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

Virtual Meeting of the
Advisory Council for the Elimination of Tuberculosis
December 14-15, 2021

Record of the Proceedings

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ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
December 14-15, 2021

Minutes of the Virtual Meeting

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC), National Center for HIV, Viral Hepatitis, STD and TB Prevention (NCHHSTP), Division of Tuberculosis Elimination (DTBE) convened a virtual meeting of the Advisory Council for the Elimination of Tuberculosis (ACET). The proceedings were held on December 14-15, 2021 beginning at 10:00 a.m. Eastern Time (ET).

ACET is formally chartered under the Federal Advisory Committee Act (FACA) to provide advice and recommendations to the HHS Secretary, HHS Assistant Secretary for Health, and the CDC Director regarding the elimination of tuberculosis (TB). The charter authorizes ACET to make recommendations regarding policies, strategies, objectives and priorities; address the development and application of new technologies; provide guidance and review of CDC's TB Prevention Research portfolio and program priorities; and review the extent to which progress has been made toward TB elimination.

Information for the public to attend the virtual ACET meeting via webinar or teleconference was published in the *Federal Register* in accordance with FACA regulations and rules. All sessions of the meeting were open to the public (*Attachment 1: Participants' Directory*).

December 14, 2021 Opening Session

Marah E. Condit, MS
Public Health Analyst, Advisory Committee Management Lead
Office of Policy, Planning, and Partnerships
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Deron Burton, MD, JD, MPH (CAPT, USPHS)
Deputy Director, National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control & Prevention
ACET Designated Federal Officer (DFO)

Robert Belknap, MD
Medical Director, Denver Metro Tuberculosis Control Program, Denver Public Health
ACET Chair

Ms. Condit called the meeting to order at 10:00 am EST on December 14, 2021 and provided meeting instructions. Dr. Burton welcomed participants and conducted a roll call to confirm the attendance of ACET voting members, *ex-officio* members, and liaison representatives. He announced that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. He reminded ACET voting members of their responsibility to disclose any potential individual and/or institutional conflicts of interest (COI) for the public record and recuse themselves from voting or participating in these matters.

ACET Voting Member Institution/Organization	Potential Conflict of Interest
Amina Ahmed, MD Levine Children's Hospital at Carolina Medical Center	No conflicts
Robert Belknap, MD Denver Metro Tuberculosis Control Program	No conflicts
Lisa Chen, MD University of California, San Francisco	No conflicts
David Horne, MD, MPH University of Washington School of Medicine	No conflicts
Lixia Liu, PhD, MP, (ASCP), D(ABMM) Indiana State Department of Health	No conflicts
Ann Loeffler, MD Multnomah County Oregon	No conflicts
Lynn Sosa-Bergeron, MD Connecticut Department of Public Health	No conflicts
Kristine Steward-East Advocate for Tuberculosis	No conflicts
Jason Stout, MD, MHS Duke University Medical Center	No conflicts
Zelalem Temesgen, MD Mayo Clinic Center for Tuberculosis	No conflicts

The roll call confirmed that the 22 voting and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 14, 2021. The roll was called subsequent to each break and lunch, with quorum established each time throughout the day.

Dr. Burton welcomed the following new members and *ex officio* members to ACET:

- Dr. Robert Belknap, incoming ACET Chair and Medical Director of the Denver Metro Tuberculosis Control Program.
- Dr. Lisa Chen, Medical Director and Principal Investigator (PI) of the Curry International Tuberculosis Center (CITC) at the University of California, San Francisco.
- Dr. Lynn Sosa-Bergeron, Deputy State Epidemiologist with the Connecticut Department of Public Health and Medical Director of the Tuberculosis and Sexually Transmitted Diseases Program.
- Dr. Jason Stout, Professor of Medicine in the Division of Infectious Diseases at the Duke University Medical Center in Durham, North Carolina. Dr. Stout also serves as the TB Controller and Medical Director for the State of North Carolina's TB Control Program.
- CAPT Edith (Edie) Lederman, Infectious Disease Program Lead for the US Immigration and Customs Enforcement (ICE) Health Service Corps (IHSC).
- The new NCHHSTP Advisory Committee Management Team: Marah Condit, Lauren Barna, and Becca Pope Alley.

In Addition, Dr. Burton made the following announcements:

- An addendum to the June 2020 ACET meeting minutes was published on June 10, 2021 and now includes the *Roadmap for Advancing TB Elimination in the United States Through Scale-Up of Testing and Treatment of Latent TB Infection*.[1] This content has been linked to the DTBE internet site to increase public accessibility.
- The response to the June 24, 2021 letter from the ACET Chair to HHS Secretary Becerra is currently being routed through HHS, with a response anticipated to be sent shortly.

Dr. Belknap welcomed members and participants to the virtual ACET meeting, emphasizing that a very full agenda had been planned for both days.

NCHHSTP Director's Report

Jonathan Mermin, MD, MPH (RADM, USPHS)
Director, National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Mermin welcomed everyone and presented the NCHHSTP update. He recognized that COVID-19 was ongoing in the background, especially for everyone focused on respiratory infections. At this time, the US was in the midst of a resurgence of COVID-19. While that started before the Omicron variant began circulating, it almost certainly would continue in that trajectory over the next few weeks and there would be a resulting need for improved public health efforts and new technologies for better control. It is disappointing for everyone working in public health to have COVID-19 continuing for 2 years, and also takes a toll on staff. It is tiring to continually have to care for people who can be so seriously ill knowing that there are preventive measures. NCHHSTP generally has 6% to 7% of its staff formally deployed at any one time, along with informal work that other staff are engaged in related to COVID-19. Some of the other centers

[1] https://www.cdc.gov/tb/publications/ltbi/pdf/Roadmap-for-Advancing-TB-Elmination.pdf

within the agency are even more involved. While this is what the public health system was built for, it teaches them that they could have done better.

Within the framework of human immunodeficiency virus (HIV), NCHHSTP published the first *Vital*signs™ under the new Administration.[2] This highlighted the trajectory of HIV incidence among men who have sex with men (MSM) stratified by race and ethnicity. This publication essentially showed that even though there were declines overall, most of those declines were among White MSM. Incidence among Black/African American MSM was stable to slightly reduced, but was increased among Hispanic/Latino MSM. This article also examined some of the underlying process indicators such as time to linkage to care, viral suppression, and other factors that could lead to why these differences might be occurring and what might be done as a nation to continue the trends in the populations where there are decreases to reverse the trends among Hispanic/Latino MSM.

NCHHSTP also published a recent HIV surveillance report[3] which showed that between 2015-2019, there was a decrease of about 9% in HIV diagnoses, including a reduction of 33% in the previously highest affected group of young gay and bisexual men. The South continues to be disproportionately affected compared to other regions in the country. While the overall incidence rate of HIV among persons who inject drugs (PWID) has been relatively stable, there continue to be very large outbreaks among PWID. These are difficult to control and take a great deal of time for local health departments, communities, and CDC staff.

New Medical Monitoring Project (MMP) data are available.[4] These data showed slight improvement in a variety of measures such as higher viral suppression rates, increasing proportion of people using pre-exposure prophylaxis (PrEP) in the prior year at about 25%, and other measures. However, these have not achieved the levels estimated to be necessary to reach the end of the HIV epidemic, defined as fewer than 3000 cases of new infections a year. The trajectory is encouraging to some extent, with some disparities getting better and others getting worse. It is important to speed up this process. To some extent this is similar to the language used for TB in that it is getting better, but it is not fast enough.

In terms of continued commitment to HIV prevention, President Biden recently announced the new *National HIV/AIDS Strategy (2022-2025)*[5], which details a roadmap to ending the epidemic by 2030. In many ways, this has the same 4 pillars as the prior strategy (e.g., making sure people are diagnosed, that people are linked to/accessing ongoing treatment, that people have prevention modalities available to them, and that outbreaks are detected and responded to more effectively). It also includes a more explicit discussion of reducing inequities within HIV, thinking about social determinants of health (SDOH), and using policy as a public health tool. CDC also issued two new cooperative agreements. One is focused on supporting community-based organizations (CBOs) and the other is focused on research related to Ending the HIV Epidemic (EHE).

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[2] https://www.cdc.gov/vitalsigns/hivgaybimen/index.html
[3] https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-32/content/national-profile.html#Diagnoses
[4] https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-special-report-number-28-factsheet.pdf; https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html
[5] https://www.hiv.gov/federal-response/national-hiv-aids-strategy/national-hiv-aids-strategy-2022-2025

A nice example of applied research being brought to scale is a public-private partnership to increase access to HIV self-tests. For the past dozen years, CDC has been involved in an initially randomized trial and evaluations[6] of sending people self-tests over the internet. This program initially focused on MSM and transgender women. There also has been exploration of targeting this to particular communities using the internet so that people from the EHE jurisdictions in particular would be able to access and order these tests. This began well before COVID-19 but became more relevant during COVID-19 because people were not getting screened as much through routine HIV screening because they were not visiting clinics as frequently. Some of the CBOs had to reduce their activities related to HIV either because concerns about COVID-19 or due to disruption in their services because of the pandemic and control factors. The study showed initially that it was very cost-effective to do this and that people used and liked the Food and Drug Administration (FDA)-approved oral or fingerstick tests.

CDC also is collaborating on a project called TakeMeHome, which also did HIV self-test distribution with MSM that was very successful. Over the past 6 months, there was a goal to distribute about 100,000 HIV tests through the internet. From February 2021-July 2021, 43,568 online orders were placed for 76,232 HIV self-test kits. Data show that people found this to be useful, effective, and to bring HIV testing to people who did not have it previously. Therefore, consideration is being given to what this means as a large-scale modality combined with other HIV testing efforts to bring testing to people who need it—especially those who need it frequently or are unable to get it per CDC guidelines.

In terms of viral hepatitis, the Association of Public Health Laboratories (APHL) brought together experts for a discussion on *Identifying High-Priority Diagnostics Approaches for Advancing Hepatitis C Elimination in the United States*. Hepatitis C diagnostics are fairly complex and in need of new technologies. In addition, the FDA has decided to reclassify two Hepatitis C tests from Class III to Class II. It is extremely expensive and prohibitive for many testing companies to bring new technologies to the US market, even when they are available in other countries. The reclassification from Class III to Class II promises to make it easier for new technologies. This conference had a discussion session about what tests might be prioritized and how they could be useful. There also is a larger scale diagnostics conference upcoming, the *2022 Advancing HIV, STI, and Viral Hepatitis Testing Conference*, which will be convened March 29, 2022 – April 1, 2022.

CDC is in the process of updating its hepatitis B virus (HBV) vaccination recommendations. This has been a risk-based recommendation for adults, even though it is also universal for infants. This was based on the continued incidence of HBV among adults, particularly those who use drugs and also others, and the inability to turn that around with risk-based recommendations. The Advisory Committee on Immunization Practices (ACIP) took time in the middle of COVID-19 to evaluate the data presented to them and make these recommendations, which hopefully will reduce new infections and some of the analyses showed that it would be cost-effective to do so. On November 3, 2021, the ACIP voted unanimously to approve the following recommendations, with release of an official *MMWR* update expected in Spring 2022:

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[6] https://www.cdc.gov/mmwr/volumes/70/wr/mm7038a2.htm

- ❑ The ACIP recommends the following groups **should** receive hepatitis B vaccines:
    - Adults 19 through 59 years of age
    - Adults 60 years of age and older with risk factors for hepatitis B infection

- ❑ The ACIP recommends the following groups **may** receive hepatitis B vaccines:
    - Adults 60 years of age and older without known risk factors for hepatitis B infection

Regarding the STD update, Dr. Leandro Mena started as the new Director of the Division of STD Prevention (DSTDP). Dr. Mena is highly experienced in STDs and most recently was an academic conducting studies in health equity and STIs and HIV. Prior to that, he ran the STI program for the State of Mississippi.

CDC received $1 billion in Disease Intervention Specialists (DIS) Workforce Development Funding over a 5-year period to support 21st century outbreak response needs by: 1) expanding and enhancing frontline public health staff; 2) conducting DIS workforce training and skills building; 3) building organizational capacity for outbreak response; and 4) evaluating and improving recruitment, training, and outbreak response efforts. The dual purpose was to tackle the COVID-19 crisis by ensuring that there are staff who can conduct the kind of investigations needed, and also to build back the staff to be able to do this in general for other infectious diseases. The hope is that these core staffing resources could have benefits for TB programs, which could be an area of discussion for ACET and certainly within NCHHSTP. Some of the resources provided will be designated for developing a research consortium to foster innovation and improvements in DIS activities and operations. [7]

Over the last decade, congenital syphilis has diffused across the nation. By 2019, 43 states and the District of Columbia (DC) reported at least one case. As of last year, there have been over 1000 congenital syphilis cases across the country. This is putting a strain on STI programs in states. Congenital syphilis is the most serious clinical manifestation of syphilis, including stillbirths, infant deaths, and long-term cognitive impairments and malformations in children. While more resources have been invested in this, it is not possible to turn the corner without a holistic approach of decreasing syphilis more broadly.

New STI treatment guidelines have been issued.[8] These take an enormous amount of time, but are highly used guidelines. Key highlights of the updated guidelines include: updated recommendations for treatment of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*; addition of metronidazole to the recommended treatment regimen for pelvic inflammatory disease (PID); expanded risk factors for syphilis testing among pregnant women; one-time testing for hepatitis C infection; and additional flexibility for Expedited Partner Therapy (EPT) for MSM.

[7] https://www.cdc.gov/std/projects/DISday.htm
[8] https://www.cdc.gov/std/treatment-guidelines/intro.htm

In terms of adolescent and school health updates, results from a new study show the positive impact of CDC programs.[9] Dr. Mermin said he thought this was one of the most creative evaluations that CDC has done of its programs over time. The Division of Adolescent and School Health (DASH) chose local educational agencies and schools based on having areas where there were high rates of infections or negative health behaviors among students, with the idea that those would be the areas that needed interventions the most. After 2 years, students in schools that implemented the DASH-funded program were less likely to: have ever had sex; have more than four lifetime sexual partners, or be currently sexually active; miss school; experience forced sex; ever use marijuana; and/or currently use marijuana. Not only were the data convincing, but also reached nearly 2 million students costing less than $10 per student. There are a lot of ideas about what it would mean to expand this to the country in order to continue to improve the health of youth.

CDC's school health infrastructure is also being leveraged to support students. Additional Coronavirus Aid, Relief, and Economic Security Act (CARES Act) funding is being allocated to school districts for mental health support in order to increase staff capacity, increase student and family access to mental health services, and enhance safe and supportive environments. A recent Surgeon General's Report[10] titled *Protecting Youth Mental Health: The U.S. Surgeon General's Advisory* tried to bring attention to the youth mental health crisis. CDC is able to conduct an online survey and some interventions with some of the COVID-19 resources that have been available. Nationally representative student data and online survey panels are being used to try to understand the impact of COVID-19 on health, mental health, and well-being. There also are research and evaluation projects to assist schools, students, and families in coping with and recovering from the adverse impacts of the pandemic.

ACET Discussion: NCHHSTP Director's Report

Dr. Belknap inquired as to whether there were specific ways in which Dr. Mermin saw the additional DIS funding and perhaps other funding to help build back the public health infrastructure, particularly the infrastructure for TB.

Dr. Mermin pointed out that there has been a large increase in attention for the need of building back a stronger public health system. There are other resources outside of NCHHSTP that are focused on that, such as resources for surveillance and other types of activities to build up other types of infrastructure and human resources. The DIS resources specifically were focused on contact tracing and case investigations, and he thought they were provided to NCHHSTP because the center supports the main extent of that in terms STI, HIV, and TB even though health departments investigate salmonella outbreaks as well for instance. The idea is that this is an opportunity to have a more holistic approach. They have been interested in DIS certification, courses, and the concept of what it would mean to be a case investigator more broadly and perhaps even with some subspecialty efforts related to certain diseases. The idea would be to support health departments in general and give them the flexibility to hire staff and focus them in the areas where they have the greatest gaps. Some of that is to help with outbreaks. For instance, there is an ongoing TB outbreak where building up that health department's TB staffing infrastructure even just a little could be beneficial because this has been persistent over

[9] https://www.sciencedirect.com/science/article/pii/S1054139X21004006?dgcid=coauthor&ACSTrackingID=USCDC_2024-DM65804&ACSTrackingLabel=September%202021%20DASH%20Partner%20Update&deliveryName=USCDC_2024-DM65804&s_cid=em-NCHHSTP-DU-202109300002

[10] https://www.hhs.gov/sites/default/files/surgeon-general-youth-mental-health-advisory.pdf

time. When surveyed, about half of health departments have stated that they still have staff who are partially or fully focused on COVID-19. The impact on the health department varies depending upon whether they are at a state or local level and how badly they have been affected by COVID-19. There are opportunities for health department TB programs to see this as a method for improving services. That said, the overall amount of $200 million is not as great as it sounds in terms of the cost of each staff person from a national perspective. Nevertheless, it could help—especially combined with some of the other resources that might be provided if a stronger public health system is built back.

Dr. Ahmed asked if/what HIV efforts are being focused specifically on the adolescent population, such as extending TakeMeHome or PrEP to populations below 18 years of age. Even though CDC recommends testing any teen for HIV who presents to the medical system in any way, a lot of teens seem to seek primary care in the emergency department (ED). For that reason, her ED has incorporated a focus on adolescent testing.

