U.S. 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

Meeting of the
Advisory Council for the Elimination of Tuberculosis
April 26, 2016

Record of the Proceedings

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US DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)
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Advisory Council for the Elimination of Tuberculosis
April 26, 2016
Atlanta, Georgia

Minutes of the Meeting

The US 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 teleconference meeting of the Advisory Council for the Elimination of Tuberculosis (ACET) on April 26, 2016.

ACET is chartered to provide advice to the Secretary of HHS and the Director of CDC regarding the elimination of tuberculosis (TB); to make recommendations regarding policies, strategy, objectives, and priorities; to address the development and application of new technologies; to provide guidance on CDC's TB Prevention Research Portfolio and program priorities; and to review the extent to which progress has been made toward eliminating TB.

Information for the public to attend the ACET meeting in person or via teleconference was published in the *Federal Register* in accordance with Federal Advisory Committee Act (FACA) regulations. All sessions of the meeting were open to the public.

Call to Order and Welcome / Roll Call

Hazel Dean, ScD, MPH
Deputy Director, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention
ACET Designated Federal Officer (DFO)

Dr. Hazel Dean called the ACET teleconference meeting to order at 10:06 a.m. on Tuesday, April 26, 2016. She reminded the meeting attendees that ACET meetings are open to the public, that all comments made during the proceedings are a matter of public record, and that members should be mindful of potential conflicts of interest identified by the CDC Committee Management Office (CMO) and recuse themselves from voting or participating in those discussions.

Dr. Dean conducted a roll call of ACET voting members, *ex officio* members, and liaison representatives. There was a quorum of ACET members and *ex officio* members. Dr. Dean reminded participants that roll call would be conducted periodically during the meeting to ensure that quorum was maintained. No ACET members disclosed conflicts of interest. A complete list of meeting attendees is appended to this document.

CONFLICT OF INTEREST DISCLOSURES	
ACET Voting Member (Institution/Organization)	**Potential Conflict of Interest**
Ana M. Alvarez, MD, FAAP (University of Florida College of Medicine)	No conflicts disclosed
Lisa Y. Armitage, MD, PhD (Heartland National Tuberculosis Center)	No conflicts disclosed
Jennifer Cochran, MPH (Massachusetts Department of Public Health)	No conflicts disclosed
Barbara Cole, RN, MSN, PHN (Riverside Co. Department of Public Health)	No conflicts disclosed
C. Robert Horsburgh, Jr, MD, MUS (Boston University School of Public Health)	No conflicts disclosed
Eric R. Houpt, MD (University of Virginia)	No conflicts disclosed
Jeffrey R. Starke, MD (Baylor College of Medicine)	No conflicts disclosed
James Sunstrum, MD (Wayne County, Michigan, TB Clinic)	No conflicts disclosed

Dr. Dean provided updates regarding ACET membership:

- Dr. Kevin Taylor, Deputy Director of Professional Medical Education, Army Public Health Center, is the new alternate *ex officio* member for Dr. Naomi Aronson from the US Department of Defense (DoD).
- Kali Crosby, a Nurse Consultant with the Division of Healthcare-Associated Infections, Center for Quality Improvement and Patient Safety, Agency for Healthcare Research and Quality (AHRQ) replaces Dr. William Baine as the ACET *ex officio* member from AHRQ. Dr. Baine retired on December 31, 2015.
- Dr. Steven Derrick joined the meeting for Dr. Karen Elkins, *ex officio* member from the US Food and Drug Administration (FDA).
- On March 25, 2016, Dr. Tara Wildes retired from the Department of Corrections. A letter was sent to the National Commission on Correctional Health to identify a replacement for her on ACET.

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Barbara Cole greeted the group and noted that her goal was to keep the meeting on time, while allowing sufficient time to address all of the important issues on the day's agenda. The agenda included updates as well as action items and discussion regarding motions from the previous meeting and advice requested of ACET.

CDC Updates

NCHHSTP Director's Update

Hazel Dean, ScD, MPH
Deputy Director, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention
ACET Designated Federal Officer (DFO)

Dr. Dean presented ACET with updates from CDC and NCHHSTP on behalf of Dr. Jono Mermin, NCHHSTP Director.

CDC Updates
CDC has been active in the fight against the Zika virus. Since May 2015, when the first Zika virus infections were confirmed in Brazil, the primarily mosquito-borne virus has spread to 24 countries and two US territories. In response, the World Health Organization (WHO) has declared the current outbreak an International Health Emergency. To date, there have been 388 travel-associated Zika virus disease cases reported in the US, of which 33 cases were among pregnant women. In the US territories, there have been 500 locally-acquired cases and three travel-associated cases. Of these cases, 48 were among pregnant women. CDC activated its Emergency Operations Center (EOC) on January 22, 2016, in response to the Zika outbreak. NCHHSTP has deployed or assigned to future deployment 77 volunteers. Of those, 24 are currently deployed. Colleagues from the Division of HIV/AIDS Prevention (DHAP), the Division of STD Prevention (DSTDP), and the National Center for Emerging and Zoonotic Infectious Diseases (NCEZID) developed CDC Interim Guidelines for Prevention of Sexual Transmission of Zika Virus.

National Action Plan for Combating Multidrug-Resistant Tuberculosis (MDR-TB)
The White House officially launched the National Action Plan for Combating MDR-TB on January 7, 2016. This plan is a comprehensive road map that identifies critical actions for federal departments and agencies to combat the global rise of MDR-TB. The launch was hosted by the US Agency for International Development (USAID). In conjunction with the new plan, the director of CDC, Dr. Tom Frieden, wrote an op-ed article on MDR-TB and the new action plan for Fox News Opinion. The article is available at: CDC Chief Frieden: World must act now to stop drug-resistant TB

NCHHSTP Highlights

The proposed Fiscal Year (FY) 2017 budget for NCHHSTP requests $1.13 billion. TB, HIV, school health, and sexually transmitted infection (STI) prevention funding levels are at FY 2016 active levels. There is a $5 million proposed increase in the viral hepatitis line.

Dr. Brian Edlin is the new NCHHSTP Chief Medical Officer. He has been involved in research, surveillance, and policy aspects of infectious diseases, including HIV and viral hepatitis, for more than 25 years. His research includes conducting community-based research for 20 years with people who inject drugs. In 2003, he joined the Center for the Study of Hepatitis C in New York to establish an epidemiologic research program. He served on the faculty of the University of California, San Francisco (UCSF), the Weill Cornell Medical School, and the State University of New York (SUNY) Downstate College of Medicine.

A few senior NCHHSTP staff members are on detail or are serving in positions that are being filled. For example, Dr. Dean is serving as the Associate Director for Planning and Policy as well as Deputy Director of the center. Eva Margolis retired in early January 2016, and it is hoped that her position will be filled soon. Dr. Patricia Dietz from DHAP is Acting Associate Director for Performance Improvement, as Dr. Rich Wolitski has joined the US Department of Health and Human Services (HHS). Craig Studer is Acting Management Officer while Michael Melneck serves on a detail to assist another CDC office. Craig is currently the Deputy Director for Management for NCHHSTP. Ann Forsythe is serving as Acting Associate Director for Communication Science while Susan Robinson serves on a detail with Zika.

Antibiotic resistance (AR) continues to be a focal point for CDC and NCHHSTP. DTBE is active in CDC's 2016 Combating Antibiotic-Resistant Bacteria (CARB) Initiative. DTBE will receive funding over the next two FYs to support these activities, which include:

- Development of a mini-stockpile to help support continuity of care for TB patients in the event of drug supply disruptions
- Enhanced surveillance and laboratory capacity for drug-resistant TB

DSTDP is also receiving funding with the CARB initiative for antimicrobial-resistant gonorrhea.

Responding to the challenges of the epidemic of opioid drug use is another CDC emphasis area. NCHHSTP recently released an analysis of the vulnerability of areas to rapid dissemination of HIV and Hepatitis C Virus (HCV) infections among persons who inject drugs. This analysis identified 220 counties in 26 states that are at particularly high risk of rapid spread of HIV and new HEV infections among persons who inject drugs, if these infections were introduced into these vulnerable populations. NCHHSTP shared this information with state health departments. Over 50% of counties were concentrated in the core of the Appalachian region that includes parts of Kentucky, Tennessee, and West Virginia. Other regional clusters of counties were identified in the Ozarks region, northern Michigan, and northern New England.

Another recent action in response to the opioid epidemic occurred in December 2015, when Congress gave states and local communities, under limited circumstances, an option to use federal funds to support certain components of syringe services programs. The use of federal funds is still prohibited for the purchase of sterile needles or syringes to inject illegal drugs, but federal funds are allowed to be devoted to other program aspects, such as staff, other supplies,

or HIV or HEV testing kits, based on demonstrated need. HHS issued guidance on the implementation of aspects of the syringe services programs: HHS Implementation Guidance to Support Certain Components of Syringe Services Programs
DHAP introduced a new HIV risk reduction tool to its website. This is a user-friendly tool for a different audience, giving risk estimates and HIV prevention messages, incorporating antiretroviral therapy (ART), pre-exposure prophylaxis (PrEP), and new prevention tools. The content is structured so that it can be tailored by the user.

The Division of Adolescent and School Health (DASH) has two new publications geared toward educators:

- Health Education Curriculum Analysis Tool (HECAT)
- Anti-Bullying Policies and Enumeration, an infobrief for local education agencies

The Annual Report to the Nation on the Status of Cancer was release in March 2016 by CDC, the American Cancer Society (ACS), and other partners. This report showed that liver cancer incidence is increasing rapidly, second only to thyroid cancer. Liver cancer increased 72% between 2003 and 2012. Almost 23,000 people died from liver cancer in 2012, a 56% increase. Hepatitis B and C are major contributing factors to liver cancer.

The STD Prevention Conference will be held in 2016 in Atlanta, Georgia. Conference registration opens in May 2016. The conference is sponsored by CDC and several partners, including WHO and the Pan-American Health Organization (PAHO).

ACET confirmed that the NCHHSTP TB budget is $142 million, and it has been flat for several years.

DTBE Director's Update

Philip LoBue, MD
Director, Division of Tuberculosis Elimination
National Center for HIV/AIDS, STD, Viral Hepatitis and TB Prevention
Centers for Disease Control and Prevention

Dr. Philip LoBue greeted the meeting attendees and provided ACET with updates on the 2015 provisional surveillance data, which were published in the *Morbidity and Mortality Weekly Report* (*MMWR*) for World TB Day; and on the US Preventive Services Task Force (USPSTF) Draft Recommendation for latent tuberculosis infection (LTBI) testing.

The provisional number of TB cases reported in 2015 was 9563, with a provisional case rate of 3.0 per 100,000. 2015 represented the first increase in the annual number of reported TB cases in the US since 1992, with an increase of 157 cases since 2014, for which the most recent data indicates 9406 TB cases. Twenty-nine states and the District of Columbia (DC) reported an increase in TB cases in 2015 compared to 2014. The case rate has essentially remained unchanged since 2013. The elimination target is based on the case rate, with the target being less than 1 case per million population. The current case rate translates to 30 cases per million

population. The data suggest a leveling in the case rate and the possibility that a limit has been reached regarding what is achievable with current, existing interventions in the US.

