeless persons, HIV-positive persons, migrants and other populations that are at risk for TB.

Dr. Castro made additional suggestions to increase awareness and dissemination of the TEP. First, the TEP and supporting data should be directly distributed to influential leaders in the AA and Hispanic communities, such as elected officials and the Congressional Black and Hispanic Caucuses. Second, the TEP should be linked to the Comprehensive TB Elimination Act that authorizes TB elimination activities at the federal level. However, a footnote should be added to the TEP to emphasize that despite this federal law, no funding has been appropriated to date for TB elimination. Third, a charter for TB patients or affected communities should be developed to accompany the TEP and document endorsement of the plan by the target audience.

Ms. Fran DuMelle, of ATS, is the ACET liaison to STOP TB USA. She announced that tools will be designed and lessons learned from previous implementation plans will be applied to enhance advocacy for and funding of the TEP at state and national levels. She asked ACET to provide input on additional tools that should be created for implementation of the TEP.

On behalf of STOP TB USA, Ms. DuMelle, presented a plaque to Dr. Reves in recognition of his dedication and commitment to updating the TEP and overseeing this grassroots initiative. The participants joined Ms. DuMelle in applauding Dr. Reves for his outstanding efforts.

Dr. Fleenor closed the discussion by confirming that the TEP would be placed on the agenda for the October 2009 meeting for ACET's review and possible adoption of a formal resolution. To ensure compliance with the charter, however, he clarified that any recommendations ACET passed on the TEP would be directed to the Director of CDC and Secretary of HHS.

Update on the National Tuberculosis Indicators Project (NTIP)

Ms. Kai Young, of DTBE, explained that DTBE formed the TB Program Evaluation Workgroup because the use of data for program improvement was limited prior to 2000. The workgroup's efforts led to the development of NTIP to facilitate a collaborative impact evaluation and enhance CDC's effectiveness in TB elimination. NTIP is a user-friendly program monitoring system that strengthens collaboration, increases the use of existing data, helps prioritize efforts for program evaluation, and facilitates the integration of monitoring and evaluation into routine program practice.

DTBE developed NTIP based on the steps in CDC's framework for program evaluation, such as engaging stakeholders, describing the program, focusing the evaluation design, gathering credible evidence, justifying conclusions, and using and sharing lessons learned. Standards in CDC's framework of utility, feasibility, propriety and accuracy also guided the design of NTIP. The workgroup identified 15 categories of high-priority objectives for TB programs and established national TB program objectives and performance targets for 2015. NTIP generates indicator reports that monitor progress toward achieving these national objectives, focus program evaluation efforts, and provide performance targets as benchmarks for assessment.

DTBE created standardized indicator measurements for NTIP by engaging stakeholders at state and local levels in an iterative process through a series of conference calls. An intensive review

of NTIP also was conducted with a larger group of external partners. NTIP indicator reports were designed based on DTBE's national TB program objectives and templates from the California TB Indicators Project. Each NTIP report contains a graph to illustrate state performance in a national objective, a table with state data, and a methods summary highlighting the national objective, indicator, cohort, data sources and calculations. States can use the NTIP reports to compare their performance with national results and targets.

DTBE will gather data from the CDC National TB Surveillance System to develop and distribute NTIP reports to all grantees for assistance in preparing progress reports. NTIP reports will have the ability to facilitate discussion, educate staff and encourage problem solving between DTBE and program areas, program managers and staff, and programs and community partners. NTIP reports also will play a role in tracking program progress, enhancing capacity to provide guidance and technical assistance, and strengthening collaboration to detect and understand barriers and improve program effectiveness.

DTBE created a process to integrate NTIP into program practice. For programs that meet NTIP targets, an evaluation will be performed to identify and widely share best practices. For programs that do not meet NTIP targets, an evaluation plan will be developed to better understand barriers and challenges. Updates on progress in the evaluation will be periodically submitted to DTBE. Upon completion of the evaluation, the program will refine current activities or develop new initiatives based on the findings and then implement improvements. Because state programs provide leadership and technical assistance to local jurisdictions in the evaluation process, NTIP reports will be distributed to regional and county levels.

DTBE launched NTIP in March 2009 for programs to pilot the system in reporting their 2008 progress. Programs are currently using NTIP to prepare applications for the 2010-2015 TB cooperative agreements. Programs will be required to report progress using NTIP beginning in 2010. County-level reports will be available to support collaborations between state and local programs. NTIP will capture real-time reporting and line-listed data. DTBE hopes NTIP will encourage programs to submit data more often to CDC.

Overall, NTIP will reinforce national TB priorities at state and local levels. Existing data will be used to measure progress and impact. Priorities will be identified for program improvement, reporting and technical assistance. NTIP also will facilitate evidence-based practice and enhance collaboration between DTBE staff and among partners at all levels. Ms. Young concluded her update by presenting a live demonstration of NTIP.

ACET made two key suggestions for DTBE to consider in the national implementation of NTIP in 2010. First, DTBE should explore the possibility of incorporating language into the TB cooperative agreements to require grantees to submit data to CDC on a timelier basis. This requirement would help DTBE to generate NTIP reports on a quarterly basis. Second, DTBE should issue clear guidance to grantees on using NTIP to submit interim progress reports to CDC.

ACET Workgroup Reports

Model TB Prevention and Control Act Workgroup. Ms. Melisa Thombly, of DTBE, reported on the status of five major activities CDC conducted to build on ACET's 1993 recommendations regarding TB laws.

In activity 1, CDC commissioned the Centers for Law and the Public's Health (CLPH) to review, organize and characterize legislative regulatory or judicial case laws for TB control in 25 selected states and jurisdictions that expressly relate to the control of TB or MDR-/XDR-TB cases through state or local health departments, other governmental actors and private sector partners. This activity focused on express TB control laws and excluded general communicable disease laws. The *Express Tuberculosis Control Laws in Selected U.S. Jurisdictions* Report was posted on the CLPH website in October 2008 and will be available on the CDC and NTCA websites in the near future.

In activity 2, CDC developed a scenario tool to assess jurisdiction-specific understanding and sufficiency of TB control laws. Officials from relevant sectors were convened to implement the scenario tool and identify potential gaps in legal authorities that might inform the development of the TB control model act. The scenario tool was piloted in Florida and Kansas in May 2008 and would be made available to other jurisdictions following implementation of the pilot.

CDC also created companion implementation guidelines for any jurisdiction that expected to use the scenario tool. In response to ACET's previous recommendation for jurisdictions to use the scenario-based assessment tool before implementing any of the options for the model TB control act, this resource will be disseminated to TB control officials in collaboration with ACET and NTCA. The tool will be posted on the websites of CDC, NTCA and other groups over the next few months.

In activity 3, CDC identified, reviewed and characterized TB control laws in selected tribes to inform the development of the TB control model act. Data sources that guided this activity included the National Tribal Justice Resource Center, Tribal Court Clearinghouse of the Tribal Law and Policy Institute, and HHS Office of the General Counsel in Region IX. CDC is currently consulting with the Indian Health Service Office of the General Counsel to identify potential concerns with posting the report on websites because tribal legal counsel did not review the document. In the event the report cannot be publicly available on websites, CDC will disseminate the report to tribal counterparts for review and feedback.

In activity 4, CDC developed a handbook and companion instructional slide unit on TB control laws that local, state and tribal public health practitioners and their legal counsel can use to improve their understanding of and competency in applying TB control laws. These resources are targeted to public health practitioners who are active in TB control at local, state and tribal levels and their legal counsel.

The materials focus on relevant local, state, tribal, federal and international laws. *Tuberculosis Control Laws and Policies: A Handbook for Public Health and Legal Practitioners* and the

companion instructional slide unit are currently in the final phase of the CDC clearance process and should be available online over the next few weeks. CDC will solicit input from ACET and NTCA on additional options to disseminate these resources.

In activity 5, CDC commissioned CLPH to develop a state “model act” on TB control to provide state and local public health officials, policymakers, legislators and others with a tool to review and potentially strengthen their respective TB prevention and control laws. After the first draft of the model act was developed and revised based on comments from CDC and key partners, CLPH informed CDC of its inability to be totally responsive to comments on the second draft in June 2009.

CLPH used its Turning Point Act to draft the TB control model act, but CDC and key partners found the broad language and numerous Constitutional provisions to be problematic for a TB control law. Moreover, CLPH’s Turning Point Act was offensive to many workgroup members because its overall tone suggested that public health officials routinely violate the Constitutional rights of patients. Several workgroup members representing ACET, NTCA and other groups informed CDC that their respective organizations would not endorse the TB control model act CLPH had written. CDC is currently consulting with its Office of General Counsel to formulate a disclaimer in the event CLPH decides to disseminate the TB control model act.

To resolve this problem, CDC will collaborate with ACET, NTCA and other key partners to develop a menu of options for state TB control laws to better address the diverse needs of states. The menu will be modeled after the methodology that was used to create CDC’s “Menu of Suggested Provisions for Public Health Mutual Aid Agreements” and also will be based on existing best practices for state control laws.

State TB control laws will be categorized using ACET’s 1993 recommendations that were published in the *MMWR*. General communicable disease control provisions will be included in the menu where appropriate. CDC will convene an in-person meeting with state TB controllers and legal counsel for state and local health departments to facilitate the development of the menu.

Dr. Fleenor confirmed that in response to Ms. Thombley’s request, the menu of options for TB control laws would be placed on future meeting agendas for ACET to provide input to CDC on an ongoing basis during the development of this activity.

IGRA Workgroup. Dr. Iram Bakhtawar is a member of both ACET and the workgroup. She presented the report on behalf of Dr. Masahiro Narita, chair of the workgroup, who was unable to attend the ACET meeting. CDC convened an expert panel in August 2008 to update its 2005 IGRA guidelines to reflect more recent data. The workgroup reviewed the initial draft and provided comments to the authors on specific areas in the IGRA guidelines that needed clarification. The revised draft was presented during the June 2009 NTCA meeting for the authors to obtain additional input.