Dr. Mermin indicated that DASH focuses almost exclusively on people in middle and high school, so there are many efforts in that setting. CDC's PrEP guidelines allow PrEP use for individuals younger than 18 years of age. Mailing a self-test is limited to adults at this point. It is important for certain groups such as youth to have a routine system implemented so that risk factors do not have to be considered, because that does not tend to work as well. There are other populations for whom that is fine. For instance, MSM are recommended to get tested at least once a year and for many every 3 to 6 months depending on risk. For youth, it is really important to add this on to routine tests that might be for something else. This can be especially helpful for STIs, a large proportion of which are still occurring among people under 18 years of age. Even adults can feel shy about discussing testing and PrEP. NCHHSTP has become increasingly interested in the ability of new diagnostic technology to make it easier. Having an FDA-approved self-test means that HIV testing can be done, but this is not available for other infections. There are not even point-of-care (POC) testing for some infections. The same thing happens at the clinical level. Routine screening has become easier, especially with large-scale high-throughput machines, but it still has to be requested. Even if testing or screening is set up with automatic standing orders, a person has to meet certain factors to trigger that. Preventive care is not always of the same urgency as curative care.

DTBE Director's Update

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

Dr. LoBue updated ACET on surveillance; selected latent TB infection (LTBI) activities; clinical trials; whole genome sequencing (WGS), drug susceptibility testing, and host-directed therapies; and guidance documents. Beginning with 2021 TB cases counts now 2 years into the COVID-19 pandemic, another substantial decrease in TB cases is not expected based on reported cases so far. It is important to understand that there tends to be a lot of reporting at the end of the year, which could change things. Provisional case counts are anticipated in 6 to 8 weeks. Publication is planned for March 2022 as is usually done around World Tuberculosis Day, and there will be a presentation to ACET during the June 2022 meeting. Another important

area for surveillance has been updating the *Report of Verified Case of Tuberculosis (RVCT).*[11] While this was originally scheduled for 2020, because of COVID-19 this has been delayed a couple of times. The goal now is to get this completed in 2022, depending upon whether the programs will be able to do this given all of the COVID-19 deployments and efforts.

With regard to selected LTBI activities, one of the areas of work over the last few years has been to increase efforts in the area of community and provider engagement. The LTBI Campaign has been progressing, for which Leeanna Allen would present more details later in the day. Dr. LoBue described a related activity, the TB Elimination Alliance (TEA). The TB Elimination Alliance is a national partnership of community leaders dedicated to increasing knowledge, testing, and treatment of TB and LTBI among Asian American, Native Hawaiian, and Pacific Islander communities. The goals of the TEA are to: 1) conduct outreach to communities most affected by TB; 2) increase awareness and understanding of LTBI testing and treatment strategies; 3) share resources and best practices among providers; and 4) develop partnerships to scale existing initiatives. This is modeled on a program developed by the Division of Viral Hepatitis (DVH) called Hep B United. The key activities for TEA have been allocation of mini-grants of about $10,000 each that have helped to jump-start some activities in local jurisdiction, technical assistance (TA) and training, a learning collaborative so groups can learn from each other, a partner summit, and a communications campaign. Another area related to LTBI is operational research. The major work currently is the TB Epidemiologic Studies Consortium III, which is in its third iteration and on which Laura Vonnahme would present later in the day.

In terms of the clinical trials update, a number of efforts have been underway within the Tuberculosis Trials Consortium (TBTC). Study 31 has been presented to ACET previously. The focus of this study is on rifapentine (RPT)-based 4-month treatment regimens for drug-susceptible TB. Additional analyses include 18-month follow-up and pharmacokinetic studies, which are in progress and should be seen in print fairly soon. Study 37 focuses on a 6-week RPT treatment for LTBI and Study 35 is a pediatric formulation of RPT and isoniazid (INH) for LTBI treatment, for which enrollment has been restarted. While Study 37 started slowly, the hope is that more sites will be brought online in the next few weeks to months in order to start ramping up enrollment. Study 38, known as CRUSH, is looking at 2 novel 4-month regimens for TB disease. Those have been moving through regulatory reviews, including a meeting with the FDA and submission for Institutional Review Board (IRB) approval, with goal to start enrollment in 2022 once regulatory reviews are completed.

With regard to WGS, drug-susceptibility testing (DST), and host-directed therapies (HDT), the TB Genotyping Information Management System (GIMS) has been released and now has the functionality to request, track, and deliver WGS single nucleotide polymorphism (wgSNP) analyses on patients to state and local TB program users. Another key piece of this effort is the implementation of a whole genome multi-locus sequence typing (wgMLST) scheme for cluster detection and a naming convention for national surveillance through TB GIMS. There are now results for 27,540 samples, which have been shared with state and local users. In addition to the molecular epidemiological piece, there is the potential to use some of this information for initial DST. The group is analyzing the results that have come out of WGS to determine whether growth-based phenotypic DST could be reduced with more routine use of rapid molecular-based DST in the US.

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[11] https://www.cdc.gov/tb/programs/rvct/default.htm

In the realm of DST, there are some newer drugs and ways need to be found to make that testing available. Regarding the addition of Bedaquiline (BDQ) DST, very few laboratories in the US perform testing for BDQ. This gap needs to be filled given its use for treatment of multidrug-resistant tuberculosis (MDR-TB). DTBE's laboratory participated in 2 studies sponsored by Janssen using the 7H9 broth microdilution method. The validation of that has been performed in compliance with Clinical Laboratory Improvement Amendments (CLIA) requirements. In the second or third quarter of 2022, the DTBE laboratory plans to add minimum inhibitory concentration (MIC) testing as routine. This will begin with reporting on BDQ, linezolid, clofazimine, levofloxacin, and moxifloxacin. Another newer drug is Pretomanid (Pa). The DTBE laboratory has been working as part of a global consortium participating in a surveillance program sponsored by TB Alliance to examine the potential resistance of this drug. CDC is conducting MIC testing of Pa in isolates from approximately 100 US MDR-TB patients per year. This method is the Becton, Dickinson and Company (BD) Mycobacterial Growth Indicator Tube™ (MGIT™) system.[12] This is the initial step, but the ultimate goal is for this to be available for clinical testing as part of the DTBE reference laboratory.

Another interesting and important project that the laboratory has been working on is the novel "Mycobacteria-in-Spheroid" 3-D granuloma bioplatform for rapid screening and characterization of anti-TB therapeutics. Some information on this has been presented previously during ACET meetings in terms of HDT. The first step taken by the immunology group in the laboratory was to develop an in vitro 3-D tuberculoma model, with which they were able to demonstrate has a lot of the same characteristics as human granulomas. They felt that this would be an even more useful model for in vitro testing of drugs rather than traditional 3-D cell culture models. With that, they started to screen a library of drugs that already were FDA-approved for other purposes to determine whether any of them potentially could be repurposed for TB treatment. They looked at many classes of drugs (e.g., anti-inflammatory, anti-depressant, anti-cancer, anti-allergy, anti-parasitic, anti-fungal). They found that most of the 465 drugs did not have any effect on reduction of TB bacterial burden in this 3-D model. Approximately 8% of drugs increased the bacterial burden (e.g., immunosuppressive, anti-cancer, anti-parasitic, anti-diabetic). A substantial number of drugs reduced the bacterial burden in the 3-D in vitro model. While most of those were modest in reducing bacterial burden in the 25% to 75% range, 9% of the drugs reduced the bacterial burden by greater than 75%. Those would have potential either on their own or more likely combined with traditional TB antibiotics to reduce the burden further and potentially have clinical use.

The next step is to move from the in vitro 3-D granuloma model into to investigations of HDT drugs (n=30) in the mouse model with low dose *M. tuberculosis* aerosol infection. The group is going to conduct 4 sub-experiments in infected C3Heb/FeJ mice with HDT treatment by daily drug gavage in infected mice for 3 weeks in an Animal Biological Safety Level-3 (ABSL-3) laboratory. They are focused on selecting the drugs that performed well in the in vitro model to look at the microbiology in terms of reduction in bacterial burden), immunology, ribonucleic acid (RNA) sequencing, histopathology, high-dimensional flow cytometry, and drug pharmacokinetics (PK) and pharmacodynamics (PD) in the serum. The hope is to identify some of these drugs that are already FDA-approved for other purposes that may have utility and ultimately could find their way into human clinical trials.

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[12] https://www.bd.com/en-uk/products/diagnostics-systems/identification-and-susceptibility-systems/mgit-(mycobacteria-growth-indicator-tube)-system

With respect to guidance documents, *Bedaquiline, Pretomanid and Linezolid (BPaL) for XDR/Difficult MDR-TB* was presented during the ACET meeting in December 2020. It is currently in the late stages of clearance, with publication anticipated on the website in December 2021 or January 2022. There are still some comments that need to be addressed. While these will not impact the substance, it may push publication closer to January 2022. One of the reasons the decision was made to publish the guidance on the website is because it will need to be updated in the near future based on the preliminary results of several clinical trials involving use of BDQ, Pa, and/or linezolid that could alter future recommendations. Posting on the website will facilitate moving reasonably quickly when those trials are peer-reviewed and published. The draft guidance of *Study 31 Regimen for Treatment of Drug-Susceptible TB* would be presented later in the day by Dr. Wendy Carr, for which the current projected publication is the first quarter of 2022 if everything goes smoothly. In terms of the use of electronic directly observed therapy (eDOT), Dr. Joan Mangan would provide a presentation later in the day on the final results of the CDC/New York City (NYC) study. Given that this study is soon to be published, planning for development of guidance based on the results hopefully can begin in 2022.

ACET Discussion: DTBE Director's Update

Dr. Sosa-Bergeron asked whether there was any ongoing work for adding any of the DST panels to the molecular detection of drug resistance (MDDR) test panel that CDC does.

Dr. LoBue indicated that the goal would be to have those available for both molecular testing and culture-based testing. CDC is now moving more toward MICs for the culture-based, which traditionally has not been done.

With regard to the BPaL data and guidelines having been available for over a year, Dr. Stout asked whether any thought had been given to how the guideline process could be accelerated. This is information that clinicians need and it seems like the delays are impeding the ability to disseminate information in an appropriate and timely fashion. Other guidelines also have taken a very long time. The clearance process seemed to be the "800 pound gorilla" and he wondered whether there was anything ACET could do to promote revisions in order to streamline the process, given that it is impeding the scientific and public health processes.

Dr. LoBue agreed that it would be nice to get these completed faster. COVID-19 impacted the BPaL guidelines, which probably would have been months ahead if not for the pandemic. Unfortunately, the people who were leading this effort who have the clinical expertise were called out almost continuously into COVID-19 work. It is not easy to substitute people in and out, because a lot of time is lost bringing people up to speed. Having said that, the process still should be faster. There is a fairly long clearance process within CDC and the rules are not going to change around that element, which does add time to the process. In anticipation of additional information being forthcoming on BPaL, the plan to post this electronically will make it easier to incorporate revisions and should result in faster dissemination than going through publication of an *MMWR*. CDC is aware of concerns with the length of the clearance process. There was a recent internal review of the clearance process and the length of time it takes. While potential changes are under consideration, it is not clear how much that would impact guidelines because guidelines require extensive clearance with division-level, center-level, and CDC Office of Science-level clearance. Although this takes a long time and ACET generally can recommend whatever the members feel is appropriate, CDC is unlikely to be open to changing major procedures with regard to the process for guideline clearance at this point.

In terms of the WGS, Dr. Liu observed that most of the TB assessments are from isolates sent into the genotyping laboratory. Given technological advances, many local state laboratories are able to do this work. She asked whether Dr. LoBue foresaw extension of the WGS methods in use within DTBE at the local level.

Dr. LoBue indicated that this is being considered, given that many resources are being made available such that state and local laboratories can adopt these technologies to conduct their own WGS. He emphasized that while he is always careful about predicting the future, he thinks ultimately there probably will be some type of hybrid system in which numerous sites will be able to perform their own sequencing and provide CDC with the sequences. Other sites will continue to need the service made available to them. A plan and smooth transition are needed to achieve that goal, and there are internal discussions about how that can be done.

Dr. Belknap requested additional information about the TEA mini-grants program in terms of whether this is a sustainable process that will continue, and whether there is a plan for dissemination of the information outside of that network.

Dr. LoBue said he thinks the TEA has done a great job, but everything depends upon funds ultimately. Ideally, he would like to see the TEA expanded beyond the current focus on Asian American, Native Hawaiian, and Pacific Islander communities to engage with other groups with disparities such as Hispanic Americans and US-born African American communities. This is the hope depending upon funding. As part of that effort, they would like to see the mini-grants continue. While the mini-grants involve small amounts of funding under $10,000, it has helped get efforts started at the local-level. For instance, these funds may pay for a part-time person who can engage a community health center that serves these populations to connect them to testing. The funds can be used for training and education of providers, engage in outreach with community leaders, et cetera. These small amounts of money have gone a surprising long way, which they would like to continue.

Study 31 Regimen Guidance

Wendy Carr, PhD
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Dr. Carr presented an update on Study 31 regimen guidance. Summary study results were presented to ACET and were published earlier in 2021 in the *New England Journal of Medicine* (*NEJM*). As a reminder, Study 31/A5349 (ClinicalTrials.gov NCT02410772) was an international, open-label, Phase 3 non-inferiority clinical trial sponsored by CDC and conducted in collaboration with the National Institutes of Health (NIH)-sponsored AIDS Clinical Trials Group (ACTG). The results of Study 31/A5349 demonstrated that 4-month daily treatment regimen with high-dose rifapentine (RPT) and moxifloxacin (MOX) is as effective as (non-inferior to) standard daily 6-month regimen in curing drug-susceptible TB. In terms of the study design, 2,516 participants were randomized at 34 clinical sites in 13 countries (829 Control, 838 RPT, and 849 RPT-MOX). There were 3 arms with the participants randomized equally into either the control arm or 1 of 2 investigational arms. The control arm was a standard 6-month regimen of daily treatment with isoniazid,

rifampicin, ethambutol, and pyrazinamide (HRZE) followed by 4 months of HR. The two investigations arms were each 4 months in duration. The RPT arm was 2 months of isoniazid rifapentine, ethambutol, and pyrazinamide (HPZE) followed by 2 months of HP. The RPT-MOX was 2 months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide (HPMZ) followed by 2 months of HPM. All treatments were given daily 7 days a week and 5 out of 7 doses were given by directly observed therapy (DOT). The rifapentine dose was 1200 mg and the moxifloxacin dose was 400 mg. RPT was given with food and RIF was given without food. All participants were followed for 18 months post-randomization, and the primary efficacy endpoint was assessed at 12 months post-randomization.

The inclusion criteria for study enrollment were a positive sputum smear for acid-fast bacillus (AFB) or positive Xpert MTB with medium or high result; age ≥12 years; if HIV-positive, CD4 T-cell count of ≥100 cells/mm3; and receipt or planned initiation of efavirenz-based antiretroviral therapy (ART).The exclusion criteria were >5 days of TB treatment within the previous 6 months; >5 days treatment with anti-TB drugs within the previous 30 days; known history of prolonged QT syndrome; TB of the central nervous system (CNS), bones or joints, miliary, pericardial; weight <40 kg; or pregnant or breastfeeding. Among the enrolled participants, the baseline characteristics were well-balanced across study arms with 71% males, 2.7% adolescents 12-17 years of age, 62% adults 18-25 years of age, 35% adults greater than 35 years of age, 8% people living with HIV with a median CD4 count of 344, 73% with cavitation on X-ray, and a median weight of 53 kg.

In terms of the efficacy results for the 4 populations from Study 31/A5349, the microbiologically eligible population included all participants who received a treatment assignment. The assessable population was a subset of the microbiologically eligible population and excluded participants who experienced an event unlikely to be related to their intervention. The other 2 populations were the per protocol 95% and the per protocol 75% populations. RPT-MOX was shown to be non-inferior in all populations based on the results for the 12-month primary outcomes. However, the results are very similar for the 18-month outcomes and were recently presented at the Union Conference in October.

For the safety analysis, the only exclusions were for those participants who never started study medication. The analysis population included 825 Control (2HRZE/4HR) participants and 846 RPT-MOX (2HPZM/2HPM) participants. The primary safety outcome was the proportion of participants with Grade 3 or higher adverse events (AEs) during study drug treatment, which occurred in 19.3% of the Control participants versus 18.8% of the RPT-MOX participants. The adjusted difference in proportion (95% CI) is -0.6 (-4.3, 3.2). Secondary safety outcomes were as follows:

- ❑ Treatment-related Grade 3 or higher AEs, which occurred in 9.8% of Controls versus 12.9% in the RPT-MOX group.
- ❑ Tolerability (discontinuation of treatment for a reason other than microbiological ineligibility), which occurred in 7.9% of Controls versus 7.0% of the RPT-MOX group.
- ❑ Any serious adverse events (SAEs) during study treatment, which occurred in 6.8% of Controls versus 4.4% in the RPT-MOX group.
- ❑ All-cause death during treatment and follow-up, which was 1.4% in Controls versus 1.5% in the RPT-MOX group
- ❑ Liver enzyme abnormalities, including ALT or AST elevations, for which there were no difference across groups.