In stratifying the TB cases by country of birth, 66% of cases occurred in persons born outside the US, and 34% of cases occurred among US-born persons. This stratification has been similar for the last several years. In 2015, the foreign-born case rate is 15.1 per 100,000, and the US-born case rate is 1.2 per 100,000. From 2012 to 2014, there were decreases in TB cases among US-born persons; however, there was an increase of 24 cases in 2015. There were increases in TB cases among foreign-born individuals from 2013 to 2014, and there was another increase from 2014 to 2015. The actual case rate has been decreasing because the relative population among the foreign-born has been increasing more rapidly than the TB cases. Twenty-seven cases are in individuals of unknown national origin. The 2015 data are provisional, so it is likely that some, if not the majority, of those 27 cases will be redistributed between US- and foreign-born populations when the final data are received. The complete data set will be examined in greater detail. The provisional report focuses on a handful of variables, such as the overall case count, the overall case rate, distribution by state, US-born versus foreign-born, race, and ethnicity. The more detailed examination of the final data will shed light on where the case increases are occurring.

Four US states reported 500 or more TB cases: California, Texas, Florida, and New York. They account for almost 51% of cases, as has been the case in recent years. The top five countries of origin among the foreign-born cases are:

- México (1,250 cases, 19.7%)
- The Philippines (819 cases, 12.9%)
- India (578 cases, 9.1%)
- Vietnam (513 cases, 8.1%)
- China (424 cases, 6.7%)

These top five countries have been the top five for a number of years, and they accounted for 56.6% of foreign-born TB cases. In terms of percentage of foreign-born cases, México has represented as many as 23% to 24% of cases in the past. The trend of cases from México appears to be drifting downward, and the foreign-born cases may be shifting more toward Asia.

The USPSTF recommendation on LTBI testing was opened for the public comment period on March 8, 2016. The comment period closed on April 4, 2016. The draft recommendation, which has a grade of B, is:

The USPSTF recommends screening for LTBI in populations that are at increased risk.

The USPSTF uses the following chart to explain its recommendations:

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I Statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

A grade of B indicates that the USPSTF recommends offering or providing the service. A recommendation of A reflects more certainty regarding substantial benefit, but ultimately, a service is recommended with a grade of A or B.

The "population at risk" applies to adults aged 18 years and up who are at increased risk for TB. The recommendation does not apply to individuals with symptoms who are suspected to have active TB. It applies only to asymptomatic adults. The populations at risk include populations with increased prevalence of active TB disease and increased risk of exposure, which includes persons who were born in, or are former residents of, countries with increased TB prevalence and persons who live in, or have lived in, high-risk congregate settings, such as homeless shelters and correctional facilities. There are other populations at increased risk that the USPSTF did not include. For instance, known contacts are at increased risk. The task force views contacts as a public health department function and not part of primary care screening procedures. A number of other populations include those with various conditions, medical diseases, or who are taking medications that might put them at increased risk for activation of TB if they are infected. Specific examples include HIV, persons on immunosuppressive medications, chemotherapy, et cetera. Within the USPSTF framework, these persons are considered to be under medical care for this condition and that testing for LTBI should be part of that medical care. These populations are, therefore, distinct from a primary care screening scheme. Similarly, the task force recommendation does not include occupational screening.

Regarding the screening tests, the recommendation refers both to the tuberculin skin test (TST) and the interferon-gamma release assay (IGRA), which are FDA-approved and recommended by CDC. USPSTF also notes that CDC documents a preference for IGRA in people who have received a bacille Calmette-Guérin (BCG) vaccination or who are unlikely to return for a TST interpretation. Those two groups largely overlap with the groups that the task force specifically mentions in the recommendation: 1) foreign-born, who are more likely to have had BCG, and 2) populations such as the homeless, who are unlikely to return for TST interpretation.

The USPSTF recommendation does not indicate an optimal frequency of screening; rather, the frequency depends upon risk factors and could range from a one-time test for individuals whose risk has already occurred and who do not have future risk, to people with continued risk of exposure who could need testing as frequently as annually.

The USPSTF recommendations refer to CDC recommendations for treatment regimens, noting that there are several available regimens, including rifampin (RIF), isoniazid (INH), or INH plus rifapentine (RPT). The duration varies from three months to nine months. The CDC currently recommends directly-observed therapy (DOT) for non-daily dosing regimens.

It is important how this recommendation relates to coverage under the Patient Protection and Affordable Care Act (ACA). The work of the USPSTF is recognized under the ACA. Under the ACA, preventive services with a grade of A or B must be covered without cost-sharing; that is, without a copayment or deductible, under and new health insurance plans or policies.

The USPSTF recommendation refers only to adults. The ACA recognizes recommendations from groups other than the USPSTF. Bright Futures is a national health promotion and prevention initiative led by the American Academy of Pediatrics (AAP) and supported by the Maternal and Child Health Bureau (MCHB) of the Health Resources and Services Administration. Bright Futures Guidelines provide and evidence-driven guidance for preventive care screenings and well-child visits. ACA coverage requirements also apply to these Bright Futures recommendations, and Bright Futures has specific recommendations for TB, particularly testing for children who are at risk. For example, Bright Futures recommends a risk assessment at the 12-month visit. If the child was born in a country that is not low-risk, or has traveled to high-risk TB countries, or if a family member has had TB, or if the child is HIV infected, then the TST is recommended.

ACET discussed Dr. LoBue's presentation.

- Regarding foreign-born incidence, there is a calculation of the total foreign-born population is in the US. ACET asked who calculates that number, how accurate it is, and whether the denominator includes all foreign countries or just high-risk countries. This area of focus is important for LTBI. Dr. LoBue answered that when US Census information is available, that information is used. Between Census years, the calculation is dependent upon a number of groups that estimate these populations. The accuracy of these inter-censal estimates is an open question, and there is always the possibility for some degree of inaccuracy. The same data sources are used in order to keep the denominators as consistent as possible from year to year, but even the US Census is not accurate in its count of these populations. Denominators are critical for determining case rates, and there is always the potential for a degree of inaccuracy. The calculation is made more difficult when populations shift for various reasons. There were population shifts during the recession, and perhaps a reversal of those shifts is taking place now, which affects the denominators.
- There has been a surge of the diagnosis of ocular TB in Michigan, with iritis and uveitis. Nine percent of the state cases are considered in this category. New México is approaching 10%. Ophthalmologists have discovered the IGRA assays and are making delayed diagnoses in patients. The leveling off or rise in TB cases could be due to increased diagnosis across the country. DTBE could examine the data on this point. This

issue is difficult, because those diagnoses are clinical and are based on a positive test for infection, plus what an ophthalmologist sees, as opposed to having a more objective diagnosis confirmed by a microbiologic specimen. DTBE can examine trends based on disease site to see whether there are effects. Clinical diagnoses may vary based on clinical practices or be an artifact of case ascertainment because there was the decision, perhaps due to awareness, to make a clinical diagnosis.

- Regarding the USPSTF recommendation, ACET asked for additional insight into the meaning or intent of the screening. If the screening is positive and an individual then needs a chest x-ray and a medical evaluation, are the next steps considered part of the screening process because they lead to a diagnosis? Dr. LoBue responded that in terms of coverage, only the initial testing is considered the screening. USPSTF has a different framework for approaching these issues. For example, in breast cancer, the task force recommends mammograms, which are not in themselves a diagnostic for breast cancer. Individuals then need biopsies or surgical excisions, which are more costly than a mammogram. They are part of the process to reach a diagnosis of breast cancer, however. The USPSTF recommends only mammograms, and this LTBI recommendation is somewhat analogous.
- ACET noted the shift among foreign-born cases to Asian countries and asked about the potential impacts on DTBE's strategies. Dr. LoBue commented on the complicated issues related to potentially screening overseas, which will require a great deal of thought and resources. There is interest in considering groups other than permanent immigrants and refugees. More students and long-term visa holders may be coming from some of these countries, which may necessitate expanding overseas screening. If the expansion were to occur, which countries would be given priority at first? Further, in terms of expanding LTBI testing and treatment, it will be important to set priorities for countries and groups.
- ACET inquired about visitor visas, which do not require TB screening, and whether there is a sense of the TB burden from visitors. ACET has also discussed the H1-B work visa in the past and issues associated with it. Dr. LoBue replied that a variable was added in 2009 to learn more about foreign-born people arriving in the US. There are a number of limitations to this work, however, because there was variation in how the numbers were reported. There are legitimate concerns associated with identifying individuals as being undocumented. Many people are placed in the "other" category in order to avoid specific designations of categories that have particular stigma. DTBE can examine the issue to look for changes in categories, such as students or other types of visas, which are not permanent immigrants. There are categories for students; permanent immigrants and refugees; undocumented persons, which is probably not accurate; and "other," a variable that could possibly be teased out. A study was conducted under the Tuberculosis Epidemiologic Studies Consortium (TBESC) which included careful interviews with persons to acquire this specific information. The study was conducted some time ago, so its results may not reflect the situation in 2015.
- ACET asked if the data are broken out by MDR-TB in terms of where people come from and also by state to get a sense of where there may be clusters of MDR-TB. Dr. LoBue answered that the final culture results are not available for 2015 to confirm MDR-TB or extensively drug-resistant tuberculosis (XDR-TB) cases. The preliminary data suggest that the numbers have not changed a great deal. Usually, there are 85 to 100 cases of MDR-TB per year, and generally, 85% to 90% of the cases occur among foreign-born persons. They were born in a mix of countries, predominantly from the top countries of

origin, but also from other countries in Eastern Europe and some other parts of Asia. The numbers are small, at slightly over 1%.

- At a previous ACET meeting, it was discussed that many of these cases developed in people who have been in the US for a number of years. ACET wondered if that information is available for the 2015 data and how that information might impact screening in the US, overseas, or among students. If the cases are occurring in individuals who have been in the US for some time, the strategies may not meet the actual demographics of the problem. Dr. LoBue answered that the data will be available in the final analysis. He agreed that the majority of cases occur among people who have been in the US for at least more than two years, and frequently more than five years. There are limitations to what overseas screening can do; nevertheless, at this point, it is important to capture as many cases as possible, and there are different ways to accomplish that goal. The most recent analysis of 2011-2014 data suggests that approximately 86% of TB cases are not due to recent transmission in the US, but to reactivation. LTBI is the critical issue. There is close to 90% treatment completion. In an ideal situation, there would be no delays in diagnosis and contact investigation could improve; however, based on what is known from genotyping data about cases occurring from recent transmission versus reactivation, those cases are occurring among foreign-born populations who have been in the US for some years. There are clear limits on what overseas screening can do to reduce cases, which makes the LTBI issue so critical, and one of the reasons why CDC was happy to see USPSTF take it on as a topic.

ACET Discussion

Discussion on US Preventive Services Task Force (USPSTF) Recommendations

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Cole led ACET in a discussion of the implications of the USPSTF recommendations on screening for LTBI. She asked for ACET's input regarding what is missing from the recommendations. The open comment period for USPSTF is closed, but there still may be an opportunity for ACET to provide comment. The National Tuberculosis Controllers Association (NTCA) provided comments during the public comment period and addressed missing elements from the recommendations. That letter has been provided to ACET.