Dr. Bakhtawar concluded that the workgroup is now asking ACET to adopt a formal resolution for CDC to publish useful IGRA guidelines as soon as possible. In preparation of ACET taking

formal action on the IGRA guidelines during the business session on the following day, Dr. Fleenor confirmed that the most recent draft would be distributed to ACET for review before the meeting was recessed.

Foreign-Born Workgroup. Dr. Dolly Katz, of DTBE, reported that the workgroup was formed to update CDC's 1998 guidelines on TB control in FBP to reflect more recent changes in the epidemiology of TB in FBP and new tests for LTBI. The workgroup is currently revising the draft guidelines and will convene an in-person meeting with ACET members, TB controllers and CDC staff on July 27, 2009 to reach consensus on three major areas of the guidelines that have not been resolved to date.

The first unresolved issue is "who should be screened." The current guidance is intended for the management of FBP who present to any type of healthcare provider for services of any kind. The workgroup has proposed a recommendation to screen all FBP for LTBI at least once except those from low-risk countries. During the meeting, the workgroup will attempt to reach consensus on whether the guidelines should reflect the best approach to the prevention of TB in FBP irrespective of individual capacity or if capacity should be taken into account.

The second unresolved issue is "what screening method" should be used (i.e., IGRA versus tuberculin skin test (TST)). During the meeting, the workgroup will attempt to reach consensus on whether the guidelines should be permissive or specifically advocate for the use of IGRA in FBP.

The third unresolved issue is "who should be treated." A decision to test will no longer serve as a decision to treat. The workgroup has proposed a recommendation to base the decision to treat on the risk of progression to active TB. High-risk FBP would be treated as well, such as recent arrivals from foreign countries, younger persons and individuals with HIV or diabetes.

During the meeting, the workgroup will attempt to reach consensus on the extent to which the guidelines should be prescriptive, such as establishing an age cutoff for treatment, describing each foreign-born subgroup that should and should not be treated, or offering general guidance to provide physicians with flexibility in making informed decisions regarding treatment based on dialogue with their patients. After consensus is reached in these three areas, the workgroup will revise and distribute the guidelines to a wider audience for broader input.

Some ACET members expressed reservations about unresolved issue 1 in which a decision has not been made on whether to consider capacity in the recommendation for any type of healthcare provider to screen FBP for LTBI. The members emphasized that individual capacity of providers should be taken into account because internists, pediatricians and other physicians with no expertise in infectious diseases are not necessarily equipped to screen FBP for LTBI. If consensus is reached not to consider individual capacity of providers, however, ACET advised the workgroup to recommend that healthcare providers give patients a written copy of their TB test results. This guidance would resolve a capacity issue for providers who do not have electronic medical record systems that are linked to health departments.

Most ACET members expressed serious concerns about unresolved issue 3 in which a decision to test would no longer serve as a decision to treat. The members strongly urged the workgroup to avoid decoupling TB screening and treatment in the guidelines. The ACET members made additional suggestions and comments for the workgroup to consider and discuss during the consensus meeting.

- The workgroup should review CDC's published data that showed the environment places FBP at greater risk for TB rather than time of arrival in the United States. The paper pointed out that FBP continue to be exposed to TB due to frequent visits to their countries of origin or relatives and friends who visit the United States, but are not screened for TB overseas.
- The workgroup should take caution in not recommending LTBI screening of FBP from low-risk countries. Canada, Sweden and other low-risk countries could have subgroups of FBP who are at high risk for TB, such as substance abusers, minorities and refugees.
- The workgroup should attempt to compile data to determine the extent to which interferon-based tests versus TST with the Mantoux method are being used at this time.
- The workgroup should explore the possibility of adding foreign-born HCP as another special population in the guidelines.
- The workgroup should ensure that the foreign-born guidelines are consistent with other CDC guidance. For example, the draft IGRA guidelines recommend IGRA as the preferred screening method for persons who have been vaccinated with BCG, while the workgroup has not yet reached consensus on whether the foreign-born guidelines should be permissive or specifically advocate for the use of IGRA in FBP.
- The workgroup should use the consensus meeting as an opportunity to discuss payment of targeted testing of FBP in the context of healthcare reform.
- CDC should update its 2000 guidelines for targeted testing and treatment of persons with LTBI to be consistent with the new foreign-born guidelines.
- The workgroup should solicit input and obtain endorsement of the guidelines from professional associations whose members will be responsible for the implementation of the recommendations in routine practice. Examples of these organizations include:
 - The Society of General and Internal Medicine and American Academy of Pediatrics for implementation of the guidelines by primary care physicians.
 - The American College Health Association for implementation of the guidelines by providers who screen foreign-born students for TB.
 - The foreign-born medical community for implementation of the guidelines by foreign-born physicians with patient populations from India and other high-burden countries.

Dr. Castro made two additional suggestions for the workgroup to consider and discuss during the consensus meeting. First, Dr. Jerry Mazurek or Dr. Andrew Vernon, of DTBE, should be asked to make a presentation during the consensus meeting on the provisional guidelines for the use of IGRA. Language in the current guidelines favors the use of IGRA in persons vaccinated with BCG. Second, representatives from ATS and the Infectious Disease Society of America (IDSA) should be invited to the consensus meeting because both of these organizations played a critical role in developing the 2000 guidelines for targeted testing and treatment of persons with LTBI.

Drs. Fleenor and Katz confirmed that ACET's concerns, comments and suggestions on the foreign-born guidelines would be discussed during the workgroup's consensus meeting. Dr. Fleenor also noted that the outcomes of the consensus meeting would be reported to ACET during the October 2009 meeting.

BCG Workgroup. Dr. Barbara Seaworth is an ACET member and chair of the workgroup. She reported that the workgroup was formed in 2008 with an initial charge to review new literature on the efficacy of BCG and apply more recent data to update CDC's 1996 BCG guidelines. During the March 2009 meeting, however, ACET unanimously adopted the following resolution. The workgroup's charge would be modified to decrease the focus on the use of BCG and formulate more general recommendations on approaches to protect humanitarian and scientific travelers who travel from the United States to work in endemic areas of the world where MDR-/XDR-TB exposure and infection would be more likely.

In response to the modified charge, the workgroup expanded its membership to include experts from CDC's DGMQ, Division of Healthcare Quality Promotion (DHQP), and Division of Respiratory Disease Studies in the National Institute for Occupational Safety and Health. The workgroup also engaged Dr. Daniel Hoft as an expert reviewer for the BCG section of the guidelines.

Dr. Seaworth outlined the workgroup's proposed plan to fulfill its modified charge based on previous input from ACET and CDC. The new title of the guidelines will be *Screening and Infection Control Guidelines for Healthcare Workers and Volunteers Who Travel to Work in Healthcare Facilities in Regions in Which Drug-Resistant TB is Endemic*. The guidelines will be shortened to specifically focus on issues that are pertinent to screening and infection control for the prevention of MDR-/XDR-TB in HCP and other volunteers. Emphasis will be placed on strategies for the management of persons who travel to high-risk areas to provide health care or humanitarian aid.

BCG will be discussed in the guidelines as only one of several options for HCP and other volunteers to consider. Other pertinent preventive measures that will be highlighted include infection control precautions, personal respiratory protection, education, airborne infection isolation rooms, and serial testing to monitor for new infections. The BCG section will contain new data on the potential efficacy of BCG and a description of the benefits, contraindications and risks of vaccination. Existing knowledge and data on the risks of BCG to HCP will be described as well. The references will be updated as needed.

The workgroup recognizes the need to resolve a number of concerns ACET raised during previous meetings. The efficacy of BCG continues to be a source of debate. Sufficient data have not been collected to date to formulate evidence-based recommendations, demonstrate actual risks to travelers, or provide guidance on the management and treatment of LTBI in HCP and other volunteers with possible MDR-TB. The workgroup also has not determined the duration of exposure that might possibly be considered.

The recommendations section of the guidelines will provide guidance in the following areas. The initial assessment prior to departure will focus on an evaluation of risk at specific sites,

education regarding measures to limit risk, fit testing with a personal respirator and education regarding its use, and provision of a respirator. The assessment for LTBI or TB disease prior to departure will focus on TST and IGRA as screening methods. The workgroup has not yet made a decision on whether LTBI treatment should be recommended prior to departure.

Options for BCG vaccination will focus on education regarding risks and benefits as well as a discussion and documentation of contraindications. The assessment upon return from travel will focus on repeating TST or IGRA if the prior test was negative and conducting an evaluation to exclude disease based on conversion of TST or IGRA results. The workgroup has not yet made a decision on whether ≥ 1 drugs or which specific drugs should be recommended for treatment of newly acquired TB infection. The guidelines will emphasize the critical need to collect additional data to answer these research questions.

Dr. Seaworth concluded her update by requesting ACET's guidance in two areas before the workgroup takes further action on revising the expanded guidelines. The workgroup needs additional feedback from ACET to resolve concerns or opposing viewpoints that were raised during previous meetings. The workgroup needs ACET's input on whether the proposed plan to revise the expanded guidelines is appropriate.

ACET commended Dr. Seaworth, Dr. Elsa Villarino, of DTBE, and other members of the workgroup for their dedication and commitment to this activity, particularly in light of the enormous amount of time and effort required to expand the guidelines from a narrow focus on BCG vaccination to a broader focus on TB prevention in endemic areas.

ACET fully supported the workgroup's proposed plan to revise the guidelines with a broader focus on the prevention of TB in HCP and other volunteers who travel to regions of the world where drug-resistant TB is endemic. Due to the lack of evidence on BCG, ACET also was in favor of recommending BCG as an optional preventive measure. Several ACET members pointed out the tremendous value in issuing the expanded guidelines. Most notably, the practice of travel medicine is overwhelmingly poor in the United States with the exception of New York City and few other large jurisdictions.

ACET advised the workgroup to seriously discuss the risks of issuing guidance to students who travel to areas of the world that are endemic for drug-resistant TB and need respiratory protection. The guidelines should advise students to reconsider their plans to travel to these high-risk areas. The guidelines also should provide a list of sites and other resources where students can be educated on potential health risks prior to travel.