Now turning to draft CDC guidance development. The current CDC guidelines, *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis*, were published in October 2016.[13] This guidance describes treatment for the intensive phase of 2 months of treatment (3-4 drugs), followed by continuation phase of 4 months (2 drugs). The interim guidance presented during this session describes a 4-month regimen developed by an internal CDC/DTBE committee with feedback by individual subject matter experts (SMEs). The expert panel individually reviewed and provided written comments. The web supplement is under development to provide background and practical information for patients and clinicians.

The draft guidance recommends the 4-month RPT-MOX for treating patients who are 12 years of age and older with a body weight at or above 40 kg, who have pulmonary TB caused by organisms not known or suspected to be drug-resistant and who have no contraindications to this regimen. Treatment consists of an intensive phase composed of 8 weeks of daily treatment with RPT, INH, PZA, and MOX and a continuation phase of 9 weeks of daily treatment with RPT, INH, and MOX. Anti-TB drugs should be administered once daily with food 7 days per week for a total of 119 treatment doses. Similar to the standard 6-month regimen, at least 5 daily doses per week should be administered under direct observation. The draft interim guidance follows for dosing, guidance recommendation, considerations, evaluations, duration and definition of completion of therapy, and poor treatment response or discontinuation follow:

Dosing Recommendations

Medication	Body weight, kg	Dose	Intensive phase	Continuation phase	Total doses
Rifapentine	≥40	1200 mg	7 days/week for 8 weeks (56 doses)	7 days/week for 9 weeks (63 doses)	119
Isoniazid	≥40	300 mg			
Moxifloxacin	≥40	400 mg			
Pyrazinamide	40-<55	1000 mg			
	≥55–75	1500 mg			
	>75	2000 mg			

[13] Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, Chaisson LH, Chaisson RE, Daley CL, Grzemska M, Higashi JM, Ho CS, Hopewell PC, Keshavjee SA, Lienhardt C, Menzies R, Merrifield C, Narita M, O'Brien R, Peloquin CA, Raftery A, Saukkonen J, Schaaf HS, Sotgiu G, Starke JR, Migliori GB, Vernon A. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195.

Draft CDC Guidance Recommendation

- ❑ The 4-month regimen **can be used** in HIV-positive individuals with CD4 counts ≥100 cells/μL receiving or planning to initiate efavirenz as part of their antiretroviral therapy (ART) regimen in the absence of any other known drug-drug interactions between antituberculosis and antiretroviral medications.

Draft CDC Guidance – Considerations

- ❑ The 4-month regimen was not studied in and CDC **does not recommend** this regimen for the following patient groups:
  - Body weight below 40 kg
  - Less than 12 years old
  - Pregnant or breastfeeding
  - Suspected or documented extrapulmonary TB (e.g., TB involving the central nervous system, bones, joints, pericardium, or miliary TB)
  - History of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications (in addition to moxifloxacin)
  - Receiving HIV protease inhibitors, HIV integrase inhibitors, HIV entry and fusion inhibitors, or HIV nonnucleoside reverse transcriptase inhibitors other than efavirenz
  - With a baseline *M. tuberculosis* isolate known or suspected to be resistant to rifampin (RIF), INH, PZA, or fluoroquinolones
- ❑ The 4-month regimen was not studied in and CDC recommends that clinical consultation be obtained to determine if this regimen is an acceptable treatment option for the following patient groups:
  - Increased risk of *M. tuberculosis* resistance to any drug in the regimen including persons who received:
    - more than 5 doses of treatment directed against TB in the prior 6 months
    - more than 5 doses of latent tuberculosis infection (LTBI) treatment in the prior 6 months
    - more than 5 doses of treatment with any one or more of the following drugs for any reason (e.g., urinary tract infection, pneumonia) in the prior 30 days:
      → INH, RIF, rifabutin, RPT, PZA, or any fluoroquinolone
  - Serum or plasma alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 3 times the upper limit of normal or total bilirubin more than 2.5 times the upper limit of normal, or with preexisting advanced liver disease
  - Renal insufficiency or end-stage renal disease, or with serum or plasma creatinine level more than 2 times the upper limit of normal
  - Plasma potassium level less than 3.5 meq/L
  - Specimen unable to be submitted for any M. tuberculosis resistance testing prior to initiating treatment
- ❑ The 4-month regimen was not studied in patients with a negative sputum culture, but who in the judgment of the clinician likely represent paucibacillary or low mycobacterial burden pulmonary TB disease
- ❑ A 4-month regimen for smear-negative, culture-negative, noncavitary TB exists in current CDC guidelines and CDC recommends that the 4-month rifapentine-moxifloxacin regimen may also be used unless patients are in one of the non-recommended patient groups

Evaluations - Microbiology

- ❑ During treatment, a respiratory specimen for acid-fast bacilli smear microscopy and culture should be obtained at baseline and at monthly intervals
- ❑ Baseline molecular drug susceptibility testing for rapid identification of mutations associated with resistance to at least RIF, INH, PZA, and fluoroquinolones (FQ) is advisable
- ❑ Phenotypic DST should follow with a panel to include at least RIF (as surrogate for RPT), INH, PZA, and MOX as the preferred fluoroquinolone
    - CDC's Division of Tuberculosis Elimination Laboratory (TBLab@cdc.gov) can assist with identifying laboratories to perform this testing for TB programs that intend to implement the 4-month regimen.

Evaluations – Imaging

- ❑ Chest radiograph
    - At baseline for all patients
    - At month 2 if baseline cultures are negative
    - End-of-treatment chest radiograph is optional
- ❑ Electrocardiogram (ECG) is not routinely recommended for all patients; it should be done if clinically indicated

Evaluations – Clinical Assessments

- ❑ Weight:
    - Monitor weight monthly to assess response to treatment
    - Adjust pyrazinamide dose if needed
- ❑ Symptoms, adverse events:
    - Improvement in TB symptoms
        - e.g., cough, fever, fatigue, night sweats
    - Development of medication adverse effects
        - e.g., jaundice, dark urine, nausea, vomiting, abdominal pain, diarrhea, anorexia, dizziness, seizures, fever, rash, malaise, neuropathy, arthralgias, tendinopathy, heart palpitations, irregular heartbeat, weakness, syncope
- ❑ Adherence

Evaluations – Laboratory Testing

- ❑ Liver function tests (LFTs): ALT, AST, bilirubin, alkaline phosphate
    - Only at baseline unless:
        - abnormalities at baseline
        - symptoms consistent with hepatotoxicity develop
        - patients who chronically consume alcohol, take other potentially hepatotoxic medications, or have viral hepatitis or history of liver disease, HIV infection, or prior drug-induced liver injury
- ❑ Platelet count
- ❑ Creatinine
- ❑ Potassium, calcium, magnesium
    - Baseline; further monitoring if baseline abnormalities or as clinically indicated

Evaluations – Baseline Laboratory Testing

- ❑ HIV testing in all patients
  - CD4 lymphocyte count and HIV RNA load if positive
- ❑ Hepatitis screening for all patients per CDC guidelines
- ❑ Diabetes screening for all patients
  - Fasting glucose or hemoglobin A1c for patients with risk factors for diabetes according to the American Diabetes Association
  - For patients with diabetes, glucose monitoring is indicated
- ❑ Pregnancy testing for women of reproductive age
  - Women of child-bearing potential should be advised to practice barrier contraception method or non-hormonal intrauterine device or abstain from heterosexual intercourse during treatment

Duration and Definition of Completion of Therapy

- ❑ The 4-month regimen considered complete based on total number of doses taken (119)
  - Recommended treatment duration is independent of any cavitation on baseline chest radiograph
- ❑ Duration of Therapy
  - Intensive phase doses (56) should be administered within 70 days from treatment initiation
  - Continuation phase doses (63) should be administered within 84 days from intensive phase completion, so that the regimen is completed within 5 months
- ❑ If these targets are not met, the patient should be considered to have interrupted therapy and managed as described in CDC drug-susceptible TB treatment guidelines
- ❑ Confirmation of continued susceptibility to all drugs in the 4-month regimen is required prior to restarting this regimen

Poor Treatment Response or Discontinuation

- ❑ Patients with any positive culture at completion of 2 months of therapy, with or without ongoing symptoms, should be carefully evaluated to identify the cause of delayed response
  - Mycobacterial isolates obtained after 2 months should be sent to a reference laboratory for DST
  - If drug resistance to INH, RIF, PZA, or any FQ is detected by any testing method (phenotypic or molecular) in baseline or follow-up specimens, the 4-month regimen should be stopped, and patients should be started on appropriate treatment regimen that accounts for identified drug resistance pattern
- ❑ Women who become pregnant while on treatment should stop the 4- month regimen and be treated with an alternative regimen that is considered safer for pregnant women

To summarize, the 4-month rifapentine-moxifloxacin regimen is a treatment option for patients 12 years and older with drug-susceptible pulmonary TB. Additional studies are needed to understand the pharmacokinetics and efficacy of the 4-month regimen in patients for whom this regimen is not currently recommended, including young children, pregnant persons, patients with extrapulmonary TB, and HIV-positive patients taking non-efavirenz based ART. Clinicians should carefully review a patient's clinical history, concurrent medications, social determinants of health, and risk factors for adverse drug reactions in making the decision to use this regimen.

ACET Discussion: Study 31 Regimen Guidance

Dr. Stout pointed out that in considering implementation of the guidance, there are key factors outside the science that he wondered if CDC was considering. The first regards cost in that this regimen's 340B price is 20-fold more expensive than standard 6-month treatment. Every TB program he knows of across the country has a shrinking budget. The second regards logistics. RPT has been in shortage many times over the last few years. This regimen requires continued access and supply of drugs to be successful. The third issue is fluoroquinolone resistance testing, because these drugs are so commonly used for other indications. This also pertains to some of the previous talks on surveillance of resistance. It is known that molecular surveillance for fluoroquinolone resistance is about 80% sensitive and is not routinely tested for as part of the first 5 panels. Therefore, he wondered whether fluoroquinolone resistance surveillance would be coupled with this regimen.

Dr. LoBue agreed that these are all valid points and concerns. This is being recommended as an option rather than a replacement or preference. It will be up to clinicians and programs to decide whether this regimen is right based on the patient. Consideration is being given to cost in terms of direct program costs, direct patient costs, societal costs, et cetera. The numbers he has seen initially from DTBE's group are nowhere near 20-fold. The issue with logistics and RPT supply is a potential issue, which ultimately will be dependent upon what Sanofi decides to do in terms of ramping up supplies. It also will depend upon demand more from the global perspective than the US. Even if there was substantial uptake of this regimen in the US, the US does not have so many cases that it would affect the global supply. Conversely, a lot of global uptake could have an impact on the US. There have been issues with just about every drug, so that could be a problem regardless of the regimen. Fluoroquinolone testing has to be available in programs planning to use this regimen. With the advent of expanded molecular testing and MDDR, that can be dealt with. Many laboratories are now developing these molecular capacities.

Dr. Chen said she has heard a lot from programs that are considering implementing this 4-month regimen in terms of the costs. She also appreciated that the CDC laboratory probably would not be able to handle numerous MDDR and liked the potential for regional laboratories to take this on. While the test exists, many do not have access to it. GeneXpert® has a cartridge that rapidly can do fluoroquinolone traditional testing, but it is difficult to get in many states in the West. It would be interesting to have DTBE and TBC to advocate for some of the global innovations to which others have access for domestic use.

Dr. LoBue emphasized that it often comes down to financial issues. In addition, those types of things have to go through FDA approval for availability/use in the US. The companies always ask whether the US market is worth the cost of having to go through FDA approval. The sad part about it is that when a lot of these things initially were developed, the funding source was the US government. There is not an existing mechanism, carrot or stick, to make that happen. If Sanofi decides RPT is not worth it from an economic standpoint, they could decide to stop manufacturing it.

Dr. Loeffler asked about the potential for using this regimen for other intrathoracic diseases such as intrathoracic lymphadenopathy and how many people in the trials had this or other extrapulmonary diseases.

Dr. Carr indicated that in developing the guidance, they were thinking about what the science demonstrated.

Dr. LoBue added that there probably were not enough patients to analyze this in order to get a valid conclusion and he did not think they had the data to go beyond the guidance as proposed.

Dr. Burzynski noted that molecular testing for drug susceptibility was mentioned in terms of Study 31, but mention was made that in addition there also should be a standard DST. He wondered why that was included, given that it is easier for them to get the molecular test now. As part of their normal algorithm they can get the MOX results from molecular testing fairly quickly. For the DST, they would have to venture outside of their normal algorithm because they do not have quinolines and the MGIT™ testing. They would have to set up traditional plating, which they do not do for drug-susceptible TB. That would be an additional step, so he wondered what the reason was for that or if it is a tradition that stuck. Regarding Dr. LoBue's presentation, he also wondered about the BPaL guidelines that would be forthcoming. The regimen has gained in popularity. Although the initial study was conducted on patients with XDR-TB or maybe some patients with MDR-TB, many programs in the US have adopted BPaL for use in patients who do not fall under those categories. He wondered whether there would be room in the guidance to discuss this.

Dr. Carr said that it was about envisioning certain circumstances. It was a matter of looking at how things traditionally have been done, so they were trying to address the most common scenario. It would be helpful to try to address various scenarios.

Dr. LoBue added that from the CDC's standpoint, they have to write recommendations that are based on the science. Clinicians may believe that a certain regimen works in situations outside of a limited FDA approval based on their experience, but the guidance must be based on the data. The initial FDA recommendation was based on 100 patients. Some of the abstracts are on the order of 30 patients. They are aware of some observational data, but the numbers are small. Data are still being collected, but the small numbers makes it difficult to draw definitive conclusions. He believes other clinical trials that have not yet been published that do have broader indications have the potential to support expansion of the recommendations. Clinicians have to decide for each individual patient what the limits of guidelines and recommendations are, because they cannot cover every situation and sometimes there are no data to apply to their situation.

Dr. Reves inquired as to whether it would be feasible to track implementation with the RVCT database. It seems like there is a need for Phase 4 evaluation. Without a tremendous amount of funding, it seems like it would be feasible to conduct such an evaluation with clinicians for lymphatic disease.

Dr. LoBue indicated that the 2009 RVCT is fairly limited. If people change things, it would be impossible to track. The next version and some of the ancillary efforts may be able to improve upon that, but he would have to look at the surveillance to determine the feasibility of that.

Regarding BPaL and its rollout in the US, Dr. Chen said she appreciated the clinician sitting in the room with the patient in terms of thinking about how study data and off-label use might apply to that patient. She thought at some point in the new year, there likely would be an equal number if not more patients in the US on the BPaL regimen compared to the mixed trial. The "horse is out of the barn" in terms of the rollout of having those one-on-one conversations. There have been some efforts to informally collect data, but it would have significant impact on domestic programs to fund researchers who conduct operational research to help support.

Dr. LoBue emphasized that resources are very limited and that CDC cannot do everything, especially since the agency has been fairly level-funded over the last 20 or so years. People can apply for grants from other agencies that have large amounts of money and are willing to fund investigator-initiated studies. Study 31 was done in a reasonable amount of time because NIH and DTBE were in a situation during which they had downtime between studies.

Dr. Belknap wondered whether the costs of susceptibility testing were included in the modeling of this, and agreed with the desire to utilize local/regional laboratories for the susceptibility testing versus trying to process everything through the CDC laboratory. Consideration must be given to how to garner resources to better address TB in the US.

Dr. LoBue responded that the analyses are still underway, so they are not ready to present the data publicly on this yet. This has been raised as something that should be considered, though it has not been added yet. They will have direct cost to the program such as the cost of medications, DOT visits, and other testing. Additional testing would add to that. There also will be societal costs. While this is not directly to the program, this impacts patients as well and must be considered when treating patients. It is not just all about the program. Ultimately, there would be a formal cost-effectiveness analyses, which would take longer. They are charged with serving the public and society, so it is a fair consideration.

TB Epidemiologic Studies Consortium

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Ms. Vonnahme provided an update on the Tuberculosis Epidemiologic Studies Consortium (TBESC), which began in 2001 with a mission to assist TB Elimination efforts in the US by designing and conducting epidemiological research studies to answer the most important questions to guide policy and practice. Since the beginning, TBESC has been a partnership with CDC and TB health departments and academic institutions. The first iteration of TBESC-I (2001-2011) consisted of about 30 individual research projects, each of which had different PIs and partners and the studies had no central theme and instead covered a wide range of topics (e.g., molecular epidemiology of MDR-TB, TB infection among specific high-risk groups, et cetera). TBESC-II (2011-2021) included programs in 11 states and that program ended in September 2021. The approach in TBESC-II was more centralized and was to identify and inform comprehensive strategies for elimination with a 3-pronged approach, including: 1) identifying better diagnostics; 2) improving testing and treatment of high-risk populations in TB programs; and 3) engaging with community health clinics serving high-risk populations.

The new cycle of TBESC-III (2021-2026) launched in October 2021. This contract differs in that it is for approximately 5 years rather than 10 years. In addition, the scope of partners has been expanded to include those in primary care settings. To provide some background that sets the stage for the mission and objectives of the TBESC-III contracts, it is estimated that 5% (14.1 million persons) of the US population has LTBI. Given that 80% of TB cases are attributed to LTBI reactivation, identifying and treating persons with LTBI is a critical step for achieving elimination. Non-US-born individuals are at higher risk for TB infection, with 70% of reported TB

cases in the US occurring among non-US-born persons. That is about 14 times higher than the US-born population. DTBE has done a lot of work with TB clinics and health departments to describe TB infection, testing, and prevalence. However, it is known that populations receive care in other settings such as primary care and community health clinics. Therefore, the work with TBESC-III has shifted toward how to best implement interventions to improve adherence to TB screening guidelines and subsequently increase TB screening and LTBI treatment in practices outside the health departments.