Ms. Cole reminded ACET that a B rating carries with it the same suggestion for practice as an A rating. No ACET members expressed concern about the B rating.

When ACET discussed the initial draft, the group expressed concern that children were not included. ACET also submitted input regarding the need to include contacts, who should be screened in settings other than public health. Further, immunosuppressed individuals and those with HIV were proposed to be included because that coverage is part of the standard of care.

- ACET supported including contacts in the recommendation. In practice, coverage is often denied when a person is identified as a contact. With a shift toward conducting more testing in primary care settings, the omission of contacts represents a gap in coverage.
- ACET noted that the points made by NTCA are relevant. When an individual is identified by screening, there is no mechanism in place to link the evaluation to assessment and treatment. Individuals identified as infected should receive the necessary x-rays and treatment for LTBI in order to move toward TB elimination.
- If the USPSTF recommendation is limited or the coverage is limited to screening, it will require public health to scale up to respond to the needs for further evaluation, access for treatment, adherent support measures, and other issues. The implications of the USPSTF recommendations are profound for public health, as public health will need to re-examine the application of resources toward treating LTBI.
- The NTCA letter also refers to the need for a standardized risk assessment screening tool. Different states are working on such tools. For example, California has developed one. ACET could address this issue, learning about the available tools that might be shared across states so that there is some consistency, especially given that the population is mobile. Pediatrics has utilized this approach for some time with good success, as a great deal of testing is conducted in clinics and doctors' offices. The approach has applied research-validated tools, with the exception of the length of time of travel, which is a problem. In this day and age, younger physicians especially are accustomed to standardized approaches and checklists. A validated tool would be very useful.
- ACET can further consider the integration of these tools into electronic health records (EHRs) or electronic medical records (EMRs), so that a trigger to apply the standardized risk assessment tool could be built into the system. Local epidemiology will play a role in some of the risk factors in triggering practitioners to think of screening for LTBI, but some elements apply regardless of where people live.
- ACET asked for clarification regarding Bright Futures and whether that recommendation covers children equivalently for the ACA in terms of requiring and paying for LTBI screening. Dr. LoBue confirmed that Bright Futures is equivalent to USPSTF, the Advisory Committee on Immunization Practices (ACIP), and HRSA in terms of coverage under the ACA.

Ms. Cole noted that the public comment period for the recommendations had closed, but that ACET could still go on the record with these expressed concerns. These issues also can be addressed in the upcoming meeting with the HHS Secretary or Deputy. She asked ACET to reflect on how to communicate the USPSTF recommendations and rating when they are finalized, and how that outreach and awareness might translate to practice.

- Overall, it is good news that the LTBI screening recommendations received a B rating. The next question to consider is how this rating "lands" on the preventive medicine guidelines that are taught in programs, the guidelines for lipid screening, A1C screening, universal HIV screening, et cetera. TB screening isn't currently "on the map." What is the mechanism by which LTBI screening is added to those "radar screens?" Dr. LoBue said that DTBE has begun to think these questions through, talking to colleagues who have responded to previous recommendations in their areas. DTBE is in the process of developing a strategy for moving forward. There are other payers to consider. For instance, the Centers for Medicare and Medicaid Services (CMS) does not automatically adopt the USPSTF recommendations, but there are mechanisms for them to adopt them,

and DTBE is moving in that direction. Regarding primary care providers, working through professional groups and some federal agencies that operate clinics, such as HRSA, may be beneficial. Even when screening is recommended, it is not assured that the providers remember the recommendations when they are seeing patients. Therefore, it is important to automate the recommendations into EHRs with clinical decision support tools and alerts. There are many pieces to the initial strategy, and DTBE is prioritizing their approach. Perhaps a draft of the suggested strategy could be presented for ACET's input. Additionally, AHRQ, which oversees the USPSTF, will have a communication strategy related to the recommendations. When they are ready to move forward, they have expressed a clear willingness to work with CDC.

- ACET discussed the possibility of working with EMR companies. Epic is the primary EMR provider. ACET wondered whether Epic's modules automatically include elements that are part of USPSTF recommendations and whether there can be built-in reminders in the modules. Dr. LoBue replied that Dr. Mermin has initiated some of these discussions regarding EMRs. Additionally, foreign-born populations are an important target group, but that information is not generally included in the EMR systems. That information needs to be included in the system in order to trigger the recommendation. This piece is critical, and all divisions of NCHHSTP are working together, and with EMR vendors. Ms. Cole asked whether this effort is part of the larger effort to consider the standard data elements that should broadly be included in EMRs. Dr. LoBue said that if there are specific triggers needed for screening for different diseases, there must be standard data elements. Both the data elements and a clinical decision support tool trigger are needed.
- The representative from the International Union Against TB and Lung Disease (The Union) recalled an AHRQ-funded project in 2002 and 2003 that involved collecting the country of birth at registration. The study demonstrated that using an EMR system would increase the frequency with which primary care providers recognize patients at risk for TB and conducted testing. Denver Health is in the process of transitioning to Epic, and the TB program has worked hard to ensure that the information is collected through the new Epic system. Denver Health has collected the information for many years, and it has been very helpful not to ask the patient, "What country were you born in?" every time he or she presents to the facility.
- ACET supported the idea of working with Epic. Another potential partner is the American Diabetes Association (ADA). They have standards of care and guidelines for diabetes. They mention hepatitis screening, for instance, but make no mention of TB.
- Regarding upgrading to Epic, ACET observed that the system has a health maintenance section which reminds users of tests such as A1C, hepatitis C, and mammogram. TB is not included in this section, but it potentially could be used as a reminder. Information about country of origin is still needed in order to determine who should be screened, however, and that issue will still need to be resolved.
- ACET asked about the status of reporting positives for TB screening. There have been discussions at previous meetings about reporting. If screening increases, there will be questions about reporting and access to treatment. Dr. LoBue answered that DTBE continues to work on TB reporting. An update can be provided at a future ACET meeting. Initially, there likely will be a multi-tiered system. A software package will be available for detailed reporting, but not all programs will want such a package. A multi-tiered system would collect a small number of variables from a larger number of programs, and more detailed information from a smaller number of programs. Ultimately, the reporting endeavor will require cooperation from local and state programs, as it is a state decision

to make conditions and diseases reportable. When this issue was discussed previously, the reporting would be voluntary, not mandatory. Each state or local jurisdiction could mandate reporting. Among the issues associated with reporting is the preparedness at the local and state levels to process the information. ACET would welcome an update on the status of this plan.

- ACET observed that the Bright Futures recommendations do not address IGRAs. IGRAs are not routinely recommended for children aged five and younger, but what about children aged 6 to 18? Dr. LoBue said that Bright Futures recommends repeated risk assessments at different ages.
- ACET added that the AAP recommendations are evolving. The last statement was released on December 1, 2014. It is not clear how often Bright Futures recommendations are updated and whether they have been updated subsequent to the statement, which is more "permissive" and states that some experts perform IGRAs in children down to two years of age. The 2018 Red Book will be even more permissive. Data are being reported from different sources about the use of these tests, indicating that they are appropriate. It would be helpful to learn more about the AAP's direction, as that group will see, screen, and re-screen children, and pediatricians rely a great deal on the Red Book.
- ACET observed that the recommendation-setting mechanism for adults, the USPSTF, has a public comment element, where Bright Futures, the mechanism for pediatric populations, does not have a public comment period. The recommendations are set differently by the different groups.

Ms. Cole summarized key issues regarding the USPSTF B rating for LTBI screening:

- Omitted groups
- Children: Bright Futures may address this issue, but ACET may need to consider communication options in this area
- Contacts: Primary care physicians do evaluate contacts, so there needs to be outreach to that group.
- Immunocompromised individuals, whether due to HIV or certain medications
- ACET raised these issues in feedback on the initial draft of the USPSTF recommendations; the USPSTF provides a rationale for not including them
- Concerns regarding next steps after a positive TST or IGRA: X-rays and treatment of LTBI are not included in the recommendations
- Strategies for outreach and promotion of the USPSTF recommendations: DTBE is developing strategies in this area, which will be shared with ACET at an upcoming meeting; key target groups for outreach include CMS, primary care providers, HRSA, funders, and payers
- Creating a standard risk assessment that can be tied to the EMR, with triggers for conducting testing; many health systems are using, or transitioning to, Epic. A group at CDC is considering all necessary data elements.
- LTBI reporting: As more screening is conducted, how will that information be linked and used?; there will be an update at a future ACET meeting regarding CDC's plans in terms of reporting

Discussion on Meeting with the HHS Secretary

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Cole directed ACET's attention to the letter that ACET sent to HHS Secretary Burwell on March 5, 2015. The letter described ACET's major concerns that they hope to address in collaboration with HHS, including:

- Intermittent shortages of anti-TB drugs, particularly second-line drugs
- TB in correctional and detention facilities
- TB along the Mexican border of the US
- Maintaining a strong public health infrastructure to carry out the recommendations in the 2000 Institute of Medicine (IOM) TB Elimination Report.

The letter welcomed the opportunity to meet with the Secretary to discuss these concerns, as well as HHS priorities. A response was received in August 2015. It acknowledges receipt of the letter and thanks ACET for raising concerns related to the elimination of TB in the US. The response also refers to challenges regarding TB at the local, state, national, and global levels. The response was favorable and indicated interest in meeting with ACET to discuss these concerns. Ms. Cole and Dr. Dean will represent ACET at the meeting. A date for the meeting has not yet been set. Ms. Cole asked for ACET's feedback regarding the topics that should be prioritized and shared with the Deputy Secretary of HHS. She asked ACET if the initial letter still reflected their priorities, or whether USPSTF recommendation should be a top priority.

- The priority focus on public health infrastructure can be tied to the USPSTF B recommendation. There is a new recommendation for screening, but no recommendation for evaluation and treatment. Much of this work will fall to the public health sector, which must be strong enough to absorb the burden of newly-identified individuals and will serve as the source of knowledge as community entities evaluate and treat patients.
- This administration has had flat DTBE budgets for years. There also has been a flattening of domestic TB cases. A 19% cut was proposed for USAID funding for TB programs at the same time that the response letter refers to developing and strengthening capacity abroad. There is a dichotomy between what is being said and what the budgets are proposing. The funding is going in the wrong direction for the degree of the problem. Especially given the trends in TB cases and shifts to Asian countries, now is a bad time to cut funding to USAID. TB also disproportionately affects children. The problem is not being conceptualized correctly, and the budgetary approach is at odds with the HHS response letter. It was clarified that the USAID budget is part of the Department of State, not HHS. These issues can be blurred because USAID works in the health area.
- ACET noted that CARB and the National Action Plan for Combating MDR-TB was released more recently than the 2000 IOM report. The MDR-TB crisis should also be discussed with the HHS Secretary.