Dr. Fleenor closed the discussion by acknowledging ACET's strong support for the workgroup to implement its proposed plan to revise the guidelines for TB prevention in HCP and other volunteers who travel to regions of the world where drug-resistant TB is endemic. He confirmed that updates by the workgroup would continue to be placed on future agendas for ACET to provide ongoing input and guidance as various drafts of the guidelines are completed. Dr. Castro confirmed that CDC would continue to provide the workgroup with staff support and other resources to revise the guidelines.

Overview of the Mycobacteriology Laboratory Branch (MLB) External Peer Review

Ms. Bonnie Plikaytis, Acting Chief of MLB, provided an overview of MLB's external peer review that would be held on August 21, 2009. CDC's 2002 peer review policy of research and scientific programs requires all research and scientific programs conducted or funded by CDC to undergo an external peer review at least once every five years to evaluate scientific and technical quality as part of the Board of Scientific Counselors (BSC) administered review of scientific programs.

Ms. Plikaytis noted that Dr. Fleenor would serve as the chair of the MLB external peer review panel and the five panel members would represent the Coordinating Center for Infectious Diseases (CCID) BSC, Association of Public Health Laboratories (APHL), academia, and a state public health department.

Ms. Plikaytis summarized the information MLB would present to the external review panel to inform its deliberations. MLB's workforce of 33 personnel includes 26 full-time equivalents, five ORISE Fellows, one American Society for Microbiology postdoctoral fellow, and one Emerging Infectious Diseases postdoctoral fellow.

Of DTBE's ~\$12.3 million allocation to MLB in FY2009, ~\$7.6 million was for cooperative agreements, ~\$3 million was for employee salaries and benefits, ~\$1.1 million was for the National Genotyping Service contract, \$348,000 was for supplies and equipment, and \$62,000 was for travel. MLB leveraged additional funding in FY2009 of \$189,000 from the DTBE TB Leads Program, \$100,000 from the Global AIDS Program, \$120,000 from the Office of Antibiotic Resistance, and \$50,000 from the Georgia Research Alliance.

MLB's organizational structure of the Reference Laboratory Team and Applied Research Team collaboratively conducts activities in six areas. MLB designed the conventional laboratory and molecular diagnostic activities to serve as a reference laboratory for DST to U.S. public health laboratories and provide DST and genotyping support for DTBE studies. MLB also uses these activities to identify non-tuberculous mycobacteria (NTM), but this service will be transferred to DHQP in the near future.

MLB will launch a new service for molecular detection of drug resistance on September 1, 2009. DNA sequencing-based assays will be provided to detect mutations associated with drug resistance of rifampin, isoniazid (INH), amikacin, fluoroquinolones, kanamycin and capreomycin. MLB designed the platform to be easily expanded.

MLB designed the laboratory capacity activity to provide oversight and administration of the laboratory component of TB cooperative agreements, train U.S. public health laboratory staff, conduct the model performance program for DST, and perform operational research by surveying the quality of TB services in public and private sector laboratories.

MLB uses this activity to secure funding and assist in planning co-located meetings sponsored by NTCA and APHL to assure that laboratory aspects of TB are included in TB control efforts. MLB also uses this activity to participate on the APHL TB Steering Committee. MLB has assigned and funded a TB laboratory consultant for each state and jurisdiction to collaborate with program consultants in reviewing reports, conducting site visits and providing consultation as needed.

MLB designed the molecular genetics activity to elucidate the mechanisms of drug resistance through several strategies. DNA sequencing of ~320 isolates is performed to map mutations associated with drug resistance. These data will provide a basis for interpreting sequencing results generated by MLB's new molecular detection of drug resistance service. A new mechanism was developed to detect low-level kanamycin resistance based on an over-expression of acetyltransferase that inactivates the drug. MLB has incorporated this mechanism into the new molecular detection of drug resistance service that will be launched in September 2009. Studies on mechanisms of resistance to first- and second-line are ongoing with a focus on functional genetics and genomic sequencing of drug-resistant isolates.

MLB designed the immunology and cell biology activity to evaluate *Mycobacterium tuberculosis* (*M.tb*) proteins for use as a second-generation TB vaccine. Under this activity, MLB and the Emory Vaccine Center collaborated to identify four proteins that elicit promising immunogenicity and antigenicity profiles in the mouse model. Protection studies that were initiated in February 2009 in the mouse model to evaluate proteins are expected to be completed in late 2009 or early 2010. The Georgia Research Alliance awarded funding to support this project and CCID filed a patent application in January 2009 to protect the intellectual property rights of the study.

MLB designed the genotyping activity to support the National TB Genotyping Service contract that was renewed in October 2008 with an expanded focus on MIRU typing of isolates. MLB also uses this activity to support Task Order 2 and TB Trials Consortium (TBTC) studies on human genotyping.

MLB will target its future activities to two major areas. In the "service component," conventional DST and molecular detection of drug resistance for *M.tb* isolates will continue to be provided and services will be expanded as needed. Education and training in laboratory practice and science will be provided to laboratory personnel, TB controllers and physicians to enhance understanding and accurate interpretation of molecular tests. Oversight of the TB cooperative agreements and consultation to U.S. public health laboratories will continue to be provided. Efforts will be made to strengthen U.S. mycobacteriology laboratory systems in collaboration with APHL.

In the "research component," translational and operational research will focus on implementing new diagnostic technologies and administering the comprehensive survey of laboratory practices and services in public and private sectors. Laboratory methods to diagnose TB and MDR-/XDR-TB and genotype *M.tb* isolates will be developed and evaluated. Mechanisms of resistance and virulence factors for *M.tb* will continue to be characterized. A second-generation TB vaccine will be produced and evaluated in a Phase I trial in collaboration with industry and other external partners.

Ms. Plikaytis concluded her overview by summarizing three key questions the MLB external peer review panel would be charged with answering. One, are MLB's activities and research agenda aligned with DTBE's mission, goals, strategic priorities and core activities? Two, what are the strengths and successes of MLB's activities? Three, what are the weaknesses and deficiencies of MLB's activities, including any significant program or research gaps?

Ms. Plikaytis added that the external peer review panel also would be asked to offer guidance on whether MLB should continue, discontinue, modify or add specific program and research activities to its existing portfolio. After the panel submitted its report to DTBE four to six weeks after the external review, MLB and DTBE would produce a formal response. MLB hopes to present a summary of the panel's report to ACET during the October 2009 meeting.

In preparation of transferring the service of identifying NTM, ACET advised MLB to provide state laboratories with background information on DHQP, including its mission and current capacity.

Dr. Fleenor pointed out that based on CDC's presentations and the workgroup reports on day 1 of the meeting, the number of issues requiring ACET's formal action during the business session on the following day was already extensive. He agreed with Dr. Castro that ACET would have time to formulate, discuss and adopt resolutions for high-priority issues only, such as the role of TB programs in contributing to the H1N1 influenza response, while continuing to provide TB case management.

To ensure that the business session was productive and efficient, Dr. Fleenor asked the ACET members to provide him with their "rankings" of high-priority issues before the meeting was reconvened on the following day. He clarified that any topics the ACET members ranked as "low" would be deferred until the October 2009 meeting.

With no further discussion or business brought before ACET, Dr. Fleenor recessed the meeting at 4:48 p.m. on July 14, 2009.

Update on TBTC

Dr. Fleenor reconvened the ACET meeting at 8:31 a.m. on July 15, 2009 and yielded the floor to the first presenter.

Dr. Vernon covered the following areas in his update. TBTC was formed in 1998 with a mission to collaboratively conduct programmatically relevant clinical, laboratory and epidemiologic research on the diagnosis, clinical management and prevention of TB infection and disease. TBTC's infrastructure includes 27 clinical sites in the United States, Canada, Brazil, South Africa and Spain.

TBTC's organizational structure includes a Steering Committee within the Executive Affairs Group to oversee daily functions and nine Executive Committees and workgroups to advance the scientific agenda. NIH-funded AIDS Clinical Trials Groups, particularly the Community

Programs for Clinical Research on AIDS and the AIDS Clinical Trials Group, were used as models to create TBTC's formal bylaws.

Major studies conducted in the current cycle of TBTC are highlighted as follows. TBTC Study 26 is a preventive therapy trial comparing a standard nine-month regimen of INH to a three-month regimen of once weekly INH and rifapentine for treatment of LTBI. The follow-up of Study 26 will end in December 2010 and the results will be presented in the spring of 2011.

TBTC Study 29 is comparing a daily rifapentine regimen with doses of 450 or 600 milligrams five days per week to a standard rifampin regimen with the primary outcome of two-month culture conversion. To date, ~200 patients of the total sample size of ~480 patients have been enrolled and two safety reviews have been completed. Enrollment is expected to be completed by February 2010. TBTC Study 31 is currently under development and will serve as a follow-on to Study 29. Study 31 will be designed as a Phase III trial with a high-frequency rifapentine-based regimen.

TBTC Study 30 is an MDR-TB study with a low-dose linezolid regimen. Challenges of the study include a number of implementation issues, such as development of the protocol, toxicity of second-line regimens, drug procurement, preparation of a placebo and reorganization of the laboratory. Moreover, the Medicines Control Council required ~12 months to issue regulatory approvals to import drugs for use in the clinical trial. Enrollment of patients in Study 30 is competing with the TMC-207 trial that is underway at the same site in Durbin, South Africa. DTBE and the CDC Emerging Infectious Disease Program agreed to support the study.

DTBE acknowledges that existing guidelines on the treatment of LTBI and TB disease will need to be updated based on outcomes of ongoing TBTC trials. However, the chair of the TBTC Advocacy and External Relations Committee engaged in dialogue with ATS and learned that no funds are available to develop and implement new Microbiology Tuberculosis and Pulmonary Infections projects in FY2009.

DTBE is currently recompeting TBTC for the next ten-year cycle. The Technical Evaluation Panel met in June 2009 and determined that a number of excellent proposals were submitted for the contract site component of TBTC. CDC expects to announce the new TBTC awards in September 2009. Several excellent proposals also were submitted for the ten-year recompetition of the Department of Veterans Affairs component of TBTC.