The mission of TBESC-III is to assist TB elimination efforts in the US centered on LTBI in high-risk non-US-born populations in primary care settings. The objective is to use implementation science to identify primary care interventions that increase LTBI targeted testing and treatment that are both effective and efficient. The specific aims are to: 1) identify primary care settings serving non-US-born persons at risk for LTBI; 2) collect retrospective and prospective electronic medical record (EMR) data; 3) design and implement clinical care-based interventions to improve performance measures across the LTBI care cascade; and 4) monitor and evaluate intervention performance over time to identify efficient and effective strategies that can be deployed across the US. Over the course of the 4.5 year TBESC-III work plan, sites will design and propose interventions that improve adoption of CDC LTBI recommendations. This includes increased targeted testing of non-US-born populations, the use of interferon-γ release assays (IGRAs) for TB testing, and the use of "preferred" rifamycin-based short-course treatment regimens for LTBI.

Data collection for TBESC-III is focused on collecting unified data among all sites to monitor and evaluate intervention implementation along the LTBI care cascade. There are two components of data collections for the study, the first of which is EMR data. Sites will map their existing EMR data to a CDC EMR data dictionary and submit data quarterly to CDC. The second component is cost data, for which sites will identify and map cost data to a CDC cost data dictionary and submit data to CDC every 6 months. The anticipated long-term outcomes expected for TBESC-III include: 1) increased availability of policy-based screening programs; 2) increased percentage of non-US-born populations screened for LTBI; 3) increased treatment completion for LTBI; 4) decreased progression from LTBI to TB disease; and 5) decreased incidence of TB disease in the US.

Sites were selected based on several criteria. They had to be a primary care setting. They had to have access to non-US-born target population and serve at least 10,000 unique patients from this population per year who were born in countries with at least 10 TB cases per 100,000 in the United States.[14] They had to have the ability to implement and monitor interventions along the LTBI care cascade. They had to have an existing EMR system for data collection, modification, and data extraction and submission to CDC. A very strong group of institutions was selected, with staff at these sites having a strong relationship with CDC already and long histories of great research. TBESC-III was launched in October 2021 with the following 4 sites:

[14] Tsang CA, Langer AJ, Kammerer JS, Navin TR. US tuberculosis rates among persons born outside the United States compared with rates in their countries of birth, 2012–2016. Emerg Infect Dis. 2020;26:533–40

- ❑ Denver Health and Hospital Authority (DHHA)
  - PI: Bob Belknap; DHHA Primary Care
- ❑ Kaiser Foundation Research Institute
  - PI: Jacek Skarbinski; Kaiser Permanente Northern California (KPNC)
- ❑ Public Health – Seattle & King County
  - PI: Masa Narita; International Community Health Services (ICHS)
- ❑ The Regents of the University of California, San Francisco
  - PI: Priya Shete; North East Medical Services (NEMS)

In terms of the timeline from the launch of the contracts in October 2021 through the end of the contracts in March 2026, the focus of the base period from October 2021-March 2023, the focus is on accomplishing start-up activities, including electronic submission of EMR and cost data and report templates. Start-up activities include establishing memorandums of understanding (MOUs) as necessary, submitting the protocol for the intervention design to CDC, creating site-specific work plans, and conducting kick-off meetings. All of the MOUs have been submitted and the site-specific kick-off meetings have been completed. For the electronic submission of the EMR and cost data during the base period, sites will provide documentation of mapping to standard variables, with CDC providing standard variables and formats.

Sites also will be required to submit data for a minimum 12-month baseline EMR cohort, as well as baseline cost data. Data will be transferred securely via the Secure Access Management Services (SAMS) portal and uploaded into the TBESC-III data pipeline. As of December, CDC already has provided the standard variables and formats in the form of an EMR data dictionary and templates for the data documentation procedures and data mapping. In addition, the CDC team has been working internally for many months to develop the data pipeline for receipt of data from sites starting with the sample data in March 2022. Several reports templates will be due during the baseline period, including the baseline reports, implementation and monitoring reports, and evaluation reports. The main deliverables overall for the base period include a minimum 12-month baseline EMR data cohort, baseline cost data, a baseline LTBI care cascade report, a cost data collection plan, and an intervention and implementation plan. Sites also must have a CDC-approved monitoring and evaluation report template. Sites must implement and start monitoring interventions no later than 12 months from award, which will be October 2022.

Moving into the Option Periods 1-3 from March 2023-March 2026, all interventions must already have been implemented and have been continuously monitored. In addition, all reports and EMR and cost data will be routinely submitted to CDC. This includes implementation monitoring and evaluation reports, as well as EMR and cost electronic data submissions to CDC SAMS. The final deliverables during Option Period 3 include final reports and evaluation of the interventions, plus final electronic data submissions. The aim is for at least one peer-reviewed journal article per site, as well as contributions to other consortium member publications. In terms of a broad overview of the entire timeline for the contact, EMR and cost data will be collected and submitted throughout the 4.5 year contract starting in 2022. After the intervention has been implemented, sites also will be submitting quarterly implementation, monitoring, and evaluation reports.

Overall, this work is a part of NCHHSTP's framework for *Improving Recommendation-Based Screening in Healthcare Settings*. The development of this contract was guided by collaborations across NCHHSTP, including the FOCUS study, hepatitis, and HIV intervention projects. There are some possible challenges with TBESC-III. This is a new and unique way of operating the consortium. These are all diverse sites and clinics that are all implementing semi-

independent studies. There is not a single protocol across all of the sites, which may present new coordination challenges. For the first time, the CDC team is providing technical assistance (TA) for implementation science. That is a skill they all have been gearing up to provide. EMR data are large, complicated, and can be clinic or EMR system-specific. It is anticipated that this may pose many challenges related to standardization, as well as defining the LTBI care cascade. However, the CDC team has considerable experience working with EMR data which they are using to develop a robust EMR data dictionary for the sites to use. In addition, some newer technology (Azure Cloud and EDAV) at CDC is being used for the first time to manage these very large datasets. It has been a big lift to initiate the data pipeline, so the need to continue to troubleshoot problems is anticipated as they arise once CDC starts to accept data from the sites.

TBESC-III also has a lot of strengths. Sites will provide a diverse sample for understanding real-world primary care interventions. While EMR data has a lot of challenges, it is a very rich data source for understanding changes over time, EMR-based improvements, and longitudinal patient data to identify gaps in LTBI care cascade and specific risk factors for TB infection. In addition, TBESC-III will emphasize the use of implementation science to produce actionable intervention models that can be implemented in a variety of settings to actually prevent TB among persons at risk. A smaller number of awarded sites and a multi-year, but not too long, a follow-up period allows for flexibility and collaboration with an ability to make adjustments to intervention designs and see improvements to the care cascade over time. The cost-effectiveness component of TBESC-III will ensure that interventions are effective, practical, and efficient to implement given available resources. This should make them more accessible to sites outside of TBESC-III.

ACET Discussion: TB Epidemiologic Studies Consortium

Dr. Ritger asked if consideration was given to whether West Coast and Mountain area participants might be applicable to the entire US population. In addition, she inquired as to what specific sub-populations or sub-analyses might be accomplished with the non-US-born populations.

Ms. Vonnahme replied that geographic location was not taken into consideration. While the results from TEBSC-III may not be generalizable to all of the US, the goal is to focus on a specific population of non-US-born persons. All of the selected sites have a population that is known to be at high-risk and they all are on the West Coast, but the hope is that they still will be applicable to a site in the South or on the East Coast if the population is similar to those on the West Coast. All 4 sites see a lot of non-US patients, they are more specific to race and ethnicity and the clinics see more refugees. For instance, the KPNC site sees a lot more of the Asian population. In terms of sub-populations or analyses, they would like to assess the Asian-American population. They also are interested in non-US-born individuals in the context of how long they have been in the US in terms of their risk factors. People tend to progress to TB disease within the first 2 years, but they would like to assess other potential factors that affect that as well. Beyond that, they also are very interested in assessing the very complex screening recommendations to ascertain whether they are actually identifying people at risk, whether they need to be as complex as they are, whether they are outdated, and whether there are other risk factors that are more important.

Dr. Belknap asked whether there were questions for ACET with regard to the TBESC-III iteration that might be helpful or supporting for ACET to try to help provide. He wondered whether there are others within CDC within the branch and/or within other branches that are doing similar work with large EMR databases where there could be cross-collaboration or discussions. He noted that all of the TBESC-III sites are using Epic platforms, which is the predominant system across the US, but he asked whether there is experience with other non-Epic systems.

Ms. Vonnahme pointed out that while they do have some experience with a large EMR dataset, they are still learning about EMR data in terms of how to identify someone who has TB or LTBI within an EMR. Anyone with a wide breadth of experience with EMR data, especially on the back end and with the nuances, the team would welcome hearing individual experiences to ensure that they capture the appropriate numerators and denominators. In terms of cross-collaborations or discussions within CDC, they are part of a group within NCHHSTP that is engaged in clinical-based interventions to enhance screening recommendations across CDC for HIV and hepatitis. The most work has been done for hepatitis in terms of exploring clinical interventions and implementing them in the EMR such that there will be automatic orders for hepatitis B or C based on an individual's specific risk factors. A lot of knowledge has been gained from them in terms of what has been most successful in terms of increasing screening among their high-risk populations. The limitation is that their interventions are often in a smaller setting, such as a single clinic where a standing order is a much more doable process than in a very large network. Unfortunately, TB and LTBI are complex with regard to identifying cases and make this very unique in terms of trying to mine EMR data. HIV and hepatitis are more straightforward. Ms. Vonnahme said she would have to ask about experience with other non-Epic systems. Every Epic system is also very specific to each clinic. Even if an EMR alert is implemented in a clinic in California, a clinic a few miles away also using the Epic platform could have a completely different interface and structure. That is another issue that makes EMRs challenging.

Dr. Benjamin, Stop TB USA, suggested partnering with the diabetes community. For instance, Dick Brostrom has done some seminal work in diabetes and TB. This represents very "low-hanging fruit" in terms of prevention.

Ms. Vonnahme thought this was a great idea, though they have not worked specifically with him at the CDC-level. The reason they wanted to select sites with primary care clinics for TBESC-III was because they also see other diseases such as diabetes. Having a clinician who is aware of the connection with diabetes and TB would be helpful. The TBESC-III sites are the first step into partnering with a clinical population where diabetic patients are also seen. A lot of those variables have been incorporated into the EMR data dictionary, so they are looking for International Statistical Classification of Diseases (ICD) codes for individuals who have diabetes. The hope is to incorporate that into the analyses to determine risk and address this for diabetics if that becomes relevant as well.

In response to Dr. Chen's question about whether they also would be looking for hepatitis co-infection, Ms. Vonnahme indicated that hepatis ICD code variables were included in the EMR data dictionary.

LTBI Campaign

Leeanna Allen, MPH
Communications, Education, and Behavioral Studies Branch
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Ms. Allen provided an update on the LTBI Communications Campaign. The campaign graphics, materials, and resources shown were still under development and were not yet ready for distribution. The campaign is called “Think. Test. Treat TB.” A consumer communications campaign is fairly new for the TB world. The campaign goals are to: 1) raise awareness about latent TB infection, risk, and the link between LTBI and TB disease in order to address misperceptions, decrease stigma, and encourage testing and treatment; 2) increase awareness of treatment for LTBI, especially shorter regimens; and 3) encourage healthcare providers to test and treat LTBI among populations at risk.

Given that there are limited resources for this campaign, the objective is to determine what will and will not work well. The campaign audiences are people born in the Philippines and Vietnam who are 20-64 years of age who consume ethnic media occasionally or regularly. In addition, it is important to reach their healthcare providers (HCP), including primary care providers, family providers, internal medicine providers, physician’s assistants, nurses, and patient educators who serve populations at risk. The markets for paid media distribution primarily will include distribution in Seattle, Washington and Los Angeles, California. Some distribution channels may be nationwide and/or statewide, depending on the platform. All of the materials that are developed will be available nationally on the CDC website.

Development of the campaign began a few years ago, with a focus on it being data-driven and based on the needs of the community. From 2019-2020, 12 focus groups sessions were conducted with consumers and HCP (e.g., physicians, providers, nurses, other HCP). Earlier in 2021, the campaign concept was tested with those same focus groups to ensure that the campaign was answering their questions and meeting their needs. For a couple of insights into the responses, people have an awareness of TB and generally have some knowledge about it. However, there is very little awareness that TB can be inactive or latent. A lot of terminology also was tested that could be used to describe LTBI. For consumers, the word “inactive” made a lot of sense to them over the word “latent.” People generally did not know what “latent” meant, but “inactive” made sense in the sense that it could become active. There is a lot of confusion around what is and is not contagious. The COVID-19 pandemic has affected general attitudes on health concerns, with people using terms like “contact tracing” and “infectious disease” in focus groups now that those have become part of the vocabulary due to the pandemic.

Numerous barriers were identified that may need to be addressed through campaign. There are misperceptions about testing or vaccinations. Participants did not know one could have TB even if they have been vaccinated or know the TB vaccine could weaken over time. Participants expressed a strong sense of cultural pride and resisted messaging that separated them because of their heritage. They do not want to be targeted due to a fear of stigma that also has been reflected during the pandemic. The things that can motivate people to get tested and complete treatment include family safety, especially in terms of preventing the spread of a deadly and dreadful disease. TB’s prevalence in certain communities and the potential for

“hidden” LTBI also were identified as motivating facts. Ease of treatment and low cost could be a motivator as well.

In terms of provider awareness and knowledge, physicians mentioned that the biggest indicator of someone who may be at risk is if they are from a country with high TB prevalence, while nurses (prescribing and non-prescribing) and physician’s assistants (PAs) were faster to associate the risk with immunocompromised individuals. Most physicians and prescribing nurses who said they recommend LTBI treatment are at least somewhat familiar with shorter treatment regimens, but acknowledge that treatment adherence is a challenge. A number of barriers also were identified among provider audiences. There is a perception that the prevalence of TB and LTBI in their practices is low. There are challenges with their patients’ mindsets that stem from cultural factors. Environmental and structural barriers, such as time and a number of other priorities, deprioritize LTBI testing for providers. With regard to motivators, what worked for providers were messages that tied testing for LTBI as a way to help curb the spread of TB, particularly among vulnerable patient populations. Messages with a clear call to action acknowledging physicians’ role in TB elimination was a motivator. Having screening tools and educational materials for patients to help them better communicate with patients and the ability to give them information if a visit ran short.

The campaign concept of “Think. Test. Treat TB.” is about making TB testing a part of things that are done every day to prevent disease in the same way as blood pressure checks, tests for diabetes, cholesterol tests, et cetera. This concept addresses the ways in which people at risk minimize the existence of TB and fail to see it as a serious issue. Healthcare providers often do not include testing and LTBI treatment during check-ups. It will be critical for patients and providers alike to “check the box” in terms of thinking about the risk factors and talk about TB, testing for TB infection, and treating LTBI to prevent the development of TB disease. In terms of a high-level overview of campaign implementation activities, it is anticipated that the campaign will be launched in early 2022 beginning with engaging partners and distributing the campaign, having the website go live. Earned and paid media will kick in around World TB Day in March. There will be another push in May through the Summer around Asian American and Pacific Islander Heritage Month in May.

To reach consumer audiences, there are a few strategies. The idea is to meet consumers where they are, so a lot of the marketing for some of the print and additional materials will be targeted to out of home venues such as supermarkets, shopping centers, grocery stores, clinics, and other places where people in the community spend time using static, mobile, and digital signage. There also are plans to use social media (Instagram and Facebook), digital ads (display banners and video), YouTube (video displayed on various devices), television (Filipino Channel, Crossings TV, Little Saigon), and print (in-language publications). Providers indicated that they look to professional journals, medical websites, and provider education resources as good channels that they visit fairly regularly. Consideration is being given to advertising with digital ads on the American Academy of Family Physicians (AAFP) website, the *Journal of Primary Care and Community Health* (*JPC*), Medscape, state medical association websites in Washington and California, and other provider association channels. Providers also will be a very important way to reach provider audiences. With a reminder that these were drafts and not to be shared, Ms. Allen showed several samples of the campaign public service announcements (PSAs), digital materials, social media messaging, print materials, and educational materials.

As part of these materials, a partner toolkit will be developed with resources, materials, and other customizable assets such as the following:

- ❑ Key messages
- ❑ Quotes from CDC, State, Local SMEs to be used in communication materials and/or media outreach
- ❑ Social media assets
- ❑ Newsletter / blog content
- ❑ Educational materials
- ❑ Campaign resources sheet
- ❑ Co-signed letter from CDC, Local/State Health Departments, and other TB partners with more information on TB resources and about key partners (i.e., TEA, TB Centers of Excellence)

CDC will be engaging a lot of its existing partners through the TB Centers of Excellence, national partners, state and local partners, and the TB Alliance. CDC partners can amplify campaign messages to reach intended audiences and extend the impact of the consumer campaign. CDC is also looking at the campaign as an opportunity to engage new partners such as Seattle- and Los Angeles-based organizations and medical associations, national medical organizations and societies, and the Asian American and Pacific Islander medical associations and groups.