- Dr. LoBue said that he is not advocating or requesting that anyone request additional funding for DTBE. It is important to make an honest assessment of what can and cannot be done with the current resources. In particular, there is a critical role for public health departments in oversight, guidance, outreach to the community, and support regarding LTBI screening, even if much of the testing and treatment is carried out in the primary care setting. No funding is available within DTBE or health departments to fulfill this critical role. A dramatic expansion in addressing LTBI cannot be accomplished with current resources. If addressing LTBI is critical to resume the downward trend in TB case rates, then it will not occur. Regarding CARB and the National Action Plan, there are financial challenges for small programs that have one or fewer MDR-TB or XDR-TB cases. These cases represent 1% of TB cases. Even if they are eradicated, the effect would not be dramatic on the case rate or the overall number cases. There is clearly a lack of resources to address MDR-TB and XDR-TB in a number of circumstances, and these cases are difficult and complicated, but a focus only on these cases and on nothing else will not move toward the goal of TB elimination.
- ACET added that even in gearing up screening for LTBI, a person infected with MDR-TB can be treated with available regimens, but it is not likely to prevent him or her from developing disease, because it is not known whether the individual is infected with an MDR-TB strain.
- Regarding USAID and global TB control, Dr. LoBue said that up to 90% of MDR-TB cases are among the foreign-born. Most of them were infected overseas. The US is not in a situation of creating drug-resistant TB. He expressed concern that with deterioration of the public health infrastructure, the risk will become real. The LTBI realm should not be expanded at the expense of basic TB control activities, which have been successful so that the US has reached a point where drug-resistant TB is not being created.
- Dr. Andy Vernon, Clinical Research Branch, DTBE, commented on MDR-TB and LTBI. Assuring a reasonable supply of new agents, ideally that are relatively non-toxic, inexpensive, and effective, is the solution to patients infected with LTBI and MDR-TB. This supply will require a substantial change to the way that drugs are developed currently. This issue is related to infrastructure problems as well. In discussing issues regarding the infrastructure, he wondered how the USPSTF posed the questions for consideration as they developed their recommendations. The groups of highest priority were excluded by the task force on the grounds that they would be "dealt with by the health departments." Health departments have experienced significant budget cuts that resulted in substantial declines in what they are able to take on. At some point, the expectation was that the ACA would help health departments cope with these burdens.
- Regarding the meeting with HHS leadership, the liaison representative from The Union pointed out that ACET's role is to advise on the National TB Elimination Plan. The problem is not with 157 additional TB cases in 2015, but with the over 8600 cases that should not have occurred, but did occur because of the failure to implement the elimination plan. There should have been only 956 cases. There were probably over 500 excess TB deaths. These TB cases and deaths are preventable, but they continue to occur because the national plan has not been implemented.
- Dr. Sundari Mase, DTBE, agreed with the focus on LTBI. She added that multi-drug resistant (MDR)-LTBI is an important area for consideration. It is not known whether contacts of MDR cases are treated and what their outcomes are. A registry that captures those contacts better would be helpful. More data are being gathered related to the treatment of MDR-LTBI with fluoroquinolone (FQ)-based regimens. MDR is not the only

concern regarding drug resistance. There is over 10% INH resistance and other forms of drug resistance. These resistances should be examined. A recent survey of a representative sampling of consults to the Regional Training and Medical Consultation Centers (RTMCC) database found a striking number of cases that acquired resistance prior to RTMCC consultation. Up to five to seven of the 150 cases reviewed had documented acquired drug resistance. There is potential for improvement in the care and management of patients in the private sector, academic settings, and the public health departments. For every MDR-TB case that is confirmed, there is probably one functional MDR-TB case; that is, there is no reason to think that a person that cannot take INH and RIF will have a better outcome than a person with confirmed MDR-TB.

- Regarding intermittent shortages of drugs, ACET asked for information about the mini-stockpile. Dr. LoBue answered that the stockpile will be very limited. For example, DTBE estimated that complete coverage of all drugs for even six months would cost on the order of over $20 million. The stockpile has an approximately $1.7 million budget from the CARB initiative. The five initial drugs to be purchased will be INH, RIF, RPT, amikacin, and capreomycin. The drugs were selected with input from NTCA. Drug-susceptible TB can be treated with INH/RIF, without other drugs. In the absence of ethambutol, fluoroquinolones could initially protect against INH resistance. Fluoroquinolones are at less risk because they are used in other situations, and there are two different FDA-approved drugs available. RPT is increasingly being used for LTBI treatment, plus it can be used for treatment of TB disease. The other two drugs are injectables and a concern for shortage, particularly capreomycin, which is not used for any other diseases or conditions. DTBE is working with NTCA to develop a procedure manual for when and how the stockpile might be accessed, the priorities for releasing it, and under what circumstances it might be released. Should additional funds become available in the future to purchase additional drugs, there are three options: purchase more of the five initial drugs, purchase additional drugs, or do both. NTCA's thoughts will be important in this area. The stockpile can be shipped to any location where it is needed. The complicating element regards *when*. The stockpile is not large and may not be the answer to every problem, such as increases in drug prices. Issues such as the recent problem with cycloserine prices can be mitigated with other means. Further, it is important to understand whether there is a true shortage of a product, or a distribution problem, which would not merit release of the stockpile. Workgroups have been convened to create a plans for the stockpile.
- Ms. Cole asked ACET whether the creation of the mini-stockpile decreases the urgency of intermittent shortages, or whether that issue should remain at the top of the list. The issue of intermittent shortages could be moved down the list of priorities and replaced with infrastructure budget concerns. The stockpile is small, and a crisis could decimate it. The budget is limited, so the ability to protect the US people is limited. There has been no progress on TB case rates as the budgets have remained flat. Because the field has reached the maximum of what can be accomplished with the current resources, the public health infrastructure needs to be a priority, as well as funding to support the programs that are needed to continue to make progress. Some areas are losing ground as opposed to just flattening.
- Regarding the Biomedical Advanced Research and Development Authority (BARDA) and the shortage issue, Dr. LoBue reminded ACET that BARDA spoke at the last ACET meeting regarding its stockpile options. It was clear that BARDA was not a solution to fill the gap in TB drugs.

- The numbers of TB cases in detention facilities and correctional settings warrant attention.
- TB along the US-México border is still a priority area. There is a shift in the countries of origin of foreign-born TB cases, but the majority of these cases still come from México. The shift toward Asian countries should be mentioned in the HHS leadership meeting.

Ms. Cole observed that the USPSTF recommendation brings to five the number of concern areas to be raised at the meeting. ACET suggested tying the USPSTF recommendation to the public health infrastructure concerns because of the potential of the recommendation to impact local health departments to provide oversight, guidance, and support for LTBI screening, treatment, and follow-up. If there is not time to talk about all five areas of concern, the issues of the USPSTF recommendations and infrastructure, and implications for TB elimination, are the top priority. She asked ACET to suggest the next priority area.

- The ACET workgroup focused on the drug supply has been meeting, and there has been activity. It might be timely to keep this point high on the list, referencing the mini-stockpile as an important and valuable step forward. The limited funding and time raise concerns about how to rectify issues in the longer term. Progress can be celebrated even as concern is expressed about the future.
- The concern about TB along the US-México border encompasses not only the Mexican-born, but also individuals who cross into the US from other countries across the US-México border.
- Given all of ACET's conversations, the public health infrastructure issue is probably paramount. It might be rephrased, however, and framed more broadly and strongly. The reference to the 2000 IOM report does not bring real urgency to the issue. The infrastructure issue includes ensuring treatment, preventing transmission, and preventing the development of MDR-TB. Ms. Cole explained the rationale for referring to the 2000 IOM report. A status report on progress on the various action items in the IOM report showed that even 16 years later, some things had not been done that need to be done to move toward TB elimination. Rates are flattening, and TB is not declining, much like in the 1990s, and it is important to learn from that experience (when cases declined, budgets declined, and then TB rates increased) and not to repeat it. The urgency comes from framing the IOM report in these terms, even though it seems old. The interventions are solid.
- ACET encouraged that the fact that the numbers have been reversed should not be minimized. In the 1990s, the numbers stabilized and then increased at the point at which budgets were cut. Making a strong correlation between those two events in considering the current situation will be important.
- Regarding the reference to the 2000 IOM report, Dr. LoBue said that Stop TB USA re-examined the report in 2010. That effort was the origin of the first progress report. The conclusion has been, "There was a plan in 2000. It was partially implemented, and we got partial results." The conclusion in 2010 was that the IOM report included fundamental interventions which work and have not changed, but were not completely implemented. DTBE looked at the IOM report in 2015 as part of the division's strategic planning process, and it was agreed that the basic, fundamental interventions in that report are effective but have not been fully implemented due to a lack of resources. The 2000 report may seem like an anachronism, but it has been evaluated and reconsidered over the years, and the conclusions have been the same.

- The liaison representative from The Union said that it is important not to begin with the assumption that funding will be flat and to lay out priorities based on that assumption. Other issues do not have that mindset, and TB elimination should share the mindset that all elements of programming are important.
- Ms. Cole said that ACET's letter to HHS referred to competing priorities. At the time, Ebola was receiving attention and resources as a public health emergency, and now Zika is an emergency. By the time ACET meets with HHS, there may be a new priority. Somehow, TB should have the same visibility and urgency of other emerging infectious diseases. Ebola and Zika clearly needed, and need, attention and interventions, but the concern and urgency around TB must be elevated. She hoped to leave the HHS leadership with that message. There is no time frame for the HHS meeting. ACET will meet again in August 2016, and the suggested talking points for the meeting will be presented for ACET's consideration and comment.
- Dr. Suzanne Marks, DTBE, suggested including MDR-TB and XDR-TB. ACET agreed, noting that the numbers of MDR-TB are small compared to drug-susceptible TB, and most cases are among the foreign-born, but the issues regarding MDR-TB could be leveraged to elevate the overall level of concern regarding TB. MDR-TB relates to other emerging infections and to drug resistance for other pathogens. Highlighting MDR-TB from the perspective of the White House National TB Action Plan would be useful, bringing attention to the issue so open discussion about the scope of the problem. Dr. LoBue agreed but urged caution, because people tend to hear only about MDR-TB. Only funding the National Action Plan for MDR-TB will not eliminate TB in the US. The issue is extremely important, it causes many problems, it can overwhelm TB programs, and it needs adequate resources to be addressed. It is also important to ensure that policymakers not "put blinders on" where MDR-TB is concerned.
- Ms. Cole added that MDR-TB can be integrated into the other talking points and tied to challenges with drug shortages and the infrastructure and the impact that one MDR case has on local jurisdictions. The problem with MDR is not only the number of cases, but their impact.

There were no further comments or questions from ACET. The group took a break for lunch at 12:09 p.m. and reconvened at 12:45 p.m. Dr. Dean conducted a roll call of ACET members and *ex officio* members. A quorum was present.

Draft of TB Treatment Guidelines

Andy Vernon, MD
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control and Prevention

Dr. Andy Vernon presented the draft of new guidelines for the treatment of drug-susceptible TB. The guidelines are being produced in coordination with the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA). Endorsement was initially sought from the AAP and the European Respiratory Society (ERS), as well as NTCA. While AAP participated

actively in the production of the guidelines, they have decided not to review them and co-publish them with CDC because of the 9 to 12 months that the process would add to the timeline.