DTBE is continuing to explore the possibility of developing a field station component for the next generation of TBTC. However, efforts to advance TBTC with three components simultaneously are presenting both financial and data management challenges to DTBE. For example, traditional contracting mechanisms that focus on the ability of grantees to present and document their capacity and experience does not support the approach of developing new TBTC sites in a substantial manner.

TBTC, the Pan African Consortium for the Evaluation of Antituberculosis Antibiotics, Oflotub Consortium, AIDS Clinical Trials Group, MDR groups and other trial groups are conducting trials to accelerate the development of promising new TB agents, including TMC-207, OPC-67683, SQ-109, PA-824, PNU-480, AZ oxazolidinone, rifapentine, high-dose rifampin and moxifloxacin.

These TB trials will provide an opportunity for FDA, the European Medicines Agency and other national agencies to consider new or modify existing regulatory approaches to safely and effectively accelerate the development of promising new TB agents. The TB Alliance and Bill and Melinda Gates Foundation have developed a joint proposal to open dialogue on new regulatory approaches.

The FDA Anti-Infectives Advisory Panel held a meeting in June 2009 to consider criteria for approval of an MDR candidate. FDA will convene a public meeting on July 30-31, 2009 to discuss issues regarding the design of clinical trials of antimycobacterial drugs for the treatment of TB. NIH will convene a pediatric TB workshop on July 29, 2009.

Dr. Vernon concluded his update by requesting ACET's assistance in the following areas to strengthen the new ten-year cycle of TBTC. ACET should adopt a formal resolution for ATS, CDC and IDSA to prepare for updating guidelines on the treatment of LTBI and TB disease based on results of the TBTC trials. ACET should provide input to DTBE on conducting Phase IV evaluations in the United States, particularly for an LTBI regimen. ACET should provide guidance on the development of new TBTC trial sites and offer strategies to ensure careful and efficient coordination between TBTC and other trial groups. ACET should help to define the role and responsibilities of the public sector and other partners in the development of new TB drugs.

ACET made suggestions for DTBE to consider in the new ten-year cycle of TBESC. DTBE should ensure that capacity is built to administer new drugs for TB and MDR-TB.

Dr. Castro raised the possibility of ACET devoting a substantial portion of a future meeting to engage ATS, IDSA and experts from other professional societies to evaluate data from the ongoing TBTC trials and develop preliminary guidelines. He noted that guidelines from a federal advisory committee with input from external experts could play a significant role in leveraging additional resources for TBTC and promoting the use of promising new TB agents.

Update on TBESC Task Order 23

Dr. Katz reminded ACET that TBESC Task Order 23 was designed as a national study to identify determinants of early diagnosis, prevention and treatment of TB in the AA community. TB rates in U.S.-born AAs have been declining, but TB rates are still ~8 times higher in this population compared to U.S.-born whites. The study will be conducted based on the hypothesis that delays in the diagnosis and treatment of active TB and LTBI are major determinants of higher rates of TB and a slower decline in rates among U.S.-born AAs.

The goals of the study are to understand factors associated with diagnosis and treatment delays among AA to facilitate developing education programs for patients and providers; proposing performance goals and indicators for TB programs; and identifying missed opportunities for TB screening. The objectives of the study are to recruit a sample size of 500 U.S.-born AAs and a comparison group of 175 U.S.-born whites. In-depth interviews will be conducted and health department medical records of patients will be abstracted to measure the time between

diagnosis and treatment in the study population; determine delays among patients, providers and TB programs; and assess the impact of delays on the spread of TB. The study will be controlled for HIV, diabetes and other co-morbid conditions in the sample size.

Questionnaires will be administered to both adults and children and a survey will be administered to TB programs. The study will be conducted in eight urban and rural areas in Georgia, Maryland, New Jersey, New York City, North Carolina, Tennessee, Texas and Virginia. These sites were selected based on their large proportions of TB cases among U.S.-born AAs.

DTBE has taken the following actions to date to conduct the study. Initial approval for the study was obtained from 17 Institutional Review Boards. Interviewers were trained in using the data abstraction forms and administering the questionnaires and surveys. A data entry system was developed for the pilot project and an implementation plan was created for all eight sites. Recruitment of the pilot was initiated with the completion of 15 of 40 planned interviews.

DTBE's next steps will be to complete the pilot at all eight sites by the end of July 2009 and analyze data. The questionnaires, data abstraction forms and implementation plan will be revised based on results of the pilot. The study protocol will be resubmitted to Institutional Review Boards and recruitment for the full study will be initiated on September 1, 2009. DTBE expects to complete the full study in September 2011.

ACET made a number of suggestions for DTBE to consider in implementing the full study in September 2009.

- DTBE should engage Dr. Kathleen McDavid Harrison, Associate Director of Disparities in NCHHSTP, to provide expertise on the SDH component of the study.
- DTBE should design the study to focus on institutional differences among states in implementing the TB diagnostic process.
- DTBE should use the study as an opportunity to perform modeling to identify variables for late health seeking behaviors among AAs and delays in diagnosis, such as racial segregation that serves as a barrier to care.
- DTBE should make every effort to store serum and other specimens collected during the study for DNA analysis to inform future genetic studies. These data could help to answer important research questions on the influence of ethnic factors in certain populations being susceptible to TB.

Update on TBESC

Dr. Denise Garrett, Team Lead of the DTBE Epidemiology Team, covered the following areas in her update. Of 28 TBESC studies that have been launched over the past eight years, seven have been completed, seven are nearly complete, ten are ongoing and four will be initiated in FY2009. DTBE will convene a meeting in July 2009 with all TBESC principal investigators to discuss the status of each active study, identify potential barriers to and develop a plan of action for completion, and ensure adequate funding of ongoing studies.

Major studies conducted in the current cycle of TBESC are highlighted as follows. TBESC Task Order 9 focused on missed opportunities for the prevention of TB in FBP. The objectives of the study were to describe the epidemiology of TB in FBP; identify barriers and opportunities for prevention; and inform the development of recommendations on immigration medical screening policies, TB control policies and TB surveillance practices. Data from the study were used to estimate additional benefits from improved overseas screening.

Prior to the study, only 33% of FBP with TB were immigrants or refugees who were eligible for overseas screening. Of this population, 20% developed TB within one year of entry into the United States that suggested these persons had active TB upon arrival. The study showed that more sensitive pre-entry screening measures would provide an additional benefit of 6.7% in detecting active TB in FBP upon their arrival to the United States. The study further demonstrated that overseas screening of TB disease would play an important, but limited role in further reduction of TB rates in the United States. LTBI screening of foreign-born residents in the United States might be a more effective approach to accelerate reduction of TB in FBP.

TBESC Task Order 13 was a three-phase study that focused on factors associated with acceptance of and adherence to LTBI treatment. Phase 1 was designed to estimate the impact of LTBI treatment. Clinics in catchment areas that treat LTBI were identified and these results were extrapolated to the U.S. population. The study concluded that LTBI treatment prevented 10,000 TB cases in 2002.

Phase 2 was designed to estimate the proportion of LTBI patients who complete treatment. Based on a chart review of 2,385 patients who were offered treatment, 83% accepted treatment and 47% completed treatment. The study found an association between shorter regimens and completion of treatment. Phase 3 is ongoing and was designed as a prospective cohort study of factors associated with acceptance of and completion of LTBI treatment from 2007-2009.

TBESC Task Order 18 evaluated IGRA in the diagnosis of LTBI in HCP. The objectives of the study were to compare QuantiFERON, T-SPOT and TST in the detection of LTBI in HCP by examining conversion and reversion rates, the ability to reproduce simultaneous tests, the ability to repeat serial tests, acceptability of the tests, and the costs and cost-effectiveness of the tests.

Baseline positive rates of the three tests ranged from 6.9%-8.9%. Intra-laboratory variability in the same draws ranged from 4%-11% with QuantiFERON and T-SPOT. Conversion rates of IGRA were six times higher than TST at the six-month follow-up. The study concluded that cutoff points for conversion should be further evaluated and alternative criteria need to be developed for conversion and reversion rates of tests.

A recent analysis focusing on the impact of recent TST on IGRA results showed that TST might boost a subsequent IGRA because IGRA boosting occurs within two weeks of TST. The analysis concluded that TST boosting of IGRA results could affect interpretation of serial testing. These data could be helpful in informing the development of guidelines on the use of TST with IGRA. DTBE noted that the United Kingdom and Canada currently recommend confirmatory IGRA for TST-positive results.

DTBE is currently preparing for the new cycle of TBESC and is extremely pleased with the valuable studies that were conducted in the first ten-year cycle to date. DTBE will apply a number of lessons learned to improve TBESC in the future, such as the importance of a solid data management system, the need to take advantage of the full strength of TBESC, the need to consider the impact of TBESC research, and the need to narrow the TBESC research focus.

Based on these lessons learned, DTBE will make the following changes in the new cycle of TBESC. Multiple oversight committees will be replaced with one Board of Directors. Numerous protocols will be replaced with one standard protocol with sub-studies. The requirement for TBESC sites to compete for studies will be replaced with a new policy in which all sites will participate in the main study. The decentralized data management system will be replaced with a centralized system. Multiple research topics will be replaced with one research topic.

To obtain external input on the TBESC recompetition process, DTBE formed a Strategic Planning Workgroup. The workgroup is represented by two ACET members, TB controllers, and other domestic and international experts in the fields of science, public health and TB research. The workgroup agreed that the new cycle of TBESC should focus on LTBI and proposed several possible interventions, such as screening of high-risk populations, targeted testing and treatment, contact and outbreak investigations, diagnostics, treatment and adherence. Regardless of the research topic that is ultimately selected for the new cycle of TBESC, a registry match outcome will be created to follow-up patients for two years.

DTBE's next steps in the TBESC recompetition process are to develop proposals of potential research topics into a detailed research plan, select the new TBESC research topic and establish rigorous criteria, issue a request for application for new sites, and select and fund the new TBESC sites by September 2010. During the last year of the current cycle of TBESC, old and new sites will overlap. Because the new TBESC awards will not be announced until September 2010, Dr. Garrett explained that she is prohibited from disclosing the names of the Strategic Planning Workgroup members, identifying the new TBESC research topic, or discussing any other confidential aspects of the recompetition process.

Dr. Castro clarified that ACET is welcome to propose names of other persons who could serve on the Strategic Planning Workgroup to represent affected communities so long as these individuals are impartial and have no conflict of interest in the TBESC recompetition process.

Update on TBESC Task Order 2

Dr. Mary Reichler, of DBTE, provided an update on TBESC Task Order 2 that was designed as a prospective evaluation of epidemiologic, genetic and immunologic factors associated with TB infection and disease. The natural history of TB begins with a TB patient who infects an exposed contact. Of the exposed contacts, 60% will remain TST-negative, while 40% will develop LTBI and become TST-positive. Of the TST-positive persons, 10% will develop TB. Of these TB patients, 15% will develop severe TB that is difficult to treat. The determinants of TB

transmission include exposure, infectiousness of patients, host factors, and the environment. These determinants result in TB disease that eventually could lead to outbreaks.

To better understand the epidemiology of TB, dynamics of transmission and progression to TB disease, DTBE launched Task Order 2 at nine TBESC sites. The objectives of this large multi-site study are to evaluate contact investigation outcomes, identify epidemiologic risk factors for *M.tb* transmission, identify genetic determinants of susceptibility to infection and disease, and evaluate surrogate markers of protective immune response to *M.tb*.

The study design includes culture-positive pulmonary TB cases ≥ 15 years of age, all contacts of these cases, interviews with both cases and contacts, environmental assessments, TB and HIV registry matches, and collection of whole blood to test three cytokine surrogate markers and 52 genetic polymorphisms.

U.S.-born, Canadian-born and foreign-populations enrolled in the study were well characterized with regard to the frequency, duration and timing of TB exposure, the infectiousness of TB cases, the susceptibility of hosts and environmental exposures. The U.S.-born and Canadian-born populations had no BCG vaccination. The study population had a low risk of continual exposure to *M.tb*. Enrollment of 948 TB cases and 5,491 contacts has been completed. To date, 1,986 genetic specimens and 2,250 immunologic specimens have been collected; 32 of 52 genetic polymorphisms have been tested; and all three cytokine surrogate markers have been tested.

DTBE formed four writing groups with 17 manuscript teams. The Contact Investigation Outcomes Writing Group will produce five manuscripts; the Epidemiologic Risk Factors Writing Group will produce three manuscripts; the Immunologic Surrogate Markers Writing Group will produce five manuscripts; and the Genetic Determinants Writing Group will produce four manuscripts. Preliminary data analyses were performed on epidemiologic, genetic and immunologic outcomes. Of eight abstracts that were developed, five have been presented and three were recently submitted for presentation at major international meetings. DTBE expects to produce the results of 10-12 additional analyses in the next 6-12 months.

Preliminary results of a TBESC Task Order 2 sub-study were recently presented during the May 2009 ATS meeting and are highlighted as follows. The sub-study emphasized that close contacts of infectious TB patients are at high risk of LTBI and TB disease. The lifetime risk of TB after recent exposure is estimated to be 10%, but 50% of this risk occurs in the first two years after exposure. A series of retrospective studies published in 2000-2003 documented that the reported proportion of contacts of infectious TB patients with TB disease ranges from 1%-2% in low-incidence settings.

The timing and rates of TB disease among recently exposed contacts are not well established. The relative proportion of TB cases among exposed contacts that can still be prevented at the time contact investigations are initiated is unknown. In an effort to fill these data gaps, the TBESC Task Order 2 sub-study was designed to achieve four key objectives. The yield of contact investigations for new cases of active TB would be determined. The rates and timing between TB disease among contacts and active pulmonary TB patients would be evaluated.

The number of TB cases among contacts that could still be prevented at the time of contact investigations would be determined. Epidemiologic characteristics of contacts with newly diagnosed TB disease would be described.

For purposes of the sub-study, a “TB contact-case” was defined as culture-confirmed or clinically diagnosed pulmonary or extrapulmonary TB in a contact to an enrolled culture-confirmed TB patient. Dates of treatment initiation were used to define the onset of TB disease in TB patients and contacts. Dates of the first TST or first chest radiograph if no TST was performed were used to define the timing of contact investigations.

“Preventable” cases were defined as contact-cases with treatment >30 days after TB patient treatment initiation with no evidence of TB disease at an initial timely evaluation. “Possibly preventable” cases were defined as contact-cases with treatment >30 days after TB patient treatment with delayed or no initial evaluation and a subsequent abnormal chest x-ray. “Not preventable” cases were defined as contact-cases with treatment before or <30 days after TB patient treatment initiation or an abnormal chest x-ray <30 days after TB patient treatment initiation.

Rates of TB disease among contacts were calculated using the number of contacts with TB during the observation interval as the numerator and the total number of priority 1 contacts multiplied by the observation interval as the denominator multiplied by 1,000. This calculation provided rates per 1,000 person-months.

Of 4,544 priority 1 contacts, 70% completed TST screening, 8% were not screened, 6% had prior TB or TST-positive results, and 16% had no post-exposure TST. Of 3,225 priority 1 contacts who completed screening, 51% had TST-negative results, 6% were documented converters, 38% initially had TST-positive results, and 5% had active TB. An analysis of the timing of TB among contacts from TB patient treatment initiation showed that the largest number of contact-cases were within the 1- to 30-day interval after TB treatment.

A registry match at two years detected 39 additional cases for a total of 199 TB cases among contacts. Of 199 contact-cases identified during the investigation and registry match, 45% had secondary TB; 40% had co-prevalent TB occurring either within one month before or one month after diagnosis of the index case; and 15% had prior TB occurring before diagnosis of the index case.

An analysis was performed to determine TB case rates among 4,544 contacts by interval from TB patient treatment initiation. The analysis showed that the TB case rate of 12.1/1,000 person-months was highest in the 1- to 30-day interval with 55 cases. Case rates from TB patient treatment initiation remained high at 7.9/1,000 person-months in the 31- to 60-day interval with 36 cases; 4.2/1,000 person-months in the 61- to 90-day interval with 19 cases; and 0.7/1,000 person-months in the 91- to 180-day interval with 10 cases.

The case rate from TB patient treatment initiation of 0.07/1,000 person-months was lowest in the 366- to 730-day interval with four cases. Recalculation of these results showed an extraordinarily high case rate of 2,971/100,000 population in the 1- to 365-day interval after TB

treatment of the index case and an elevated case rate of 88/100,000 population in the 366- to 730-day interval.

Of 90 contacts with secondary TB detected in the initial contact investigation, 74% had TB at the time of initial screening, 12% were TST-positive, 4% were not screened and later developed TB, 3% were TST-negative and later developed TB, 2% were converters with no evidence of TB at initial evaluation, 2% had incomplete screening, and 2% had prior TB or TST-positive results. Of 199 TB cases among contacts detected in the contact investigation, 63% were not preventable, 23% were possibly preventable, and 14% were preventable. A preliminary analysis of the epidemiologic results showed increased rates of progression to TB disease in AAs compared to whites. Of children enrolled in the study, 50% rapidly developed TB within the first three months.

Overall, the TBESC Task Order 2 sub-study showed that contact investigations have a high yield for new TB cases. Relatively few of these new TB cases can be prevented, but the development of interventions to shorten the time between positive TST results and chest radiograph could increase the number of TB cases prevented. Moreover, contact investigations are an extremely important approach to identifying co-prevalent and secondary TB cases and placing these cases on treatment to prevent further transmission.

TB case detection rates among exposed contacts are highest in the month following TB patient diagnosis. These rates steadily fall, but remain elevated for at least two years. Additional operational research should be conducted on contact investigations and risk factors for TB transmission to learn more about the timing and rates of TB infection and disease and assist programs in developing algorithms to prioritize contact investigations.

ACET made two key suggestions for DTBE to consider in refining TBESC Task Order 2 and presenting data from these studies. First, DTBE should design a new TBESC sub-study to determine factors that would encourage contacts to present for TB testing more quickly. Results of this study would be particularly helpful to local public health departments.

Second, DTBE should frame the context of TBESC Task Order 2 to ensure that data are presented in a positive manner. For example, programs might view contact investigations as unnecessary if only a “relatively few” number of new TB cases can be prevented. DTBE should emphasize that contact investigations are a key case finding tool in helping to reduce both TB illness and secondary cases.

Dr. Castro further advised DTBE to use results of TBESC Task Order 2 to conduct a stratified analysis that specifically focuses on the issue of race/ethnicity. This approach could inform TBESC Task Order 23 that is being designed to identify determinants of early diagnosis, prevention and treatment of TB in the AA community.

Overview of the Critical Path to TB Drug Regimens Initiative

Dr. Jan Gheuens is the Senior Program Officer for TB at the Bill and Melinda Gates Foundation and served as the keynote speaker during the ACET meeting. He pointed out that the Gates Foundation has played a critical role in the dramatic evolution of TB research and development (R&D) over the past seven years. In 2002, only a few credible products had actual development plans in the product component of TB R&D. Industry-style programs were minimal and scattered in the process component of TB R&D. The small, but active group of TB researchers was academically focused in the research component of TB R&D.

An overarching vision was established to strengthen the product, process and research components of TB R&D. TB-specific product development partnerships (PDPs) would be formed to develop products and a process. The Gates Foundation "Grand Challenges and Innovations Program" would encourage scientific engagement. Several efforts have been made to date to achieve this vision. A more credible and industry-style development plan was designed for the product component of TB R&D. A rational approval process was created for the process component of TB R&D. The small, but active group of TB researchers was enhanced with a more solid network and a stronger focus for the research component of TB R&D.

Of the Gates Foundation's total TB investment of \$768 million, ~\$587 million is devoted to TB drugs, vaccines and diagnostics. A portion of this investment has been targeted to new tools through the development of three TB-specific PDPs. The Aeras Global TB Vaccine Foundation develops, tests, characterizes, licenses, manufactures and distributes at least one new TB vaccine regimen for infants and adolescents and ensure its availability to all persons in need.

The Foundation for Innovative New Diagnostics ensures equitable access to high-quality diagnosis worldwide and drives the development and implementation of accurate and affordable diagnostic tests that are appropriate to patient care in low-resource settings. The Global Alliance for TB Drug Development (GATB) ensures widespread availability of affordable, faster and better TB drug regimens that will advance global health and prosperity.

TB stakeholders recognize that a truly novel TB regimen might be licensed in 2018 based on drugs in the pre-clinical and clinical development stages at this time. Based on a number of critical trends, the need for new combination therapies is more compelling than individual new drugs. Drug-resistant TB has emerged as an important issue over the past few years. Current second-line treatment regimens are impractical and difficult to scale-up. The risk for inducing resistance to a new drug occurs shortly after introduction.

Classical sequential development of a TB regimen cannot be achieved. The current four-drug regimens were empirically developed with a standard that was established in the 1970s. The individual contribution of each drug to the entire TB regimen is not understood. The sequential development of a new TB combination would require decades based on the current state of TB clinical trial methodologies.

The Gates Foundation met with FDA to discuss regulatory challenges to the development of TB drug regimens. For example, limited availability of biomarkers hinders the development of vaccines, makes vaccine development fully empirical, complicates assessments of vaccine trial endpoints, and increases the difficulty of clinical development. Outcome endpoints produced after one or two years of TB clinical trials are used in Phase III studies. With this approach, failure to cure and relapse rates are combined. All unfavorable outcomes, including lost to follow-up rates and deaths from all causes, are combined as well.

Bacterial endpoints, such as serial sputum colony counts and sputum conversion rates, are used in Phase I and II studies. The Gates Foundation and FDA discussed the possibility of whether bacteriological endpoints could be qualified to support approval. To address drug-resistant TB, an FDA advisory committee recently recommended the acceptance of sputum conversion for approval under Subpart H that would require an additional confirmatory study after approval of a TB drug regimen. However, this recommendation did not address drug-sensitive TB.

Despite these challenges, opportunities exist to develop TB drug regimens because nine new TB drug candidates representing various biological classes are in pre-clinical or clinical stages at this time. The current list of TB drug candidates is expected to be dynamic as new compounds will be selected, while others might fail. The Gates Foundation recognizes that four key questions must be answered to determine whether the development of TB drug regimens is actually feasible.

First, are companies with TB drug candidates willing to test their pre-approval compounds in combination with other experimental compounds? Historically, industry has been reluctant to take this approach based on legal, antitrust and safety concerns. For example, a pre-approval compound might taint another compound. Second, has a regulatory pathway to approval been established? Regulations for the development of drug regimens exist at this time. The role of each individual component in a drug regimen must be known, but acceptable evidence to fill this data gap in TB has not been collected to date.

Third, what is the state of TB science to support this approach and regulatory decision-making? The predictive value of pre-clinical *in vitro* and *in vivo* studies is uncertain. The ability to customarily accept endpoints for Phase II and III studies on drug-sensitive TB and MDR-/XDR-TB is unknown. More data are needed to address the limited availability of biomarkers. Fourth, what mechanisms are available to fund this effort? TB drugs have limited commercial value for large companies. No company can afford or is willing to fund completion of projects, including Phase III studies. Traditional donor funds could not adequately support Phase III programs.

Due to the strong belief that the development of TB drug regimens can be achieved, a number of partners are currently in the planning stage of designing the Critical Path to TB Drug Regimens (CPTR) Initiative. This collaborative effort aims to accelerate the development of new, safe and highly-effective regimens for TB by early combination testing. During a closed meeting in June 2009, the Gates Foundation, NIH, FDA, Critical Path Institute (C-Path), and four of eight companies with TB drug candidates agreed to collaborate in CPTR.

The partners plan to expand CPTR in the future to include patient representatives, scientific advisors from academia and government agencies, and additional regulatory agencies and organizations at domestic and international levels to provide expertise, leverage additional funding and facilitate programmatic implementation through networks and organizations. Due to the large investment that will be required by both public and private sectors in the TB community, the partners are aware of the need to establish a solid funding coalition to support CPTR.

The mission and purpose of two of the eight current CPTR partners are outlined as follows. Partner 1 is FDA's Critical Path Initiative (CPI) that was established to innovate science and tools and define a rigorous evidence base for regulatory decisions based on new science rather than shortcuts. CPI has a simple concept, but is difficult to implement. FDA published 76 CPI models in 2006, but these solutions are only effective based on adoption by FDA review divisions and other authorities. Although the CPI Office spans across most of FDA's centers, CPI's applied science that could lead to better and faster regulatory decision-making receives relatively little funding.

FDA's key CPI models are highlighted as follows. The Predictive Safety Testing Consortium includes 16 companies and three academic groups that are organized as nephrotoxicity, hepatotoxicity and other organ toxicity workgroups. CDISC is a set of worldwide data standards that are supported by 250 member organizations to enhance electronic acquisition, exchange, submission and archival of clinical data.

QSAR is a computational toxicology model that uses all chemical structures and all toxicology data FDA has reviewed to date. This model has the ability to predict carcinogenicity, genetic toxicity, reproductive toxicity and development toxicity for new structures if these structures are related to known outcomes. SENTINEL is a new approach to active safety surveillance.

Partner 2 is C-Path that is a non-profit organization with a mission of organizing and managing FDA's CPI projects. C-Path created innovative methods for highly-competitive companies and regulatory agencies to share pre-competitive data and knowledge. C-Path's success is based on its creation and management of formal legal consortia with academic advisors, regulatory agency representatives, 500 participating scientists from 26 pharmaceutical companies, and six patient advocacy organizations.

C-Path developed a three-pronged approach to fulfill its mission: (1) develop a legal agreement to enable rapid, broad and open sharing of scientific data and knowledge by all parties; (2) reach scientific consensus among scientists from industry, academia and regulatory agencies on preferred testing methods of new products; and (3) obtain mutual acceptance of innovative testing methods, such as FDA-qualified biomarkers.

To date, the CPTR partners have broadly communicated the initiative to TB stakeholders and proposed the following process. A consortium would be formed similar to other CPI projects. C-Path would organize and manage the consortium. The Gates Foundation would retain its role as a catalyst and convener, but would not have responsibility for the operation and oversight of

CPTR. GATB and companies with TB drug candidates would form partnerships based on the production of promising data.

The next steps to advance CPTR are to convene a meeting to clarify the scope of CPTR; outline the structure, roles and operating principles of the consortium; define various work streams; and identify “low-hanging” activities the partners could immediately initiate. The meeting also will provide an opportunity for the CPTR partners to focus on clinical development plans and study designs; site capacity, regulatory capacity and logistical issues; and acceleration of applied science. The CPTR partners will hold an additional meeting to conduct an in-depth review of currently available data on different drugs and their backups. The CPTR partners also would form a workgroup to identify potential solutions to fund the development of TB drug regimens at \$500-\$600 million per year.

The partners have agreed that “success” of CPTR will be defined based on the following outcomes. The CPTR approach will be established as the gold standard for rapid, safe and efficient evaluation and development of new TB drug combinations. Consensus-based and validated methods will be designed to test new TB drugs individually and in combinations that maximize learning and minimize delay.

Novel regimens of TB drugs for treatment of drug-sensitive and drug-resistant disease will be developed, approved by regulatory agencies and endorsed by WHO. Novel biomarkers for TB that are qualified for use in TB productive development will be created. Diagnostic tests for TB will be designed and approved by regulatory agencies.

Overall, a new era for TB product development has begun. GATB, companies with TB drug candidates and other TB stakeholders have expressed strong enthusiasm and support for advancing from the development of individual TB drugs to TB regimens. Because the partners are still in the planning stage of determining whether CPTR will serve as the collaborative effort to enable rapid development of TB regimens, Dr. Gheuens emphasized that ACET’s valuable input and expertise would be welcome at this point.

Due to time constraints, Dr. Fleenor exercised the chair’s prerogative and tabled ACET’s comments and suggestions on Dr. Gheuens’ presentation until the discussion period following the next presentation.

Update on the Role of Federal Agencies in Global TB Control and Research

NIH/National Institute of Allergy and Infectious Diseases (NIAID). Dr. Christine Sizemore is Chief of the TB, Leprosy and Other Mycobacterial Diseases Section of NIAID. She explained that NIH is a biomedical research institution with 27 institutes and centers. NIAID has lead responsibility for TB biomedical research at NIH and is the largest global funder of this activity. Other NIH institutes that play a significant role in TB science include the National Heart, Lung and Blood Institute, Fogarty International Center, and National Institute of Child Health and Human Development.

NIH's mission is to help lead the way toward important medical discoveries that improve the health of individuals and save lives. NIAID supports NIH's mission in two major areas: (1) conducting and supporting research to study the cause, diagnosis, treatment and prevention of infections, immunologic and allergic diseases and (2) providing critical resources to fill gaps in basic, translational and clinical research.

Of NIAID's ~\$115 million TB research budget, 10% is devoted to intramural research conducted by NIAID and 90% is devoted to extramural research conducted in both U.S. and international settings by universities, pharmaceutical companies, individual investigators, public-private partnerships, research organizations and small businesses. Of NIAID's ~\$115 million TB research budget, basic research accounts for 57%, drug development accounts for 20%, vaccine development accounts for 12% and diagnostics account for 11%.

All NIAID extramural research activities are legally required to undergo a solicited or unsolicited research grant application process. Applications are evaluated based on a thorough scientific peer review and scoring process. Funding decisions are based on the merit and score of each application. NIAID also awards funds through specific solicitations and contracts to support research infrastructures, research support services and pre-clinical development activities.

NIAID established its four TB program priorities based on a translational research paradigm. Fundamental science focuses on host-pathogen interactions in immunology, microbiology and tools. Translational science focuses on drugs, vaccines and diagnostic candidates to support discovery, pre-clinical validation and the selection of candidates. Clinical studies focus on pathogenesis, disease, immune markers, HIV/TB co-infection, and clinical trials of new candidates and regimens. Research support focuses on TB-specific and generic contracts across NIAID for research reagents, product testing, models, pre-clinical support and training.

NIAID has a number of "hand-off" partners and beneficiaries to facilitate its translational research paradigm. Grants and contracts are awarded to global biomedical TB research organizations and Gates-funded programs to conduct discovery research. Solicited grants and contracts are awarded to pharmaceutical and biotech companies, the Stop TB Partnership and Gates-funded programs to conduct translational research.