In terms of evaluation of the campaign, baseline data came from proxy data sources such as campaign formative research and pilot testing, TBESC patient/provider interviews, styles audience surveys. For process evaluation, metrics will be tracked across distribution channels in all markets during campaign implementation in order to track awareness, reach, and engagement. An effort will be made to assess whether there is an opportunity to demonstrate behavior change, which is somewhat of a challenge since the campaign will be in the field for a fairly short amount of time. Impact evaluation will be focused on the Seattle market and will be done through consumer and provider surveys to ascertain whether any evaluation data can be tied back to the campaign focused on behavior change. Impact evaluation questions will assess the following:

- ❑ Exposure to the campaign
- ❑ Attending to campaign (recall of provided information)
- ❑ Comprehending contents / generating related cognition (perceived risk)
- ❑ Credibility / agreeing with campaign messages
- ❑ Decisions and rationale for decisions related to campaign messages
- ❑ Actions taken / behavioral intentions in response to the campaign
- ❑ Advising others to take action

ACET Discussion: LTBI Campaign

Regarding an inquiry from Dr. Belknap about whether these activities are aligned and coordinated with the TEA, Ms. Allen indicated that they have been working closely with TEA since the beginning of the campaign. Some of the key partners observed a lot of the focus groups in the early stages of the campaign and provided some input, particularly on how to reach provider audiences in community health clinics. A lot of TEA members come from that area. They also had several sessions with TEA for them to look at the provider and patient education materials and some of the overall campaign planning and ideas and provide input. They received some very helpful input, such as making sure that some of the digital assets

would be appropriate to share on clinic digital signage, making sure that materials are translated, and ensuring that materials are short and concise as possible. TEA also will be a very important partner in terms of implementation. Several TEA members are looking forward to using these materials in their own clinics and sharing through their own channels.

Ms. Ross, BOP, said that anytime she hears "LTBI" she always thinks about corrections. There is not necessarily a large Asian/Pacific Islander population, but there is a large at-risk population in corrections. The BOP probably has one of the largest populations who are tested for LTBI, but follow-up for treatment is not always great after that testing is done. With that in mind, she wondered whether corrections was considered in terms of LTBI education. Dr. Watts, National Health Care for the Homeless Council (NHCHC), raised the same issue with regard to whether there are plans for targeted education and outreach to those living and working in shelters.

Ms. Allen indicated that while this effort is not specifically targeted at the corrections population, it is included in a lot of patient education campaign materials in terms of talking to patients about their risks if they have spent time in a prison, jail, or other such facility. There is a team at DTBE in the Communications, Education, and Behavioral Studies Branch (CEBSB) who looks at materials more broadly. If there are specific needs for the correctional population, she will be happy to connect them with the right people. Homeless shelters also are mentioned as part of the patient education materials being used in terms of the campaign, though the campaign is not focused specifically on those living and working in shelters. There are a number of other CDC resources and materials, such as a homelessness toolkit.

In response to a question from Dr. Benjamin, Stop TB USA, regarding whether the research was leading them toward the use of "inactive" versus "latent" and if that might be recommended for everyone, Ms. Allen emphasized that there was a lot of discussion about this internally and externally with partners. At this point, they are not recommending a wholesale change or redoing the entire TB website. However, they did feel strongly from consumers that they do not like "latent." The campaign will test this in that the materials targeting consumers will use the term "inactive TB." A lot of the message for consumers explains that this is inactive TB, which is sometimes called "latent TB infection" so that people are exposed to both terminologies. Because they want to direct providers back to guidance on testing and treatment, the term "latent TB infection" is still being used. There will be information on the campaign website that explains this terminology. Dr. Benjamin emphasized that scientifically, there is nothing latent about TB infection. Dr. Loeffler commented that the 2021 AAP RedBook is saying "TB infection (TBI)." To her, TBI also means traumatic brain injury. Ms. Allen indicated that TBI was tested, but people seemed to like "inactive TB" as a way to refer to "LTBI."

Dr. Ritger, NACCHO, recalled that focus groups were previously held with Mexican and Central American groups and asked whether more materials would be forthcoming or if this was the extent of the focus of this LTBI campaign.

Ms. Allen reminded everyone that their first round of research from 2019-2020 included a larger population, including people born in Mexico and Guatemala. Due to the resources available, it was necessary to narrow the scope of the campaign to a much smaller population. The campaign concept and implementation have moved ahead with people born in the Philippines and Vietnam. The great thing about having that extant research is that if additional resources become available, the campaign could be expanded to include other languages. All of the campaign materials will be available online and others with resources available to translate the materials into Spanish certainly would have that option.

NCHHSTP and DTBE Equity Activities

NCHHSTP Equity Activities

Donna Hubbard McCree, PhD, MPH, RPh
Associate Director for Health Equity
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. McCree presented an overview of NCHHSTP equity activities. The mission of the NCCHSTP Office of Health Equity (OHE) is to promote health equity, the absence of systematic unfair disparities in health, and reduce health disparities among populations disproportionately affected by HIV, viral hepatitis, sexually transmitted diseases, tuberculosis, and other related conditions. The NCHHSTP OHE supports activities which aim to reduce health inequities among affected populations in NCHHSTP research and surveillance, policy, health communication, prevention and intervention programs, capacity-building, and partnerships. The OHE also leads activities in collaborations with all divisions in the center.

The NCHHSTP Equity Initiative is a transformational long-term strategy to achieve equity within the NCHHSTP workplace and eliminate health disparities in the diseases and infections addressed by the center. This purposely was not called a "health equity initiative." Instead, "equity initiative" was used because it involves both workplace culture, policies, and procedures and also efforts to eliminate health disparities. The NCHHSTP Equity Initiative was launched in February 2021 after 2 years of intensive planning. Dr. Burton lead this the planning effort in his previous role as NCHHSTP Associate Director for Health Equity, which included visits to several health departments to inform the work that is being done. It is very exciting to see this plan coming to the implementation stage and to look at some of the outcomes of the work that is being done.

There is a full implementation plan for the Equity Initiative that includes 3 focus areas and goals. Focus Area 1 is focused on workplace culture; Focus Area 2 focuses on workplace policies and procedures; and Focus Area 3 focuses on research, policy, programs, and partnerships. Each of these focus areas has a set of goals and activities, responsible parties, metrics, and a timeline for completion of the activity.[15] The implementation plan established some key organizational structures that were put in place to get the work done. There is a Coordinating Group that includes 2 representatives from each of the divisions and the Office of the Director (OD). They serve in an advisory capacity to ensure that the activities under the plan are executed as delineated. They also serve as the liaison for the work being done under this initiative to their own division. The implementation plan also established OD and Division Equity Change Teams. The OD and each division has an Equity Change Team that is responsible for guiding the activities being implemented under the implementation plan within their organizational units. There also is an Evaluation Team that is responsible for monitoring and evaluating the outcomes of the work completed under this initiative, using the CDC *Framework for Program Evaluation in Public Health*[16] as a guide.

[15] https://intranet.cdc.gov/nchhstp/od/equityinitiative/index.htm
[16] https://www.cdc.gov/eval/framework/

The NCHHSTP Equity Initiative has a dedicated internal website that staff can access to look for status updates, and status updates are also provided during Center-wide all-hands meetings. The Equity Change Teams allow for Division and OD staff to provide comments and recommendations on the activities that are moving forward in their organizational units. NCHHSTP is very proud of an Equity Training Toolkit that was developed by the Equity Initiative Planning Team, which includes trainings focused on the science of health equity, workplace culture, increasing cultural diversity, et cetera. This tool is available on the internal website and is being used across the agency. NCHHSTP also developed an Equity Dashboard with indicators, measures, and targets to monitor progress. This is the first of its kind in that the Dashboard uses disparity measures to monitor the Center's process in reducing disparities.

The agency released a CDC CORE Health Equity and Science Intervention Strategy[17] in 2021, a very comprehensive strategy that the agency is implementing to advance the science of health equity. NCHHSTP has been very much involved in that effort. Drs. McCree and Burton serve as the center's points of contact for the CORE Initiative. All NCHHSTP's divisions and the OD have CORE goals and targets. Progress on these goals will be monitored as a part of the agency's health equity science and intervention strategy.

The agency also recently released an initiative titled, "Better Together: CDC Diversity, Equity, and Inclusion." This is important and unique because it addresses both public health and workforce equity issues. Dr. Burton serves as a representative to that initiative as well. Further, during the past year, all CDC Data Driven Regular Reviews (D2R2) | PPEO | OADPS (cdc.gov) were focused for the first time on health equity. This provided an opportunity for NCHHSTP to highlight the work the center is doing around health equity, with a focus on the NCHHSTP Equity Initiative, Implementation Plan, and Focus Areas. As a part of that work, NCHHSTP highlighted some of the activities within the divisions. A particular project that was highlighted for TB elimination was the LTBI Campaign. The center also released its Equity Dashboard during that meeting and had an opportunity to discuss it, along with the indicators and targets and how those were set.

NCHHSTP is performing a health disparity trend analysis in which they are documenting existing disparity trends and identifying important gaps. The hope as an outcome from this is to develop and prioritize a center-wide list of additional disparity trend analyses that can be done. The results will align with the center's new Strategic Plan that is currently in development, the CDC CORE Strategies, and the Equity Initiative. Of the trends being analyzed, 7 are from work that was done by colleagues in DTBE. NCHHSTP also is conducting a cost-benefit analysis as part of its NCHHSTP Epidemiologic and Economic Modeling Agreements (NEEMA) project, which is a modeling project looking at closing gaps in the health disparity indicators for priority racial and ethnic minority populations. Thinking about the work being done around decreasing disparities, it is known where the greatest disparities are and the causes. Consideration must be given to where to intervene in order to have the greatest impact. Some modeling needs to be done to facilitate that work, which is where this project is filling a gap.

NCHHSTP has a Correctional Health Coordinator position that was filled in 2021. The center had a Corrections Workgroup that was inactive for a while, but was reactivated in 2019. This group has been working to advance the science of health equity as it relates to correctional health work. In terms of prioritization, a "Roadmap" was developed to address 12 priority

[17] https://www.cdc.gov/healthequity/core/index.html

activities that were identified. The Correctional Health Coordinator, Dr. Mariel Marlow, is in the process of leading the development of a Correctional Health Agenda for the center. NCHHSTP had panel discussions accepted at one of the leading correctional health conferences that will be held in Atlanta in 2022. The panels will describe the work that CDC is doing around correctional health. Dr. Marlowe is also doing work around standardizing corrections surveillance terminology and serving as a liaison to the NCHHSTP Strategic Partnership Initiative (SPI).

NCHHSTP is involved in several workgroups and other activities. There is a CDC Health Equity Leadership Network, which includes those who are engaged in health equity work across the agencies. This Network provides a great opportunity to exchange information about ongoing work, hear about activities that are being established, and to learn from best practices and lessons learned from work that has been completed by other colleagues. The agency also convened a Social Determinants of Health (SDOH) Working Group that is charged with developing a framework for using social determinants as a pathway to reducing disparities. The framework will define how SDOH may be leveraged to reduce disparities, and the science needed to support the work.

In addition, the agency has a very active Climate and Health Workgroup in which NCHHSTP representatives are involved. The Workgroup has several subgroups, including an Environmental Justice Subgroup in which NCHHSTP is very active. There is an HHS Reentry Workgroup that focuses on persons who are justice-involved once they are released from the system in terms of best practices for reentry. There is now a CDC Governance Board that is assessing workplace culture and the importance of having a diverse workforce that can do the kind of work that needs to be done to move the needle in terms of health equity. There are several Executive Orders around health equity in which NCHHSTP is involved. NCHHSTP also attends Tribal Advisory Committee meetings. In addition, NCHHSTP reviews documents and manuscripts that have a focus on health equity and/or on advancing the science of health equity.

Within the center and across the agency, NCHHSTP has robust opportunities to engage in collaborative efforts and believes that this allows them to do their work effectively and efficiently. The OD leadership has been very much involved from the beginning in making sure that the NCHHSTP Equity Initiative had the resources, staff, and other elements needed to get the implementation plan in place and implemented. Dr. McCree emphasized that the Equity Initiative Coordinating Group has been groundbreaking, certainly in her 4 decades of work in public health, in terms of how that group has been able to coalesce and work together to get the Equity Initiative implementation off the ground, get buy-in from the divisions, and serve as a continuous feedback loop between what is needed, how well the center is doing, what adjustments need to be made, and what next steps are needed moving forward.

DTBE Equity Activities

Awal Khan, PhD
Health Equity Coordinator/Senior Health Scientist
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Khan presented an overview of DTBE's health equity activities for the DTBE Health Equity Workgroup/Equity Change Team. The mission of the DTBE Health Equity Workgroup is to: 1) educate CDC staff and the public about populations who experience TB health disparities and inequities; 2) improve health equity by eliminating TB health disparities and inequities, and 3) establish an Equity Change Team to plan, coordinate, and implement equity activities in alignment with the goals and objectives of the NCHHSTP Equity Initiative. DTBE Health Equity Workgroup, comprising of two members from its 5 branches and a member from the Office of Director. With the charter of the NCHHSTP Equity Initiative, DTBE Health Equity Workgroup serves as DTBE Equity Change Team.

In terms of progress toward TB elimination in the US, TB incidence rates have declined by about 80% from 1982-2020. In 1992, the incidence rate was 10.4 per 100,000 population. In 2020, the incidence rate was 2.2 per 100,000 population. Although TB incidence rates declined progressively, TB disproportionately affects people from racial/ethnic groups. Native Hawaiian and other Pacific Islander and Asian populations have consistently experienced higher TB incidence rates, followed by Hispanic/Latino, Black/African American, and American Indian/Alaskan Native persons. The white persons had the lowest incidence rates. Non-US-born persons account for more than 70% of TB cases in the US. Rates among both US-born and non-US-born groups have declined over time, but US-born persons had a steeper decline compared with non-US-born persons.

As Dr. Hubbard McCree mentioned, CDC has launched agency-wide CORE strategic goals to integrate health equity. Guidance for developing DTBE goals was to complete a Year 1 plan with follow-up potential, incorporate 4 core elements (e.g., healthy equity focus, goal statement, annual milestones, and key partnerships, and complete the CDC health equity science and interventions (HESI) Commitment Worksheet. Based on these criteria, DTBE developed core strategic goals and they are to: 1) decrease the TB incidence rate among non-US-born Asian-American persons from 26.2 per 100,000 (2019) to 20.8 per 100,000 by December 2025; 2) decrease the TB incidence rate among non-US-born Hispanic/Latino persons from 10.2 Per 100,000 (2019) to 8.2 per 100,000 by December 2025; and 3) decrease the TB incidence rate among US-born non-Hispanic Blacks or African American persons from 2.6 per 100,000 (2019) to 2.0 per 100,000 by December 2025.

Guidance for the DTBE Equity Change Team's workplan was to use the NCHHSTP Equity Initiative Implementation Plan; plan and coordinate equity activities for DTBE; focus on the Equity Initiative Implementation Plan objectives 2.3.4, 2.3.6, and 3.1.1; and contribute other NCHHSTP Equity Initiative Implementation Plan goals and objectives. The workplan was developed by the DTBE Equity Change Team, received feedback and input from Branch Chiefs, was approved by DTBE Director, and was submitted to the Equity Initiative Coordinating Group.

The 11 activities proposed in the DTBE Equity Change Team workplan for the NCHHSTP Equity Initiative include the following:

1. Ensure to update DTBE website items related to TB in specific populations and risk groups, including race/ethnicity, immigrants/refugees, etc.

2. Complete the development of a public health framework to advance TB health equity.

3. Conduct a review to identify activities related to reduction of health disparities and promotion of health equity in TB annual progress reports submitted by CDC-funded TB programs.

4. Describe interventions to address TB health disparities and improve health equity in specific U.S. populations (Asians, Native Hawaiian, Pacific Islanders, Hispanics, non-US-born persons).

5. Develop DTBE's Health Equity website to display all health disparity/health equity documents and projects in one place.

6. Identify and use the suitable measures of disparity from a list of health disparity measures, such as relative risk, absolute risk, index of disparity, Gini coefficient, etc.

7. Develop and maintain a list of health equity training courses available to DTBE staff, and post on the DTBE intranet site. Work with DTBE OD to sponsor at least one health equity-related training course per year.

8. Complete a comprehensive analysis using DTBE data to identify where staffing disparities may exist, by series and grade.

9. Based on the results of activity 9, develop a plan to address staffing disparities. The plan could include improving recruitment of qualified candidates from under-represented groups.

10. Reduce potential bias in the selection process. Update division hiring standard operating procedures (SOP) incorporating best practices.

11. Identify training for selecting officials and ensure each selection process is documented.

ACET Discussion: NCHHSTP and DTBE Equity Activities

Dr. Belknap inquired about potential opportunities to share best practices and/or lessons learned, given that the activities described while amazing seem more internally-facing. While there is a lot of work within his own organization, it is at a much earlier stage than where CDC, NCHHSTP, and DTBE are. Other programs could use a lot of the training and tools and do not have the resources that CDC has been able to devote to this.