The prior ATS/CDC/IDSA Guidelines for Treatment of TB were published in the *MMWR* in 2003. The volume included a section on treatment of drug-resistant TB and a brief section on international guidelines. Because a separate guideline is being developed to address drug-resistant TB, this guideline specifically excludes drug-resistant TB, including INH-resistant TB. To respond to recent trends in guideline methodology, this document was developed with formal Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods for assessment of the quality of evidence.

This guideline provides recommendations on the clinical and public health management of TB in children and adults in well-resourced settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. Nine questions addressing Population, Intervention, Comparators, an Outcomes (PICO) and associated recommendations were developed on the basis of the evidence that was appraised using GRADE methodology. A carefully selected panel of experts, screened for conflicts of interest, including specialists in pulmonary medicine, infectious diseases, pharmacokinetics, pediatrics, primary care, public health and systematic review methodology were assembled and worked together to create the recommendations.

The GRADE-based recommendations are called "strong" or "conditional." For a strong recommendation, it is assumed that most individuals would want the recommended course of action, and most should receive it. For a conditional or a weak recommendation, a majority of individuals would want the suggested action, but different choices are recognized as appropriate for some individual patients, and there may be discussion regarding the appropriate course in those situations. It is expected that a strong recommendation would be readily adopted by policymakers, while a conditional or weak recommendation would give rise to more debate and involvement of various stakeholders.

A GRADE evidence profile was developed for each of the PICO questions. The profile considers the quality of the evidence, provides information regarding the number of treatment arms or reviews that were consulted, considers the study designs associated with them, considers a number of elements that would diminish the reliability of any findings, including the risk of bias, inconsistency among studies / heterogeneity of findings, indirectness, which refers to a finding that is thought to be relevant to the outcome of interest, but is not actually the outcome; imprecision, with issues related to sample sizes, confidence intervals, and the like; and other considerations, which often include elements related to patient acceptance, cost, and other issues. The tables present information on efficacy outcomes for the particular element being considered and estimates of the relative and absolute effects. Quality is related to the ranking of the quality of the evidence. Importance is related to the grading of the importance of the outcome. In these cases, failure, relapse, and acquired drug resistance were all considered to be critically important outcomes.

The committee included five co-chairs. Payam Nahid was responsible for assuring the careful adherence to GRADE methodologies and assessment of the evidence, as well as recruitment of several members of the GRADE methodology group. Richard Menzies was a notable member of the GRADE group, and the writing group included the co-chairs as well as other individuals.

PICO Question 1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with TB?

- Recommendation 1: We suggest using case management interventions during treatment of patients with TB (Conditional recommendation / Very low quality of evidence).

Several systematic reviews were available to consider this question, with small numbers of studies. The recommendation is therefore highly qualified.

PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to DOT in patients with various forms of TB?

- Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of TB (Conditional recommendation / Low quality of evidence).

A number of international trials have examined the use of DOT. All of the trials suffer from various weaknesses in design and comparability of setting, and indirectness, therefore, for applicability to the US. None of the trials shows a distinct advantage to the use of DOT compared to SAT. The committee considered the evidence from published studies other than randomized trials, which were supportive of the use of DOT. None of these studies indicated any risk of harm from the use of DOT. This recommendation will give rise to discussion in the context of increasing attention to electronic forms of DOT.

PICO Question 3: Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary TB?

- Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary TB (Strong recommendation / Moderate quality of evidence).
- Recommendation 3b: Use of three times weekly therapy in the intensive phase may be considered in patients who are not HIV-infected and are also at low risk of relapse (Conditional recommendation / Low quality of evidence).
- Recommendation 3c: In situations where daily or three times weekly DOT therapy is difficult to achieve, use of twice weekly therapy after an initial two weeks of daily therapy may be considered for patients who are not HIV-infected and are also at low risk of relapse (Conditional recommendation / Very low quality of evidence). Note: if doses are missed in a regimen using twice weekly dosing, then therapy is equivalent to once weekly, which is clearly inferior in the systematic reviews that were reviewed.

The guidelines committee included several individuals who are prominent in the field of HIV/TB. This recommendation was supported “across the board.”

PICO Question 4: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug susceptible pulmonary TB patients?

- Recommendation 4a: We recommend the use of daily or three times weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary TB (Strong recommendation / Moderate quality of evidence).
- Recommendation 4b: If intermittent therapy is to be administered in the continuation phase, then we suggest use of three times weekly instead of twice weekly therapy

(Conditional recommendation / Low quality of evidence), allowing for the possibility of some doses being missed; with twice weekly therapy, if doses are missed, then therapy is equivalent to once weekly, which is inferior.

- Recommendation 4c: We recommend against the use of once weekly therapy with INH 900 mg and RPT 600 mg in the continuation phase (Strong recommendation / High quality of evidence). In uncommon situations where more than once-weekly DOT is difficult to achieve, once weekly continuation phase therapy with INH 900 mg plus RPT 600 mg may be considered for use only in HIV-negative persons without cavitation.

PICO Question 5: Does extending treatment beyond six months improve outcomes compared to the standard six-month treatment regimen among pulmonary TB patients co-infected with HIV?

- Recommendation 5a: For HIV-infected patients receiving ART, we suggest using the standard six-month daily regimen consisting of four drugs for the intensive phase, followed by a two-drug continuation phase. (Conditional recommendation / Very low quality of evidence).
- Recommendation 5b: In uncommon situations in which HIV-infected patients do not receive ART during TB treatment, we suggest extending the continuation phase for an additional three months for treatment of drug-susceptible pulmonary tuberculosis (Conditional recommendation / Very low quality of evidence).

Regarding recommendation 5b, a substantial systematic review has been updated in the last five years. The committee considered this review carefully. One of the few recommendations that might cause controversy is Recommendation 6:

PICO Question 6: Does initiation of ART during TB treatment compared to at the end of TB treatment improve outcomes among TB patients co-infected with HIV?

- Recommendation 6: We recommend initiating ART during TB treatment. ART should ideally be initiated within the first two weeks of TB treatment for patients with CD4 cell counts under 50, and by eight to twelve weeks of TB treatment initiation for patients with higher CD4 cell counts (Strong recommendation / High quality of evidence).

The evidence supporting this recommendation came from several trials that were recently completed and reported. An exception is patients with HIV infection and tuberculous meningitis. The pending guidelines for AIDS treatment in adults and the updated draft of the opportunistic infections (OI) treatment guidelines that will appear on the AIDSinfo webpage are both likely to indicate “within eight weeks,” rather than the eight-to-twelve week period reflected in Recommendation 6. The committee discussed this point and was aware of the inconsistency. The current wording was maintained because:

- At least two of the trials sought to begin treatment in the eight to twelve week period. Stating “within eight weeks” goes beyond the evidence.
- This kind of variation reflects genuine disagreements among various groups. It is reasonable to reflect these disagreements.

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

- Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (Conditional recommendation / Very low quality of evidence).

There was a large, recent randomized trial on this point. This evidence was considered in the development of this recommendation. The discussion regarding this recommendation provides for the use of steroids in a select group of patients thought to be at high risk for development of constricted pericarditis, which is the only serious outcome for which some evidence supports the efficacy of steroids.

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

- Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone given for six weeks for patients with tuberculous meningitis (Strong recommendation / Moderate quality of evidence).

The strength of this recommendation is particularly based on evidence from the Vietnam Trials Group, which has been accumulating for a decade and which is supported by other studies as well.

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-negative patients with aucibacillary TB (i.e., smear negative, culture negative)?

- Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-negative adult patients with acid-fast bacilli (AFB) smear- and culture-negative pulmonary TB (Conditional recommendation / Very low quality of evidence).

The committee felt that it was important to reflect that the gradation moves from more intermittent to less intermittent therapy, which reflects a progression from lesser to greater regimen effectiveness, based on the evidence that was reviewed. Many of these recommendations are considered in that context. For the purposes of this guideline, the committee considered that five times per week was equivalent to seven times per week; however, “in our hearts, we know that’s not true.” There is no direct evidence comparing five to seven times per week, so there is no basis on which to presume otherwise.

The guideline has been formally approved by ATS and IDSA. Their reviews and suggested edits have been considered and incorporated. The guideline is currently under review by ERS (several of its members were members of the development committee) and by NTCA. While AAP will not formally review the guideline, their views were strongly considered in the guideline development. This presentation provides an opportunity for public comment on the guideline and represents one of the concluding steps in the CDC clearance process. The guideline has cleared DTBE and NCHHSTP and is being considered by the CDC Office of the Associate Director for Science. This public comment opportunity is being sought because the guideline is considered to be influential scientific information, which requires opportunity for public comment under current guidelines.

- ACET clarified that the diagnosis of culture-negative TB refers just to clinical cases.
- The former guidelines are used and carefully followed by programs on a daily basis. The new guidelines appear to discourage twice-weekly therapy to a greater degree than the 2003 guidelines. This shift may have implications for programs. Opinions differ regarding twice-weekly therapy, but many programs implement it frequently with success. There will be impact if jurisdictions implement three-times-per-week therapy. The new guidelines appear to increase the extension of therapy from six months to nine months in certain populations.
- ACET asked about evidence showing high failure or relapse rates for biweekly treatment. Dr. Vernon said that such evidence has been present and published since 2009, but the response to the evidence has been slow. In 2009, a systematic review of over 200 trials included the available evidence on twice-weekly treatment. The evidence base for use of twice-weekly therapy is limited in the opinion of the guideline development committee. Study 22 looked at twice-weekly therapy compared to once-weekly INH-RPT. The once-weekly therapy performed mostly more weakly than the twice-weekly therapy. More importantly, however, a group of patients in both arms relapsed at 20% to 25%. These patients had cavitary and smear-positive disease at baseline. The new guidelines draw attention to the fact that twice-weekly is a weaker regimen, and there should be considerable thought given to how it is used, if it is used.
- The liaison representative from NTCA said that the reason for intermittent therapy is the opportunity it affords for directly-observed treatment. He agreed with the group's assessment that more drugs should be administered, when it is feasible. It will be a challenge from a programmatic perspective to administer daily therapy throughout the intensive phase and even into the continuation phase. The guideline is slightly confusing in terms of how programs will be able to balance these factors. The approach in Denver incorporates video technology to be able to observe therapy in a manner that is less resource-intensive and that allows for more frequent dosing. It will be a challenge for programs to determine how to do more frequent dosing and whether in-person DOT is affordable, if video technology is not available. The evidence base for intermittent therapy is weak, but at the same time, the absence of evidence is not evidence of absence. It does not mean that intermittent therapy in less-severe disease does not work, and programs have been using it with good success for some time. The evidence is observational at best, with no randomized trials, much in the same manner that there are no well-constructed randomized trials of DOT.
- Dr. Vernon noted the potential for engaging programs throughout the country to conduct large simple trials to address programmatic issues of importance. This question would be ideal for such an approach. It would be important to acquire evidence and make decisions based on knowledge about the relative performance. The committee appreciates the challenges posed by recommending DOT and less-intermittent therapy.
- ACET said even a massive observational study does not carry as much weight within the GRADE structure as a small randomized controlled trial (RCT). Some find it a flaw of GRADE that real-time, real-life experience is inherently downgraded in terms of the evidence. Even if all TB programs reported their data and the data were analyzed, the result would be impressive and likely convincing, but it would not count for much within GRADE. Dr. Vernon clarified that his suggestion was for a large, simple RCT that would not be costly.