Contracts and solicited grants are awarded to small businesses in the United States and academic institutions to conduct pre-clinical testing. Contracts and intramural grants are awarded to small businesses, pharmaceutical companies and CDC to conduct clinical trials and studies domestically. Contracts and intramural grants are awarded to Gates-funded programs, pharmaceutical and biotech companies, CDC, the U.S. Agency for International Development (USAID), and the European and Developing Countries Clinical Trials Partnership to conduct clinical trials and studies internationally.

CDC. Dr. Kevin Cain is the TB/HIV Team Lead for the DTBE International Research and Program Branch. He explained that CDC's global TB research portfolio is funded by two major sources. The DTBE Office of the Director provides supplies, equipment and salaries for core headquarters staff and 2.5 field staff; ~\$1.3 million per year for the Botswana Field Station; and

\$152,000 per year for travel funds. The DTBE Office of the Director also uses cooperative agreements to allocate \$176,380 per year to WHO and \$166,303 to the International Union Against Tuberculosis and Lung Disease. Through an interagency agreement with USAID, CDC receives ~\$3.8 million per year from global and regional bureaus and country-specific missions.

CDC's areas of focus in its global TB research portfolio are to decrease the incidence of U.S. foreign-born TB cases and contribute to international efforts led by the Stop TB Partnership. The international efforts are designed to strengthen national TB control programs; mitigate the impact of TB/HIV; prevent the emergence and improve detection, diagnosis and treatment of drug-resistant TB; and address infection control in institutions and communities.

CDC's global TB research activities focus on two major areas. Programmatically relevant operational and epidemiological research and training are conducted to strengthen TB control efforts, facilitate policy changes, and build capacity within national TB control programs through technical assistance. Programmatically relevant clinical and diagnostic studies are conducted as well. These activities are conducted in a limited number of countries due to the branch's small staff and level of funding.

CDC's criteria to conduct global TB research activities in certain countries are based on strategic interest, such as those that contribute to U.S. foreign-born TB cases; countries with a high burden of TB; or countries with unique opportunities to conduct important research to inform global policy. Based on 2006 data, the top ten countries contributing to foreign-born TB cases in the United States were Mexico, Vietnam, India, China, Haiti, Guatemala, South Korea, Ethiopia, Peru and the Philippines. CDC has ongoing projects and activities in eight of these top ten countries as well as 12 of 22 high-burden TB countries.

Examples of CDC's global TB research and epidemiological studies are highlighted as follows. A clinical trial in Botswana is underway to evaluate the impact of INH preventive therapy on the prevention of active TB disease in patients with HIV. The clinical trial is comparing a six-month and a continuous three-year regimen of INH preventive therapy. Results of the clinical trial will play an important role in informing international policy.

A large TB/HIV study in three countries in Southeast Asia with 2,000 patients examined the role of intensified case finding to improve the diagnosis of TB in HIV-infected persons. Different screening approaches in adults and children were evaluated. The three countries used results of the study to change screening policies. WHO has included CDC's study in an ongoing meta-analysis of multiple studies to inform the development of recommendations in which chronic cough along with other symptoms would be used to screen for TB.

CDC evaluated new rapid diagnostics, including a line probe assay for rapid diagnosis of TB and rapid MDR-TB diagnostics, to determine their effectiveness in actual practice. CDC is conducting a large MDR-TB study in multiple countries focusing on preserving effective TB treatment for second-line drugs. CDC is conducting a number of activities to enhance national TB programs, including an evaluation of TB screening practices among pediatric TB suspects and patients and an assessment of guidelines for diagnosis of smear-negative TB. CDC is continuing its research and epidemiologic studies to better understand the epidemiology of TB

in FBP in the United States and also to influence infection control policies, particularly with respect to the risk for TB among HCP in outpatient HIV care settings.

Department of Defense (DoD). Dr. Sizemore presented the overview on behalf of Col. Naomi Aronson who was unable to attend the meeting. Col. Aronson is the ACET *ex-officio* member for DoD as well as a Professor of Medicine and Director of the Infectious Diseases Division at the DoD Uniformed Services University of the Health Sciences. Based on 1998-2005 data, the rate of active TB of 1.4/100,000 in the military population was lower than the age-adjusted rate in the U.S. population. However, DoD noted a higher rate of TB outbreaks on Navy shipboards and similar risk factors for TB between the military and U.S. populations, such as foreign-born, non-white and HIV-positive persons.

DoD is an expert in purified protein derivative (PPD) testing and performs 250,000 PPD tests in new accessions annually and 500,000 PPD tests each year overall. DoD is now moving toward targeted TB testing of enlisted personnel who return from deployments. DoD's TB activities focus on three major areas. Clinical care is provided to beneficiaries through screening for LTBI and treatment of active disease. The military treats ~20,000 persons for LTBI each year.

DoD conducts TB research, but this activity has no focused program or devoted funding. However, DoD's TB research makes a significant contribution to LTBI diagnostics and TB/HIV co-infection, enhancement of laboratory capacity, and the development of best practices for TB control in the military population. DoD performs surveillance through its large network of military bases worldwide. For example, DoD is currently comparing various technologies, such as surveys, PPD testing and ELISPOT assays, to screen for new TB infections and LTBI in Fort Jackson, South Carolina.

The U.S. Army and Navy have a strong international presence with overseas medical research laboratories in Egypt, Indonesia, Kenya, Peru and Thailand. DoD's collaborations with federal partners for other infectious diseases are important to TB. The U.S. Military HIV Research Program partners with the President's Emergency Plan for AIDS Relief to provide HIV treatment services for military and civilian personnel in Africa. DoD's medical capabilities play a critical role in the global fight against HIV. DoD is exploring the possibility of using its existing influenza surveillance network to facilitate the collection of additional respiratory specimens, surveillance and diagnosis of TB and drug-resistant TB.

USAID. Dr. Sizemore presented the overview on behalf of Dr. Christy Hanson, a TB Research Advisor in USAID, who was unable to attend the meeting. Of USAID's \$162 million TB budget, ~\$116 million is devoted to country programs, ~\$22 million is devoted to global leadership activities, ~\$15 million is devoted to the Global TB Drug Facility, and ~\$9 million is devoted to the development of new tools and approaches.

USAID conducts TB activities in 19 focus countries that account for 61% of the global TB burden as well as 17 additional countries. USAID presented its 2006 research strategy to Congress to emphasize the comparative advantage of its field presence and highlight its five key focus areas: (1) research with programmatic implications within three to five years; (2) research to bridge product development after NIH studies for implementation in the field; (3)

studies with global and national policy implications; (4) late stage trials; and (5) operational research.

USAID is currently conducting four flagship TB research projects. USAID is conducting clinical trials focusing on TB re-treatment regimens and individualized versus standard regimens for MDR-TB. To advance TB diagnostics, USAID is performing systematic reviews to initiate diagnostic clinical trials and identify gaps that limit progress on policies. USAID also is developing models to determine the best use of current tools to maximize case detection based on the current epidemiology of TB, available health systems and existing capacity. USAID is conducting operational and evaluation research at the country level to apply study results to actual practice in international settings. CDC will take leadership of USAID's infection control activities in the future.

Based on overviews of four federal agencies, Dr. Sizemore emphasized that FTBTF partners ensure global coordination of TB control and research activities by creating domestic and international networks with public and private healthcare providers, academia, pharmaceutical companies, the Stop TB Partnership and WHO. She was pleased to report that FTBTF is making tremendous progress on defining specific global TB control and research projects for implementation in the future.

Drs. Castro, Cain and Sizemore provided additional details on the role of federal agencies in global TB control and research activities in response to specific questions raised by the ACET members.

- The federal partners are continuing to use FTBTF as a forum to share data and closely collaborate. This approach ensures that global TB control and research activities conducted by various federal agencies are complimentary and lessons learned are immediately disseminated to programs through technical assistance to enhance TB care and treatment in the field. During the August 2009 FTBTF meeting, the federal partners will primarily discuss additional mechanisms, such as a website or listserve, to enhance information exchange among their respective agencies. The new FTBTF website will be open to the public to ensure transparency to TB advocates, stakeholders, constituents and the TB community at large.
- The Office of the U.S. Global AIDS Coordinator is continuing to serve on FTBTF and has expressed a strong interest in devoting a portion of its resources to the public health evaluation of global TB control and research activities.
- The public can monitor funding of global TB research activities through the Treatment Action Group's tracking system and the up-to-date clinical trials registration system that is supported by NIH, WHO and several other groups.

ACET commended the Gates Foundation and NIH on their roles as the top two leading funders in global TB research. Dr. Fleenor apologized that time did not permit ACET to engage in a more extensive discussion to make substantive comments and suggestions on the new CPTR Initiative or the role of federal agencies in global TB control and research activities. However, he confirmed that ACET would discuss these issues in more detail during the October 2009 meeting to formulate formal recommendations.

Update on the National TB Archive (NTBA)

Dr. Damian Gessler is a Semantic Web Architect at the University of Arizona. He explained that the prior vision for maintenance of TB data was to collect and genotype isolates from every TB case in the United States to develop the Universal Genotyping Program. The prior vision was enhanced to achieve the current vision of making data web-accessible and developing TB-GIMS. The TB community now recognizes the need to advance the current vision to achieve a future vision in which web-accessible data entered into TB-GIMs will be archived, sequenced, integrated and presented to facilitate the development of NTBA.

A study published in *Science* in March 2006 provided solid evidence to support the need to create the nation's first comprehensive and integration information and biological resource for an infectious disease. The study documented the important role of archiving in three major areas. Archiving formalizes the systematic collection and preservation of etiologic agents that cause disease in communities. Archiving enables future technologies to be retroactively applied for a comprehensive and temporarily complete baseline. Archiving has the ability to ground evidence-based decision-making on persistent data.

The 2006 study was later supported in a February 2009 press release. Illumina, Inc. presented a development roadmap for scaling its genome analyzer and noted that innovations would substantially increase output, decrease cost and expand applications. Illumina estimated that coverage of a human genome with these developments would cost <\$10,000 in 2009.

As of February 2009, a 20-gigabyte single run on human data was achieved in three to seven days at a cost of \$30,000-\$50,000. For *M.tb*, genome sequencing at 4.4Mbp would be required at least 12 times with the Illumina high throughput technology. At 20 times the coverage, a 95-gigabyte single run would yield ~1,100 genomes at an expected cost of \$10,000 per run using bar code multiplexing. The approximate raw cost of \$9.26 per genome was based on a cost of \$10,000 per run. Each new TB case could be sequenced for ~\$120,000 with raw sequencing.

Emphasis is placed on the three components of integration in the current era of limited resources and the need to rapidly make decisions. Integration is needed across genomic, phylogenetic, clinical and epidemiological data. Actionable intelligence is needed to facilitate timely delivery of information for discriminatory decision-making. Evidence-based decision-making is needed to facilitate efficient allocation of resources for targeted preparation and effective response.

NTBA would be implemented by placing isolates states previously submitted to the Universal Genotyping Program into an archival system that is professionally managed. The isolates would be sequenced to build a population-based biological repository. The sequences would be annotated into epidemiological and clinical data. NTBA would be successful because unlike HIV, hepatitis C, influenza or other infectious diseases, the existing TB infrastructure to gather isolates or collect epidemiological and clinical data is superb.

The ongoing intelligence and value of NTBA at the local level would provide an incentive for physicians, nurses and TB controllers to submit isolates and for researchers, policymakers and communities to advocate for policy changes. NTBA ultimately would lead to the collection of important genomic, phylogenetic, clinical and epidemiologic data and serve as a new approach to TB control in the 21st century.

Dr. Gessler presented a series of maps to illustrate the capacity of NTBA in pinpointing locations of H1N1 influenza virus outbreaks and identifying areas to enhance TB contact investigations with geographic information systems at the local level. He concluded that NTBA has a simple design of integrating biological and informatic resources under a national and coordinated scope. Moreover, NTBA allows for spatial integration of contact investigations at local and trans-jurisdictional levels and also facilitates temporal integration by utilizing existing repositories to build a record and baseline data for the future.

NTBA encourages conceptual integration across science, medicine and public health and enables evidence-based decision-making that is responsive to local needs and requirements. The next steps to advance NTBA are to obtain recommendations, endorsement, refinement and direction from ACET and leverage collaborative relationships with federal, state and local agencies for actual implementation.

Dr. Castro fully supported the concept of NTBA, but he was uncertain of the actual steps for implementation. He emphasized the critical need to obtain input from TB controllers and affected communities on potential barriers to accessing NTBA's epidemiologic data. For example, California accounts for the most TB morbidity in the United States, but does not share the HIV status of TB patients with CDC or any other entity. However, the collection of the HIV status of TB patients will be a crucial component of NTBA. Dr. Castro further emphasized that in adherence to existing agreements with states, CDC would not release RVCT data without direction from TB controllers.

Several ACET members were pleased with the possible abilities of NTBA, particularly its potential to strengthen knowledge on the mechanisms of TB drug resistance. However, Dr. Fleenor agreed with Dr. Castro regarding the need to obtain feedback on major barriers to implementation of NTBA from a broader group of TB controllers.

To facilitate this effort, Dr. Fleenor encouraged Drs. Gessler and Gary Simpson, of Texas Tech University Health Sciences Center, to open discussions with Mr. Phillip Griffin, the ACET liaison to NTCA. Drs. Gessler and Simpson would be placed on future ACET agendas to provide updates on NTBA and report the outcomes of their conversations with NTCA. Dr. Fleenor confirmed that ACET would take formal action on NTBA based on the outcomes of these updates.

ACET Business Session

Dr. Fleenor opened the business session by reviewing nine items that would require ACET's formal action.

ISSUE 1: Dr. Fleenor entertained a motion for ACET to approve the previous meeting minutes, but he proposed a change in which attachments or addenda referenced on page 15 of the minutes would be deleted.

A motion was properly placed on the floor and seconded by Mr. Kinney and Dr. Bakhtawar, respectively, for ACET to accept the previous minutes with the change Dr. Fleenor proposed for the record. ACET **unanimously approved** the March 3-4, 2009 Draft Meeting Minutes as amended with no further discussion or changes.

ISSUE 2: The following motion was properly placed on the floor and seconded by Drs. Fleenor and Bakhtawar, respectively:

WHEREAS, access to care for all in the United States (US) is an admirable and desirable health policy goal;

WHEREAS, access to care for the treatment of TB is necessary to achieve health equity and assure the public's health in the US;

WHEREAS, treatment of TB is the most effective way of interrupting transmission in a community; and

THEREFORE, ACET recommends that the Secretary of HHS advise executive and legislative branch health policymakers that any national health plan assuring unrestricted access to diagnosis and treatment of TB include:

- Underinsured and uninsured US residents
- Legal non-residents (e.g., students and work visa holders)
- Undocumented aliens
- Individuals undergoing repatriation to or from the US
- Individuals entering the US under the Compact of Federal Free Association states

ACET **unanimously approved** the motion for issue 2 with no further discussion.

ISSUE 3: The following motion was properly placed on the floor and seconded by Drs. Bakhtawar and Seaworth, respectively. "ACET endorses the provisional Interferon Gamma Release Assay Guidelines to detect *Mycobacterium Tuberculosis* among persons in the United States and requests that CDC/DTBE publish these guidelines as soon as practicable."

ACET **unanimously approved** the motion for issue 3, but the members agreed to submit language to refine the section of the guidelines that advises against making decisions based on positive IGRA or TST results alone and recommends additional evaluation, including chest x-rays or sputum smears. ACET agreed to provide Dr. Bakhtawar with any additional comments on this section of the guidelines within the next two weeks.

ISSUE 4: The following motion was properly placed on the floor and seconded by Drs. Fleenor and Seaworth, respectively. “ACET recommends that DTBE remain active participants on the NCHHSTP Workgroup for Persons Using Drugs and report its plans to ACET on incorporating specific interventions in its future programs for improving TB outcomes in this high-risk group.”

ACET **unanimously approved** the motion for issue 4. Dr. Fleenor confirmed that DTBE’s update on TB and substance abuse would be placed on the ACET agenda for the October 2009 meeting or the first meeting in 2010.

ISSUE 5: The following motion was properly placed on the floor and seconded by Drs. Bakhtawar and Hahn, respectively. “ACET recommends that DTBE approach industries hiring employees from countries under the Compact of Free Association, particularly the Federated States of Micronesia, Republic of the Marshall Islands and Republic of Palau, to perform post-hire pre-employment TB screening.”

The motion for issue 5 failed by a vote of 3 members opposed and 2 members in favor. ACET agreed that this issue would be revisited during the October 2009 meeting after Dr. Bakhtawar presented data to support the motion.

ISSUE 6: The following motion was properly placed on the floor and seconded by Drs. Seaworth and Hahn, respectively:

WHEREAS, HIV status is a critical value used in diagnostic and treatment decisions for the care of tuberculosis disease; and

THEREFORE, ACET requests that CDC/DGMQ recommend HIV testing in diagnostic requirements of all refugees and immigrants entering the United States who are assigned a “TB classification” during the overseas screening process.

ACET **unanimously approved** the motion for issue 6 with no further discussion.

ISSUE 7: The following motion was properly placed on the floor and seconded by Mr. Jones and Dr. Hahn, respectively. “ACET recommends that CDC, through DTBE or other sources at its disposal, allocate funds to allow distribution of the “TB Toolkit” for use in educating appropriate parties working with African Americans at risk for TB and for DTBE to subsequently evaluate the results.”

ACET **unanimously approved** the motion for issue 7. In follow-up to the resolution, ACET asked DTBE to develop and present a concrete work plan and timeline to fund, disseminate and evaluate the TB Toolkit.

ISSUE 8: The following motion was properly placed on the floor and seconded by Drs. Fleenor and Hahn, respectively. "ACET recommends that CDC ask the Office of the HHS Secretary to consider and approve the Association of State and Territorial Health Officials and the Council for State and Territorial Epidemiologists as new ACET liaison members."

ACET **unanimously approved** the motion for issue 8 with no further discussion.

ISSUE 9: The following motion was properly placed on the floor and seconded by Drs. Hahn and Seaworth, respectively. "ACET recommends that DTBE send a Dear Colleague letter to state and local TB controllers to encourage proactive collaboration with their preparedness planning groups and other staff to plan for the fall influenza season and determine functions that could be managed by hiring temporary staff or contractors using supplemental pandemic influenza stimulus dollars instead of pulling key TB program staff during the influenza season."

ACET **unanimously approved** the motion for issue 9. Dr. Castro confirmed that he would share the "Dear Colleague" letter with CDC staff members who are leading the pandemic influenza preparedness planning effort for broader distribution to their constituents.

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

Action Items

- Ms. Ann Cronin, of DTBE, will provide ACET with its comments that were given to Dr. Frieden in preparation of his presentation during the June 2009 NTCA meeting. The written briefing to Dr. Frieden included current surveillance data in the context of TB elimination and DTBE's concerns regarding existing capacity to eliminate TB.
- Ms. Margie Scott-Cseh, the ACET Committee Management Specialist, will distribute DTBE's TB-specific pandemic influenza operational plan to ACET.
- Dr. Vernon will provide Ms. Katz with contact information for members of the American College Health Association who can serve as reviewers of the foreign-born guidelines.
- Ms. Scott-Cseh will e-mail Dr. Reichler's slides to ACET.

Agenda Items

- An overview of strategies local health departments implemented to maintain their core TB functions during the H1N1 influenza outbreak while personnel were deployed to the response.
- Update by DTBE on its progress in responding to recommendations made by the African American Workgroup.

Public Comment Session

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

Closing Session

The participants applauded Dr. Fleenor for his outstanding leadership and efficiency in resolving a large number of resolutions during the short time of the business session. The next ACET meeting would be held on October 27-28, 2009 in Atlanta, Georgia.

With no further discussion or business brought before ACET, Dr. Fleenor adjourned the meeting at 2:08 p.m. on July 15, 2009.

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