Dr. Hubbard McCree said she thought the toolkit they developed around the training certainly could be shared. NCHHSTP is currently working on messaging and communication around equity within the equity mission for the center in order to be able to share aspects of it with external partners. They hope to publish the trend analysis and process for doing that, which could be very helpful as well. They are very proud of the dashboard they developed and she has discussed with Drs. Mermin and Burton that there should be some discussions with external partners and some publication regarding the process used to develop some of the indicators,

measures, targets, data, methods, et cetera. The Equity Change Teams are developing a document that will discuss collaborative efforts in which they will be involved, within DTBE and other divisions, in terms of how those can be used to advance this type of work in other areas.

Mr. Watts, NHCHC, commended CDC, NCHHSTP, and DTBE for including activities focused on the workplace. The NHCHC conducts trainings for primary care organizations, which have centered on equity and diversity over the last 3 years. One thing they have found is that it is very disheartening for staff of color when the leadership says one thing externally, but does not practice it internally. He asked whether there has been any mandatory training considered or developed around this.

Dr. Hubbard McCree indicated that all supervisors at CDC are required to take unconscious bias training. This is a 3-part series that is one of the best training programs she has had, because it provides some clear examples and solutions to create an environment that is inclusive, diverse, and ensures that supervisors understand their own role in making sure that happens. The Coordinating Group also is taking training. The training topics in the toolkit includes racial equity, health equity, health disparities, sexual and gender identities, cultural diversity competence, and cultural bias. Some of these trainings have been made available online, which allows people to complete them when it is convenient for them and to revisit the material several times if there were areas of interest they wished to review. These are internal on the intranet, but they should be able to share externally because of the way the document is constructed. She will confirm this and follow up with ACET. The OD Change Team is focused on activities just in the NCHHSTP center's OD. While it was not required, they completed the training so that they could coalesce. They have told the story of how difficult it was to talk about these issues. Once the group took the training and individuals started to discuss their own lived experiences, it helped the group to coalesce around the idea itself. They then built out some excellent activities that can be implemented to move the needle in terms of workplace culture policies and features. She stressed that Drs. Mermin and Burton were part of this in the beginning when the initiative was under development, with people who were part of the workgroup sitting in on those uncomfortable conversations. This showed that they had buy-in from the beginning and made it easier to do the work, because the staff members were able to see the support from leadership from the outset.

Dr. LoBue added that the unconscious bias training is required of the DTBE supervisors as well. In addition, DTBE held their own similar trainings. While they were not required, the participation rate was extremely high at close to 100%. A follow-up session was incorporated into DTBE's all-hands meeting that was attended by the trainer and where people could discuss their concerns and questions. Again, participation was extremely high. While a lot has been done, there is always more that can be done. The plan is to build this in as part of the annual training curriculum.

eDOT Study

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Drs. Mangan and Burzynski presented the final results of the eDOT study, implications for programs, and next steps. As many ACET members are aware, the use of video-enabled eDOT has been increasing. However, the evidence surrounding its efficacy is somewhat limited. This trial began with the hypothesis that eDOT is non-inferior to in-person DOT (ipDOT) for monitoring TB treatment adherence. This was a randomized, two-period crossover, non-inferiority trial. The non-inferiority margin was <10% difference between DOT methods. Randomization was either to ipDOT or eDOT at the time outpatient TB treatment began at 4 health department TB clinics in NYC. Following randomization, participants aimed to complete 20 medication doses with 1 DOT method and switched DOT methods for another 20 doses. Following these 2 crossover periods, participants chose the method of DOT they used for the remainder of their treatment. The primary objective was to estimate the percent-difference of non-holiday, weekday medication doses completed by ipDOT versus eDOT.

In terms of the methods, 4 analytical approaches were used to test for non-inferiority. In the modified intention-to-treat (mITT) analysis, the DOT method for each dose was represented according to the participant's randomization assignment. The per protocol (PP) analysis was restricted to participants who completed 100% of their doses using the DOT method according to their randomization assignment. The per protocol 85% (PP85) analysis was restricted in such a way that a minimum of 85% of each patient's doses complied with their assigned DOT method and a maximum of 15% of the doses were represented according to the method the patients actually used. The empirical (E) analysis assessed all eligible participants where the DOT at each dose was represented according to the method actually used, regardless of randomization assignment. Patients in the E analyses are the same as in the mITT analysis except that the representation of the DOT method differs. Within the 4 analytic approaches, each scheduled observable dose of medication was realized as a binary outcome. Staff observed the patient completely ingest the dose or they did not. The binary outcome was analyzed with a generalized linear mixed effects regression model. To evaluate the non-inferiority of eDOT, the percentage of medication doses staff observed patients completely ingest while using eDOT was subtracted from the percentage observed from ipDOT. The variation of the percent difference was then estimated in the form of a 95% confidence interval using a bootstrap technique.

The participant profile summarizes the characteristics of all 216 persons who enrolled in the study alongside the 173 participants who were included in the mITT and E analyses, the 43 participants including the PP analysis, the 138 participants included in the PP85 analysis, and the persons who were not treated for TB by the NYC Bureau of Tuberculosis Control (BTBC). Compared to other patients, study participants were slightly younger, more often male, less likely to be born in an Asian country, and more often employed. The other variables were quite similar. In terms of the results, the proportion of doses observed by the 2 methods was quite good. The percent difference between the 2 DOT methods ranged from −1.91% (−4.51, 0.92) to −4.90% (−11.74, 2.83), which was well below non-inferiority of ≤10%, indicating that eDOT is non-inferior (or as good as) ipDOT.

All studies have strengths and limitations and this one is no exception. With regard to limitations, the availability of eDOT without study enrollment did have an impact on recruitment. Some participants either switched or simply continued their preferred DOT method during the crossover period. Additionally, the study focused on adherence following initiation of outpatient treatment. On the positive side, the evaluation was conducted under pragmatic conditions. The patient population was diverse. Data were derived from participants using both DOT methods. The comparator to eDOT was the participant's choice of community-based or clinic-based in-person DOT.

When considering the implications of this study for TB programs, the data were assessed with regard to the parameters of cost, logistics, case management, and patient-centered care. In terms of patient and program costs, the data were not restricted to NYC. The Departments of Public Health in San Francisco and Rhode Island joined this evaluation, which allowed the investigators to look at patient and health department costs relative to low, medium, and high incidence settings. Both types of video DOT were associated with lower costs than traditional forms of DOT. The highest cost observed in the analysis was patient cost for clinic DOT, which averaged $33.98 per session. It is important to note that the cost of DOT varies by site. While the cost of video DOT with recorded videos was significantly lower than the cost of community-based DOT for both the NYC and San Francisco sites, the cost of video DOT with recorded video was not statistically different from the cost of community DOT in Rhode Island. The costs by site illustrate an economy of scale in that when there were fewer patients over which to spread the fixed costs, the cost per dose was higher. From a programmatic perspective, programs in low TB incidence settings might partner with other programs to gain better prices on equipment and software, in turn reducing the cost per DOT session.[18]

Turning to the logistics, as part of the study data were collected related to the organization and coordination of DOT services. Approximately a third of study participants needed to borrow a video-enabled cell phone through the health department in order to participate in DOT. As programs plan to implement or scale up eDOT services, this provides some guidance on the purchase of video-enabled phones, data plans, protection plans, or insurance for repairs. While the investigators do not have data on the number of phones lost, conversations with Study Coordinators revealed that there could be more of a need for phone repairs than issues with lost phones that were loaned. In NYC, patients are referred to the DOT team, who arrange for initiation of ipDOT visits or eDOT. Staff responsible for community-based DOT cover a

[18] Beeler Asay GR, Lam CK, Stewart B, Mangan JM, Romo L, Marks SM, Morris SB, Gummo CL, Keh CE, Hill AN, Thomas A, Macaraig M, St John K, J Ampie T, Chuck C, Burzynski J. Cost of Tuberculosis Therapy Directly Observed on Video for Health Departments and Patients in New York City; San Francisco, California; and Rhode Island (2017-2018). Am J Public Health. 2020 Nov;110(11):1696-1703. doi: 10.2105/AJPH.2020.305877. Epub 2020 Sep 17. PMID: 32941064; PMCID: PMC7542290.

somewhat large and population-dense area. This referral system and staff are efficient in NYC. The time between study enrollment and first DOT session recorded in the study database do not indicate one DOT method is better than the other. Advocates note that eDOT offers an advantage over ipDOT when inclement weather occurs or when patients take vacation or travel for holidays. An ad hoc analysis found no significant effect of season on dose observations among this cohort of patients. Delving further into the data to evaluate live and recorded video DOT, both were found to be non-inferior to ipDOT. The proportion of doses that the staff observed participants completely ingest was a little bit higher for recorded DOT compared to live video DOT.

The data collected for each DOT session were granular. This included documenting any factors or challenges that potentially hindered adherence. Approximately 89% of study participants experienced one or more challenges with a DOT session, and 10% of all DOT observations experienced a challenge. The proportion of doses that had some type of challenge arise by DOT type were 19% with field DOT, 10% with live video, 8% with recorded video, and 6% with clinic DOT. Among the 216 participants, there were 29,900 prescribed doses of medication. Of those, 20,344 of these doses were expected to be observed by DOT and 2,034 (10%) of the doses experienced a challenge. Among all doses that had a challenge, 57% (1,161) doses ended up not observed as planned. Among those doses, there were 1,301 challenges documented. Of these challenges, 27% were technology-related, 13% were staff/program-related, and 61% were patient-related. These data highlight the need for good communication between patients and staff, as well as good contingency planning when patients use any DOT modality.

Turning now to data that looks at DOT in the context of facilitating care, in NYC patients are asked to report any AE at the beginning of the DOT session and during monthly clinic visits. For this study, Coordinators prospectively documented AEs on a study-specific form. Clinicians reviewed the study's forms and graded symptom severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). AE type and severity did not differ significantly by DOT methods. The number of days between symptom onset and receipt of medical attention was similar by DOT method, with the average being 1 day. No participants were switched from eDOT to ipDOT due to AEs and/or concerns about monitoring. In terms of completed doses among patient subgroups, no discernable graphical patterns in dose completion were detected among participants based upon substance abuse, age group, a primary language other than English, or educational attainment. Statistical analyses are pending.

A variety of individuals were either excluded from the study or not offered enrollment despite being eligible. However, relatively few patients had characteristics that made eDOT a non-viable or less-optimal option for monitoring treatment. Before the study began, eDOT was available to patients in NYC. Thus, it would have been unethical to make this intervention available only to those who participated in the trial. This led the investigators to capture detailed reasons why patients elected to decline study enrollment. The top 5 reasons patients declined study participation included inconvenience of DOT, patient preferred a specific form of DOT, patient did not want to be randomized, patient preferred routine care, and missing work or school would be a problem. Among those who did not enroll because they preferred a specific form of DOT, the top 2 choices were recorded and live DOT. As noted earlier, participants could choose the method of medication administration for the remainder of their treatment following the crossover period. Among the participants, 84% chose eDOT, 4% chose to self-administer their medication, and 6% chose ipDOT. When asked to rate their overall satisfaction with eDOT and ipDOT, 95% of those who used live video DOT indicated they were satisfied versus 92% of those who used

recorded DOT. In comparison, 79% of those who used community-based ipDOT indicated that they were satisfied with this method and 67% of those who chose clinic-based ipDOT were satisfied.

When asked to compare eDOT to ipDOT, 59%-89% of participants overall felt that eDOT offered a greater opportunity to maintain independence, keep their schedule as it was prior to their illness, keep their diagnosis and treatment private, cope with the treatment, and take the treatment more easily. In contrast, 57%-66% of participants noted no difference between ipDOT and eDOT or rated ipDOT higher with regard to being able to talk to staff about treatment concerns, feeling emotionally supported by TB program staff, having staff listen to concerns or worries, staff knowing and caring about a patient's situation, and staff checking on patients for side effects of medications. Certainly, each method of DOT has its strengths.

Now turning to the NYC experience during the eDOT study. Prior to the start of the eDOT study, the NYC BTBC had piloted and implemented an eDOT program with both recorded and live video platforms. Prior to the study, some limits were set on which patients could use eDOT. Limits on policies were loosened somewhat to accommodate the study. However, a number of program practices were integrated into the study protocol and data were routinely collected during clinic visits and were transferred into the study database to align the study and clinic operations. As part of the programmatic approach, the aim was to recruit participants who would reflect the greater patient population. The challenges were documented that needed to be addressed, and investigators were able to capitalize on the expertise that the BTBC staff had developed. The program did derive a number of benefits from the study. Not only were the BTBC clinic staff engaged, but also the study highlighted the importance of quality assurance in providing eDOT to patients. Not only was eDOT expanded to a larger cross-section of patients, but also the proportion of patients using eDOT increased during the course of the study. The study ended right before the pandemic began and because of the study, the NYC BTBC program was well-positioned to further expand telemedicine and move almost completely to eDOT for DOT needs. Now eDOT has become the standard of care in the BTBC.

This study demonstrated that eDOT is non-inferior to ipDOT in the context of an urban TB program with a history of successful ipDOT practice. Study data also help to address practical considerations for TB implementation and questions about eDOT. In settings where ipDOT operations are not as robust and/or logistics are challenging, the variables presented could be used as metrics to monitor initial implementation and scale up of eDOT activities. The study also demonstrated that a combination of DOT methods enabled the program in NYC to achieve high rates of direct observation. There were a number of instances in which ipDOT was a better option, which points to the need for programs to retain some capacity for ipDOT. While there are many advantages of eDOT and digital adherence technologies, the literature points out a number of unintended consequences of relying on technology. Among the top are social isolation, decreased attention, and privacy issues. These need to be considered in the context of eDOT so that its use and related policies and procedures may be adapted and optimized.

In terms of next steps, the investigators have been working on a number of manuscripts. The main manuscript has been accepted and is currently pending publication in the *Journal of the American Medical Association* (*JAMA*) Network Open. The publication data has not yet been determined. Publishing in an open-access journal will allow TB program staff to readily obtain the report. Other manuscripts in process include: 1) Assessing adverse events among patients using in-person and electronic directly observed therapy; 2) Comparing electronic directly observed therapy (DOT) to in-person DOT: Patients' perspectives; and 3) Technical, programmatic, and patient challenges across four types of directly observed therapy. ACET

members were invited to share their views of additional implications based upon the data presented, and to make suggestions for additional analyses using the study data.

ACET Discussion: eDOT Study

Related to some of the changes mentioned and what is being done now that the study is completed, Dr. Belknap inquired as to whether the NYC program is offering eDOT from the beginning in patients newly diagnosed with TB if they do not have the barriers described. He also asked whether there are any exclusion criteria based on disease site.

Dr. Burzynski indicated that eDOT is being offered during the first day in the clinic. It usually takes a day to do this. That was something that changed. Before the study began, NYC and other programs were cautious with eDOT and had a policy stating that patients had to be on DOT for 2 weeks and if that seemed to be going well, consideration would be given to eDOT. All of that has now changed such that eDOT is offered/started on Day 1. With the pandemic, they prefer eDOT for everyone. They do not exclude anyone based on disease site with the exception perhaps of CNS, but they do not see much of that. Importantly, they showed that there was no difference in reporting of AEs for persons on eDOT versus ipDOT.

Ms. Ross, BOP, asked whether this study been considered for replication in rural areas. Given that it is known that there is often disparity in rural health care, availability of this technology may be helpful.

Dr. Burzynski indicated that while they did not perform a rural evaluation in NYC, he thought it would be even more valuable in a rural setting where the issues related to travel are so important. With eDOT, the logistics are much simpler. The cost study was conducted with Rhode Island and San Francisco. There are some advantages of using eDOT when there is the economy of scale as far as cost issues are concerned. It seems that in rural areas, this would be especially beneficial for programs. While not the same as rural, several patients traveled outside of the city during the study who were continued on eDOT.

Dr. Mangan agreed and added that when this study was first started, there was the idea of potential conducting it in two locations. However, the ability to do this was restricted by the budget. They did try to compensate by conducting the economic evaluation looking at high, medium, and low incidence settings. The one caveat on who was invited to participate in the economic evaluation was that a program had to have an eDOT system up and running because they did not have the funds to stand up a program.

Dr. Ahmed asked the age of the youngest patient, pointing out that there is no reason not to bring a child on board as well—especially if a parent is receiving eDOT. She wondered whether there would be room for extending this into the school system and LTBI, especially to children under 5 years of age. There was agreement from other ACET members that eDOT definitely should be considered for younger children.

Dr. Burzynski indicated that the youngest patient was 12 years of age. While they were somewhat reluctant to go that young, there were a few participants under 18 years of age as long as the parents agreed to it. For LTBI, eDOT is used for 3HP pretty successfully in their clinics. Using it in schools would be great where permitted but likely would vary depending on geography, policies on using cell phones in schools, and the Health Insurance Portability and Accountability Act (HIPAA). They have been told that Google Meet is HIPAA-compliant, so NYC has been using that platform for their eDOT program. FaceTime also is HIPAA-compliant.