- In response to a question from ACET, Dr. Vernon said that the committee interpreted studies using five or seven days per week of therapy as daily therapy, and they were analyzed in that way. Studies vary in their approaches to the issue, but for purposes of the implementation of recommendations in the guideline, "daily" can be interpreted as five to seven days of therapy. Programs will use their discretion in determining their approaches. The phrasing still indicates that five days are considered equivalent to seven days if the doses are observed, but there has been no comparison of five days versus seven days, so data are not available to address the point in an evidence-based fashion.
- ACET observed that the evidence profile 6 in the table shows a 3% to 9% relapse rate with intermittent therapy, which seems higher than what programs experience. Dr. Vernon said that the evidence profile was for daily therapy versus three-times-weekly throughout the duration of the intensive and continuation phases. The realm of relapse rates is consistent with the results of Study 22 and in clinical trials that use substantially intermittent therapies. The relapse rates for daily therapy seem somewhat high, but the review includes a large number of trials, including many conducted outside the US. The interest is less in the individual value for one regimen or the other, but the comparison of regimens. In this case, there was not a significant difference in relapse, but there was a difference in acquired drug resistance.
- The liaison representative from The Union commented that the last version of the guidelines were released 13 years ago and asked about plans for more timely updates in the future. Dr. Vernon replied that the revised guidelines took two and a half years to complete. It would be ideal to maintain and produce future edits to the guideline more expeditiously. There has been discussion and support regarding a living document, but it is not clear who will pay for and maintain it. There are some collaborative approaches among HHS agencies that might be appropriate, but they involve complexities of collaboration and costs.

Ms. Cole asked ACET whether additional in-depth review and comment is needed for the new guidelines. No additional comments were offered. Dr. Vernon explained that a public comment opportunity was needed for the guideline in order to satisfy agency requirements regarding guidelines that involve influential scientific information. DTBE does not seek additional action from ACET and is always open to comments from ACET members, whose views are highly valued.

Update on ACET Workgroups

Congregate Settings Workgroup
Lisa Y. Armitige, MD, PhD
ACET Member
Chair, Congregate Settings Workgroup

The Congregate Settings Workgroup has met and discussed several issues, including the use of a 12-dose regimen of weekly rifapentine plus INH (3HP) in congregate settings. A pilot study regarding 3HP in congregate settings was conducted at seven Federal Bureau of Prisons (BOP) facilities from July 2012 – February 2015. Inmates were transitioned from a regimen of nine months of INH given twice weekly to the 3HP regimen. The study documented DOT visits, weekly

symptom screenings, monthly liver function tests, and demographic, behavioral, and medical risk factors. The study group was 70% male and 67% foreign-born. Twenty percent were known contacts to a TB case, and their ages ranged from 20 to 71 years, with a median age of 36. 463 patients started on 3HP, and 92% of them completed the regimen. Thirty-nine participants discontinued: 17 due to adverse events and the rest due to loss to follow-up, refusal, or provider error. Approximately half of the patients reported at least one symptom or complaint during treatment, with 42% reporting two or more complaints. Only 17 individuals stopped treatment, however. The complaints include abdominal pain, nausea, and rash.

The study concluded that the 3HP regimen was tolerable among the population. There were significantly higher completion rates compared to the INH regimen, likely because of the transient nature of the population. Although half of inmates reported symptom complaints during the course of treatment, only 4% discontinued treatment. The completion rate was high, even among patients with co-morbid conditions, including a history of alcohol abuse and hepatitis C. 3HP is a shorter regimen that is appropriate for inmates who are transient or who have shorter stays in the BOP system, with a better opportunity to complete the regimen. The study also showed reduced costs for fewer liver function tests and reduced staff time for DOT. The BOP Health Services staff was enthusiastic about the change as well.

A study by Maria Juarez-Reyes and colleagues was conducted in a jail in Santa Clara, California. The results were published in *Open Forum Infectious Diseases*. The jail had an average population of approximately 4600 individuals, with an average length of stay of 110 days. The study goal was to determine the safety, tolerability, and completion rates of 3HP in this population. Many of the individuals had co-existing diseases and conditions, such as diabetes, current smokers, hepatitis C, and histories of alcohol or injection drug use. The study examined a historic cohort from January 2010 to December 2011 of 154 individuals who had been on nine months of INH. The 3HP cohort was studied from June 2012 through March 2014. There was an 18% completion rate for the group on the regimen of nine months of INH. The 3HP cohort achieved a completion rate of 85%, even in this more transient population. Most of the individuals who did not complete 3HP were transferred. Few individuals stopped treatment for reasons other than transfer.

Regarding 3HP in homeless populations, S. Bamrah Morris and N. Nwana provided data from a study conducted from July 2011 through December 2013. In the study, of 3327 individuals started the 3HP regimen. Of the individuals who began the study, 3288 were eligible to complete treatment, and 2389 individuals provided additional data. The use of directly observed 3HP to treat LTBI resulted in a high rate (73%) of treatment completion among homeless persons. There has been anecdotal feedback from other programs with completion rates of over 70%. TB programs should prioritize efforts and target resources in this subpopulation during treatment to optimize completion of treatment.

The incarcerated and homeless populations are fluid. Frequently, individuals are represented in both groups. When there are opportunities to treat them successfully, then those opportunities must be utilized. Especially in the BOP system, where there are longer stays, these populations can be targeted successfully.

The ACET Congregate Settings Workgroup asks that CDC embrace the use of 3HP in corrections and homeless populations. The workgroup asks that CDC develop a plan, such as providing materials messaged to individuals serving these populations, to show that this approach is

worthwhile and should be pursued. Other strategies could include giving presentations at relevant national meetings and working with individual groups.

A motion was properly placed on the floor between Dr. Lisa Armitige and seconded by Dr. Ana Alvarez to recommend that CDC embrace the use of 3HP in congregate settings and develop a plan to reach out and communicate to various groups that could implement the regimen. **The motion carried unanimously with no abstentions.**

- John Lozier from the National Healthcare for the Homeless Council indicated that group's support for the motion and willingness to help implement it was appreciated.
- Dr. Vernon asked for ACET's thoughts regarding how this recommendation could interdigitate with the nearly-completed LTBI guideline revision. Dr. LoBue said that 3HP is an option in the guideline, which has not been finalized. He noted that CDC already embraces 3HP in any population with LTBI that is susceptible to INH and RIF. The congregate settings population is considered a priority because of low historical completion rates.
- Input from members of the Congregate Setting Workgroup can be provided through the CDC representatives participating on the workgroup.

Dr. Armitage noted that the workgroup's next focus areas include concerns associated with individuals who are diagnosed with active TB disease in one agency who are transferred to another agency. The concerns include follow-up, infection control, treatment completion, and contact investigations.

TB Drug Supply Workgroup
Jennifer Cochran, MPH
ACET Member
Co-Chair, ACET TB Drug Supply Workgroup

Ms. Jennifer Cochran reported that the TB Drug Supply Workgroup was reconvened at the December 2015 ACET meeting. The focus of the group was reframed from drug shortage to a broader scope, incorporating an uninterrupted and affordable supply of essential drugs to treat TB.

Challenges associated with drug shortages and supply interruptions are woven into the workgroup's work. Affordability is a concern both for public health programs and for patients. The workgroup consists of a knowledgeable and committed group of experts, with representation from TB programs, TB clinicians, TB pharmacists, and partners and allies from the Treatment Action Group (TAG), the National Alliance of State and Territorial AIDS Directors (NASTAD), CDC, and the Public Health Agency of Canada (PHAC). The response from workgroup participants has been positive, and there is recognition of the need for the workgroup.

The workgroup has discussed several issues thus far. Regarding the drug supply, the group will consider the possibility of US access to the Global Drug Facility (GDF) drugs. Any drug available to the US market requires FDA approval. The workgroup is examining which drugs might be good candidates for bringing to the US. They have also reviewed the vulnerability chart completed and presented to ACET by Ann Cronin and Justin Davis in 2014. That chart was helpful in learning where there are single producers and which drugs could be lost if something happens to that

production. The workgroup has also considered demand. If drugs could be acquired through the GDF, how could public health programs procure and manage them, given that there are different methodologies for the process of ordering, the frequency of ordering, and the size and scale of the orders. Other considerations include the logistics of receiving the drugs from international sources and distributing them for final delivery. The workgroup appreciates the range of complexities associated with the GDF supply.

The workgroup agrees that the mini-stockpile is a welcome development, but there is concern about certain details, such as the logistics, processes for requesting drugs, and sustainability. Regarding drug costs and access, the workgroup will learn from experiences of colleagues in the HIV/AIDS arena. There are many challenges for the 340B programs. NTCA has offered comments on proposed rule changes associated with 340B and the implications of the changes. From the patient perspective, the workgroup is thinking of out-of-pocket costs, such as copays and deductibles, which prevent people from accessing an uninterrupted drug supply, whether for active TB or LTBI. If more care is given in the private sector through insurance reimbursement, there may be accompanying challenges.

The TB Drug Supply Workgroup is meeting monthly and will propose recommendations to ACET in a future meeting.

- ACET noted that the US has other stockpiles of antiviral and antibacterial agents. There was discussion regarding how they are administered, and under which agency. Dr. LoBue said that CDC investigated other stockpiles and their willingness to take on the TB drug stockpile. The other stockpiles declined, so CDC took its own approach. A Federal Supply Center in Maryland manages not only drugs, other types of devices and supplies for federal agencies, including the United States Department of Veterans Affairs (VA). This center manages the logistics of stocking drugs, shipping drugs, rotating inventory, and extending inventory life. CDC is creating a procedure manual for determining who receives the drugs and when shipping will occur. The manual will be created with input from NTCA and other groups working on drug shortage issues.
- In response to a question from ACET, Dr. LoBue clarified that all drugs in the stockpile have a shelf life. If they are not used, then they are often destroyed. This waste should be avoided. There is some ability to sell drugs that are nearing their expiration dates and to replace them with newer drugs. This approach cannot be utilized for 100% of the stockpile, but it will be done as much as possible. FDA has a process for extending the expiration date of drugs that have been kept under certain conditions. CDC will try to use this mechanism as well.
- ACET commented on the drugs that are not ordered often and that are, therefore, difficult to acquire. This issue is separate from issues of drugs that are out of stock or are not available. ACET asked about the calculation of the numbers of drugs that might be needed in a year and the ability to use the stockpile mechanism as a way to get those drugs quickly, and then to replace them when the insurer or payer completes reimbursement.
- Dr. LoBue clarified that CDC is not entering the drug supply business. As long as a drug is FDA-approved and available in the US, it can be purchased. Further, CDC cannot sell the drugs. Replacement drugs will need to be purchased when drugs are used from the stockpile.

Essential Components Workgroup

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Cole explained that the Essential Components Workgroup was reconvened. Diana Nilsen with NTCA is the co-chair. Currently, the workgroup is reviewing work that was completed in May 2013. Each chapter was assigned to a workgroup member for review and edit. By June 2016, a draft document will be reviewed by subject matter experts, with the goal of presenting it at the August 2016 ACET meeting for review and comment. At that time, ACET will be asked to provide recommendations on changes to the document and ultimately to approve the final document. Plans will be developed regarding publication of the document.

Children and Adolescent TB Workgroup

Dr. Jeffrey Starke
ACET member
Chair, ACET Children and Adolescent TB Workgroup

Dr. Starke indicated that the ACET Children and Adolescent TB Workgroup is beginning its work, exchanging emails and ideas regarding priority areas. The workgroup includes ACET members, patient advocates, and CDC representatives, who have suggested adding other members of CDC, especially if the workgroup takes on issues such as foreign adoption or other issues that are outside DTBE's purview.

Dr. Starke added that a study is ongoing of contacts is yielding information about young children. The workgroup is not calling for such a study, he clarified. The workgroup will hold a conference call in the coming weeks to set its agenda.

With no additional comments or questions, the group took a break at 2:04 p.m. and reconvened at 2:24 p.m. Dr. Dean conducted a roll call and confirmed the presence of a quorum of ACET voting and *ex officio* members.

Business Session

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Cole led the Business Section of the ACET meeting.

A motion was properly placed on the floor and seconded to accept the December 15-16, 2015, ACET meeting minutes. **The motion carried unanimously with no abstentions.**

Charter Amendment

Ms. Cole reminded ACET of the proposed wording change to the ACET charter. Dr. Dean read the current wording of the charter:

> "The Council shall consist of ten voting members including the Chair. Members and the Chair shall be selected by the Secretary from authorities knowledgeable in the fields of public health, epidemiology, immunology, infectious diseases, pulmonary disease, pediatrics, tuberculosis, microbiology, and preventive health care delivery. Members shall be deemed Special Government Employees."

The suggested change to the charter is as follows, with the proposed new sentence in italics:

> "The Council shall consist of ten voting members including the Chair. Members and the Chair shall be selected by the Secretary from authorities knowledgeable in the fields of public health, epidemiology, immunology, infectious diseases, pulmonary disease, pediatrics, tuberculosis, microbiology, and preventive health care delivery. *The exception to this requirement is that one member other than the Chair may be selected by the Secretary from persons who have had tuberculosis disease, or parents of children who have had tuberculosis disease.* Members shall be deemed Special Government Employees."

In order to change the charter, a letter must be written to the Secretary. The ACET charter is up for renewal at the end of 2016, so the proposed change will likely be included as part of the charter renewal process. The CDC Management Analysis and Services Office (MASO) indicated that the most recent charter amendment process took approximately five months.

- ACET observed that the current wording of the ACET charter refers to persons who are knowledgeable in TB. Someone who is a TB patient or a parent of a TB patient could be interpreted in that light, given their intimate knowledge and personal experience with the disease. Perhaps this avenue could be utilized to speed the process.
- Dr. Dean clarified that the original wording refers to authorities who are knowledgeable in the field and probably would not incorporate parents of children with TB. Ms. Cole added that the patient or parent member would not have to be an expert in one of the scientific areas. They will bring their personal experience with TB to ACET. There will still be ten ACET voting members. Dr. LoBue said that the new wording will make it explicit that a patient or parent will be included on ACET so that the question of whether they are classified as an "authority" will not be an issue. There will not likely be a vacant position on ACET before the end of the year.
- The liaison representative from the National Medical Association suggested that a TB patient or parent of a child with TB could still participate as an *ex officio* ACET member or liaison representative. ACET voting members vote on specific issues that are relayed to the HHS Secretary, and that position might not be appropriate for a patient or parent. Having that person serve in a different capacity could still accomplish the goal of hearing their input. Dr. Dean answered that based on the definitions of *ex officio* members and liaison representatives, a patient or parent would not qualify. Other advisory committees incorporate patients or persons impacted by the disease of interest. For example, the CDC/HRSA HIV/STD/Hepatitis Advisory Committee includes members who are

impacted by those diseases. In her years of working with them, there have not been problems with those persons understanding the issues and participating as voting members. ACET is not likely to be different. Dr. LoBue agreed and added the example of Institutional Review Boards (IRBs) that review technical and complex research studies and that include lay representatives and persons from affected communities. These participants bring important and different perspectives. The proposed charter change is in response to a request from ACET. *Ex officio* members are members based on the office that they hold in the federal government. Liaison representatives come from organizations, and there may not be such a patient organizations.

- Ms. Cole said that the TB Ambassador group is not a formal nonprofit group yet.
- ACET supported moving forward with the charter language amendment.

BSC Report

Ms. Cole shared highlights from the NCHHSTP Board of Scientific Counselors (BSC) meeting on March 28, 2016. Key topics of the meeting included an update on the CDC Syphillis Summit and action plan; discussion of the Zika virus outbreak response; highlights from the infectious disease budget and possible increases; priorities for CDC's antimicrobial resistance (AMR) work and the Congressional appropriation of approximately $168 million to fight antibiotic resistance; CARB; and a separate plan for drug resistance.

Medical Consultation Centers

Ms. Cole raised the issue of re-funding the RTMCCs and whether any changes might be made. ACET voiced no comments or concerns regarding the centers.

Advice Requested From ACET

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County (California) Department of Public Health
ACET Chair

Ms. Cole reminded ACET that DTBE had requested advice in several areas, particularly in identifying gaps, if any, in the research agenda. She recalled ACET's discussion of the need for operational research. If ACET suggests new proposals in the research agenda, elements will need to be prioritized, as there will need to be if funding remains at the same level. Input was also requested on:

- Activities to decrease the incidence of TB infections
- Decreasing morbidity and mortality from *Mycobacterium tuberculosis*
- Decreasing health disparities across groups affected by TB
- Conducting surveillance for adverse events and treatment outcomes, including post-marketing surveillance.

These topics were discussed at the previous ACET meeting. No additional comments were offered from ACET regarding the research agenda.

Ms. Cole recalled ACET's discussions regarding BARDA, such as potential collaborations and assistance from BARDA on drug supply issues associated with TB. The next steps in this area are:

- Clearly define what problem needs to be solved
- Drug shortages, diagnostics, vaccine development
- Share data that might help inform the discussions around LTBI

BARDA cannot solve the problems with drug shortages. Ms. Cole asked for comments from ACET regarding potential areas for collaboration with BARDA.

- BARDA is an HHS agency. ACET had discussed requesting that the scope for BARDA be modified to include MDR-TB and XDR-TB. This issue could be raised in the upcoming meeting with the Secretary.
- No additional comments were offered regarding BARDA.

Regarding TB in correctional settings, ACET had discussed the best ways to build strong partnerships with national corrections organizations and determining specific stakeholders for engagement and regarding which resources might best help them. Dr. Armitage confirmed that the Congregate Settings Workgroup has been working with CDC in these areas, sharing information about potential partners as well as helping to identify targets. The workgroup will report on this progress at the August ACET meeting.

ACET had identified challenges with the Webinar format, such as difficulty connecting via Live Meeting. The transition to Adobe Connect should be complete later in 2016. Regarding scheduling, ACET requested three Webinars and one in-person meeting. The next Webinar will be held in August 2016, and the in-person meeting will be held in December 2016.

- Several members of ACET indicated that they had had trouble connecting to this Webinar.
- ACET noted that the request for three Webinars was not granted. There are two Webinars in 2016. ACET will meet every four months, not every three months as requested. The gap between the meetings is longer, making it more difficult to stay abreast of events. The current scheduling represents an improvement over the previous structure, which had a six-month gap between meetings.
- ACET pointed out that if the schedule had been to meet every three months, then ACET would have met in time to provide feedback to USPSTF during the open comment period. The timing of the comment period was by chance, but if ACET met more frequently, there would be less chance that such opportunities will be missed.

Ms. Cole reviewed the motions from the last ACET meeting:

Motion	Progress
ACET recommended to CDC and the secretary of HHS to make available more resources in order to accomplish the goal of the elimination of TB.	DTBE has not received new information on this point from CDC or HHS. The FY 2017 proposed budget has no change in the TB funding allotment. Ms. Cole said that this topic may be raised in the upcoming meeting with the HHS Secretary.
Recommend that ACET form a workgroup on children and adolescents.	This workgroup was established and provided a report at today's meeting.
ACET recommends to CDC to work with the HHS Secretary's office to request an amendment to the ACET charter to allow a survivor/TB patient advocate to serve on ACET.	This item is in progress.
ACET recommend that CDC explore options to increase operational research to build an evidence base of best practices to increase the capacity within and outside health departments to increase the number of providers to reduce the prevalence of untreated LTBI in the US.	This item is under discussion (see below)

Ms. Cole asked for comments from ACET regarding possible kinds of operational research.

- ACET noted the potential research area of determining the best use of IGRAs in young children. Frequently, tools are developed, but research is not conducted on how to properly use them. NIH and many foundations do not approve funding for operational research. This kind of funding could have high impact and clear public health value. This topic could include anything and everything, such as the simple randomized trials suggested by Dr. Vernon. It would be helpful to have clear delineations regarding possible paths. Further, a clearinghouse for ideas would be helpful to the field, helping people with good ideas link to funders and supporters. Dr. LoBue concurred and added that it is unfortunate that due to the existing structures, operational research can "fall in the cracks." CDC has zero discretionary funding for TB research and would essentially need to eliminate the consortia in order to create such a mechanism. NIH has the R01 mechanism to fund investigator-initiated research, and CDC is not as well structured to do that.
- ACET suggested sharing ideas regarding operational research to TBESC. They have developed a research agenda but could potentially respond to good ideas. The sites may have data to answer some of the operational questions. TBESC can reach out to NTCA and other partners to indicate interest in such ideas. Dr. LoBue agreed that the TBESC's focus is on LTBI operational research. If an individual investigator with no relationship to CDC or the consortia wants to lead an effort, there is no existing mechanism, but TBESC does have data that could be utilized and opportunities for collaboration with existing sites. Queries can be directed to him, Christine Ho, Tom Navin, or investigators in advisory group.

- The treatment guidelines regarding bi-weekly versus tri-weekly treatment have major implications for local jurisdictions, which for the most part are doing bi-weekly DOT. Operational research on these kinds of issues could be an area for the consortia to consider. Dr. LoBue said that Tuberculosis Trials Consortium (TBTC) does clinical trials, but all of those resources have been allocated to the current trial looking at four-month therapy.
- ACET noted that in RCTs are needed to influence guidelines; most operational research is not an RCT. Operational research could influence NTCA's practical products, however.
- ACET asked about the possibility of an investigator accessing a CDC database to answer a research question, with no additional use of CDC funds. Dr. LoBue answered that it depends on the maturity and status of the database. Databases from some clinical trials have been packaged and given to groups that develop TB drug regimens. Investigators can access those data. In other cases, when studies are not complete or the data have not been clean, the databases are not ready to be shared.

- ACET recalled a plan for all of the study databases from the previous incarnation of the TBESC to be archived and made available. The plan included creating an oversight committee that investigators could apply to. Dr. LoBue said that he would assess the status of that effort. There is a great deal of work involved in meeting requirements regarding confidentiality and other requirements before data can be shared. A data set might not require an oversight committee. If it is easily transferable, then it can simply be released. The dataset must meet CDC criteria for sharing. Data from some TBTC studies were cleaned and released.
- ACET noted that the National Health and Nutrition Examination Survey (NHANES) data are available. They conducted IGRA testing, but probably not in large enough numbers to answer the operational research question.

Potential Agenda Topics for the Next Meeting

Ms. Cole said that the Agenda Setting Committee would be convened to create the next meeting agenda and asked for ACET's ideas for the agenda. Points raised included:

- Updates from DTBE regarding strategies to communicate and promote the USPSTF B rating and its implications.
- "Drilling down" on surveillance data with groups that were discussed in today's meeting, particularly the shift to increasing cases coming from Asian countries versus México. Further, learning about the availability of data on visa status to guide targeting efforts for LTBI.
- Revisit the funding formula. Dr. LoBue said that a workgroup co-chaired by Dr. Terry Chorba from CDC and NTCA has begun that process.
- Updates on data sharing and access.
- ACET suggested a follow-up on the flattening and increases of TB cases and an examination of whether MDR-TB rates are increasing widely, as the rates are increasing in some states.
- ACET suggested an update on reporting of LTBI.

- ACET suggested an update from the CDC laboratory on their molecular testing and the progress on the rapid molecular detection of drug resistance. Further, it would be useful to hear information on the use of GeneXpert® across the country, false positives of RIF resistance, and other issues.

Public Comment

Ms. Cole called for public comment at 3:16 p.m. No public comments were offered.

Meeting Adjourned

Ms. Cole thanked the attendees for their discussion and input. She reviewed additional points from the ACET meeting:

- The meeting with the HHS Secretary will focus on the importance of the public health infrastructure to moving toward TB elimination. The meeting will also include the implications for the USPSTF B rating and the expansion of LTBI screening, as well as x-rays, treatment, and other issues, and potential impacts on local health departments, especially since contacts and immunocompromised individuals are excluded. The impact of MDR-TB and XDR-TB links not only to infrastructure, but also to funding, drug supply, and TB along the US-México border. The successes in TB in correctional facilities will be highlighted, as well as the work that remains to be done. The 2000 IOM report, while 16 years old, is still relevant because it incorporates sound interventions that have not been fully implemented. We must not repeat the situation in the 1990s, when cases decreased, funding decreased, and then funding increased.
- ACET will consider ideas regarding operational research and linking investigators with appropriate resources.
- Locally, jurisdictions will consider the new treatment guidelines and the implications for increased workloads and resource demands associated with moving from bi-weekly to tri-weekly DOT.

Dr. Dean conducted a final roll call of ACET members and *ex officio* members. A quorum was present.

A motion was properly placed on the floor and seconded to adjourn the April 2016 ACET meeting. **The motion carried unanimously with no abstentions.**

The meeting stood adjourned at 3:18 p.m.

Certification

I hereby certify that, to the best of my knowledge and ability, the foregoing minutes of the April 26, 2016, meeting of the Advisory Council for the Elimination of Tuberculosis, CDC, are accurate and complete.

_____
Date

_____
Barbara Cole, RN, MSN, PHN
Chair, Advisory Council for the Elimination of Tuberculosis, CDC

Attachment 1: Participant Directory

ACET Members Present

Ms. Barbara Cole (Chair)
Dr. Ana Alvarez
Dr. Lisa Armitige
Ms. Jennifer Cochran
Dr. C. Robert Horsburgh
Dr. Eric Houpt
Dr. Jeffrey Starke
Dr. James Sunstrum
Dr. David Warshauer

ACET Members Absent

Dr. Michael Lauzardo

ACET *ex officio* Members Present

Naomi Aronson, MD
US Department of Defense

Michael Bartholomew, MD, FAAP
Indian Health Service

Amy Bloom, MD
US Agency for International Development

Kali Crosby, RN, MSN, CIC
Agency for Healthcare Research and Quality

Steven Derrick, PhD
US Food and Drug Administration

Rupali Doshi, MD, MS
HIV/AIDS Bureau, Health Resources and Services Administration

Diana Elson, DrPH, MA, CDR USPHS
US Immigration and Customs Enforcement

J. Nadine Gracia, MD, MSCE
Office of Minority Health, US Department of Health and Human Services

Stephen Martin
National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

Gary Roselle, MD
US Department of Veterans Affair

ACET ex officio Members Absent

Sarah Bur, RN, MPH
Federal Bureau of Prisons

Anthony Campbell, RPH, DO
Substance Abuse and Mental Health Services Administration

Edward Chin
US Marshals Service

Caroline Freeman
US Department of Labor, Occupational Safety and Health Administrration

Mamodikoe Makhene, MD, MPH
National Institute of Allergy and Infectious Diseases
National Institutes of Health

Bruce San Filippo, MD
US-México Border Health Commission

ACET Liaison Representatives Present

Robert Belknap, MD
National TB Controllers Association

Robert Benjamin, MD, MPH
National Association of County and City Health Officials

Jay C. Butler, MD, CPE, FAAP, FACP, FIDSA
Association of State and Territorial Health Officials

Kenyon Farrow
Treatment Action Group

John Lozier
National Coalition for the Homeless

Amee Patrawalla, MD, MPH, FCCP
American College of Chest Physicians

Susan Rappaport, MPH
American Lung Association

Randal Reves, MD
International Union Against TB and Lung Disease

Lornel Tompkins, MD
National Medical Association

ACET Liaison Members Absent

Shama Desai Ahuja, PhD, MPH
Council of State and Territorial Epidemiologists

David Bryden
RESULTS

Fran Du Melle, MS
American Thoracic Society

Mayleen Ekiek, MD
Pacific Island Health Officers Association

Eddie Hedrick, BS, MT (ASCP), CIC
Association for Professionals in Infection Control and Epidemiology

Ilse Levin, DO, MPH & TM
American Medical Association

Howard Njoo, MD, MHSc, FRCPC
Public Health Agency of Canada

Jennifer Rakeman, PhD
Association of Public Health Laboratories

Gudelia Rangel, PhD
México Section, US-México Border Health Commission

Susan Ray, MD
Infectious Disease Society of America

Michael Tapper, MD
Society for Healthcare Epidemiology of America

Tara Wildes
Jails Division, National Commission on Correctional Health

ACET Designated Federal Officer

Hazel Dean, ScD, MPH
Deputy Director, NCHHSTP

CDC Representatives

Ms. Leeanna Allen
Dr. Stuart Berman
Ms. Nwanna Bunie
Mr. Deron Burton
Ms. Tammy Cantrell
Dr. Terence Chorba
Ms. Ann Cronin
Mr. Justin Davis
Dr. Patty Dietz
Ms. Kim Distel
Mr. Jeffrey Driscoll
Dr. Wayne Duffus
Dr. Stefan Goldberg
Ms. Maryam Haddad
Ms. DeKeely Hartsfield
Dr. Michael Iademarco
Ms. Stephanie Johnston
Dr. Awal Khan
Ms. Maureen Kolasa
Ms. Kathryn Koski
Mr. Chee Kin Lam
Dr. Adam Langer
Dr. Philip LoBue
Ms. Suzanne Marks
Dr. Sundari Mase
Dr. Jerry Mazurek
Dr. Sapna Morris
Dr. Subhadra Nandakumar
Dr. Tom Navin
Dr. Kristine Schmitt
Ms. Margie Scott-Cseh
Ms. Maria Fraire Sessions
Dr. Neha Shah
Dr. Angela Starks
Ms. Dana Tumblin
Dr. Andrew Vernon
Dr. Wanda Walton
Dr. Carla Winston
Dr. Jonathan Wortham

Members of the Public

Ms. Eve Calhoun
QIAGEN

Mr. Jeff Chrismon
Northrop Grumman

Ms. Kendra Cox, MA
Cambridge Communications

Ms. Suraj Madoori
Treatment Action Group

Dr. Marlene Matosky
HIV/AIDS Bureau, Health Resources and Services Administration

Ms. Donna Wegener
National TB Controllers Association

Attachment 2: Glossary of Acronyms

Acronym	Expansion
3HP	Rifapentine Plus Isoniazid
AAP	American Academy of Pediatrics
ACA	(Patient Protection and) Affordable Care Act
ACET	Advisory Council for the Elimination of Tuberculosis
ACIP	Advisory Committee on Immunization Practices
ACS	American Cancer Society
ADA	American Diabetes Association
AFB	Acid-Fast Bacilli
AHRQ	Agency for Healthcare Research and Quality
AMR	Antimicrobial Resistance
AR	Antibiotic Resistance
ART	Antiretroviral Therapy
ATS	American Thoracic Society
BARDA	Biomedical Advanced Research and Development Authority
BCG	bacille Calmette-Guérin (vaccination)
BOP	(Federal) Bureau of Prisons
BSC	Board of Scientific Counselors
CARB	Combating Antibiotic-Resistant Bacteria
CDC	Centers for Disease Control and Prevention
CMO	Committee Management Office
CMS	Centers for Medicare and Medicaid Services
DASH	Division of Adolescent and School Health
DC	District of Columbia
DFO	Designated Federal Officer
DHAP	Division of HIV/AIDS Prevention
DoD	(United States) Department of Defense
DOT	Directly-Observed Therapy
DSTDP	Division of STD Prevention
DTBE	Division of Tuberculosis Elimination
EHR	Electronic Health Record
EMR	Electronic Medical Record
EOC	Emergency Operations Center
ERS	European Respiratory Society
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
FQ	Fluoroquinolone
FY	Fiscal Year
GDF	Global Drug Facility
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HECAT	Health Education Curriculum Analysis Tool
HEV	Hepatitis E Virus
HHS	(United States) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HRSA	Health Resources and Services Administration
IDSA	Infectious Diseases Society of America

Acronym	Expansion
IGRA	Interferon-Gamma Release Assay
INH	Isoniazid
IOM	Institute of Medicine
IRB	Institutional Review Board
LTBI	Latent Tuberculosis Infection
MASO	Management Analysis and Services Office
MCHB	Maternal and Child Health Bureau
MDR	Multidrug Resistant
MDR-TB	Multidrug-Resistant Tuberculosis
MMWR	*Morbidity and Mortality Weekly Report*
NASTAD	National Alliance of State and Territorial AIDS Directors
NCEZID	National Center for Emerging and Zoonotic Infectious Diseases
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
NHANES	National Health and Nutrition Examination Survey
NTCA	National Tuberculosis Controllers Association
OI	Opportunistic Infections
PAHO	Pan American Health Organization
PHAC	Public Health Agency of Canada
PICO	Population, Intervention, Comparators, Outcomes
PrEP	Pre-Exposure Prophylaxis
RCT	Randomized Controlled Trial
RIF	Rifampin
RPT	Rifapentine
RTMCC	Regional Training and Medical Consultation Centers
SAT	Self-Administered Therapy
STI	Sexually Transmitted Infection
SUNY	State University of New York
TAG	Treatment Action Group
TB	Tuberculosis
TBESC	Tuberculosis Epidemiologic Studies Consortium
TBTC	Tuberculosis Trials Consortium
The Union	International Union Against TB and Lung Disease
TST	Tuberculin Skin Test
UCSF	University of California, San Francisco
USAID	United States Agency for International Development
USPSTF	United States Preventive Services Task Force
VA	(United States Department of) Veterans Affairs
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant Tuberculosis