Dr. Mangan added that prior to coming to CDC she worked at the University of Alabama (UAB) in Birmingham in the Lung Health Center (LHC) where they focused on asthma, COPD, and TB. They implemented projects with elementary school children with asthma to ascertain their adherence on their rescue inhalers. It was all done over the internet and was quite successful. The biggest issue was the firewall into the schools because there are so many safety nets to keep children from going onto websites where they should not be.

Dr. Stout inquired as to whether there is any nationwide understanding of how eDOT is being utilized in different jurisdictions, which would be helpful to understand in terms of what the potential impact of this might be. North Carolina has used video DOT for a long time, much of which is done through Skype. Their attorneys ruled that as long as this is done in a certain way using free services, it is HIPAA-compliant. Some jurisdictions use asynchronous HIPAA-compliant apps that do cost more money. For instance, the cost for Rhode Island was higher because it costs money to buy the eDOT software at the outset. If free software is used, that would not be a consideration.

Dr. Mangan indicated that before this study started, the National Tuberculosis Controllers Association (NTBA) conducted a survey looking at practices, but it was more to assess what percentage of programs were using or were planning to use DOT. That was the last survey she saw that was conducted in the US.

Dr. Wegener added that the NTCA Survey Committee is considering conducting an updated assessment of that original eDOT survey work, and she would appreciate feedback on questions to include in the next survey effort.

Dr. Chen pointed out that the economy of scale may now be met in many places due to pandemic-response growth in telehealth systems.

Dr. Mermin asked whether there is a role that CDC could play in supporting the policy-related issues to eDOT in terms of following up on concerns about HIPAA compliance, health department policies and their attorney, et cetera. He also wondered whether there would be a role for CDC in terms of funding some kind of available electronic system that would make it less expensive for each jurisdiction to have the capacity to implement eDOT. As the presentation made clear, it is the upfront costs that are the problem rather than the long-term costs.

Dr. Burzynski thought it would be helpful in any guideline statements going forward to indicate that DOT is the standard of care, and that includes eDOT. Clinical trials have avoided using eDOT because there was not enough data to know whether eDOT was as good as regular DOT, and no one wanted to risk a large clinical trial without better data behind it. There have been some discussions with Dr. LoBue about this, but there is some reluctance because of the information technology (IT) management such as software updates that might be complicated.

Dr. LoBue indicated that they would plan to address the policy guidance based on the study, which is convincing. Legal support could be problematic. This issue has arisen on other efforts and the CDC Office of General Council (OGC) typically takes the position that they are council to CDC and no one else, so they are not going to provide essential legal advice to people outside of the agency. There has been some discussion about making one application available, but there were a couple of major hurdles. One was money in that the upfront cost was in the millions. The second aspect is that DTBE would be in a position that they would own this and

then would have to deal with all of the upgrades that would need to be done, which their technical people said could be very expensive. Therefore, it did not seem like that model would be supportable by DTBE.

Dr. Belknap asked whether there might be an opportunity to publish something about the decisions that legal institutions came to around the use of various platforms.

Dr. Ahmed pointed out that health departments in Mecklenburg County have to have access to local hospital EMRs, each of which has a virtual visit platform. If that is also true throughout the country, perhaps that is mechanism for completing eDOT. Cerner and Epic both have virtual visit platforms.

Dr. Stout indicated that they have Epic and considered this as an option. The technical side from the patient perspective is not easy relative to some of the other options, such as paid platforms designed specifically for this or some of the available free platforms people use.

Day 1 Recap

Robert Belknap, MD
Medical Director, Denver Metro Tuberculosis Control Program, Denver Public Health
ACET Chair

Dr. Belknap provided a brief recap of the information presented throughout the day and reviewed the agenda for the next day.

With no further business posed, a motion was made and seconded to adjourn the meeting for the day. The motion carried unanimously and the meeting was adjourned at 3:45 pm ET. ACET stood in recess until 10:00 am ET on December 15, 2021.

December 15, 2021 Opening Session

Marah E. Condit, MS
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Office of Policy, Planning, and Partnerships
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Deron Burton, MD, JD, MPH (CAPT, USPHS)
Deputy Director, National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control & Prevention
ACET Designated Federal Officer (DFO)

Ms. Condit called the meeting to order at 10:00 am ET on December 15, 2021 and provided meeting instructions. Dr. Burton welcomed participants to the second day of the ACET meeting. He then conducted a roll call to confirm attendance of the ACET voting members, *ex-officio* members, and liaison representatives. He reminded everyone that ACET meetings are open to the public and that all comments made during proceedings are a matter of public record. He informed the ACET members to be mindful of their responsibility to disclose any potential COI, as identified by the CDC Committee Management Office, and to recuse themselves from voting or participating in discussions for which they have a conflict. The roll call confirmed that the 22 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 15, 2021. No additional COIs were declared and quorum was maintained throughout the meeting.

Multi-State TB Outbreak Associated with Bone Allograft Surgery

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Medical Officer
Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Schwartz described a multi-state outbreak of spinal and disseminated TB caused by surgical implantation of a bone allograft product. In terms of how CDC became aware of this situation, the Delaware TB program notified DTBE on May 25, 2021 about an unusual cluster of 7 TB cases all in patients who had recently undergone spinal fusion surgery. Initial investigations by the hospital epidemiologist and operating room (OR) staff determined that all 7 patients had received the same lot of a bone allograft product containing live cells. Working with the Division of Healthcare Quality Promotion (DHQP) at CDC, DTBE deployed a team to Delaware to conduct a field investigation along with the Delaware TB program and the hospital. The findings from that investigation have been published in the *MMWR*. Simultaneously, their team back at headquarters issued a nationwide call for cases on May 31, 2021 on CDC's Epidemic Information Exchange (Epi-X). On June 2, 2021, the manufacturer issued a voluntary recall of the affected product lot. The same day, a second state notified DTBE about another case of TB in a recipient of the product. This confirmed the suspicion that this might be an issue with the product rather than a local issue at the hospital in Delaware.

The team worked quickly with FDA, the product manufacturer, distributor, and state and local health department TB and healthcare-associated infections (HAI) programs to rapidly track unused product and evaluate recipients nationwide. It was determined that the bone used to manufacture this product was recovered from a single deceased donor. It was manufactured in a single facility into 154 units of bone allograft, which were then distributed to 37 facilities in 20 US states. They were able to sequester 18 units that were not yet used, which were sent for mycobacterial testing or were returned to the manufacturer. The remaining 136 units already had been implanted into 113 patients at that point. Of the 113 patients, 105 were still alive and were started on TB treatment by June 10, 2021—just 8 days after the recall. Unfortunately, the other 8 patients already had died by the time of public health action.

Since early June, CDC has continued to investigate this outbreak along with FDA and state and local TB partners. Medical records have been abstracted for all 113 identified product recipients. The donor screening and tissue processing procedures have been reviewed and a variety of laboratory testing has been conducted. CDC partnered with the reference laboratory run by the US Department of Agriculture (USDA) to perform *Mycobacterium tuberculosis* (MTB) polymerase chain reaction (PCR) and culture for unused product that was sequestered from the recalled lot, as well as other products processed at same facility. WGS and phylogenetic analysis were done on MTB isolates from both product recipients and from the unused units. CDC performed MDDR testing for the first submitted unused product unit and state and local public health laboratories performed routine growth-based DST as well.

In terms of the baseline characteristics of the product recipients, recipients primarily were US-born, ranged in age from 24 to 87 years, and were 50% female and 50% male. Eighty-one percent were White non-Hispanic and 15% were Black non-Hispanic. Underlying medical conditions included diabetes (26%) and immunocompromising conditions (11%). The product was implanted primarily in the spine (99%), and 1 patient received the product in the left metatarsal of the foot (1%). Unfortunately, very high attack rates were found of both surgical site and disseminated TB among the identified product recipients. Of the 113 identified recipients, 16 (53%) had microbiologic evidence of TB disease, 87 (77%) had microbiologic or imaging evidence of TB disease, 83 (73%) had evidence of TB at the surgical site, and 28 (25%) had evidence of TB disease at other sites (e.g., lungs, brain, spinal cord, liver, and bone marrow). Complications were frequent with this level of disease with 54 (48%) identified product recipients having hospital readmissions for complications of infection, 48 (42%) having additional surgeries for treatment of infection, and 8 recipients dying after product implantation. State and local health departments reported to CDC whether TB was a cause of death (COD) based on either medical records, death certificate data, or autopsy in one case. Of the 8 deaths, 2 were attributed to TB, 4 were attributed to causes unrelated to TB, and there was insufficient data to determine whether TB was a cause of the remaining 2 deaths.

With respect to the donor's medical history, the donor was an older man with several TB risk factors, including prior residence in and frequent travel to a country with endemic TB, end-stage renal disease (ESRD) requiring hemodialysis, and diabetes mellitus type II requiring insulin. Review of his records revealed a clinical course of 70- to 80-pound weight loss over the 2 years prior to death, which was attributed by his next of kin to dietary changes. However, this can be a non-specific symptom of TB. He was admitted following 2 to 3 weeks of cough and difficulty breathing. His death was attributed by the medical team to cardiogenic shock following bradycardic arrest. No mycobacterial testing was performed during his hospitalization because TB was not suspected. Screening of this donor consisted of a standard donor risk assessment with the donor's proxy. The proxy reported no known reported history of prior TB, positive TB skin or blood test, or household exposure to TB in the previous 12 months. Cough and weight

loss were attributed to other causes as noted. On further review, CDC found out that the donor had a negative TB skin test about 4 months before his death at his dialysis center. However, false-negative TB skin test results are not uncommon in patients with ESRD. Standard donor testing was performed and was negative for hepatitis B and C, HIV, syphilis, and human T-lymphotropic virus (HTLV).

Speaking with the manufacturer, FDA, and the tissue recovery agency, CDC learned more about tissue procurement and processing. Fortunately, no solid organs were procured from this donor. The tissues procured included long bones, skin, fascia lata, and tendons. Only the bones were used to manufacture medical products. The bone tissue was processed at a single facility. The cortical bone was treated with hydrochloric acid and demineralized. The cancellous bone, the spongy interior part of the bone, was processed in order to retain live cells in the final product. Bioburden testing followed current industry standards and regulations. This included bacterial and fungal testing performed on samples that were collected during processing and also samples from the final product. Mycobacterial testing is not part of current industry standards, so this testing was not performed.

When the USDA laboratory performed testing of the unused bone allograft products that CDC was able to sequester from this donor lot, *M. tuberculosis* was detected by PCR and culture in all 8 of the bone allograft units from this donor's recalled lot. *M. tuberculosis* was not detected in 11 bone allograft products from other donors processed at the same facility during a 12-week period. Using WGS and phylogenetic analysis, *M. tuberculosis* isolates from the unused product and recipients were determined to be >99.99% identical genetically. All shared a unique genotype that has never been observed before in the US, confirming that the product was the source of the outbreak. The isolates differed by just 0 to 1 single nucleotide polymorphisms (SNP). Fortunately, no resistance to first-line or second-line TB medications was detected on the molecular and growth-based testing of isolates from the product and from patients.

To summarize, strong epidemiologic and laboratory evidence were found that *M. tuberculosis* was transmitted through bone allograft tissue from a single donor to at least 87 recipients in 15 states, resulting in substantial morbidity and mortality. Based on the review of the records, it seemed that the donor likely had unrecognized disseminated TB disease with bone marrow involvement at the time of death. It appears that current donor screening and tissue testing standards do not reliably detect *M. tuberculosis* infection or TB disease. Based on that, improvements are warranted in TB screening for tissue donors to improve tissue safety. CDC is actively engaged in discussions with regulatory bodies to explore what options might be feasible.

ACET Discussion: Multi-State TB Outbreak Associated with Bone Allograft Surgery

Dr. Stout noted that in conversations with Dr. Schwartz's team, he received some information that there may be something related to the medium used to store the bone product that perhaps was amplifying the TB and requested further information about that. He also inquired as to why Dr. Schwartz thinks this is the first time this has happened since 1953 and if perhaps it could have to do with mycobacterial load.

Dr. Schwartz responded that unfortunately, exactly what this product contains is proprietary. Based on the website of the company, the product is designed to sustain osteoprogenitor cells in order to stimulate bone growth and includes bone morphogenetic proteins (BMPs). They have not been able to find any literature about whether BMPs stimulate TB growth or affect immunity to TB. It is certainly possible that since the BMPs and other growth factors in the product are

designed to stimulate the growth of human cells, they may also be capable of sustaining or stimulating growth of MTB. It certainly contained live bone marrow cells that are likely to be able to be infected with TB as well. The product is stored at about -70^0 C, so the inoculum in the product mostly reflects what was in the donor since it was immediately frozen. It is not likely that there was a lot of MTB growth in the product between the time it was procured from the donor and implanted. After implantation, certainly all of those factors are biologically plausible in terms of stimulating MTB growth. In terms of why this has not occurred frequently, Dr. Schwartz indicated that live cell products are relatively new on the order of 10 years. Bone grafting has been around for a long time. Bone TB is relatively rare, with about 200 patients nationwide per year. It is possible that this donor had disseminated TB with higher bacterial loads in bone marrow than would be observed in typical bone TB. Other than that, he was not sure and would be speculating.

Dr. Horne emphasized that this illustrates the importance of necropsies and demonstrating what is not known when CODs are attributed, and requested information about the selection process for bone donors.

Dr. Schwartz responded that while screening is not mandated by law, many tissue donor procurement organizations use a unform interview with the donor's proxy that does assess for a few non-specific signs and symptoms of TB or other systemic illnesses like weight loss and cough. There are 2 questions that specifically ask whether the donor has a history of TB or a history of positive skin or blood testing for tuberculosis or household exposure in the last 12 months. That is the extent of typical TB screening for tissue donors. Since TB is common enough and devastating, and live cell tissues are being increasingly used, CDC is hoping that regulations might be updated to require standard TB screening for donors. He did not know specifically why one patient versus another would be selected for bone harvesting versus other tissues. There is standard testing for other pathogens that are mandated by law, which he mentioned earlier.

Dr. Loeffler asked how many days or weeks before individuals who suffered clinical disease manifested signs/symptoms, and whether the donor was hospitalized in a place where there was particularly little TB. It is not clear what else could be done to raise awareness in terms of thinking about TB.

Dr. Schwartz replied that disease progressed and manifested remarkably quickly in this outbreak. The range from product implantation to first mycobacterial evidence of TB or first imaging finding that is documented was on the order of weeks, spanning 9 to 130 days, with a median of 65 days. The donor was hospitalized in a relatively low burden state. It is an ongoing challenge to encourage people to keep TB on the differential. That said, it is easy to look at this patient in retrospect but difficult in real-time to consider TB. He presented with a picture of hypervolemia from renal and heart failure and suffered cardiac arrest and shock after that. Providers likely anchored on the most likely and common problems of this clinical presentation of cardiac and renal dysfunction. It is not clear whether they were aware of the backdrop of 2 years of weight loss or whether that only came out after the screening process.

Dr. Chen asked what actionable items the company is now implementing to change their processing and testing of materials before they sell it, whether many companies are doing the same, and whether this is being presented widely with the communities and professional societies that would influence future practice.

Dr. Schwartz indicated that CDC would be meeting with the manufacturer later in the day to hear an update. It is understood from their presentation to shareholders that they have made changes to their screening policies, but CDC does not know the details yet. CDC would like to speak with the regulatory bodies to actually change policy. The FDA and the American Association of Tissue Banks (AATB) are the primary bodies responsible for regulation of tissue- and cell-based products. They also are working closely with the Blood, Organ, and Tissue Safety Team at CDC. They have briefed FDA on the investigation and have worked closely with them and are planning to have conversations about what might be feasible in terms of what can be suggested or mandated for tissue screening in the future. Some possible options would be that every donor deserves an assessment with a history, physical exam, and a chest x-ray for history or evidence of TB. They could contemplate potentially screening with IGRAs, although they are not perfect and likely would have a lot of false negatives and indeterminant results in donors, who tend to be critically ill. There is also the question of what should trigger mycobacterial testing of either the patients or the product, and whether that is feasible. Many options are being explored, but it is early at this point. CDC also has reached out to the Organ Procurement Transplant Network (OPTN) that regulates solid organ transplantation (SOT). Even though this patient was a tissue donor and not an organ donor, a lot of these issues are relevant to both populations. CDC has investigated multiple cases of TB transmission via SOTs as well, so the possibilities are being explored with OPTN.

Dr. Belknap asked whether the current screening that is done is essentially all serologic or if there is any actual tissue screening for diseases at all routinely done, such as molecular-based testing. He emphasized that this is an amazing story and it is very important to raise awareness about this beyond the places that were directly affected.

Dr. Schwartz said his understanding is that there is serologic testing of the donor for HIV, hepatitis B and C, syphilis, and HTLV. FDA mandates that the product itself undergo USP 71 sterility testing, which involves 2 different culture media of samples from the final product that assess for bacterial (aerobic and anaerobic), and fungal contaminants. The product is supposed to be held in quarantine for 2 weeks. When the final cultures are negative, then the lot can be released and distributed. That is the extent of actual direct testing on tissue currently. For this product, there is a shelf-life of 2 years. It is plausible that mycobacterial, PCR, and culture could be done directly on tissue. That is another option being explored. There is no FDA-approved test right now other than GeneXpert®, which is only approved for use with sputum specimens. However, laboratories do develop and validate their own tests, like the USDA laboratory that tested the unused products in this case. Therefore, it is possible that this might be an option in the future. Publishing is planned to help encourage regulators and clinicians to think about this issue.

ACET Business Session

Robert Belknap, MD
Medical Director, Denver Metro Tuberculosis Control Program, Denver Public Health
ACET Chair

Dr. Belknap opened the Business Session and facilitated a review of old and current business items that warranted ACET's formal action, and allowed time for additional discussion and/or requests for future agenda items.

Business Item 1: Approval of Previous ACET Meeting Minutes

A motion was properly placed on the floor by Dr. Horne and seconded by Dr. Temesgen to accept the minutes from the June 16, 2020 ACET minutes. With no further discussion or changes, the motion to accept the minutes as written carried unanimously with no abstentions or opposition.

Business Item 2: Advice Requested from ACET

Dr. Belknap reminded the members that one of ACET's responsibilities is to provide advice to HHS and the CDC. Together they reviewed the pending pieces of advice requested from ACET and the status of each:

Topic	Proposed Action
1) **Study 31** • ACET expressed interest in making sure that the guidance for the Study 31 regimen aligns with the guidance and recommendations for the standard 6-month regimen. For instance, for paucibacillary extrapulmonary disease there are no randomized studies for any regimen in lymphatic TB or pleural TB. • Also important is the availability of medications and diagnostics, particularly if fluoroquinolones are going to be used more regularly as a first-line regimen, given that susceptibility results will be needed quickly. The lack of access to the GeneXpert® cartridge for detecting fluroquinolone resistance is a specific example. • Consider ways for which the process for approval could incentivized or simplified for TB, which is many ways is an orphan disease in the US.	• As the guidelines are being developed, ACET suggests including language that is at least consistent with the 2016 guidelines pertaining to the use of the standard regimen in such scenarios. • Given that there is no evidence, perhaps this could be coupled with a registry assessing patients who would be treated this way in order to begin obtaining evidence into the efficacy of this. • In terms of incentivizing/simplifying the process for approval of diagnostics, Dr. Elkins indicated that FDA is at the recipient of what sponsors choose to submit to them. That is typically the limitation rather than the time taken to review. FDA does not disclose confidential information about submission, status, content, et cetera. The manufacturer has to decide to discuss. • ACET should investigate the barriers from their perspective and what would be an acceptable incentive.
2) **LTBI Campaign** • ACET expressed an interest in CEBSB considering communication strategies that include and are considerate of incarcerated populations and other congregate settings such as shelters. • There is interest among ACET members in expansion of the LTBI campaign to incarcerated, shelter, ethnic, and pediatric populations.	• It is not clear whether the LTBI campaign is applicable to corrections and other congregate settings, given that it is trying to engage individuals and their providers. Corrections might be more about training and education among medical staff and persons in facilities versus television or media advertisements. • Perhaps images of children could be added to the campaign materials to express the idea of cocooning the child.

Recommendation: Study 31

A motion was properly placed on the floor by Dr. Temesgen and seconded by Dr. Horne for ACET to recommend that the group at CDC who is developing the guidelines based on the Study 31 regimen explicitly consider treatment of extrapulmonary disease and monitoring with regard to pregnancy, taking a relatively permissive position consistent with the prior 2016 guidelines. The motion carried unanimously with no abstentions or opposition.

Recommendation: LTBI Campaign

A motion was properly placed on the floor by Dr. Loeffler and second by Dr. Ahmed to consider the risk for LTBI for other populations and ways to message that risk to populations who would be most impacted, such as 1) including images of children in mentoring materials; 2) educating practitioners and providers on the importance of treating LTBI in children and adults; and 3) considering expansion of the LTBI Campaign to include others such as incarcerated, shelter, ethnic, and pediatric populations. The motion carried unanimously with no abstentions or opposition.

Business Item 2: Future Agenda Items

While the Agenda Setting Workgroup will be convened to finalize the agenda for the next meeting, Dr. Belknap invited members to suggest topics of interest. During this meeting, the following topics of interest were suggested for consideration:

Presenter	Agenda Item
Dr. Burton will check to determine whether it is appropriate to invite a manufacturer to present. Pfizer and Moderna present to the Advisory Committee on Immunization Practices (ACIP), so there is a precedent for inviting manufacturers to present. FDA Representative(s); Dr. Elkins will help to connect to the right people to include them in any meeting that is applicable.	• For Study 31, review of what is available for the supplementary material and discussion in terms of what is covered, not covered, what should be covered, et cetera. • Invite manufacturers to discuss the development of diagnostics and medications in terms of the barriers to product development and submission to the FDA. • Invite a representative from the FDA to discuss drugs and diagnostics from the regulatory perspective, which could help inform advice or recommendations from ACET that would support efforts by DTBE. • TB may be miscategorized since it is an “orphan” disease. Consider having someone speak about whether there are other easier pathways that could streamline the process that would reduce barriers.
CDC Office of Science Representative	• Include a presentation on the CDC guidance process, particularly with regard to the clearance process and discuss whether there are potential ways in which this process might be streamlined or improved. Perhaps explain the requirements for each type of document.
Division of Global Migration and Quarantine (DGMQ) The PIs from the 3 divisions involved in the 3HP regimen.	• It would be beneficial to hear a presentation on how the COVID-19 pandemic has impacted TB in terms of the US immigration population and particularly the impact of Afghanistan relocations on programs across the country. • Related to pre-immigration, a presentation on the 3HP regimen would be interesting.
Global TB Branch, the United States Agency for International Development (USAID), and/or NIH.	• Perhaps a presentation would be beneficial in terms of insight into how to optimize research/implementation occurring globally and how that could benefit domestic groups (Amy Bloom will share a graphic to illustrate how things fit across the USG).
TBD	• It would be interesting to hear a presentation on the risk of congenital TB in the context of reproductive health with respect to in vitro fertilization of infected women, potential transmission in other settings such as neonatal intensive care units (NICU), the children who are serving as a reservoir for possible future cases, pediatrics in general, et cetera.

Public Comment

Dr. Belknap read the following comment from Nick DeLuca into the record:

I am happy to hear the support for the LTBI Campaign and the TB Elimination Alliance. Regarding the discussion this afternoon, I just wanted to let you know a critical component of the campaign is for the target audience to—"Protect yourself and your family.” We will have lots of images of family and children as well.

Closing Session

The proposed dates for upcoming 2022 ACET meetings are:

- ❑ June 21-22, 2022
- ❑ December 13-14, 2022

While the preference is for these meetings to be in-person, this will be dependent upon CDC's status and what is permitted. There is not yet a timeline for when in-person meetings may be resumed at CDC, and virtual meetings will be convened only if there is no other option. It should be possible to make a decision by late February or early March 2022, and consideration can be given to a hybrid meeting that includes both in-person and virtual attendance.

With no further discussion or business brought before ACET, a motion was properly placed on the floor, seconded, and unanimously approved to adjourn the meeting at 12:00 pm on December 15, 2021.

Chair's Certification

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

Date

Robert Belknap, MD, Chair
Advisory Council for the Elimination of Tuberculosis

Attachment 1: Participants' Directory

ACET Members Present

Dr. Robert Belknap, Chair
Dr. Amina Ahmed
Dr. Lisa Chen
Dr. David Horne
Dr. Lixia Liu
Dr. Ann Loeffler
Dr. Lynn Sosa-Bergeron
Ms. Kristine Steward-East
Dr. Jason Stout
Dr. Zelalem Temesgen

ACET *Ex-Officio* Members Present

Drs. Naomi Aronson & Kevin Taylor
US Department of Defense

Dr. Amy Bloom
US Agency for International Development

Dr. Karen Elkins
Food and Drug Administration

Dr. Jonathan Iralu
Indian Health Service

Dr. Edith (Edie) Lederman
Homeland Security

Dr. Lawrence Kline
Department of Health and Human Services

Dr. Mamodikoe Makhene
National Institutes of Health

Mr. Stephen Martin & Dr. David Weissman
National Institute for Occupational Safety and Health

Dr. Gary Roselle
Department of Veteran Affairs

Dr. Stephen Kralovic & Ms. Marla Clifton
US Department of Veteran Affairs

Tara Ross
Federal Bureau of Prisons

Dr. Ronald Wilcox
Health Resources and Services Administration

CAPT David Wong
Office of the Assistant Secretary for Health

ACET *Ex-Officio* Members Absent

Dr. Thomas Nerad
US Department of Labor/Occupational Safety and Health Administration

Dr. John Palmieri
Substance Abuse and Mental Health Services Administration

ACET Liaison Representatives Present

Dr. Shama Desai Ahuja
Council of State and Territorial Epidemiologists

Dr. Robert Benjamin
Stop TB USA

Dr. Sarah Gordon & Ms. Donna Wegener
National Tuberculosis Controllers Association

Valerie Adelson & Charles Daley
American Thoracic Society
Ms. Susan Rappaport
American Lung Association

Dr. Randall Reves
International Union Against TB and Lung Disease

Dr. Kathleen Ritger
National Association of County and City Health Officials

Ms. Susan Ruwe
Association for Professionals in Infection Control and Epidemiology

Dr. Sylvie Stacy
National Commission on Correctional Health

Dr. Lornel Tompkins
National Medical Association

Mr. Bobby Watts
National Health Care for the Homeless Council

Dr. Daphne Ware
Association of Public Health Laboratories

Dr. David Weber & Dr. David Henderson
Society for Healthcare Epidemiology of America

ACET Liaison Representatives Absent

Dr. Mayleen Ekiek
Pacific Island Health Officers Association

Dr. John Hellerstedt
Association of State and Territorial Health Officials

Dr. Ilse Levin
American Medical Association

Mr. Surajkumar Madoori
Treatment Action Group

Dr. Howard Njoo
Public Health Agency of Canada

Dr. Amee Patrawalla
American College of Chest Physicians

Dr. Gudelia Rangel
Mexico Section, US-Mexico Border Health Commission

Dr. Susan Ray
Infectious Disease Society of America

ACET Designated Federal Officer

Dr. Deron Burton
NCHHSTP Deputy Director

CDC Representatives

Ms. Leeanna Allen
Ms. Rebeccann Pope Alley
Garrett Asay
Ms. Lauren Barna
Ms. Beth Bouwkamp
Kia Bryant
Dr. Deron Burton
Dr. Wendy Carr
Terry Chorba
Ms. Marah Condit
Ms. Anne Cronin
Dr. Tracy Dalton
Dr. B. Rey de Castro
Dr. Nick DeLuca
Brittany Foushee
Maria Gomez
Neela Goswami
Maryam Haddad
Tempest Hill
Dr. John Jereb
Dr. Awal Khan
Maureen Kolasa
Ms. Kathryn Koski
Dr. Ekaterina Kurbatova
Mr. Yecai Liu
Dr. Philip LoBue
Dr. Joan M. Mangan
Atanaska Marinova-Petkova
Ms. Suzanne Marks
Luc Marzano
Dr. Donna Hubbard McCree
Dr. Jonathan Mermin
Erin Miller
Mark Miner
Wan Moon
Meredith Moore
Selma Moore
Dr. Sapna Bamrah Morris
Ms. Staci Morris

Margaret Oxtoby
John Parmer
Robert Pratt
Claire Sadowski
Audilis Sanchez
Carissa Sera-Josef
Ms. Maria Sessions
Dr. Noah Schwartz
Dr. Angela Starks
Rebekah Stewart
Rita Traxler
Dr. Thara Venkatappa
Dr. Andrew Vernon
Ms. Laura Vonnahme
Dr. Carla Winston
Marilyn Wolff

Guest Presenters

Dr. Joseph Burzynski

Members of the Public

Shama Desai Ahuja
Lisa Armitige
Debra Benator
Rajita Bhavaraju
Haley Blake
Gail Burns-Grant
Brandy Cloud
Olivia Dupont
Pete Dupree, CDPHE
Diana Fortune
Annette Gaudino, TAG
Stefan Goldberg
Connie Haley
Chayelle Jagger
Payam Nahid
Masa Narita
Monica Pecha, Washington State Department of Health
Lakshima Peddareddy
Tina Shah
Ellen Smith
Cherie Stafford

Attachment 2: Glossary of Acronyms

Acronym	Definition
AAFP	American Academy of Family Physicians
AATB	American Association of Tissue Banks
ABSL-3	Animal Biological Safety Level-3
ACET	Advisory Council for the Elimination of Tuberculosis
ACIP	Advisory Committee on Immunization Practices
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AFB	Acid-Fast Bacillus
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
BD	Becton, Dickinson and Company
BDQ	Bedaquiline
BMZ	Bedaquiline, Moxifloxacin, and Pyrazinamide
BOP	Federal Bureau of Prisons
BPaL	Bedaquiline, Pretomanid, and Linezolid
BTBC	Bureau of Tuberculosis Control
CARES Act	Coronavirus Aid, Relief, and Economic Security Act
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CEBSB	Communications, Education, and Behavioral Studies Branch
CIOs	Centers, Institutes, and Offices
CITC	Curry International Tuberculosis Center
CNS	Central Nervous System
COD	Cause of Death
COI	Conflict of Interest
CTCAE	Common Terminology Criteria for Adverse Events
DASH	Division of Adolescent and School Health
DC	District of Columbia
DFO	Designated Federal Official
DGMQ	Division of Global Migration and Quarantine
DHHA	Denver Health and Hospital Authority

Acronym	Definition
DHQP	Division of Healthcare Quality Promotion
DIS	Disease Intervention Specialists
DOT	Directly Observed Therapy
DST	Drug-Susceptibility Testing
DSTDP	Division of STD Prevention
DTBE	Division of Tuberculosis Elimination
DVH	Division of Viral Hepatitis
E	Empirical
ED	Emergency Department
eDOT	Electronic Directly Observed Therapy
EHE	Ending the HIV Epidemic
EHR	Electronic Health Record
EMR	Electronic Medical Record
Epi-X	Epidemic Information Exchange
EPT	Expedited Partner Therapy
ESRD	End-Stage Renal Disease
ET	Eastern Time
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
GIMS	Genotyping Information Management System
HAI	Healthcare-Associated Infections
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCP	Healthcare Providers/Professionals
HCV	Hepatitis C Virus
HDT	Host-Directed Therapies
HESI	Health Equity Science and Interventions
HHS	(United States) Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HTLV	Human T-Lymphotropic Virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICE	Immigration and Customs Enforcement
ICHS	International Community Health Services
IGRA	Interferon-γ Release Assay
IHSC	ICE Health Service Corps
INH	Isoniazid
ipDOT	In-Person Directly Observed Therapy
IRB	Institutional Review Board
ISTM	International Society of Travel Medicine
IT	Information Technology

Acronym	Definition
JAMA	*Journal of the American Medical Association*
JPC	*Journal of Primary Care and Community Health*
KPNC	Kaiser Permanente Northern California
LHC	Lung Health Center
LTBI	Latent Tuberculosis Infection
MDDR	Molecular Detection of Drug Resistance
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT™	Mycobacterial Growth Indicator Tube™
MIC	Minimum Inhibitory Concentration
mITT	Modified Intention-To-Treat
MMP	Medical Monitoring Project
MMWR	*Morbidity and Mortality Weekly Report*
MOX	Moxifloxacin
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSM	Men who have Sex with Men
MTB	Mycobacterium Tuberculosis
NACCHO	National Association of County and City Health Officials
NCHHSTP	National Center for HIV, Viral Hepatitis, STD and TB Prevention
NCI	National Cancer Institute
NEEMA	NCHHSTP Epidemiologic and Economic Modeling Agreements
NEJM	*New England Journal of Medicine*
NEMS	North East Medical Services
NHCHC	National Health Care for the Homeless Council
NIH	National Institutes of Health
NP	Nurse Practitioner
NTCA	National Tuberculosis Controllers Association
NYC	New York City
OD	Office of the Director
OGC	Office of General Council
OHE	Office of Health Equity
OTPN	Organ Procurement Transplant Network
Pa	Pretomanid
PA	Physician's Assistant
PCP	Primary Care Providers
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PI	Principal Investigator
PID	Pelvic Inflammatory Disease
PK	Pharmacokinetics
PP	Per Protocol

Acronym	Definition
PP85	Per Protocol 85%
PrEP	Pre-Exposure Prophylaxis
PSAs	Public Service Announcements
PWID	Persons Who Inject Drugs
PZA	Pyrazinamide
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RPT	Rifapentine
RVCT	Report of Verified Case of Tuberculosis
SAMS	Secure Access Management Services
SDOH	Social Determinants of Health
SEOIB	Surveillance, Epidemiology, and Outbreak Investigations Branch
SME	Subject Matter Expert
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedures
SOT	Solid Organ Transplantation
SPI	Strategic Partnership Initiative
STD	Sexually Transmitted Disease
TA	Technical Assistance
TB	Tuberculosis
TB GIMS	TB Genotyping Information Management System
TBESC	Tuberculosis Epidemiologic Studies Consortium
TBI	Traumatic Brain Injury
TBI	Tuberculosis Infection
TBTC	Tuberculosis Trials Consortium
TEA	TB Elimination Alliance
TST	Tuberculin Skin Test
UAB	University of Alabama
US	United States
USAID	United States Agency for International Development
USDA	US Department of Agriculture
WG	Working Group
wgMLST	Whole Genome Multi-Locus Sequence Typing
WGS	Whole Genome Sequencing
wgSNP	Nucleotide Polymorphism
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB