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

Virtual Meeting of the
Advisory Council for the Elimination of Tuberculosis
December 8-9, 2020

Record of the Proceedings

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ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
December 8-9, 2020

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/AIDS, 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 8-9, 2020 beginning at 10:00 a.m. Eastern Standard Time (EST).

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 8, 2020 Opening Session

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

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County Department of Public Health

The meeting was called to order at 10:00 am EST on December 8, 2020. 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 disclosed
Lisa Armitige, MD, PhD Heartland National Tuberculosis Center	No conflicts disclosed
Robert Belknap, MD Denver Metro Tuberculosis Control Program	No conflicts disclosed
Barbara Cole, RN, MSN, PHN Riverside County Department of Public Health	No conflicts disclosed
David Horne, MD, MPH University of Washington School of Medicine	No conflicts disclosed
Robert Horsburgh, Jr., MD, MUS Boston University School of Public Health	No conflicts disclosed
Ann Loeffler, MD Multnomah County Oregon	No conflicts disclosed
Lixia Liu, PhD, MP, (ASCP), D(ABMM) New Mexico Department of Health	No conflicts disclosed
Kristine Steward-East Advocate for Tuberculosis	No conflicts disclosed
Zelalem Temesgen, MD Mayo Clinic Center for Tuberculosis	No conflicts disclosed

The roll call confirmed that the 19 voting and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 8, 2020. The roll was called subsequent to each break and lunch, with quorum established each time throughout the day.

Dr. Burton introduced and requested that everyone welcome the following new ACET *ex officio* members and liaison representatives:

- Dr. Ronald Wilcox, Medical Officer for the Office of Program and Support of the HIV Bureau, who will serve as the *ex officio* member for the Health Resources and Services (HRSA).
- CAPT David Wong, Medical Officer for the Office of Minority Health, who will serve as the *ex officio* member for the Office of the Assistant Secretary for Health (OASH). LTC Naomi Aspaas sat in for CAPT Wong on December 8, 2020.
- Mr. Peter Dupree, TB Program Manager and Public Health TB Epidemiologist with the Colorado Department of Public Health and Environment (CDPHE), who will serve as the liaison representative for the National TB Controller's Association (NTCA).
- Dr. Sylvie Stacy, Medical Director with the Birmingham Metro Treatment Center, will serve as the liaison representative for the National Commission on Correctional Health (NTCH).
- Dr. David Weber, Professor of Medicine at the University of North Carolina (UNC) School of Medicine at UNC Chapel Hill, who will serve as the liaison representative for the Society for Healthcare Epidemiology of America (SHAE).

The following announcements were made:

- Several *ex officio* members and liaison representatives rotated off of ACET, including Dr. Ulana Bodnar, Ms. Sarah Bur, Dr. Laura Cheever, Dr. Julie Higashi, Dr. Robert Morris, and Dr. Michael Tapper. Dr. Burton expressed gratitude for their service.
- CDC sent a letter to the Substance Abuse and Mental Health Services Administration (SAMHSA) with a request to identify a replacement.
- CDC sent a letter to the Agency for Healthcare Research and Quality (AHRQ) to identify a replacement.
- The ACET Charter expires on March 15, 2021. The renewal package has been submitted and is currently under review.
- Mr. Dupree, current NTCA President, recognized and congratulated Barbara Cole who won the well-deserved President's Award during the NTCA virtual conference in November.

Ms. Cole welcomed participants to the virtual ACET meeting and reviewed the agenda items planned for both days of the meeting.

NCHHSTP Director's Report

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

Dr. Mermin introduced and welcomed Dr. Burton, the new Deputy Director for NCHHSTP and ACET DFO, and Dr. Demetre Daskalakis, who officially will begin his role as the new Director for the Division of HIV/AIDS Prevention (DHAP) on December 21, 2020.

CDC continues to be involved heavily in the COVID-19 response. The number of infections, hospitalizations, and deaths in the United States (US) are at the worst they have been thus far. It is a very difficult time for those who care about public health and the wellbeing of people in the country and the world, and it has taken a toll on the ability to implement other important services

for HIV, viral hepatitis, STDs, and TB. A fair proportion of the NCHHSTP's staff continue to be actively deployed, with many having deployed more than once. The actual response system itself has increasingly improved its organizational structures, but it is very difficult to implement preventive measures at the same time that there are massive preparations for vaccines.

NCHHSTP recently published a supplement on the infectious disease consequences of injection drug use (IDU) titled, "Infectious Diseases and Injection Drug Use: Public Health Burden and Response." This was a tour de force in that it includes 34 articles from multiple national and global organizations, 10 of which are CDC articles. This is a comprehensive supplement that sets the stage for what has been occurring over the past few years, including creative ways of treating the infectious disease consequences of the opioid crisis and IDU, lessons learned from outbreaks, cost-effectiveness of various interventions, developing models for predicting or assessing what is occurring geographically and in various populations, and ideas about how to better conduct surveillance and other activities related to this issue. It was published in the time of COVID-19, so perhaps it did not receive the splash it might have otherwise, but it is a comprehensive document that represents a lot of fine work from multiple people [The *Journal of Infectious Diseases*, Volume 222, Issue Supplement_5, 1 October 2020].

Along with the National Alliance of State and Territorial AIDS Directors (NASTAD) and the University of Washington, NCHHSTP issued a new National Harm Reduction Cooperative Agreement that focuses on developing the technical assistance (TA) necessary to standardize as much as possible and normalize syringe service programs (SSPs) as a basic component of the public health system in the same way that a TB or STD clinic would be part of that. In addition to TA, this involves monitoring and supporting SSPs to determine whether they are being implemented and what their services are, and some special studies on what is occurring with different infections among people who inject drugs (PWID). NCHHSTP issued a Health Alert related to multiple outbreaks of HIV during the COVID-19 pandemic among PWID. Despite improvements in the ability to control outbreaks, both HIV and hepatitis C have continued to be transmitted during IDU in multiple areas of the country.

NCHHSTP issued what is a basically a modified *Vital*signs™ due to COVID-19. This is an assessment of what has happened with HIV-related deaths in the US over the past decade. This report shows that between 2010 and 2017, there was a major reduction in the overall HIV-related death rate by about 50%. There also was a reduction in relative and absolute disparities among African Americans compared to White persons with HIV for HIV-related mortality. The absolute difference in the disparity measure between Black persons and White persons decreased 66%, while the relative disparity measure decreased 23.2%. This is consistent with how they have tried to work within NCHHSTP to achieve reductions in incidence in morbidity and mortality and also to increase equity simultaneously [Bosh KA, Johnson AS, Hernandez AL, et al. Vital Signs: Deaths Among Persons with Diagnosed HIV Infection, United States, 2010–2018. *MMWR* Morb Mortal Wkly Rep 2020;69:1717–1724. DOI: http://dx.doi.org/10.15585/mmwr].

As part of the new Ending the HIV Epidemic initiative, NCHHSTP received $109 million that they allocated to several health departments throughout the country. This is the start of a large scale effort. This included HIV-specific activities and support for STD clinics, accepting the understanding that not only is there a syndemic in that both are transmitted from sexual behavior, but also that STDs double one's risk for transmission of HIV. The greatly increasing problem with STDs in the nation also is epidemiologically driving some of the cases of HIV

infection, so tackling the STD crisis more effectively also can result in reductions in HIV incidence.

NCHHSTP has what is known as its flagship community-based organization (CBO) funding announcement every 5 years, which has been reissued. It is anticipated that it will be possible to award funding to approximately 90 CBOs. There were many applications this year, which are being reviewed and for which there will be a modified version of pre-decisional site visits for some of the organizations to ensure that they have the capacity to do a good job. Eligible states/jurisdictions include approximately 96% of the total number of HIV diagnoses as of 2018 [https://www.cdc.gov/hiv/funding/announcements/ps21-2102/index.html].

In terms of viral hepatitis, there continues to be increasing incidence of hepatitis C in the country. American Indian/Alaska Native (AI/AN) populations are the most disproportionately affected, followed by non-Hispanic Whites, and about the same rates for other racial and ethnic groups. Since about 2006, relative and absolute increases in rates have been observed among AI/AN and among non-Hispanic White Americans.[1] A new funding announcement has been issued for the Division of Viral Hepatitis (DVH) that combines surveillance and prevention funding in order to take a more integrated approach similar to the way that TB is conceptualized in health departments and at the CDC level, although the resources are much less for viral hepatitis at $21 million than for TB. The applications were due December 1, 2020 and awards are anticipated to be made by May 2021.[2] NCHHSTP also has issued a progress report for viral hepatitis with specific indicators, which for viral hepatitis is somewhat mixed. In some areas, there have been some fairly impressive responses, particularly for reduction in HCV-related deaths. That is primarily because more people are being diagnosed and there is now the availability of direct acting agents that are highly effective and safe in curing people of hepatitis C. However, other areas continue to have trouble such as incidence of hepatitis C and A. The large multi-state hepatitis A outbreak that started about 3 years ago has now reduced its incidence overall by about 70%, but there are still about 150 cases a week and a lot of jurisdictions continue to struggle with cases of hepatitis A even though the level is lower than previously[3] [[1]Centers for Disease Control and Prevention. Viral Hepatitis Surveillance – United States, 2018. https://www.cdc.gov/ hepatitis/statistics/ SurveillanceRpts.htm; [2]https://www.cdc.gov/hepatitis/policy/FO-CDC-RFA-PS21-2103.htm; [3] https://www.cdc.gov/ hepatitis/policy/NationalProgressReport.htm?s_cid=em-NCHHSTP-DU-202009020002].

The Division of Adolescent and School Health (DASH) has continued to work on the Youth Risk Behavioral Survey (YRBS), which is conducted every 2 years. The data collected are analyzed for a variety of behaviors and outcomes for youth, as well as trends across the past decade. To highlight some of the findings, sexual risk continues to decline in terms of the portion of high school students who report having sex, having 4 or more lifetime sexual partners, or being currently sexually active. For those who have had sex, there also has been a small decline in the use of condoms and concomitant with that increase in the use of hormonal birth control. A trend that appears to be occurring across the country is that the age of onset of sex and the number of sexual partners has decreased over the past 3 years. High risk substance use also is declining in terms of the proportion of high school students who reported using illicit drugs or injecting drugs, but misuse of prescription opioids has remained relatively stable for the past 2 times that question has been included in the YRBS. Adolescents continue to experience a fair amount of violence. A somewhat stable portion of students reported being threatened or injured in school, electronically bullied, or physically bullied. Rape has remained consistent at about 7% of students reporting having been forced to have sex, with somewhat higher reporting having experienced dating violence. Adolescent mental health trends are moving in the wrong direction

and are being monitored closely. These data are before COVID-19 for which there are more recent data from a special survey. YRBS shows that mental health has worsened for youth over the past 10 years. Attempting suicide has increased and about a third of students reported having experienced persistent feelings of sadness or hopelessness. One area of success occurred in New York City (NYC) schools that received CDC funding, which reported increases in condom use during the last sexual encounter compared with a decrease among schools without CDC funding [https://www.cdc.gov/healthyyouth/data/yrbs/results.htm].

NCHHSTP convened a virtual STD prevention conference on September 14-24, 2020 that went very well. The theme was 2020 Vision: Disrupting Epidemics and Dismantling Disparities. Areas of focus included telemedicine, developments in STI diagnostics and testing, exciting possibilities for STD treatments, and COVID-19. People in the STD community are having a difficult time coping with the fact that there have been 5 years of increasing incidence of bacterial STDs, but continue to be energized with some new technologies and new approaches to STD prevention.

Data reported to CDC from January-June 2020 show that there was a decrease in primary and secondary syphilis, gonorrhea, and chlamydia diagnoses and cases are now close to being back up to prior rates. The decrease from March to April is thought to be a combination of people not being diagnosed due to decreased visits to clinics and perhaps due to social distancing [Weinstock, et. al., (Sept. 24, 2020). Impact of COVID-19 on STD Surveillance. 2020 National STD Prevention Conference, virtual].

In terms of activities on the horizon, NCHHSTP anticipates revising CDC's "Preexposure Prophylaxis for the Prevention of HIV Infection in the United States—2017 Update." This guideline helps the nation move forward in terms of getting access to pre-exposure prophylaxis (PrEP) for people who could benefit and offers guidance to providers. In addition, an update is underway to CDC's "Treatment Guidelines for Gonococcal Infection" that will be published soon. In collaboration with multiple other agencies and led by the OASH, there will be 3 "HHS National Strategic Plans: 2021-2025" issued in the next month or two for each of these topics: HIV/AIDS, STI, and Viral Hepatitis.

ACET Discussion: NCHHSTP Director's Report

In terms of the CBOs being funded to support HIV work with CDC, Dr. Goswami inquired as to whether there will be any stipulations in the Notice of Award or through programmatic monitoring of those activities about COVID-19 precautions the CBOs engaging in community work should implement or explicit line items to fund preventive measures (e.g., COVID-19 testing for staff, protective measures, et cetera). Dr. Mermin said that while he was not sure whether it was in the Notice of Funding Opportunity (NOFO), guidance has been issued to support adapting programs to the time of COVID-19. For instance, "Dear Colleague" letters have been sent from DTBE, DHAP, and DVH to partners to ensure that there is support for safe and effective implementation of programs. Sometimes, that means modifying the program itself. For example, adaptations can be made to field HIV or STD testing such as self-collected samples, mailing tests to people, modifying the SSPs, et cetera.

Dr. Belknap inquired as to whether there will be any opportunities to leverage current COVID-19 activities to strengthen TB prevention in communities at risk, and pointed out that there is a lot of overlap in the populations that are disproportionately affected by TB and COVID-19. Dr. Mermin replied that there are a lot of opportunities. The work of many TB experts has now been shifted to help with COVID-19 because much of the experience is similar. A lot of health

departments have turned to the TB expertise. It has been hard to expand on the synergies between COVID-19 and some of the other public health work in the agency, given that much of the focus has been on trying to tackle COVID-19 itself. While there are some areas where there has been overlap, there has not been as much overlap for NCHHSTP. Some of that has to do with the fact that the driving forces for transmission of SARS-CoV-2 are similar to active transmission of TB, not reactivation. They have not done as well as they could have in using the opportunity to "lift all boats" and make public health better in general. Some of that is simply the massive and overwhelming importance of trying to tackle the COVID-19 pandemic first. Many people have said they wish they had done more and that they probably will regret later not having done so.

Dr. Horsburgh congratulated NCHHSTP for all of its accomplishments in the midst of COVID-19 An impressive body of work has been done in advancing HIV, STDs, and harm reduction. He observed that the harm reduction program is highly encouraging. Drug use is a risk factor for TB as well, so the harm reduction program may have benefits in reducing TB transmission.

DTBE Director's Update

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

Dr. LoBue updated ACET on the FY2021 budget proposals, the impact of COVID-19 with a focus on what is being observed in terms of TB cases and surveillance, recent shortages of Rifamycins and AccuProbe, and the Research Consortia re-competition. In terms of the FY2021 budget, CDC is under a Continuing Resolution (CR) through December 11, 2020 with level funding. Additional appropriations for the remainder of the fiscal year remain unknown, but Dr. LoBue anticipates that funding will remain level for FY2021.

Regarding the impact of COVID-19 on DTE activities, laboratory services initially were limited to those focused on direct patient care or public health interventions such as outbreak investigations only. Most research activities in the laboratory have restarted, within the limitations of the number people who are allowed to be in the building at one time. It is substantially more than it was 6 months ago. All clinical trial enrollment has been suspended, which is based on what is occurring at sites. Throughout the country and in many parts of the world, COVID-19 is worse than it was even in the Spring. Therefore, it is not possible for those sites to enroll patients. The plan is to restart enrollment at individual sites when it is safe and practical to do so. However, this is not likely to occur in the US any time soon. A number of the epidemiological studies involved focus groups and surveys that could be done virtually and did not have to involve in-person interactions. Therefore, a lot of that work was able to continue.

One of the major efforts anticipated for 2020 was implementation of the new reporting form for verified cases of TB. However, this was delayed in most jurisdictions due to COVID-19. Only a couple of jurisdictions were able to move forward with the effort, so this is on hold by and large. All travel has been suspended except that related to COVID-19 and other urgent disease responses. Numerous conferences, site visits, trainings, and meetings have either been postponed, canceled, or moved to a virtual format.

It was apparent early on that the COVID-19 pandemic was straining the capacity of TB programs in many ways, including surveillance. As things progressed into the summary, DBTE wanted to be more proactive in terms of monitoring and evaluating potential COVID-related effects on TB surveillance to the extent possible. This began with an initial query of the National Tuberculosis Surveillance System (NTSS) data warehouse for 2020 cases reported as of May 31, 2020. This was updated again July 31, 2020 and has been updated monthly thereafter. The number of cases had decreased by 13.9% as of 5/31/20 compared to the 2016-2019 average for the same period. The percentage decline was 14.7% by 7/31/20, 18.5% by 8/21/2020, 19.4% by 9/30/20, and by 19.7% by 10/31/20. This was much greater than the expected small trend downward in case numbers of approximately 1% to 2%. At different timepoints, there is more year-to-year variability because there tends to be bulk and batch reporting of cases sometimes because programs tend to wait until the of the year. There also have been some special circumstances in certain jurisdictions this year, which has resulted in lower reporting of cases. Nevertheless, none of these considerations would come close to accounting for this type of decline.

In terms of the approach to investigating the unexpected decline in TB cases, a number of hypotheses were considered. The first was underreporting or delayed reporting TB cases within the public health system such that cases are being reported to local jurisdictions, but are just not getting up to the states and CDC in the usual way. Given the tremendous strain on local programs with staff being either referred over to COVID-19 activities or because of budget issues being reduced or furloughed, that certainly could be a significant contributor to this. There could be underreporting or delayed reporting to public health departments from private or commercial laboratories, private providers, prisons, jails, Indian Health Service (IHS), Veterans Affairs (VA) hospitals, or other healthcare facilities.

Another hypothesis is that there could be underdiagnosis. Fewer healthcare workers and others are familiar with TB, given that people have less experiences as the number of cases have decreased. However, this much of a change would not be expected in one year. TB being misdiagnosed as COVID-19 or missed in patients who are coinfected is new and certainly could account for delayed diagnosis. Anecdotally, DTBE has heard from jurisdictions about this. There even have been situations in which individuals patients have had 10 or 20 negative COVID-19 tests before a decision was made to look for something else. In some of those cases, TB has been diagnosed eventually.

The reduction in public health capacity has definitely impacted the ability to do active case finding (e.g., contact investigations and targeted testing for latent TB among populations at higher risk), which could have led to delays in diagnosis. There also has been a reduction in the likelihood that patients with chronic respiratory illness that could be TB would seek medical care, given that they fear seeking medical care could lead to contracting COVID-19. Anecdotally, CDC has heard of instances in which patients who turned out to have TB said they waited to seek medical care until they were very ill because they were more afraid of being exposed to COVID-19. Empiric treatment of presumed community-acquired pneumonia with fluoroquinolones (moxifloxacin) could initially mask TB symptoms and cause delayed TB diagnoses. This has been observed in the past and is not new, so there is no reason to think that this in particular would be increased in 2020.

There certainly could have been a true decline in incidence for a number of reasons, so this could reflect reality. For instance, the decline in international travel has resulted in a reduction in new arrivals from high-TB incidence countries and of US residents traveling to high-incidence areas. About 10% of TB cases occur in non-US born persons who have been in the US for less than a year. There has been a major reduction in new arrivals in the US through the various ways in which people enter the US (e.g., primary immigration, refugee status, work, temporary visas, et cetera). Improved TB control also has been theorized, but is the least likely hypothesis because health departments are having more difficulties conducting their TB prevention and control activities. Technical instructions have definitely had an impact in the past in decreasing TB cases, which is related to overseas screening of immigrants and refugees. However, those started implementation in 2007 and within 7 years were largely fully implemented. While there was an impact, it plateaued years ago and is not expected to have changed in the more recent term. It also is possible that measures being take for COVID-19 could affect domestic transmission (e.g., social distancing, wearing masks, et cetera). If the population at risk for reactivation has experienced a lot of COVID-19 and a lot of mortality, they may not survive to the point where their TB reactivates. However, this would be unlikely to have more than a minor effect.

In terms of planned activities to address this going forward in 2020-2021, the Surveillance, Epidemiology, and Outbreak Investigations Branch (SEOIB) Surveillance Team will: 1) continue to compare 2020 NTSS live production case counts and demographic/risk factor distributions to prior years, which is ongoing; 2) compare cluster alerts in the TB Genotyping Information Management System (TB GIMS) for 2020 data to prior years, which is in the planning stages; 3) conduct key informant interviews with TB program staff, which is in progress; 4) compare 2020 Electronic Disease Notification (EDN) data on “Class B” arrivals to prior years, which is in the planning stages; and 5) compare 2020 inpatient hospitalization data for TB-related diagnoses to prior years, which is in the planning stages. The Data Management, Statistics, and Evaluation Branch (DMSEB) Statistics Team and the SEOIB Surveillance Team will compare 2020 outpatient pharmacy dispensing data from IQVIA for anti-TB drugs to prior years.

Regarding shortages, Sanofi is the single approved manufacturer of rifapentine in the US. An initial shortage in rifapentine was caused by excess global demand due to the popularity of the different latent tuberculosis infection (LTBI) regimens that use rifapentine. However, there was a halt in product release by the manufacturer after nitrosamine impurities were identified. Since then, the Food and Drug Administration (FDA) has announced that they will allow distribution of the drug with an interim level of 20 parts per million (ppm) of the impurity. The manufacturer has not yet indicated its plans for releasing additional product. There are multiple manufacturers of rifampin and that product has continued to be released after the nitrosamine impurity was identified. The FDA set an interim level of 5 ppm. One manufacturer withdrew from the US market because their share of the market was small. FDA has indicated that the rifampin supply is tight, but the drug is still flowing.

AccuProbe® is the most used technology in the US for identifying *M. tuberculosis* and some non-tuberculous mycobacteria growing in culture. It is manufactured by Hologic, which plans to discontinue this product in approximately 1 to 2 years. They are open to making a replacement, but this depends upon compatibility with existing platforms in TB laboratories. The imminent shortage is due to the fact that the manufacturer temporarily shut down their production line to make COVID-19 tests. The disruption in the supply chain because of the demand for shared components for COVID-19 testing slows restarting production. It is possible that there will be a resolution by the end of first quarter of 2021. DTBE’s laboratory is working with the Association

of Public Health Laboratories (APHL) to find alternatives for public health laboratories to identify TB. Also under discussion is that a longer term solution must be found, especially if the AccuProbe® is going to be discontinued.

In terms of the Research Consortia re-competition, the next contract for the TB Trials Consortium is anticipated to begin in early 2021. Applications have been closed, reviewed, and ranked. DTBE is awaiting the selection announcement from the Office of Acquisition Services (OAS). For the TB Epidemiologic Studies Consortium, a process is underway to prepare for announcement of a request for new contract proposals in 2021. The anticipated start of the new contract will be late 2021 or early 2022. COVID-19 demands could delay that process, given that COVID-19 contracts and grants have priority.

ACET Discussion: DTBE Director's Update

Dr. Mermin commended DTBE's fantastically well-thought-out work and anticipation of important issues and congratulated Dr. LoBue and his team. There have been some good data to suggest that preventive efforts for SARS-CoV-2 infection has dramatically decreased the incidence of influenza. There is essentially not an influenza outbreak this season, and this is not due to increased vaccination. He wondered whether the factors Dr. LoBue discussed could be modeled (e.g., how many people are informally or formally immigrating who may have had LTBI or sub-clinical TB, or what proportion of the new infections or diagnoses are from well-documented reactivation versus active transmission) to get a sense of what is occurring. Currently, it is estimated that 1 in 5 are from active cases versus reactivation. He asked whether the ACET members, who are all out in the field, have a sense of whether that has changed.

Dr. LoBue indicated that if they have complete data, it should be possible to assess US-born versus non-US born and time in the US. For instance, a massive decrease in non-US born cases in the last year points to a certain answer. If not, that would raise more questions. EDN will be supplementary to that because they will know how many people are actually screening and coming through. In terms of recent transmission versus reactivation, the TB GIMS data will be assessed. Pretty well-documented examples have been received from the program related to delays in diagnoses. It will be necessary to rely on partners to convey how much less they have been able to do with regard to contact investigation, through which about 1% of new TB cases are found. There are some outbreak examples with clear incidence and ongoing transmission, so it is not gone. Whether it is less will take a while to sort out and require a considerable amount of genotyping data.

Ms. Cole reported that California initiated a survey to assess the reasons for reduced/delayed diagnoses at health departments, and suggested that consideration might be given to doing this on a more widespread basis.

Ms. Wegener added that there is an opportunity to expand the California data collection activities. NTCA has developed a national survey they hope to launch this week, which includes some of the questions used by the California survey for comparison purposes. The hope is to assess the impact of COVID on NTCA's programs and to obtain information about COVID-TB co-infections nationally.

Dr. Horsburgh commented that in overseas sites that are enrolling TB patients in cohort studies and clinical trials, there was no enrollment during the lockdowns that occurred in various countries. As soon as countries were reopened, there was a very robust response which suggests delayed diagnoses.

Dr. Ritger pointed out that delays in elective or semi-elective bronchoscopies may be impacting the rates, as a fair number of cases are typically diagnosed in this way. Decline in international arrivals also seems to be playing a role. Chicago Department of Public Health (CDPH) would be interested in participating in examining this more closely.

Dr. Ahuja indicated that NYC added that they assessed the first couple of quarters of the year and found that only about 18% of their patients had less than 5 single-nucleotide polymorphism (SNPs) different based on sequencing data. Therefore, it does appear that there is less active transmission than is usually seen in the 25% to 30% realm based on genotyping. In addition, cases are down about 20% though there has not been a big difference in the clinical characteristics of cases. In terms of the demographics, they are seeing fewer cases in the 18 to 41 year old and 45 to 64 year old age groups. It is possible that there may be more household transmissions because people are at home. They are still exploring and are working to assemble some data for an abstract and also are interested in participating in efforts to examine this more broadly.

Dr. Armitige reported that Heartland National Tuberculosis Center (HNTC) is seeing delays in diagnosis along the lines of those mentioned by others, such as averaging about 3 to 4 COVID-19 tests before another diagnosis is considered. The case numbers have decreased by nearly half. They are seeing more household transmission, an increase in LTBI in children, and a signal from homeless shelters with young people.

Responding to Dr. Dasgupta-Tsinikas's inquiry about whether there has been any signal in mortality among TB cases in NTSS, Dr. LoBue indicated that they have not looked at this yet. One way they can look at this is by assessing death at diagnosis, which can be done sooner. The other way is to examine death as an outcome after someone has been diagnosed, which typically takes at least a year after the data being assessed, so they are unlikely to have good data on this before 2022.

Dr. Kline inquired as to whether there are more detailed geographic data on the reduction of TB cases from 2016-2019 in border states versus non-border states, for instance. Dr. LoBue indicated that there are more data, but he purposely did not show it because it can be misleading due to peculiarities in some states in terms of how they report. Some tend to batch and a lot of reporting is submitted late in the year, while others have specific problems with their data systems in submitting data to CDC. Each one requires so much explanation, he did not think it would be helpful. Enough states are observing a reduction in TB cases across the country and fewer cases are being reported to CDC, so this appears to be real.

In response to a question from Dr. Dasgupta-Tsinikas regarding whether there is any evidence for TB survivors to be considered a special population for COVID-19 immunization, Dr. LoBue pointed out that the numbers are likely to be small once they have the data. While it may be difficult to prove given the data, anyone with an underlying respiratory condition could be at risk. It is known that acutely while people have the disease and after people with substantial pulmonary TB recover, they frequently have chronic pulmonary dysfunction. There is ample reason to consider them at higher risk the same as people with other underlying chronic respiratory diseases.

Dr. Belknap reported that Colorado has found that the biggest decline has been in pulmonary TB diagnoses among people who have been there for 5 or more years, which suggests missed or delayed diagnoses. He wondered whether there are plans to communicate this information more broadly to inform providers now rather than waiting until more complex analyses can be completed. Dr. LoBue replied that it seems reasonable for anyone with state or local data to alert state and local providers. DTBE's data are not at a point that they could say this definitively, given that it is difficult to extract this from the data they have. The fact that this is being seen is based mainly on anecdotal reports that have come from state and local health departments. If at any point they can show that this is true based on the data, DTBE would communicate that. That should not discourage those who have local data to put out local alerts.

Recalling the "Think TB" campaign from decades ago, Dr. Benjamin suggested that it may be time to reinstate that campaign as "All Coughs Are Not COVID."

TBTC S31/ACTG A5349 Update

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In terms of background, Dr. Kurbatova emphasized that reducing the length of time for treating TB has been a longstanding public health goal. Shorter regimens alone can cure patients faster, and have the potential to reduce treatment costs, improve patient quality of life, and increase completion of therapy. The key study question for S31 was, "Does optimized rifapentine allow treatment shortening to 4 months for drug-susceptible TB?" This is an international, multicenter, Phase 3 randomized controlled trial (RCT). It has an open-label design, but only the Data Safety and Monitoring Board (DSMB) reviewed aggregate data during the active trial. The trial had a non-inferiority design with a margin of 6.6% and it has FDA registration quality.

S31 had 3 arms with randomization of 1:1:1 into the control group, the RPT investigational arm, or the RTP-MOX investigation arm. The control arm was a standard 6-month regimen of daily treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide. The RPT only arm was a 4-month regimen with a single substitution of rifapentine for rifampicin. The RPT-MOX arm was a rifapentine-containing regimen that in addition substituted moxifloxacin for ethambutol and continued moxifloxacin during the continuation phase. All treatment was given daily 7 days per week. At least 5 of 7 doses were required to be given by directly observed therapy (DOT). Rifapentine had a flat dose of 1200 mg and the moxifloxacin dose was 400 mg daily. Rifapentine was given with food and rifampicin 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.

Eligibility criteria included a positive sputum smear for AFB or positive *Xpert* MTB with a medium or high result. One of the strengths of S31 was enrollment of adolescents ≥12 years of age. HIV-positive participants were required to have a CD4 T-cell count ≥100 cells/mm3. Participants were excluded if they had received over 5 days of systemic TB treatment within the previous 6 months, more than 5 days of treatment with anti-TB drugs within the previous 30 days, had extrapulmonary TB, or weighed <40 kg.

S31 was built upon a strong partnership between CDC's TBTC and the National Institutes of Health's ACTG network. These are two large clinical trial networks with 10 TBTC clinical trial research sites and 24 ACTG clinical sites for a total of 34 sites. The 34 clinical research sites are located in 13 countries on 4 continents and include a broadly representative patient population. In terms of recruitment by country, about one-third of participants were from South Africa (N=949), followed by Uganda (N=553) and Haiti (N=279). About half of screened participants were enrolled, with a total of 2516 undergoing randomized. Of those, 829 were assigned to the control arm, 838 were assigned to the RPT arm, and 849 were assigned to the RPT-MOX arm. Of note, 2.7% of participants were 12 to 17 years of age and 8% were HIV-infected with a median CD4 count of 344.

The primary efficacy analysis plan required that non-inferiority must be demonstrated in both primary analysis populations (e.g., *Microbiologically Eligible* and *Assessable*) in order to declare non-inferiority for an intervention regimen. The comparison for RPT-MOX versus the control regimen would be considered first. If the non-inferiority criteria were met in this, then the comparison of the RPT arm versus the control arm would be considered. The primary analysis was stratified by the randomization stratification factors of HIV status and presence of cavitation. Each eligible participant was classified into one of 3 outcome categories: *Cured/Favorable*, *Absence of Cure/Unfavorable*, or *Not Assessable*. *Not Assessable* participants were classified as *Unfavorable* for the *Microbiologically Eligible* analysis population and were excluded from the *Assessable* analysis population. Overall, 6.9% were excluded from the *Microbiologically Eligible* analysis population. These exclusions were mainly due to drug-resistance. In addition, 4.3% were excluded from the *Assessable* analysis population. The secondary efficacy analyses included two per-protocol populations, PP95 and PP75, with 95% and 75% of the study dose received.

In terms of categories of outcomes by treatment arm, of the 109 participants classified as not assessable, the main reason was loss to follow-up with last culture being negative for mycobacterium tuberculosis (MTB). Additional reasons for being classified as non-accessible included removal from treatment due to pregnancy, death not related to TB during the follow-up period, violent or accidental death during treatment, and exogenous re-infection with MTB. Among participants with favorable outcome, the absolute majority had microbiological confirmation, and only 34 participants were clinical cures who could not expectorate sputum by the end of follow-up. Overall, 11.9% of participants experienced unfavorable outcomes, with this proportion being 9.6% among patients in the control arm, 14.2% in the RPT arm, and 11.6% in the RPT-MOX arm. Unfavorable outcomes were separated into TB-related and not TB-related. The majority of participants in the TB-related unfavorable outcomes had 2 positive cultures at or after Week 17. Other categories included loss to follow-up with last culture being positive for MTB, and change of treatment due to clinical recurrence. Not TB-related unfavorable outcomes included not completed or changed treatment due to withdrawal of informed consent, adverse event (AE), death, moving away, or loss to follow-up.

Regarding primary efficacy results for the comparison RPT-MOX regimen versus the control group, the upper bound of the 95% confidence interval for the *Accessible* and *Microbiologically Eligible* groups was below the margin of 6.6%. This means that RPT-MOX met the non-inferiority criteria for efficacy in all primary analyses. For the RTP groups, the upper bound of the confidence interval was above or at 6.6% in both primary analysis populations. Thus, the RTP only arm did not meet the non-inferiority criteria for efficacy in any primary analyses. Regarding the per-protocol efficacy results for the RPT-MOX versus the control group, this arm again met the non-inferiority criteria for efficacy in all analyses. In a similar per-protocol

comparison for the RPT only arm versus controls, RPT did not meet the non-inferiority criteria for efficacy an any analyses. Next, 14 sensitivity analyses were performed. RPT-MOX again met the non-inferiority criteria for efficacy in all 14 sensitivity analyses, while RPT alone did not meet the non-inferiority criteria in any of the 14 sensitivity analyses.

In the sub-group analyses, all interaction tests were non-significant for the RPT-MOX regimen and there was no evidence that the treatment effect differed by any sub-group. For the subgroup analysis for the RPT alone regimen, there was evidence that the treatment effect for RPT regimen differed among some sub-groups. There was a suggestion that the RPT regimen was non-inferior for female participants, participants with more than one race, those without cavities on chest X-ray (CXR), those with a low baseline acid-fast bacilli (AFB) smear grade, and participants with high time to detect (TTD) on Mycobacteria Growth Indicator Tube (MGIT) liquid medium. The retention level was high throughout the follow-up period, with 94% and 93% of participants respectively seen at the 12-Month and 18-Month visits.

The safety analysis population included all randomized participants who received at least 1 dose of the study medication. Only 10 participants never started medication and were excluded from the safety analysis and they were evenly distributed across the arms, and 2510 participants were included in the safety analysis. The primary safety outcome was the proportion of participants with Grade 3 or higher AEs during study drug treatment for up to 14 days after the last study dose. It was hypothesized that RPT-based regimens would have safety at least as good as the control regimen, but no inferiority margin was pre-specified. The objective was to estimate the difference between the regimens and describe the estimates using the 95% confidence interval. The secondary safety outcomes included treatment-related Grade 3 or higher AEs, tolerability (discontinuation of assigned treatment for a reason other than microbiological ineligibility), any serious adverse events (SAEs), all-cause death during treatment and follow-up, or liver enzyme abnormalities.

The proportion of participants with any Grade 3-5 AEs during study treatment was comparable for the RPT-MOX and control arms and was slightly lower for the RPT alone arm. The adjusted differences in the proportion of AEs between the RPT and control arms was -5.1% and the difference between the RPT-MOX and control arms was -0.6%. Thus, the primary safety outcome was quite comparable for the RPT-MOX and control arms and was slightly lower for the RPT only arm. In terms of the time to the first all-cause Grade 3 or higher AE during treatment and follow-up, AEs were persistently collected for all participants during the follow-up period of 18 months. The RPT-MOX arm had a slightly higher rate of Grade 3-5 AEs compared to the control arm, but the difference was not statistically significant. The rate of severe events in the RPT only arm was not significantly lower than in the control arm.

The primary safety outcome comparison was Grade 3-5 AEs during treatment, which was 17 weeks for the experimental arms and 26 weeks for the control arms. Similar proportions of participants with events by Week 17 were seen for the RPT-MOX and by Week 26 were seen for the control arm. In terms of secondary safety analyses, the RPT-MOX arm had a slightly higher proportion of Grade 3-5 AEs classified as treatment-related. This was an open-label trial, so this may have to do with awareness of study investigators to the treatment arm and relatedness determined by these investigators. The proportion of participants with treatment discontinuations due to any SAEs or death was slightly lower in each RPT arm as compared to controls. Overall, all-cause mortality during treatment and follow-up was 1.4% and was similar in each arm at 1.3% among controls, 1.4% in the RPT arm, and 1.5% in the RPT-MOX arms.

A closer look was taken at liver chemistries across treatment groups as several of the drugs have the potential for hepatotoxicity. Using indicators recommended by the FDA *Guidance for Industry*, this was assessed in 3 main ways. First, participants were assessed for early aminotransferase volume increase 3 or more times above normal during study treatment. There was not much difference across groups, though the control group was slightly higher. Next, high thresholds were assessed of 3, 10, and 30 times the upper limit of normal. Again, little difference was observed across the arms. Finally, combined aminotransferase and bilirubin elevations were assessed. There was a slight trend toward high frequencies in both RPT arms compared to the control arm. However, these events in the RPT arm were mainly low-level bilirubin elevations and mild to modest aminotransferase elevations.

In summary, the RPT-MOX regimen consistently met the non-inferiority criteria for efficacy in all primary and secondary analysis populations, all 14 sensitivity analyses, and all sub-group analyses. The RPT regimen did not meet the non-inferiority criteria for efficacy; non-inferiority was not met in any analysis, except certain participant sub-groups. High-dose RPT regimens were safe and well-tolerated. In terms of implications for programs, the new 4-month regimen is the first successful short treatment regimen for drug-susceptible TB disease identified in almost 40 years. The results of this study will help inform future TB disease treatment guidelines and innovations for designing future clinical trials. The study also highlights the great power of collaboration between two leading US health agencies, CDC and NIH.

ACET Discussion: TBTC/ACTG Study 31

Dr. Reves inquired as to what the outcomes were for the microbiologic failures that occurred before the 4-month regimen was complete or very shortly thereafter. Dr. Kurbatova indicated that it depended upon the specific clinical circumstance. If the event occurred at 17 weeks or later and the microbiology was positive, they would be classified in that category. If it was early treatment failure and a clinician made any treatment changes, the participant would still be classified as unfavorable on that basis. Any treatment change would lead to a participant being classified as unfavorable. The post-study outcomes varied for these individuals from site to site. Some sites had the capacity to manage treatment failures or relapses at the site, while other sites without the capacity to treat would refer participants with resurgence of TB to the national TB control program. These patients were still followed with all study-specified procedures so they would know what happened with each participant. Some participants were followed beyond the 18 months.

Dr. Horne asked if there are any data on whether participants with cavitary disease and delayed conversion at 2 months into treatment who remained culture positive were at higher risk for poor outcome and whether treatment extension would be indicated as is done with HRZE (Isoniazid + Rifampin + Pyrazinamide + Ethambutol). Dr. Kurbatova said that during the study, the extension or change in treatment was considered an unfavorable outcome. The site investigators could make this decision if they were concerned clinically about the patient. The protocol did not envision any extensions if participants still had positive cultures in 2 months. The investigational RPT-based treatment had significantly faster time to sputum culture conversion consistent with Phase 2 clinical trials on RPT.

In response to Dr. Dasgupta-Tsinikas's request for further comment on the power calculations for the primary efficacy analysis, Dr. Kurbatova indicated that the power calculations included assumptions that 12% of participants may be late exclusions, so they would be excluded from the microbiological population, and a further 12% were envisioned to not meet the criteria for the accessible population. The proportion of unfavorable outcomes in the investigational arm was

assumed to be 15%. The late exclusions in the non-assessable group were almost twice less than those envisioned by the power calculations. The microbiologically eligible population had few exclusions due to *Xpert* use, RPT resistance was quickly screened out and many sites had low non-assessables that was attributable to exceptionally high quality of implementation, very low loss to follow-up, and rigorous microbiological evaluations for all participants. The margin of 6.6% was based on multiple factors such as FDA *Guidance for Clinical Trials* on TB, previous clinical trials for treatment shortening, and feasibility.

Dr. Belknap found it interesting that the outcomes were similar in those with 75% + protocol adherence versus 95%+ adherence. He requested further information about how those groups were defined and what this is thought to mean in terms of implementing this regimen in clinical practice. Dr. Kurbatova said that they have to be cautious about interpretation of the results. There was significant overlap in between the populations. About 150 participants were in the 75% compliant population but not in the 95% population. The reason for this was the very stringent DOT implementation in Study 31. Each site did its best to make sure participants actually received doses, but each site had its own way of implementing DOT that worked for their own settings. If participants took doses, they usually took all doses. She cautioned against interpreting that RPT-MOX was a forgiving regimen. The percentage relates to every dose, so 119 doses for short regimens and 186 doses for an extended regimen. The compliance with DOT was over 95%, which means that at least 95% of the participants took the appropriate number of DOT doses. The investigators are quite confident that sites did their best to ensure that self-administered therapy (SAT) doses were ingested, because they were well-packed, participants were well-instructed, and sites checked the packaging when participants returned to the site on Mondays. There is high confidence that the SAT doses that were counted were actually taken.

Dr. Dasgupta-Tsinikas inquired as to whether all study drugs in the HMP arm were administered with food and if baseline DST or molecular resistance testing for fluoroquinolones was performed for enrolled patients. Dr. Kurbatova indicated that for both arms, sites provided some food. There were no specific requirements for the type of food. This was left to the discretion of each site. If participants declined food, a snack or sandwich was provided for them to eat within an hour. Every participant had molecular tests for fluoroquinolones. Some sites where resistance rates are high chose to use a rapid screening test for fluoroquinolones.

Dr. Vernon indicated that Study 31 has PK on all participants. The PK data and the adherence data have not yet been fully analyzed, so this will inform the issues around failures in a uniquely valuable manner. They would be interested in ACET members' thoughts on the potential for use of this regimen in the US. With eDOT increasingly available, the use of DOT should be easier and less costly in the future.

Dr. Goswami indicated that they have received questions from field staff on if there will be any CDC guidelines regarding 4 month regimen and what the timing would be. She invited thoughts from ACET members.

LTBI Campaign & Community Engagement Network Updates

CDC's Latent TB Infection Communications Campaign

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

Ms. Allen provided an update on CDC's LTBI communications campaign. In terms of background, eliminating TB requires expanding the testing and treatment of LTBI. CDC and the US Preventive Services Task Force (USPSTF) recommend testing populations who may be at increased risk. The hope is to develop a targeted campaign for LTBI and work with providers and community partners to increase awareness and encourage testing and treatment of populations at risk. The objectives of this campaign are to: 1) raise awareness about LTBI, the risk factors, and the link between infection and disease to ensure the importance of getting treatment; 2) increase the awareness of treatments for LTBI, particularly among providers, and especially about shorter regimens; and 3) encourage providers to test and treat LTBI among populations at risk.

To accomplish all of this, CDC is collecting considerable data and doing extensive audience testing. Ms. Allen shared a few findings from the most recent round of audience testing that was done in the summer, including highlights from those focus groups and interviews and how that will impact the campaign going forward. All campaign materials will be culturally and linguistically appropriate, so they will be developed in-language depending on the specific population. They are pulling from best practices like CDC's "Know Hepatitis B Campaign" as a model. An earlier CDC campaign, "Hep B United, has a similar target audience of Asian Americans and others at risk for chronic hepatitis B. Recently, that has been expanded to include other populations. Currently, this campaign is available in Chinese, Korean, and Vietnamese. The team is pulling from many different organizations and groups within CDC who have done this before to borrow as many good ideas as possible.

The high-level project timeline for the campaign has three stages, with one stage each year. Formative research was conducted in Year 1, during which some data collection instruments were designed, focus groups and interviews were conducted with the target audiences, and an analysis was conducted. This year will be focused on campaign development and pilot testing, This is in the early stages of assessing the information learned from the formative research to figure out how to interpret that to create engaging and motivating creative materials, such as public service announcements (PSAs), print advertisements, and so forth. Next year will be the implementation of the campaign in selected markets.

To provide some background on what has been done, some messages were tested with a couple of different target audiences, the largest being consumers. Virtual focus groups were conducted due to COVID-19. In-language focus groups were conducted with people born in China, the Philippines, Vietnam, India, Mexico, and Guatemala. All of these focus groups were conducted in-language except for the Filipino and Indian audiences, which were conducted in

English based upon these communities' comfortability with English. The focus groups were about two hours long. There were 7 participants per group from target markets in Los Angeles, Houston, and New York. For physician audiences, 1-hour interviews were conducted virtually due to COVID-19. In addition, there were 4 focus groups with Nurses, Physician's Assistants (PAs), and Nurse Practitioners (NPs) in these specific markets that were 2 hours long. Interviews also were conducted with 9 Civil Surgeons via phone to get an initial sense of what they feel their role is in LTBI testing and treatment and any thoughts or concerns about the technical instructions that were released recently.
A number of formative questions were posed to help inform campaign development, including the following:

- ❑ What factors influence decisions about whether to test and treat LTBI?
- ❑ What barriers and facilitators exist related to testing and treating LTBI?
- ❑ What are trusted sources of health information and communication channels?

To highlight the interviews and focus groups conducted with provider audiences, essentially providers buy into the value of testing. They were pretty well-informed about CDC guidelines, although the physicians interviewed seemed somewhat more knowledgeable than the nurses and PA groups. One important thing that came up in just about every interview and all of the focus groups is that one of the barriers to testing and treatment is physicians and healthcare providers (HCPs) not being sure or confident that insurance would cover the cost of testing and treatment for their patients. They are very worried about potentially putting any kind of a financial burden on their patients, particularly with the clientele and patient populations that these providers serve. Most do a mix of the blood test and skin test depending on a variety of reasons (e.g., resources, existing clinical protocols, insurance, et cetera), Most of the providers noted that if the patient reported a Bacillus Calmette–Guérin (BCG) vaccination, they would use the blood test. There were many questions about not being sure if a particular test or treatments were covered by insurance or state Medicare/Medicaid. All providers saw the importance of treatment, but noted that there are some adherence challenges among their patients. They reported that patients may be reluctant to take treatment when they do not have any symptoms, there may be cost concerns, or there may be concerns about potential side effects.

From the consumer side, the bottom line was that consumers are really not aware at all of TB or LTBI. They were concerned about chronic health conditions like diabetes, high blood pressure, and cancer. Therefore, there is a lot of work to be done with consumer audiences on even bringing TB as a thought into people's minds. A lot of consumer audience noted that they visit a clinic or their physician's office pretty regularly for an annual checkup and preventive tests like blood work, cholesterol testing, et cetera. Younger participants in the focus groups tended to be less likely to seek annual care, but they would seek care if they were sick or thought something was wrong. Consumers reported that they are pretty happy with their HCP and rely on them to tell them what kind of tests that they need. They mentioned that their HCP have not suggested that they may be at risk for TB or should get tested.

It was clear that the messages and themes of this campaign for consumers need to communicate that people must be made aware that TB is still an issue in the US and that it can live in one's body without making them sick and then become active. These virtual focus groups were conducted in August, so it was post-onset of the COVID-19 pandemic. They heard from people that CDC and their HCP are credible authorities. Consumers also expressed concerns about the potential of stigma related to singling out the country of origin for people at higher risk of TB. This was especially apparent among people born in China. Otherwise, no notable

differences were identified across consumer groups based on culture, language, or their region of the country they were in. Providers wanted a clear call to action and thought the CDC would be a good messenger, but also noted good relationships with their state and local health care departments. The message framework moving forward for consumers will be focused on getting their attention, providing education, motivating people to take action, and making sure that people know that if they do get a positive TB test and their diagnosis is LTBI, treatments are available. Providers expressed interest in seeing data, having a direct call to action, and making sure that they have access to official guidance.

The next steps for this year will be to finalize the campaign strategy for 2 selected Asian American audiences based on the resources available for this year. The decision was made to move forward to develop a campaign focused on reaching people born in the Philippines and Vietnam. All of this formative research has been done and is available for many different audiences, so the strategy can be expanded if more resources become available. Efforts also are underway for developing a campaign strategy for HCP, developing campaign creative materials, testing campaign materials, developing social and digital media materials, and strategies, and obtaining the needed HHS/CDC clearances to launch the campaign—hopefully next fall.

TB Community Engagement Network

Ms. Evelyn Moua
Program Manager
Tuberculosis Elimination
Association of Asian Pacific Community Health Organizations

Ms. Moua noted that the Association of Asian Pacific Community Health Organizations (AAPCHO) is 1 of 4 organizations that are leading the TB Community Engagement Network. The other 3 organizations include the AAPCHO's partners at the Asian and Pacific Islander American Health Forum (APIAHF), the Hepatitis B Foundation, and Stop TB USA. The TB Community Engagement Network's (TB CEN's) response to Asian American, Native Hawaiian, and Pacific Islander health inequities is strategically implemented by the TB CEN Steering Committee. The Steering Committee members are responsible for leveraging their individual passions and community health experience to strategically design the building blocks and implement an impact of the TB CEN in partnership with their CDC Project Officer and team; providing access to a vast network of community health centers, community-based organizations, health departments, and academic institutions; advising on effective coalition-building tactics; leaning on the medical expertise and wisdom of physicians; and driving the collective work with core values in mind as the North Star, such as placing community at the center of all intentions.

During this session, Ms. Moua provided key updates on the TB CEN inaugural membership, results of TB CEN's early strategy conversations and the vision of the TB CEN as recommended by network members, an overview of the first mini-grants program that launched in November, and the TB Summit that was convened in November. While there were some delays in launching the TB CEN earlier this year due to the pandemic, it officially launched in July. Here is a list of the 14 organizations that were identified and accepted the first round of membership invitations earlier this year:

- ❑ Arkansas Coalition of Marshallese (AR)
- ❑ Loma Linda University, School of Nursing (CA)
- ❑ Hepatitis B Initiative of Washington, DC (DC)
- ❑ Asian Services in Action (OH)
- ❑ Community Clinic (AR)
- ❑ New Jersey Hepatitis B Coalition (NJ)
- ❑ Eastern Michigan University (EMU): Center for Health Disparities Innovation and Studies (MI)
- ❑ North East Medical Services (CA)
- ❑ California Department of Public Health – TB Free California (CA)
- ❑ Florida Asian Services (FL)
- ❑ Asian American Health Coalition - HOPE Clinic (TX)
- ❑ Center for Pan Asian Community Services Inc. (GA)
- ❑ SF Hep B Free – Bay Area (CA)
- ❑ Hep Free Hawaii (HI)

Members are located in states with the highest TB incidence rates. They have demonstrated leadership in the areas of addressing both TB and hepatitis B, demonstrated knowledge of the particular subgroups that the initiative is targeting, and carry TB and LTBI expertise through their everyday research, programming, and outreach efforts. The TB CEN has geographic diversity. The TB and hepatitis B coalitions recruited allow the TB CEN to disseminate information, resources, and training opportunities more easily across hard-to-reach communities. The TB CEN's member organizations serve patients with limited English proficiency and demonstrate culturally and linguistically appropriate services to reach monolingual populations. They serve immigrants and refugees through services that promote self-sufficiency, equity, and quality of care that is trauma-informed. Many of the members are Federally Qualified Health Centers (FQHC) that serve people with limited or no health coverage. There also are members who serve people who are living with or are at risk for HIV and AIDS and community members struggling with substance abuse. In terms of ethnic groups, the subgroups the member organizations serve include Filipinx, Indians, Vietnamese, Chinese, Nepalese, Burmese, and Marshallese. Some additional subgroups served include Hispanic immigrants and African refugees.

In terms of the member organizations' capacity to serve, across the 14 organizations the TB CEN is calculated to represent a workforce of more than 2,000 clinicians, non-clinical providers, board members, administrators, partners, and volunteers. Some key titles of people who play an active role include Physicians, Health Educators, Care Coordinators, Epidemiologists, and Coalition Directors. There are 5 CHCs serving racially and ethnically diverse communities, which totals more than 141,000 patients in medically underserved areas, with 55% of those patients self-identifying as AAs and NHPIs.

The TB CEN strategies are threefold and include communications, partnerships, and programs and services. For communications, the goal is to build capacity to reach underserved AA and NHPI communities with the highest TB burden through the sharing of best practices, development of a TB CEN website, and social media campaigns. For partnerships, the TB CEN membership includes 14 organizations and 4 steering committee organizations across 10 states, and inclusion last month of 10 mini-grantees across 6 states. The TB CEN members and mini-grantees meet monthly to share resources and best practices among staff and providers. For programs and services, the TB CEN is developing partnerships to scale existing initiatives, such as mini-grants, the annual summit, and training and technical assistance.

The TB CEN hosted a collective visioning exercise with members to hear from them their vision for TB CEN. Their vision is to eliminate TB, advocate for LTBI screening and standard of care protocols for TB, and have trained and accessible HCP specialized in TB. They value learning and sharing creative strategies. Members have expertise in content, collaborations and partnerships, culturally and linguistically appropriate services, and community. Members also want to develop achievable goals.

As mentioned earlier, the mini-grants program launched in November with the purpose of increasing awareness and building provider capacity on LTBI testing, TB testing, and treatment to organizations serving AA and NPHI communities. The proposals must also have identified and aligned with TB CEN priority areas and activities to reflect 3 category areas. Of the proposals received, 10 were selected. Each award amount was between $8000 to $12,000. This mini-grants program has created an opportunity for innovation, interdisciplinary collaboration, new partnerships, and strategies that are community-driven. Many of the grantees are partnered with CHCs, CBOs, and local health departments. There is geographic diversity with the selected grantees, 5 of which are also TB CEN members. The first category area is community engagement and education. For instance, the Arkansas Coalition of Marshallese will host a Facebook and radio live effect and create a TV education video for the Marshallese community in Arkansas. The second category is provider education. HOPE Clinic in Texas will provide TB education to new and existing practitioners and their community partners through their collaboration with their local health authority. The last category is quality improvement. North East Medical Services in the Bay Area is working with their electronic health record (EHR) team and the San Francisco Department of Public Health to simplify their TB screening form and improve clinic intake procedures.

The annual “TB Summit: Eliminating TB Together” took place virtually on November 18-19, 2020. It was originally planned to be in-person in Atlanta and small and intimate. Given the pandemic, it was hosted virtually and was able to accommodate a larger audience of 146 attendees. The goal of the summit was to bring TB CEN members together; develop a strategic plan; provide a space for multiple national partners, state and local health departments, and community partners to come together grounded in the work and efforts of communities; highlight innovation; and share best practices. The kickoff to the summit was the convening of TB CEN members. The first official day of the summit consisted of two workshops on program innovation and partnerships and provider education. There was a poster exhibitor presentation and multiple networking and virtualization opportunities. The last day featured two different workshops on quality improvement and community engagement. The day was closed with a federal and regional partners panel to address updates, opportunities, and how they will continue to uplift the community. They also were able to offer continuing education credits for the summit to providers who attended live and who will watch the workshop recordings. The summit went beyond the initial expectations.

ACET Discussion: LTBI Campaign & Community Engagement Network

Ms. Cole reminded everyone that when people provide information or presentations, one of the tasks of ACET is to provide and respond to any advice they request. She recapped that there is a sense that the general population may not be aware that TB is still very much a public health concern for their health, and that it is challenging to convince people with LTBI who are not symptomatic about why they should take medication.

Dr. Reves requested that examples be shared of findings that illustrate the importance of surveying the different populations by country of origin. He has been told by an activist in Denver that there is not a single approach that works for the Korean, Chinese, Indians, and Nepalese because each culture has its own approach.

Ms. Allen indicated that they are examining this in a couple of ways. First, their contractor is working with a communications firm that has a lot of experience with Asian American audiences and a lot of depth about the different nuances and considerations that have to be made. One of the reasons the focus groups were stratified by country of origin was because they wanted to conduct these focus groups in-language and determine whether major cultural differences could be identified that may impact messaging. The provider audiences were screened to select providers who treat patients who are at risk for TB. As they move forward with development, they are being very mindful of trying not to do anything that would stigmatize the population or make people feel singled out or targeted, while at the same time designing a campaign that speaks to these groups and can motivate them and their providers to take action. They did observe differences in terms of the types of providers people see and the types of clinical environments. Overall, consumers trust whatever kind of provider they see. Those avenues will be really important to engage those providers so that they can be that trusted source of information for the patient. The campaign that is created is anticipated to be tested in the spring, and CDC is relying on the expertise of its partners with the TB CEN to help inform this as well.

Dr. Belknap emphasized that a challenge identified due to the COVID-19 pandemic regards the importance of multi-language, multicultural messaging and the negative impact the lack of that early on had on certain populations that have been disproportionately affected. He wondered whether there would be an opportunity to leverage the work related to community engagement around COVID-19 that could be transitioned to other health conditions, including TB when the timing is right. It would be prudent to have something ready at the end of the pandemic to avoid missing a window of opportunity, particularly because everyone is already exhausted.

Ms. Allen acknowledged that this was on the minds of consumers and providers when they spoke to them in August. There was a lot more general awareness around terms like “contact tracing” and “infectious disease.” In some sense, there already is more knowledge in the community about some of the terms that are with regard to TB disease and LTBI than there was pre-pandemic. There is intent to assess how the idea of increased testing and treatment for LTBI is being/should be approached in terms of whether the goal is to normalize it like a cholesterol or diabetes test as a preventative measure for staying healthy, versus a self-empowerment message that everyone must do their part to prevent TB, versus other concepts. The findings from that assessment will inform whether it is necessary to tie that in with or separate it from COVID-19. Many of the TB CEN partners are dealing with COVID-19 simultaneously with LTBI. A lot of the mini-grant recipients have been very creative with their strategies to deal with COVID-19 while also raising awareness about LTBI.

Ms. Moua added that the partners and mini-grant recipients have figured out creative ways to incorporate TB screening with drive through influenza clinics, hepatitis B screenings, and/or other current practices.

Ms. Cole observed that one of the things that happened with COVID-19 is the use of a virtual assistant to send out a text message and a survey. She wondered whether similar technology had been explored with the TB CEN membership that would be acceptable to the target audience. Perhaps that type of screening could be used for TB screening as well.

Ms. Moua said that while she had not heard of the members implementing such a technological enhancement yet, she thought this would be a great suggestion to take back to the members for consideration with their respective populations.

In response to a question from Dr. Benjamin regarding whether the use of the word “latent” might have impacted outcomes and participation, Ms. Allen indicated that they used the term “inactive TB” in the consumer group and defined LTBI as part of their level-setting.

Dr. Belknap pointed out that an important challenge to expanded treatment will be the issue of nitrosamines that are impacting all LTBI short course regimens. The surveys showed that cancer is a high priority but TB is not. While ACET would hear more about nitrosamines later in the day, this has been incredibly difficult to understand and to message appropriately to patients.

BPal Clinical Guidance Update

Sapna Bamrah Morris, MD, MBA, FIDSA
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National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Morris provided a brief presentation about draft guidance on the use of pretomanid in the combination of bedaquiline, pretomanid, and linezolid (BPaL) for the treatment of extensively drug-resistant TB (XDR-TB). In terms of history, the Global TB Alliance developed pretomanid for use. It was first discovered in 1995 by researchers at PathoGenesis Corporation. It is a nitroimidazooxazine antimycobacterial that kills actively replicating MTB by blocking cell wall production and also has some activity against non-replicating MTB. The preclinical data showed a very strong bactericidal effect. There was quite a gap between 1995 and the initial animal models in about 2000 and initiation of Phase 1 trials in the US in June 2005. Orphan drug status was obtained in July 2007. Between 2012-2014, a Phase 2b trial was conducted with pretomanid, moxifloxacin, and pyrazinamide (PaMZ) and a Phase 3 trial was planned. The Nix-TB trial began in 2016, the ZeNix-TB trial was announced in February 2018, preliminary Nix-TB results were shared in October 2018 and full results in 2019. An application was submitted for FDA approval through a Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) in June 2019.

The Nix-TB study is the most important information around the use of BPaL. In 2015, enrollment began in this open-label, single group study of the regimen of bedaquiline, pretomanid, and linezolid in the treatment of patients with XDR-TB or non-responsive MDR-TB in 3 sites in South Africa. The primary endpoint was treatment failure or relapse, so primary endpoints were negative outcomes. The 26 weeks of treatment could have been extended to 39 weeks, but this occurred in only two situations. There were 26 weeks of follow-up. There also were secondary safety outcomes. A favorable outcome was culture negative at 6 months and resolution of clinical disease, as well as no relapse within that 26-week follow-up.

In terms of the BPaL trial key findings, 109 patients were ultimately enrolled and 34 were excluded for the 26-week regimen, 71 (65%) had XDR-TB, 92 (84%) had cavitary lesions, and 100 patients received other treatment within the week prior to initiating BPaL. The majority of these patients had received multiple regimens of multiple drugs over long periods of time and had pretty devastating disease. Upon enrollment in this trial, these patients were considered to have no alternatives left. Of the 109 total participants enrolled, 56 (51%) were HIV-infected and all but 2 were on ART prior to BPaL treatment. For the treatment course, all received 200 milligrams of pretomanid daily; 400 milligrams of bedaquiline daily for 2 weeks, followed by 200 milligrams 3 times per week for the remaining time; and 44 received 600 milligrams of linezolid by mouth 2 times per day; and 65 received 1200 milligrams of linezolid daily. Two patients had positive cultures during treatment, so they extended to 39 weeks of treatment.

There were 95 patients with favorable outcomes and 12 patients with unfavorable outcomes. Among the unfavorable outcomes were 8 deaths (6 during treatment and 2 during follow-up), 1 withdrawal of consent, 1 loss to follow-up, 2 relapses in the initial 6-month follow-up, and 1 additional in the 24-month follow-up. All participants had AEs and 19 (17%) had SAEs. Among the participants, 62 (57%) had Grade 3 or higher AEs, 17 had a toxicity with ATL/AST elevations to 3 times the upper limit of normal, and only 1 patient had treatment interruption for more than 35 days. For the linezolid dosing, 16 (15%) completed 26 weeks at 1200 milligrams, 37 (34%) patients completed 26 weeks with a reduction in dose, and 56 patients had linezolid interrupted and restarted at a reduction. About half of reductions or interruptions of linezolid were due to peripheral neuropathy and about a quarter or so were due to myelosuppression [Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. The New England journal of medicine. 2020 Mar 5;382(10):893-902].

It is important to note that the way this study was written, it was initially decided that the linezolid dosing would begin at 1200 milligrams by mouth 2 times a day, knowing full well that everyone has side effects with this dose. However, the majority of data on linezolid does not come from treatment in TB. It comes from the bactericidal effect for Staphylococcus aureus (S. aureus) and enterococcus. The standard dosing for S. aureus and enterococcus is 600 milligrams BID for up to 28 days. Because of the overwhelming data there as well as the study bactericidal effect in mouse models, the investigators opted for these very sick, very drug-resistant patients to use 600 milligrams PO BID. They looked at the potential for toxicity that is known to exist with linezolid and felt that concentration above the curve would actually be reduced if it was used once a day versus the BID regimen. That is why there is a split in how people were enrolled. When they wrote the protocol, everyone who was in the study had to complete 28 days. Because of that kind of experience and maximum dosing with other bactericidal, it was made part of the inclusion criteria that everyone had to complete the milligrams at 28 days and then they could have dose reduction or interruption and potentially restart at a reduction.

Toward the end of the preliminary results, the TB Alliance applied for and received approval through FDA's LPAD to approve drugs when no other regimen exists for life-saving treatment [(FDA) USFaDA. FDA approves new drugs for treatment-resistant forms of tuberculosis that affects the lungs. https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-resistant-formstuberculosis-affects-lungs]. Language from that approval reads:

> "Use of Pretomanid Tablets as part of a combination regimen with bedaquiline and linezolid, for the treatment of adults with pulmonary extensively drug resistant (XDR), or treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis."
>
> "Approval of this indication is based on limited clinical safety and efficacy data. This drug is indicated for use in a limited and specific population of patients."

The FDA approval letter lists conditional approval based on results of further studies, 4 of which are listed here with the timelines, which may be adjusted due to COVID-19:

- ❑ Conduct a study to evaluate pharmacokinetics and safety of pretomanid in subjects with hepatic and renal impairment, with results by December 2021
- ❑ Conduct 5-year global surveillance study after the introduction of pretomanid to the market to monitor changes in M. tuberculosis susceptibility to pretomanid, which requires annual reporting and in which CDC is participating
- ❑ Conduct the ZeNix trial to evaluate various doses and durations of linezolid [+ bedaquiline, pretomanid] for treatment of pulmonary XDR-TB, which requires interim analyses and final results by July 2023
- ❑ Conduct the SimpliciTB trial to evaluate pretomanid, bedaquiline, moxifloxacin, and pyrazinamide for treatment of drug-resistant pulmonary tuberculosis, with results expected by December 2023

CDC's Draft Guidance was intended to be completed much earlier in the Spring and was initially drafted for the summer. However, it has taken this long to draft and present to ACET. CDC did draft a short Policy Brief to say something about the use of BPaL. Normally, the guideline process requires a systematic review of the literature. However, there essentially is this one study to contribute to the writing of this Guidance or Policy Brief. They opted for something that was basically targeted at commenting on the FDA approval and leave it very succinct. "ATS/CDC/IDSA Treatment of Drug-Resistance Guidelines" were published in December 2019. At the time the guidelines had gone through HHS, CDC, and IDSA, there was no time to include even the preliminary results. Right now the guideline states, "5 effective drugs for the initial 4 to 6 months of treatment, followed by 4 oral drugs for 12-18 months." There was a lot of discussion previously about how to incorporate Nix-TB. The timing of how that happened was just unfortunate.

Despite FDA approval, there is inadequate evidence to support systematic review of the literature and changing the guideline. This is what prompted the short Policy Brief. The guidance was developed by an internal CDC/DTBE committee and allows for feedback by individual SMEs, ACET, and the public. The expert panel individually reviewed the guidance and provided written comments. Because this is a short Policy Brief, it is anticipated that there probably are other additional questions on the use of this regimen. CDC has been drafting a web supplement to provide background and practical guidance to clinicians around dosing and AE monitoring. Dr. Morris just finished incorporating comments from experts and anticipates that the guidance will be submitted for clearance this week for publication in the *Morbidity and Mortality Weekly Report* (*MMWR*).

Draft Guidance:

- Pretomanid 200mg daily should be used for 26 weeks in the treatment of adults with pulmonary XDR or TI/NR MDR TB when ***a safe and effective treatment regimen cannot otherwise be provided and when administered in combination with bedaquiline and linezolid (BPaL)***
  - Bedaquiline 400mg orally daily for 2 weeks; 200mg thrice weekly for 24 weeks
  - Linezolid 1200mg daily for up to 26 weeks, with dose adjustments for toxicities or severe adverse events
  - Treatment with BPaL can be extended to 9 months (39 weeks) based on treatment response within the first 8 weeks

- Pretomanid does not have a licensed indication for
  - Use with other anti-TB meds (e.g., rifampin, fluoroquinolones, pyrazinamide)
  - Use in the treatment of drug-susceptible TB
  - Use in the treatment of extrapulmonary TB disease
  - MDR TB that is not treatment-intolerant or non-responsive to standard therapy
  - Latent TB infection

- Pretomanid has not been studied in children and pregnant patients

- Pretomanid within the BPaL regimen can be used in persons living with HIV/AIDS (PLWHA) diagnosed with XDR TB or TI/NR MDR TB disease
  - Over 50% of the participants in the Nix-TB study were PLWHA both on and off antiretroviral therapy (ART) and reported 90% favorable outcomes
  - Currently, there are no pharmacokinetic data on pretomanid in combination with ART; draft guidance has been based on interactions with bedaquiline
  - Known drug interactions with bedaquiline, both efavirenz and cobicistat (COBI) should be avoided in the ART regimen for a patient receiving BPaL

Laboratory Considerations:

- Initial and monthly MTB specimens should be sent for evaluation of resistance during treatment to one or more of the BPaL regimen drugs
  - We expect baseline resistance to any of the drugs to be minimal
    - Bedaquiline (BDQ) resistance is rare at baseline, but is increasing in areas where it is being utilized*
    - LNZ resistance is considered rare and really has not been described in the US
    - Pretomanid has not been widely tested
  - 1 of 3 relapse in the Nix-TB study had increased BDQ minimum inhibitory concentration (MIC)

[*1. Nimmo C, Millard J, van Dorp L, et al. Population-level emergence of bedaquiline and clofazimine resistance-associated variants among patients with drug-resistant tuberculosis in southern Africa: a phenotypic and phylogenetic analysis. Lancet Microbe. 2020 Aug;1(4):e165-e174. doi: 10.1016/S2666-5247(20)30031-8. PMID: 32803174; PMCID: PMC7416634.
2. Veziris, Bernard, Guglielmetti, et al. Rapid emergence of Mycobacterium tuberculosis bedaquiline resistance: lessons to avoid repeating past errors.
European Respiratory Journal Mar 2017, 49 (3) 1601719; DOI: 10.1183/13993003.01719-2016. https://erj.ersjournals.com/content/49/3/1601719
3. Ghajavand, Kamakoli, Khanipour, et al. High Prevalence of Bedaquiline Resistance in Treatment-Naive Tuberculosis Patients and Verapamil Effectiveness. Antimicrobial Agents and . . .]

Patient Monitoring:

- Safety risks associated with the regimen include peripheral neuropathy, myelosuppression, hepatotoxicity, QTc prolongation, lactic acidosis, and optic neuropathy
- Monthly monitoring for symptoms: nausea, headache, hemoptysis, chest pain, peripheral neuropathy, arthralgia, and rash
- Baseline and monthly laboratory assessment: complete blood count, comprehensive metabolic panel with liver function tests
- Baseline and follow-up evaluation: examination for peripheral neuropathy, electrocardiogram (QTc prolongation); follow-up at 1 and 2 years post-treatment completion to evaluate for relapse
- Anticipated suggestion: Sputum monitoring monthly for resistance

In terms of ongoing CDC activities, a web supplement is being completed and by the same committee. TB Centers of Excellence medical consultants are assisting providers with patients who are receiving BPaL. The CDC Laboratory Branch is evaluating MICs of BPaL and monitoring for resistance. DTBE is collecting post-marketing surveillance data on US TB patients receiving the BPaL regimen through the BAM Project. TB programs are requested to contact the DTBE Field Services Branch Medical Team at BAMproject@cdc.gov when notified of patients initiating BPaL. The lead on that project is Neela Goswami: nef7@cdc.gov

ACET Discussion: BPal Clinical Guidance

In terms of the comment about AEs being anticipated, Ms. Cole inquired as to how much of that information was included in the informed consent process when enrolling patients in the study and how much of this has gone through an Institutional Review Board (IRB). Dr. Morris emphasized that historically, outcomes among XDR patients and MDR non-responsive patients have been overwhelmingly negative, particularly in South Africa. The discussion of these AEs was certainly part of informed consent. These patients were facing a situation in which there were really no other treatment alternatives left, or in many situations may not have any other treatment alternatives. Because of the limited data thus far, it is important to make sure that patients are informed of the possible side effects of the regimen.

Regarding Dr. Horsburgh's inquiry about the availability of pretomanid, Dr. Ashkin indicated that pretomanid is available from CVS and Walgreens. Dr. Mangan added that it has been much easier in New York to get pretomanid than bedaquiline or clofazimine, which are much more difficult.

Dr. Horne reported that there have been 4 cases in Washington State and they have been in contact with other people, including Dr. Ashkin who have been using the BPaL regimen. It will be important to collect data on the actual dosing that is being used since there is a variety of dosing. In Washington State's cases, 600 milligrams daily were used initially. Subsequently, a trough-guided dosing level was used. Given that this regimen is roughly one-third the length of a standard MDR-TB regimen, he wondered if an increase in its use during COVID-19 has been observed because of social distancing and decreased resources. Dr. Ashkin indicated that they are following dosing, side effects, and outcomes in a joint project with CDC. In Florida, there would have been a lot of difficulty getting people through the MDR/XDR treatments during COVID-19 if not for BPaL. All of their patients and health departments have been very appreciative of the much less needed resources to take care of BPaL. Dr. Morris added that everyone is excited about ZeNix and anticipates positive outcomes with lower initiation of dosing. Until all of the relapse data and ZeNix, some clinicians think that it may be worth starting it at the recommended 1 month at the higher dose and then lower with reductions.

Dr. Dasgupta-Tsinikas wondered if beyond culture conversion there are any data on infectiousness and de-isolation of patients after enrollment, and what proportion of patients in the trial were hospitalized at the initiation of study regimen and for how long. She pointed out that culture-conversion is an imperfect measure of infectiousness. Dr. Morris indicated that at least half of the patients were hospitalized at the time of initiation. In terms of infectiousness, they did monitor for culture negativity. The supplemental materials for the trial show the rate at which the culture conversion occurred. As noted earlier, only 2 patients were extended to 39 weeks of treatment and 1 of those had a culture positivity at 3 months and 1 at 4 months. Everyone else in the study had culture conversion by 2 months. The median time to culture conversion was 6 weeks.

Regarding an inquiry from Dr. Mangan about what options there are if patients do not tolerate the BPaL regimen, Dr. Ashkin indicated that they have limited experience with about 30 patients throughout the US who have been started on BPaL and over half of them have completed. The tolerance has been amazing, so it is not clear what they would do for intolerance. There are a lot of options in the US, but the issue of intolerance has not arisen. They have a number of patients, including physicians, who had MDR and were surprised at how easy the regimen is.

Dr. Goswami commented that it is important to note that even when the BDQ in a patient's BPaL regimen is "stopped" and other agents are being looked at, the BDQ will hang around for a long time given its long half-life.

Dr. LoBue emphasized that medicine is both science and art. Unfortunately for this particular regimen, science is extremely limited at this point. The study that the FDA approval is based on has 100 patients in a single arm study compared to the Study 31 RCT with almost 2500 patients. The FDA moved on this because these people are in desperate straits and do not have a lot of other options. Having said that, once pretomanid was approved as part of this regimen, like all other drugs, physicians are free to use drugs off-label in ways that they think are appropriate. That is the art of it based on other experience they have in treating patients. In terms of FDA and CDC, it is pretty clear what the indication for this drug is, which is very limited. It is not for all MDR patients. When CDC provides guidance, it must be done based on science. Right now, the data are extremely limited and do not support straying much from what the FDA has put forward. Hopefully this can be expanded as more information becomes available from ZeNix and observational data.

Dr. Armitige reiterated that the BPaL regimen is based on a single paper and was approved for a single purpose. If one strays from the spirit of this approval, that must be noted. Good information is imperative and the more variability there is, the less likely it will be possible to understand what is important about the regimen itself.

Dr. Dasgupta-Tsinikas reported that in Los Angeles County, they have very limited but favorable experience using Pa off-label as a component of a "BPaL-Plus" strategy in highly selected patients. She knows that this may be controversial. Interestingly, use of BPaL entails an off-label use of BDQ, which is supposed to be used alongside more than 2 effective companion drugs.

Dr. Haley indicated that the Southeastern National Tuberculosis Center (SNTC) has guided use of BPaL in 22 patients in their region, and has started 600mg per day, measured drug levels at 2 weeks and adjusted either the dose or the dosing interval to ensure the peak is 12-26 and the trough is <2 (associated with lower risk of adverse events). Their patients did generally have less burden of disease compared to South Africa, though they did have about 1/3 with cavitation.

Nitrosamine Impurities in Rifamycins

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Division of Pharmacology/Toxicology for Infectious Diseases
Food and Drug Administration

Dr. McMaster presented pharmacology and toxicology considerations for nitrosamines in rifamycins in terms of nitrosamines and carcinogenicity, nitrosamine impurities in drugs, the FDA response, and recommendations for mitigation.

The term “nitrosamine” refers to any molecule containing the nitroso functional group (NO+) bonded to an amine. The compounds can form by a nitrosating reaction between amines (secondary, tertiary, or quaternary amines) and nitrous acid (nitrite salts under acidic conditions). FDA has identified 7 nitrosamine impurities that theoretically could be present in drug products: NDMA, N-nitrosodiethylamine (NDEA), N-nitroso-N-methyl-4-aminobutanoic acid (NMBA), N-nitrosoisopropylethyl amine (NIPEA), N-nitrosodiisopropylamine (NDIPA), N-nitrosodibutylamine (NDBA), and Nnitrosomethylphenylamine (NMPA). Five of them (NDMA, NDEA, NMBA, NIPEA, and NMPA) have actually been detected in drug substances or drug products.

Nitrosamines are found in many things that people encounter in their daily lives. Among foods, high nitrosamine levels have been detected in bacon, bacon grease, blood sausage, turkey, ham, and fried chicken. Higher temperatures increase nitrosamine formation in foods. For example, nitrosamine levels in fried bacon are almost 6 times the level as bacon cooked in microwaves. In the saliva, 5% of nitrates are reduced to nitrites. These nitrites react in solution with secondary and tertiary amines to form *N*-nitroso groups within the gastrointestinal (GI) tract. Often, manufacturers will add ascorbic acid to prevent nitrosamine formation. Nitrosamines are also found in agricultural chemicals, tobacco, detergents, cosmetics, et cetera.

There is concern about these nitrosamine impurities because many nitrosamines cause a high incidence of tumors in animals at low doses after short durations, including single doses. Early evidence was seen as far back as 1956 by British scientists John Barnes and Peter Magee who were screening chemicals being proposed for use solvents as in dry cleaning when they discovered that dimethyl nitrosamine at doses as low as 50 ppm produced a very high incidence of hepatic tumors in rats.[1] Over the years, it has become clear that many other nitrosamines exhibit carcinogenic potential. Results from a lifetime drinking water study published in 1983 showed that even very low doses of NDMA of less than 1 milligram per kilogram per day resulted in liver carcinomas in 88% of the animals[2] [[1]Magee, P.N. and Barnes, J.M. 1956. The Production of Malignant Primary Hepatic tumors in the Rat by Feeding Dimethyl nitrosamine. Br J Cancer 1956 Mar; 10(1): 114–122; [2]Brantom, P.G., (1983) Dose-response relationships in

nitrosamine carcinogenesis. PhD thesis. University of Surrey, Guildford. Carshalton, UK (BIBRA), 158 pp].

Other publications have shown that even single doses of then dimethyl nitrosamine can produce adenomas and carcinomas. Studies have also shown that MDMA intake was correlated with a subsequent incidence of colorectal cancer. Intake of smoked and salted fish was also significantly correlated with increases in colorectal cancer. Smoked and salted fish are well known to contain high levels of nitrosamine. While the intake of cured meat is also associated with an increase in the risk of colorectal cancer, the increase was not statistically significant [Knekt, P et al. (1999) Risk of colorectal and other gastro-intestinal cancers after exposure to nitrate, nitrite and N-nitroso compounds: a follow-up study. Int. J. Cancer. 80(6):852-6].

Recently, FDA was notified that nitrosamine impurities were present in certain samples of rifampin and rifapentine. FDA saw the need to address the issue because of carcinogenic potential of these compounds. A Public Notice was posted on the FDA website in August 2020. Despite this high carcinogenic risk, 1.4 million people were dying from TB in 2019. Therefore, the risk-benefit ratio needs to be considered very carefully. Given the very important nature of maintaining cases on TB drugs, cases were advised to stay on their medications and to consult their physicians about future actions regarding these impurities. FDA's response to the discovery of these impurities has been robust. First, FDA and the manufacturers are investigating the origins of these impurities. FDA is developing testing methods for regulators and industry, and has continued ongoing review, surveillance, and compliance efforts in order to ensure that safe drugs are available to the American public.

There were no carcinogenicity data available regarding these specific impurities, so FDA had to use a surrogate. NDMA was selected as a conservative surrogate for MNP and CPNP. The acceptable intakes were determined to be 0.16 ppm for MNT and 0.1 ppm for CPNP. To avoid shortages and to ensure access, the agency will not object to certain manufacturers distributing rifampin containing MNP below 5 ppm or rifapentine containing CPNP below 14 ppm until they can reduce or eliminate these impurities. Manufacturers should contact the Center for Drug Evaluation and Research (CDER) if they find that the nitrosamine impurity levels in their drugs exceed the acceptable intake limits of 0.16 ppm for MNP and 0.1 ppm for CPNP. Another thing the agency did was to publish a guidance for industry. The guidance discusses potential causes of impurities, makes recommendations to manufacturers, and provides recommended timelines for risk assessment.

One of the most frequently asked questions FDA gets from sponsors or interested groups is, "How do you determine the acceptable intakes for these various impurities?" The acceptable intake is a daily exposure to a compound that approximates a 1:100,000 cancer risk after 70 years of exposure. It is consistent with ICH Guidelines. Using NDMA as an example, FDA looks at non-clinical data. In this case, the began with the TD_{50} value, which is the dose giving 50% tumor incidents equivalent to a cancer risk probability of 1 in 2. In this case, TD_{50} value for NDMA was 0.0959 mg/kg/day in a rat based on a publication by Peto et al and 0.0959 for the mouse, which was obtained from the Carcinogenic Potency Database (CPDB). FDA chose to use the more conservative rat value for this calculation. TD_{50} value was divided by 50,000 and then multiplied by 50-kg body weight, which represents the weight of the most vulnerable patients. This results in 0.0000959 mg/day NDMA. Hence, a daily lifelong intake of 96 ng/day NDMA corresponds to a theoretical cancer risk of 1 in 100,000 and represents an acceptable intake when this is present as an impurity. The FDA guidance can be consulted for more details regarding these calculations. If there is an impurity, FDA first determines if there are actual data

for TD_{50} associated with that impurity. If not, then a surrogate is chosen such as in this case with NDMA. In this instance, 0.96 ng/day NDMA over the 0.16 ppm acceptable intake.

Another question FDA is frequently asked regards whether the treatment duration affects this this calculation. For instance, is it necessary to worry about it if the drug is being given for only a week? The FDA calculation is a lifetime-based extrapolation. The agency is not considering the AI based on a less-than-lifetime duration for a number of reasons. First, nitrosamines are listed in the cohorts of concern in the ICH M7(R1) among a group of highly potent mutagenic carcinogens. It is classified as a probable human carcinogen. Several studies have shown nitrosamines to cause tumors at low doses and after short durations. The problem with using a less-than-lifetime approach is that it could result in a high acute used nitrosamine intake, particularly from medicines that are given for short durations. Because there is uncertainty about how the cancer risk of the cohort of concern carcinogen changes with short durations of exposure, FDA has decided to take the conservative position to use a lifetime approach as opposed to a less-than-lifetime approach.

Each drug will end up with a different acceptable intake based on the drug's maximum daily dose (MDD). The other point is that the limits are applicable only if a drug product contains a single nitrosamine. If nitrosamines without published AI limits are found in drug products, the manufacturer should use the approach outlined in ICH M7(R1) looking at similar products and also should consult with the agency regarding the acceptability of their proposed amendment. The agency also published an FDA testing method to provide an option for regulators and industry to detect nitrosamines. There often are some inconsistencies going from lab to lab and test to test. Therefore, FDA wanted to ensure that the best methods are available. This is available on FDA's website: https://www.fda.gov/media/138617/download

The FDA also has published *Control of Nitrosamine Impurities in Human Drugs* which discusses the causes of the presence of nitrosamines in drugs, including sources of amines that can form in nitrosamines, contaminated solvents, contaminated catalysts, other reagents, contaminated raw materials, contaminated excipients, et cetera. There also are recommendations for mitigations to drug manufacturers and other players in the drug supply chain for addressing these issues. The guidance also recommends timelines. For example, manufacturers of approved drugs are expected to conclude a risk assessment within 6 months of the publication of this guidance. If applicants need more time, they should contact the agency to discuss possible extensions with the relevant disciplines. Depending on many factors, the risk may be higher or lower. For those in the pre-NDA stage, risk assessments should be conducted as needed prior to the submission of the NDA. Applicants with pending applications should conduct the risk assessment expeditiously and inform the agency if confirmatory tests find nitrosamine levels above the acceptable AI limits and to amend the application as appropriate. Some companies are making progress. For example, GlaxoSmithKline (GSK) is already getting a better understanding of the root causes of the presence of nitrosamine impurities in its rifapentine product [King, F. et al, Ranitidine—Investigations into the Root Cause for the Presence of N-Nitroso-N,N-dimethylamine in Ranitidine Hydrochloride Drug Substances and Associated Drug Products. Org. Process Res. Dev. 2020, 24, 12, 2915–2926]. In this case, the root cause analysis suggested that the presence of the NDMA resulted from a slow degradation of the rifapentine molecule.

In closing, Dr. McMaster stressed that the FDA encourages all interested parties to discuss any quality problems with any of their products, the review, and/or with the FDA Adverse Event Reporting System (FAERS). FDA is always willing to work with sponsors and applicants to maintain the necessary supply of safe and effective drugs.

ACET Discussion: Nitrosamine Impurities in Rifamycins

Regarding an inquiry about whether this is a new problem or a newly discovered issue, Dr. McMaster indicated that the technology has changed and has been improved. FDA was notified of this problem starting a couple of years ago. It remains an unanswered question that has been raised many times before. More recent papers about nitrosamines refer to different technology being used to measure nitrosamines compared to what was done earlier. The position FDA is in is that they know right now there are higher than acceptable levels of nitrosamines, so they are working as hard as they can to get rid of them because they think that there is a risk.

Dr. Marks inquired as to whether the amount of nitrosamine intake when taking a typical DS TB regimen can be compared to intake of a strip of bacon daily for 6 months. Dr. McMaster referred to a paper in 2019 in the journal *Food Additives and Contaminants* that lists fried chicken as having 1.3 micrograms of NMDA per kilogram and fried bacon as 1.8 micrograms of NMDA per kilogram. He chose fried chicken as more dangerous because people tend to eat more fried chicken then bacon. His understanding is that a chicken breast from Kentucky Fried Chicken is over the 0.16 limit.

Regarding a question about whether risk is dependent upon body weight, if there are differences in how people metabolize the substance, and if different races and ethnicities are impacted differently, Dr. McMaster indicated that body weight is an issue and the formula includes 50 milligram body weight. However, the agency has taken a very conservative approach and basically factored all those things in. Using the very conservative position of 0.16, weight, ethnicity, and duration of dosing should not matter.

In terms of whether this discussion pertains to rifampicin only or all rifamycins, Dr. McMaster indicated that other classes of drugs have been found to have nitrosamine impurities. There are other drugs among the TB drugs. FDA also has looked at how a drug may be generated. There are theoretical points in the in the manufacture of the rifamycins where they see that nitrosamines could possibly be regenerated. As they continue to probe various drugs and have asked people to look, they fully expect that there are going to be other drugs with high levels of nitrosamines. The theoretical formation of nitrosamine is very present for all of the synthetic methods as well.

Dr. Belknap wondered what would occur if the manufacturers are not able to achieve the acceptable limit targets, and how to have conversations with patients about the meaning of allowable levels. Dr. McMaster indicated that FDA is working very closely with manufacturers. The manufacturers provide updates and can request more time if needed if they are having problems. He did not think they had gotten to the place where people have not been able to do this and are going to give up. Some manufacturers have reported that they are having a difficult time achieving these goals, but FDA is working with them and provides extensions as necessary. They must balance the need to provide these very important life-saving drugs with trying to reduce the risk of potentially carcinogenic compounds.

Dr. Vernon asked whether there are any studies demonstrating an association of higher nitrosamine levels and human exposures, whether the levels in salted fish over a lifetime are higher than the levels in 6 months of rifamycins, and if so whether FDA has taken any action on this. Dr. McMaster emphasized that salted and fermented fish are very high. The reviews of nitrosamine levels increased from 1985 onward. Due to the awareness of nitrosamines, less nitrites are being used in bacon, smoking technology has changed such that smoked fish is not the same as it was 20 years ago, and sauerkraut remains an issue. Salted fish and fermented fish are extremely high, but people do not tend to eat too much salty fish and that mitigates it to some extent.

Regarding a question about whether there is evidence to support the approach being used to estimate the risk by dividing the TD_{50} by 50,000, Dr. McMaster clarified that the 50,000 is used because they are trying to estimate a 1 in 100,000 risk. This is the approach recommended by ICH M7 (R1). An international group of toxicologists looked at this and determined that this is the approach that is useful in order to approach determining what the risk is for carcinogenicity: https://www.ema.europa.eu/en/ich-m7-assessment-control-dna-reactive-mutagenic-impurities-pharmaceuticals-limit-potential

Dr. Ray proposed suggesting a “nitrosamine” exchange approach to patients similar to carbon credits.

Dr. Vernon noted that in the case of tobacco, the evidence became clear as efforts were made to assess this possibility. His sense was that this has not happened with the nitrosamine issue. Perhaps they are looking where the light is instead of where the keys were lost. An experienced academic toxicologist told him and a colleague that the problem with food is not nitrosamine in the food, but the nitrites used to preserve many foods and the fact that these are converted to nitrosamine in the stomach and intestine, and that this endogenous production is the real problem.

Dr. Benjamin asked if by salted fish he meant dry preserved salted fish. Dr. McMaster indicated that the paper refers to “salted fish” (NDMA up to 39 µg/kg), which he assumes means dried preserved salted fish. Dried shrimp (up to 132 µg/kg) and broiled squid (up to 300 µg/kg) were even higher [Please See: Tricker, A. et al. Carcinogenic N-nitrosamines in the diet: occurrence, formation, mechanisms and carcinogenic potential. Mutat Res. Mar-Apr 1991;259(3-4):277-89].

Dr. Temesgen inquired as to how the FDA position on nitrosamines compares to that of the European Medicines Agency’s (EMA’s) position. Dr. McMaster replied that the FDA has regular meetings with the EMA to discuss this matter. The approaches are very similar. For example, they also do not use a less-than-lifetime approach to compensate for short treatment durations.

Dr. McMaster shared another useful recent reference for nitrosamines in foods: Lee, H. Literature compilation of volatile N-nitrosamines in processed meat and poultry products - an update. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2019 Oct;36(10):1491-1500.

eDOT Study Update

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Communications, Education & Behavioral Studies Branch
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
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Drs. Mangan and Burzynski provided an outline of the study itself, shared the results of the analyses relative to the primary objective, provided highlights from the preliminary analyses relative to select secondary objectives, and discussed the next steps going into the next year. Work on developing the study protocol and data collection tools began in early 2016. Recruitment began in July 2017 and concluded in October 2019. The participants recruited toward the end of the study were followed until January 2020. The past few months have been spent on data cleaning and analyses, as well as presenting some of the preliminary results at the International Union Against Tuberculosis and Lung Disease (IUATLD; The Union) World Conference in October 2020.

The use of video enabled or electronic directly observed therapy (eDOT) has been increasing, yet evidence surrounding the efficacy of eDOT is limited. The investigators began with the hypothesis that eDOT is non-inferior to or as good as traditional in-person DOT (ipDOT) for monitoring treatment adherence. To test this hypothesis, they conducted a randomized, two-period crossover, non-inferiority trial. The non-inferiority margin was set at ≤10% difference between the two DOT methods. Following the randomization, participants aimed to complete 20 medication doses with one DOT method and then switch DOT methods for another 20 doses. Following these two crossover periods, participants chose the method of DOT they would use the remainder of their treatment. The study was conducted in 4 TB clinics in NYC and patients were enrolled at the time they began outpatient treatment.

The primary objective was to estimate the difference in the percentage of non-holiday, weekday medication doses completed when observed by eDOT versus ipDOT. The analysis was restricted to patients with 10 or more medication doses observed with each DOT method in each of the crossover periods. Doses were not included if the treating clinician withheld medications or the patient was admitted for in-patient care or was incarcerated. The secondary objectives included comparing the type, frequency, and time between initial symptoms of AEs and discussions with the medical provider across the DOT methods; participants' perceptions of the care received and their overall satisfaction by DOT method; their choice of DOT method following the crossover period; adherence using live video versus recorded DOT; patient characteristics associated with adherence; and treatment outcomes by DOT method. Also, an economic evaluation was conducted to assess both program and patient costs.

As noted, participants aimed to complete 20 medication doses with each DOT method. During ipDOT, participants were able to choose between clinic or community-based DOT. For eDOT, participants could choose either live video conferencing or recorded videos. All medical care was provided in accordance with the NYC Bureau of Tuberculosis Control (BTBC) case management policies. Patients were eligible for inclusion if they were 12 years of age or older, had a laboratory-confirmed or clinical diagnosis of TB, had a residence that was accessible for visiting, and had no plans to move from the area within 9 months of study enrollment. Patients were not eligible to be enrolled if they were taking an injectable medication or had a comorbidity or circumstance that precluded a physician's comfort with eDOT. Also excluded were those with a cognitive or physical disability that prevented their use of eDOT and who did not have a caretaker able to assist them.

Four analytic approaches were used to test for non-inferiority. In the intention to treat (ITT), the DOT method of each dose was represented according to the participant's randomization assignment rather than the actual DOT method a participant may have used. The per protocol (PP) analysis was restricted to patients who completed 100% of doses using the DOT method according to their randomization assignment. The per protocol 85% analysis (PP85) 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 15% of doses were represented according to the methods patients actually used. In the empirical approach (E), the DOT method for each dose was represented according to the methods actually undertaken by a patient regardless of study assignment. The analysis takes into account patients whose doses were intermittently non-compliant or who chose to switch DOT methods during the study. Patients in the E analysis are the same as the ITT analysis, except the representation of DOT method differs.

Within the 4 analytic approaches, each scheduled and observable dose of medication was realized as a binary outcome. Staff observed the patient completely ingest the medication dose or they did not. The binary outcome was analyzed with the generalized linear mixed effects regression model that included fixed effect predictors representing the DOT method, the patient's randomization group, the study period, the dose outcome during each of the 2 preceding scheduled and observable doses representing carryover effects, and season represented as a calendar quarter. The potential influence of season was explored because of the anticipated demands of adhering to DOT schedules, especially for ipDOT in a seasonal climate in a large metropolitan area. Additionally, correlations were expected among doses observed with the same patient and among patients treated at the same clinic. To minimize the bias from these correlations, the model included random effects representing each tuberculosis treatment clinic and each patient nested within their respective clinics. To evaluate the non-inferiority of eDOT, the percentage of medication doses that staff observed the patients completely ingest while using eDOT was subtracted from the percentage of doses staff observed the patients ingest while using ipDOT. The variation of this percentage difference was then estimated in the form of a 95% confidence interval using bootstrap technique. As noted earlier, the limit of non-inferiority was set at 10%, which is to say that the percentage difference between ipDOT – eDOT could not be more than 10% to conclude that eDOT is non-inferior to ipDOT.

Moving on to the results, the demographic profile summarizes the characteristics of all 216 persons who enrolled in the study alongside the 173 participants who were included in the ITT and E analyses, the 43 participants including the PP analysis, and the 138 participants included in the PP85 analysis. Overall, participants ranged in age from 16 to 86 years. The majority were male, non-White, and non-US born. Approximately a third reported Hispanic or Latino ethnicity.

A little more than a third reported Asia as their global region of birth. Over half were employed at the time of study enrollment. A majority possessed or had access to a video-enabled device prior to enrollment in the study. There are some differences between the groups included in the 4 analytic approaches used. Notably, the PP analysis included a small proportion of males and persons who reported Hispanic or Latino ethnicity. This group is also comprised of a larger proportion of persons who reported being born in Asia.

Dr. Mangan next described total number of weekday, non-holiday doses that were scheduled for DOT and included in each of the 4 analyses; the total number of doses staff observed the patients completely ingest; the percent of doses taken with ipDOT and the percent taken with eDOT; and the 95% confidence. The proportion of doses observed by the 2 methods is quite good. The percentage difference between the two DOT methods ranged from -1.8% to -4.1%, which falls below the non-inferiority Δ of 10% or less. The results of the PP85 and E analyses illustrate that eDOT is not inferior yet not superior to ipDOT. The results of the ITT analysis indicate that eDOT is non-inferior and superior to ipDOT. This illustrates that eDOT is as good as ipDOT and the difference between the two DOT types is much less than 10%.

In terms of the results for some of the secondary objectives, following the two crossover periods, participants were asked to complete a survey that asked them to compare eDOT to ipDOT; their overall satisfaction with eDOT and ipDOT; their opinions about staff members' interpersonal skills, patient education provided, and patient-centered communications; their trust in the staff; self-stigmatization; and their preferred approach to medication administration for the remainder of treatment. Among the 216 enrolled participants, 122 (56%) completed 10 or more medication doses while using both ipDOT and eDOT and completed the patient questionnaire. There is a lot of detail from this questionnaire, so Dr. Mangan highlighted just a few of the results.

When asked to compare eDOT to ipDOT, overall 59% to 85% of participants felt that eDOT offered greater opportunity to maintain their independence, keep their schedule as it was prior to their illness, keep their diagnosis and treatment private, cope with the treatment, and take treatment more easily. In contrast, 57% to 66% of participants noted no difference between the 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.

When asked to rate their overall satisfaction of eDOT and ipDOT, 96% of those who used live video eDOT indicated that they were satisfied versus 92% of those who used recorded video DOT. In comparison, 79% of those used community-based ipDOT indicated that they were satisfied with this method of DOT, while 67% of those who used clinic-based ipDOT were satisfied. As noted earlier, following the crossover periods, the participants could choose the method of medication administration for the remainder of their treatment. Of the participants, 84% chose eDOT, 4% chose to self-administer their medications, 6% chose ipDOT, and an additional 6% had no preference documented. It is notable that among those patients who chose ipDOT, none chose clinic-based DOT.

Dr. Burzynski indicated that thinking about clinicians concerns regarding the use of eDOT and patient safety, the investigators also compared the type and frequency of AEs and the time between initial symptoms and discussion with medical providers across the DOT methods. To clarify, AEs were defined as "undesirable signs and symptoms associated with anti-TB

medications and health-related symptoms that arose while participants underwent TB treatment." To be clear, health-related issues were reported events that were not the result of TB disease or TB treatment. Upon enrolling into the study, participants were given instructions for how to report AEs and what types of problems to report. Study Coordinators prospectively documented AEs on a specific study data collection form. Clinicians reviewed the AE study form and graded symptom severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). AEs were analyzed by the DOT method used by patients immediately prior to the recording of the event.

Among 216 enrolled participants, 63 (30%) experienced AEs. It is not uncommon for TB patients to report multiple AEs. In this cohort, 63 participants reported a total of 87 AEs. Notably, the median age of participants who reported AEs and those who did not was 42. Among the participants who reported AEs, a higher proportion were female. Additionally, more Hispanic persons reported AEs. In terms of the DOT modality used, 40 AEs were reported by 30 patients while using ipDOT, 47 AEs were reported by 40 patients while using eDOT, 7 patients reported multiple AEs while using ipDOT and eDOT. The median time between symptom onset and patient discussions with providers was 1 day for both eDOT and ipDOT. Some eDOT AEs required more time as demonstrated by the greater IQR. Ultimately, no patients were switched from eDOT to ipDOT due to AEs. In terms of the most common symptoms, severity of the AEs reported, and management of AEs by DOT method, the most commonly reported symptoms were similar for both eDOT and ipDOT AEs. Few AEs were graded 3-5, with 13% cumulatively. Most of these events were graded 3. Few patients were hospitalized, at 10% cumulatively. One patient experienced a life-threatening event.

At the same time planning began for the randomized trial, funds were set aside to conduct an economic evaluation of eDOT in low, medium, and high TB incident settings. DTBE solicited applications from programs that were routinely using eDOT and willing to prospectively collect data. This evaluation was done in collaboration with DTBE, the Rhode Island Department of Health (RIDH), the San Francisco Department of Health (SFDPH), and the New York City Bureau of TB Control. The results were recently published in the November issue of the *American Journal of Public Health* (*AJPH*) and can be accessed at the following URL: https://ajph.aphapublications.org/doi/epub/10.2105/AJPH.2020.305877

What sets this economic evaluation apart from others in the literature is that it is done from a societal perspective. In other words, data were collected to assess both patient and health department costs. In terms of the average DOT cost per session, 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 about $34. This may help to explain the relatively low overall satisfaction with clinic-based DOT that was observed on the patient opinion survey. Notably, the Centers for Medicare and Medicaid Services (CMS) 2019 Physician Fee Schedule includes two codes that allow for Medicare billing by physicians and FQHCs for live and recorded video DOT at an average of $12.91 reimbursement per session. Given the three site average cost of $11.54 per video DOT recorded session, it appears that the Medicare reimbursement is slightly greater than the health department cost of providing the service. However, it is important to note that the cost of DOT varied 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 SF sites, the cost of video DOT with recorded videos was not statistically significantly different from the cost of community DOT Rhode Island. Why are costs per session greater for small health departments in lower incidence settings? In a

nutshell, it becomes an economy of scale. There are fewer patients over which to spread fixed costs across. These results suggest the need for low TB incidence settings to seek methods by which fixed costs, such as equipment and purchased software, could be integrated across localities therefore potentially enabling the state health departments to reduce the cost per session.

Dr. Mangan concluded that in this randomized crossover trial which was conducted in an urban TB program with a long history of successful implementation of ipDOT, eDOT was found to be non-inferior to ipDOT as an approach for monitoring treatment adherence. This finding was associated with statistical confidence of 95% and was consistent across the ITT, PP, PP85, empirical analyses. The investigators estimate that the staff-observed patients completely ingested 1.8% to 4.1% more medication doses when eDOT was used compared to an ipDOT was used. Thus, eDOT may be as effective as traditional DOT methods for improving treatment adherence, clinical outcomes, equity, and patient-centered care. It is worth noting with respect to patient-centered care that among the 173 participants included in the statistical analyses, 84% percent chose to continue treatment using eDOT at the conclusion of crossover periods. The economic evaluation linked to this trial determined that eDOT was associated with lower costs from a societal perspective. At this time, work is well underway on multiple manuscripts that the investigators hope to submit to journals in the coming months. Dr. Burzynski will present the results of the study at the IUATLD North American Region Meeting in February 2021. Given that this dataset is rich, the hope is that the investigators and many others can conduct additional analyses of interest.

Advice requested from ACET:
1. Feedback in response to the study results and/or next steps outlined in the presentation
2. Suggestions for expanding access to eDOT among programs, especially those with low TB incidence
3. Recommendations for future digital health interventions to facilitate TB control activities

ACET Discussion: eDOT Study
Dr. Horsburgh expressed some concerns about the availability of electronic connectivity to do this for all patients, and requested comments on selection bias in the study based on having the ability to access the system. Dr. Mangan responded that the study showed that a greater majority of the patients who were enrolled into the study did have electronic devices that they could use. In addition, NYC has the availability of phones that patients can take out on a loan. They sign an agreement and they are able to use the phones for the duration of their treatments, with the expectation that they return the phones when they finished. Being able to provide phones is one way to minimize bias. Connectivity is very important. One of the other analyses that is planned is that for every dose recorded, any type of problems that arose were recorded as well, such as technical issues with connectivity. An initial analysis has been done on these data that were presented at the 2018 Union conference.

Regarding an inquiry about whether there were many older patients who were not comfortable with the system, Dr. Mangan indicated that older individuals were enrolled. Though she did not immediately recall how many of those individuals chose ipDOT based, they do have these data. The demographics are being assessed more closely. The investigators received some of the initial demographics when the dataset was transferred to CDC in February. In August, there was a download of data with a lot more of the demographics included. The statistician is looking at those data now. Dr. Burzynski added that in general, they were pleasantly surprised at how many older individuals were able to use video DOT either with some family help or the

instruction of the clinical staff.

Ms. Cole inquired as to whether there were any problems with misuse of the loaner phones. Dr. Burzynski indicated that they had the ability to block international calls with the loner phones. While they lost a few phones, the problems were few and far between and they are not aware of any inappropriate use.

Mr. Watts indicated that the National Health Care for the Homeless Council found that telehealth during COVID-19 resulted in reduced barriers for many patients experiencing homelessness. He wondered whether the investigators looked at housing status and if so, whether they observed any differences by housing status. Dr. Mangan indicated that housing status was not something that they collected specifically in this study. One of the things that they did have was an inclusion criteria that potential participants had to have a residence that was available for visitation. People who were stably housed in a shelter could be enrolled in the study, but that was not something very specific that they looked at. It will not be possible to ascertain how COVID-19 might have impacted that because data collection ended on January 10, 2020. Mr. Watts suggested that they could determine which addresses were shelter sites and stratify their experience. Since it is difficult and expensive to reach this population that is at higher risk, it may be helpful to see if the benefits extended to patients in the study who were experiencing homelessness in the study.

Regarding Dr. Belknap's question about what platforms were used for the synchronous and asynchronous eDOT, Dr. Burzynski indicated that for the synchronous they used Skype for Business, which worked pretty well. It is somewhat cumbersome to use, but it was approved by their Information Technology (IT) department and is Health Insurance Portability and Accountability Act (HIPAA)-complaint. For the asynchronous, they used SureAdhere which worked very well. With that, they were able to load the app onto patients' phones, often their own phones. They patients would record the videos and the team would watch them the next morning, which worked very well.

Mr. Dupree offered some perspective from a low incidence area, noting that Colorado is low medium depending on the year. They were able to democratize as best they could the eDOT platform. Their vendor charges by the month for patients. The state took on the cost of that so that local public health would not see that cost passed on to them. They also made 4 smart phones available to their biggest clinic to try to level the playing field, so not owning a smartphone was not an impediment to getting eDOT when it was appropriate. That has worked out really well, because there are months where they have just a handful of people on treatment and the invoice reflects that. Recently, there has been a lot more eDOT with the COVID-19 fog everyone is in right now and the lack of capacity. It has been a win-win for Colorado and they have been very happy with their vendor.

Dr. Loeffler commented that she is from the low incidence area of Portland, Oregon. They currently have almost exclusively foreign-born, older adults and a lot of end-stage renal disease (ESRD). Some people have technical challenges and connectivity issues and many build strong bonds with ipDOT staff.

Dr. Temesgen requested a summary of the differences between the synchronous and asynchronous patients in terms of outcomes, AEs, et cetera. To him it would be major progress if the asynchronous is shown to be as good as in-person. Dr. Burzynski responded that looking at this more closely is one of the planned secondary analyses. The participants were given a

choice and about half chose synchronous and half asynchronous/synchronous. At least in theory, some people might think that a direct patient-provider interaction would be better for patients who may like talking to somebody every day and getting some feedback. The difficulty with that is having to schedule it. Patients with difficult work schedules might like the flexibility of having asynchronous eDOT that allows them to record the video almost any time of the day when they are going to take their medication, and the team can watch it the next day when they have time. That gets around having to schedule appointments, but the tradeoff is losing the direct connection between the provider and patient.

Dr. Belknap wondered whether study enrollment was restricted at all by primary or preferred language. Dr. Mangan indicated that it was not, given that the consent forms were translated into multiple languages and the clinics have the language line. Language was not a major barrier for this study.

Ms. Cole asked whether the cost of staff (nurses versus office workers), travel time for in-person DOT versus eDOT, et cetera for comparison. Dr. Burzynski indicated that this was part of the cost analysis. That paper has been published in the *AJPH*. They found that there was significant time and cost for in-person DOT. NYC has Public Health Advisors who are not nurses, so their salary is not as high as the salary of the nurses who provide DOT in the community. Those costs were all figured in. They found that the biggest cost was to the people coming into the clinic in terms of time, transportation, babysitters, et cetera. All of those things were taken into consideration and were quite high. Whether a patient was presenting to a clinic or a nurse was visiting them, the societal cost for ipDOT was considerably higher than the cost for eDOT. The only the only place that did not show up was in Rhode Island, which is a low incidence jurisdiction where the start-up cost for the video DOT was significant. This made the cost in Rhode Island similar for ipDOT and video DOT. There was cost-efficiency in NY and SF with eDOT.

Dr. Belknap asked whether there was any evidence that video calls are less secure than standard phone calls and therefore require a higher standard to be HIPAA-compliant. Dr. Burzynski said that their IT department takes this very seriously and they allow use of Skype for Business, Facetime, and Google Meet. More of these platforms are becoming increasingly secure as they realize the potential for issues with being disrupted of confidentiality. He feels confident in using them.

In response to a question about the number of doses patients were given to keep at home when they were on eDOT, Dr. Burzynski said that NYC provides patients a month's supply to take home and asks them not to take it until the DOT session. The Public Health Advisors can go to the home to do the observation or can do it through the video DOT without ever handling the medication.

Mr. Dupree indicated that Colorado has a YouTube video in English and with Spanish subtitles that demonstrates what is expect from video DOT patients and case managers. They also have "place mat" templates that show patients where to place their phone, clear drinking glass, et cetera on the website.

Day 1 Recap

Barbara Cole, RN, MSN, PHN
TB Controller
Riverside County Department of Public Health

Ms. Cole recapped that during the morning session, they had a very informative presentation from Dr. Mermin reviewing all of the activity NCHHSTP has been engaged in despite the impact of COVID. A central theme in terms of what is happening with COVID is that there is the "COVID effect" on many of the things that everyone is trying to accomplish at the local, state, national, and global levels. Everyone looks forward to the strategic plans that are coming out for HIV/AIDS, STI, and viral hepatitis. It was encouraging to see the decline in sexual risk behaviors for youth. Whether that is a COVID effect is another topic to assess. It is encouraging that various areas are receiving funding for the work that is being done. Hopefully, there will be additional funding along the way for TB. Dr. LoBue covered some of the impacts of COVID on TB services for DTBE, including laboratory enrollment in the epidemiology studies and implementation of the new TB reporting case form. There is concern about the potential for AccuProbe® to get out of the business in the next 1 to 2 years, raising uncertainty about what technology would be utilized to identify MTB if that occurs. A lot of discussion involved what the hypothesis is to explain the decrease in TB in terms of whether it is a real decrease or it is due to other factors. This definitely deserves more investigation. NTCA is conducting a survey that may provide some additional insight, which can be considered during a future meeting. Another concern is potential shortages in medications. FDA is allowing a certain percentage of nitrosamine impurities for rifapentine to continue to be used. Dr. Kurbatova presented on Study 31, which has great implications for shorter treatment. This could improve adherence and outcomes for patients. It is important to think through what the implications would be at the program level.

In terms of the afternoon, Ms. Cole recapped that they heard very informative presentations and engaged in interesting discussions. In terms of nitrosamine impurities, the guidance will be important in terms of the FDA testing methods to determine the levels. Currently, there is not an issue with the medication. Given that issues could occur, this will be important for ACET to monitor. As Dr. LoBue mentioned, some medications are available through the stockpile if needed. They also heard an update as part of the DOT participants' perceptions. It is very important to consider the study results they heard in terms of whether to give people a choice between eDOT and ipDOT. Most places have at least some eligibility criteria for eDOT. For those who do not have technology or are not familiar with it, loaner phones can be utilized. An important question was raised about the security, given all the malware and people trying to hack into and tie up health facilities and public health hospitals systems, it is important to continue to be cognizant of these potential issues. It is unlikely that anyone would be engaged in eDOT or asynchronous DOT without having their IT departments involved. ACET looks forward to hearing an update on the eDOT follow-up analyses.

With no further business posed, Dr. Temesgen moved to adjourn the meeting for the day and Dr. Horsburgh seconded. The motion carried unanimously and the meeting was adjourned at 3:40 pm EST.

December 9, 2020 Opening Session

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

The meeting was called to order at 10:00 am EST. Dr. Burton welcomed participants to the second day of the ACET meeting. He first took a moment to thank Ms. Margie Scott-Cseh for her 17 years of outstanding service to ACET. Margie has been the superglue of the committee, undertaking excellent committee management and communications between ACET members, *ex officios*, liaison members, speakers, CDC, and HHS. Everyone is delighted for Margie that she has announced her retirement in April 2021 and that she and her family will have more time to spend together in the next phase of life. CDC is grateful for her service to this agency and this federal council and will miss her terribly. CDC appreciates that she and Ms. Staci Morris have had the opportunity to overlap and that Margie is able to share her knowledge in the transition. CDC and ACET thanks Margie for all of her exemplary service. Ms. Cole added her deep appreciation for Margie's support throughout all of the years they have worked together, and said that she looks forward to working with Staci. Everyone applauded Margie and wished her well on her next journey.

Dr. Burton 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 15 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 9, 2020. No COIs were declared and a quorum was maintained throughout the meeting.

Drug Supply Update

CAPT Christine Bina, RPh, MPH
Team Leader, Drug Shortage Staff Center
Drug Evaluation and Research
Food and Drug Administration

CAPT Bina provided a background on the CDER Drug Shortage Staff (DSS), US drug shortage trends, reasons for drug shortages, CDER's approach to prevention and mitigation of drug shortages, nitrosamines, supply of rifampin and other TB drugs, and industry's role. As a reminder, FDA's mission is to ensure that safe and effective drugs are available to patients. The role of the FDA DSS is to:

- ❑ Support FDA's mission of ensuring that safe and effective drugs are available to patients
- ❑ Facilitate temporary and long-term strategies to address shortages
- ❑ Coordinate for timely and comprehensive risk/benefit decisions
- ❑ Distribute information (web posting, professional organizations)
- ❑ Work across suppliers, facilities, and issues with multiple moving parts and urgency

- ❑ Maintain availability of these important medically necessary products while minimizing risk to patients

For some history, this program started within FDA CDER in 1999. There were not a lot of shortages at that point and most shortages were of antiviral drugs, so the program was under that area at the time. The program stayed small for quite a while until 2011 when there were significant shortages due to a couple of manufacturers shutting down. There were shortages of a lot of oncology products as well as rifampin. In 2012, FDA received regulation requirements under the Food and Drug Administration Safety and Innovation Act (FDASIA) for manufacturers to report and notify the agency 6 months in advance of any supply disruption or discontinuation of a product. This has really helped with early notification to try to prevent shortages and keep supply available versus trying to fix it after it is already out in the market and could take weeks to try to get medication back into patients' hands. This reporting requirement is not limited to medically necessary products. All product companies are required to report on their products regardless of how much their market share is. While companies with small market shares may think it is not that big of a deal for them, they also are required to report because any disruption in the market can cause a problem due to different contracting wholesalers and not knowing where gaps might occur.

While notification is very helpful, there are some challenges with shortages. As Dr. McMaster mentioned the previous day, FDA does work closely with the manufacturers to address the problems. Though FDA can advise and assist in expediting inspections and reviews, the manufacturers are ultimately responsible for fixing the problem. Because of the FDASIA, FDA can require manufacturers to report supply disruptions, delays, discontinuation, and notification of certain manufacturing changes. FDA cannot require a company to make a drug, to make more of a drug, or set requirements on how much of a drug is distributed or which purchasers will be given priority. While FDA might speak to a manufacturer about the public health impact of making a specific drug or more drugs, these are ultimately business decisions. This can be challenging because there are obviously certain patient groups who face more needs than others.

A lot of the drug shortages have been due to quality and manufacturing issues. Sterility has been a problem with injectables sometimes due to bacterial or fungal contamination. Particulates in products (glass, metal, fiber in vials) have caused issues. Drugs may form crystals. Precipitate may occur, which is a reaction between the drug and the container or diluent. There may be impurities that can be toxic (heavy metals, nitrosamines). Degradants may lead to less effective drugs. Equipment may break down or there may be issues due to natural disasters such as hurricanes. Hurricane Maria hit the Baxter site in Puerto Rico, which had a major impact on IV fluid bags and medication delivery.

FDA was first notified of nitrosamines in valsartan in 2018. This was a huge alarm and concern for the agency, patients, and healthcare providers for patients on these long-term medicines. These are chronic medications that are needed by patients. At that time, a Task Force was assembled within the agency to try to deal with this issue. In 2019, ranitidine was identified as having nitrosamine. Another big concern was that many people take over-the-counter (OTC) medications or have prescriptions. This ended up in a class-wide recall. Fortunately with this product, there are alternatives and people have access to other OTCs. Since then, other drugs that have had unexpected findings of nitrosamine impurities, including nizatidine, metformin, and now rifampin and rifapentine.

As a reminder, nitrosamines are potentially cancer-causing organic compounds that people are exposed to in their everyday lives. They exist in low levels in water and foods, including meat, vegetables, and dairy products. Some nitrosamines may increase the risk of cancer if people are exposed to them above acceptable levels and over long periods of time. More information can be found on the FDA website [https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications].

In terms of the agency's approach to prevention and mitigation of nitrosamine impurities, the Task Force that was established is assessing the risk/benefit of the drug in question to try to decide whether it is worse if the patient does not receive the medication versus the elevated risk of cancer later on if they do take the medication. This is definitely a challenging question for patients, HCP, and the agency in terms of maintaining availability while maintaining the risk to the patient. FDA works closely with the firms to address the problem by advising and expediting reviews of supplements or whatever is needed to try to keep the products available. FDA encourages manufacturers to maintain open communication with the DSS regarding potential impact on supply. Specifically with nitrosamines in rifamycins, FDA wants manufacturers to reach out to the agencies if their levels are not meeting the requirements in an effort to understand what is occurring. FDA is continually evaluating supplies.

In August 2020, FDA posted information on its website discussing how the agency is working to mitigate issues with rifampicin and rifapentine after nitrosamines were identified in each of these products. This posting identifies the acceptable levels of nitrosamine and the interim limits that are acceptable until this issue can be resolved. This information is continually updated as new information becomes available. In October 2020, the interim levels of nitrosamine that are acceptable in rifapentine were updated and will continue be as new information comes into the agency [https://www.fda.gov/drugs/drug-safety-and-availability/fda-works-mitigate-shortagesrifampin-and-rifapentine-after-manufacturers-find-nitrosamine].

In September 2020, FDA published "*A Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs*." This applies to all medications. While this keeps showing up, part of the problem is that it is not the same in every product so it is difficult to understand where the nitrosamines are coming from. This is very complicated, but industry is trying to help identify where the nitrosamines might be coming.

Specific to the TB drug supply, rifapentine is a sole source product from Sanofi. It is currently posted on FDA's drug shortage page. There is some supply available, but it is on allocation by the company. FDA is continuing to work with Sanofi and hopes that this product remains available. Rifampin supplies remain tight but DSS is working with the 4 manufacturers. Supply continues to be available from all 4 suppliers. However, it has been challenging with the nitrosamines because of the additional testing that must be done. There may be some slowness in some of the lot released, but at this point all 4 companies have supply available of this important medication. Rifabutin supplies also remain tight. DSS is working with the manufacturers and supply continues to be available at this point. Manufacturers report that adequate supplies of ethambutol are available to meet demand. DSS is monitoring isonicotinylhydrazide (INH) injection and INH oral, for which supplies continue to be available.

Shortages have occurred for reasons other than nitrosamines. Many drugs are sole source, there is a lack of redundancy, and there are capacity constraints. When a quality problem occurs or a firm loses their manufacturing site or supplier, a shortage may occur. Again, FDA is committed to having safe and effective drugs available. When issues arise such as nitrosamine impurities and others, the agency makes every effort to understand the issues and provide its best recommendation to the public as quickly and accurately as possible. FDA will continue to investigate and work to ensure these types of impurities do not exceed acceptable limits so that patients can continue taking their medicines without concern. FDA communicates with its other government partners, including CDC, and other stakeholders and global regulatory groups.

The FDA drug shortage website is:
https://www.fda.gov/drugs/drug-safety-andavailability/drug-shortages

To report shortages, the e-mail account is:
Drugshortages@fda.hhs.gov

In closing, CAPT Bina emphasized that FDA wants to hear about any supply issues so that they can follow up with the manufacturer to understand what is occurring.

ACET Discussion: Drug Supply Update
Dr. Temesgen observed that the shortages and impurities are not a US-only issue and he wondered whether there is any coordination and consultation with the EMA, the World Health Organization (WHO), or other relevant agencies and organizations. CAPT Bina indicated that the FDA's Task Force often has meetings with international regulators. They exchange information on what steps they are taking and what they have determined to be acceptable. The Task Force also has been on calls with the WHO.

In response to a question about the risk/benefit of the drugs in question for TB and other diseases, CAPT Bina indicated that FDA gathers a group of experts (chemists, pharmacologist, clinicians, toxicologists) within the agency when there is a shortage or impurity, to assess the risk of not having the medication versus whatever the issue is with the product.

Dr. Reves pointed out that it is not as big a deal in terms of treating active TB. The problem lies with treating LTBI. He saw a patient recently who got this information and decided to take 6 months of INH instead of rifampin. People clearly die of INH toxicity, particularly older individuals. He lamented that he has no real feeling for how to tell a patient what the risk is of cancer developing and dying of that. While his thought was that it is extremely rare, he requested input on putting this into terms that a patient would understand. CAPT Bina agreed that this is a difficult discussion to have and that it is an easier conversation with a patient who has active TB. There is not a great response for the patient other than to have the discussion that there is a slightly elevated risk. She will talk to the Task Force to find out if they have something more specific.

Dr. Ahmed wondered what the clinician's obligation is to discuss newly posted information, which will be applicable to TB and non-TB patients for rifampin. Others agreed that programs and providers are struggling with how best to communicate/inform patients about true risk. Clinicians may have ethical and legal obligation to inform patients about the risk of cancer with rifampin.

Dr. Loeffler noted that young children take 20 to 30 mg/kg/day and wondered about risk given the young age and high weight-based dose, and Dr. Armitige expressed concern about pregnant women and their unborn babies. It would be nice to have information to provide families about these two issues.

Dr. LoBue commented on risk calculating, emphasizing that this was not a criticism—it is just the reality. There are so many one-offs, trying to nail down a number is questionable. The actual impurities are not the ones that are used to make the calculation. It is totally reasonable because they are chemically similar, but it is still a one-off. The next one-off is the calculations are based on animals not humans. There are some human data, but they are a lot murkier than the animal data. Those calculations are based on giving the animals a dose that results in one half of them getting tumors. The next one-off is dividing that by 50,000 to get the 1 in 100,000 number, which is a one-off in the sense that it is assuming some kind of linear relationship, which has not yet been proven. The next one-off is based on a daily dose for 70 years. That is not necessarily the same as taking 12 weekly doses as in the rifapentine regimen. While 1 in 100,000 can be used, there are a lot of estimations and one-offs around this that make it really difficult.

Dr. Horsburgh noted that the best human study, cited by the previous day's speaker, shows a doubling of the risk of colon cancer associated with various nitrosamines. The baseline risk of colon cancer in the US is .03% per year. So, unless a patient has a known risk factor for colon cancer, the absolute risk of this associated with nitrosamines is still small.

Dr. Belknap shared this language that they are using to discuss this issue with patients in Denver, "Rifampin and rifapentine have been found to have small amounts of chemicals called nitrosamines. Some nitrosamines have been shown to cause cancer in test animals. Nitrosamines are also found in water and many foods, including meats, dairy, and some fruits and vegetables. Everyone is exposed to some of these chemicals. Exposure at high levels and for long times (such as years) may increase the risk of cancer. Rifampin and rifapentine are still recommended as the best options for treating TB infection (or TB disease depending on the patient). The risk to you from TB is greater than the risk from these medicines. If you have questions, please ask your nurse or doctor for more information."

Dr. Loeffler shared an excerpt of the language that Portland, Multnomah County uses: "Impurities in Rifampin. You will be taking a medicine called rifampin to treat tuberculosis (TB). Rifampin is an important medicine for TB treatment. We want to let you know that the Federal Drug Administration (FDA) recently found very low amounts of impurities in some rifampin capsules. An impurity is something that is left over after making the drug. In this case, there is a small chance that the impurities could be dangerous if you took the medicine every day for many years. Treatment for TB usually lasts less than one year. We recommend that you take rifampin to treat your TB. What are the impurities? The FDA recently started testing different medicines for impurities called nitrosamines. Nitrosamines in large amounts may cause cancer. Nitrosamines are common in water and foods, including cured and grilled meats, dairy products and vegetables. Everyone is exposed to nitrosamines. We think it is likely that the nitrosamine . . ." The full statement is on the website.

Dr. Bloom asked whether there was an ability/data to conduct a retrospective study of individuals who have been treated for TB to look at development of potential rifamycin-related issues. TB generally has one of the most complete electronic and paper databases with treatment data on dose, length, patient outcomes, and contact information for follow-up. CAPT Bina said that while she did not know the extent to which FDA has the resources to conduct such a study, they do have a Safety Group within the agency that examines AE reporting and conducts retrospective studies. Dr. LoBue added that CDC's data are short-term, so they do not have the ability to conduct a retrospective study such as this. Cancers probably will take decades to develop after treatment, and they have no long-term follow-up after that period nor do they have identifiable information.

Dr. Temesgen pointed out that it would be difficult to distinguish the nitrosamines in rifampin from fried chicken and all of the other things that contain nitrosamines.

Regarding a question about whether FDA is able to share the status of each manufacturer's mitigation plans, CAPT Bina indicated that a lot of the information manufacturers provide to the DSS is confidential so FDA cannot share the specifics. However, they can share availability information that the manufacturers agree upon. The agency does identify the manufacturers with a contact phone number on the website when there is a shortage so that people can reach out directly to them. A manufacturer may be willing to supply that information directly, but FDA is bound by confidentiality of certain information.

Ms. Pritschet, the TB Controller for North Dakota, indicated that one of her roles is to ensure that their program has an adequate supply of medication available to treat TB disease and TB infected persons in the state. The previous day when placing an order for rifampin, she was informed that the manufacturer they usually order from was backordered and no date of availability could be provided. She was able to order from another manufacturer, but at almost double the cost. As a low incidence state working with a limited budget, if the cost of rifampin continues to increase, as a program they may need to look at who they are able to provide medication for to treat TB-infected persons. Others agreed and emphasized that it is important to address increased costs for dwindling/finite product. This information would help to better assess the impacts, short- and long-term for big pharma manufacturing rifampin. The great fear is that they will leave the market not seeing the value of reducing nitrosamines to zero or they reduce their nitrosamine levels to zero at great expense that is then passed on to TB programs already facing level or reduced funding.

Some sentiment was expressed that perhaps nothing should be said at all, given that there has not been a signal after 40 years of use. The honest answer is that risk is unknown. Ethically all that can be said is that there is animal risk. When given to animals on a regular basis, it produces cancer. Exactly how that translates into a humans taking 4 months of rifampin is unclear.

Recap of the follow-up questions pending FDA response to ACET:

- ❑ Concerns expressed to NTCA by programs that there are challenges procuring ethionamide
- ❑ Provide information on BCG vaccine supply/availability
- ❑ Additional information on pediatric populations and perhaps a statement that there are no data to suggest that there is an increased risk to children simply because they are small and metabolize differently
- ❑ Additional information on the impact on pregnant women and their unborn babies
- ❑ Need for information to provide to patients about risk/benefit in the context of nitrosamines

ACET Business Session

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

Ms. Cole 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. David Horne and seconded by Dr. Robert Belknap to accept 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

Ms. Cole 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:

ADVICE REQUESTED FROM ACET		
Topic	**Discussion From Minutes**	**Action**
A Tool to Assist TB Programs with Integration of Whole Genome Sequencing (WGS) Data: 1) Perhaps this type of tool could assist with contact tracing and other activities done during COVID-19: a. While the tool is specific to TB, it could be customized. b. Dr. Winglee is highly involved in the COVID-19 response. She certainly would make the tool available.	June 2020 minutes, pages 21-25	• While no action needs to be taken on customizing the tool, this should be monitored to determine whether any adaptations are actually made.
Ongoing Challenges with TB Drugs and Diagnostic Supplies: Results from National Survey.	June 2020 minutes, pages 25-28	• Information was shared about how people can access the FDA information on the website. • This action item is closed.
TB Elimination Roadmap Update: 1) Concern was expressed that a response is never going to be provided from HHS. a. A suggestion was made to consider alternative routes for publication. b. Ms. Cole reminded everyone that ACET advices CDC and HHS. c. Dr. LoBue indicated that there is a process that requires approval and clearance before publication. d. It was noted that the authors all will have rotated off of ACET by the time this is published.	June 2020 minutes, pages 30-31	• Edits were made to the draft letter that was to accompany the roadmap. • The letter and roadmap were sent to the HHS Secretary on August 17, 2020. • A response is pending. • Consider resubmitting the letter and roadmap in January 2021.

Business Item 3: Identify Charge and New Chair for the ACET Drug Supply Workgroup

The previous Chair and members have rotated off. The original charge was to assess drug shortages and ascertain mitigation strategies to address shortages, determine the cost of drugs, understand the barriers to ensuring that the drug supply is uninterrupted so that TB and LTBI wil receive treatment. ACET considered various models and outlined multiple possible avenues; however, no conclusions were reached. Feedback included the following:

- Sometimes when there is a seeming shortage, it can be a distribution problem rather than a manufacturing shortage. There is a lot of variability depending upon the supplier. Once state, area, or jurisdiction may be told that their supplier has a shortage that is not at the manufacturing level. It is not clear whether there is a role for ACET in addressing supply chain issues.
- This workgroup does not have to be reconvened, especially given that it does not have a clear purpose and charge.
- If the US makes part of its contribution to the Global Fund to be providing a supply of drugs to Mexico, in which case there would be a much larger amount of drugs to be produced.
- Dr. LoBue indicated that programs in the US can buy medications from the Global Drug Facility (GDF). However, this is not like an emergency resource. Instead, it requires advanced planning and regular shipments. Second, only FDA-approved formulations can be used in the US. The GDF does not have very many FDA-approved formulations. It would not be legal to use drugs that are not FDA-approved unless FDA waives the non-approved formulation. They would only do that in a truly dire situation in which there is truly a shortage and there are no drugs.
- NTCA has a group working on this issue. Perhaps there is something NTCA would like ACET to do that could be considered to be a charge. Connect with Mr. Dupree, ACET Liaison and the new NTCA President.
- TB Treatment Action Group (TB TAG) had a representative on the workgroup serving as an SME. Connect with Mr. Madoori, ACET Liaison from TB TAG.
- With no charge and no motion to reconvene, the decision was made to table this discussion until the next ACET meeting. In the interim, discuss a new charge with NTCA and TB TAG.

Business Item 4: ACET's Semi-Annual Report to the HHS Secretary

Ms. Cole reviewed ACET's December 8, 2020 letter to Secretary Azar. While she updated some of the data in the background section, much of it was still relevant and remained unchanged. She reminded everyone that during the last meeting, they discussed folding in some information about COVID-19. To that end, she replaced the information about Ebola and focused on COVID-19. The following input was provided:

<u>Background</u>

- Modeling was done on the impact of COVID-19 on TB worldwide, which is public. Dr. Bloom recalled that this modeling predicts an additional 1.4 million deaths globally over the next 5 years. She will email the details to Ms. Cole. Ms. Cole will determine where to add this.
- In the paragraph beginning with "Health disparities are seen in vulnerable populations for TB and COVID-19," add a bullet about the impact of COVID-19 on the AccuProbe® diagnostic method regarding the short-term problem of the current shortage and the long-term problem that in 1 to 2 years it may not be available at all. However, there may be a better place for this since it is more global than just health disparities.

Six Concerns That Continue to be Paramount in ACET's Deliberations

- Under #3 *Targeted testing of individuals at risk for progression from LTBI to active TB*, add an emphasis on a culturally sensitive LTBI-focused equity lens to reach the populations who are having more issues. Sometimes a liaison/change agent is needed to reach such populations. Suggested language. Perhaps include a couple of sentences about the current populations who need help.
- Under #5 *TB Research* reword the first sentence to add the importance of observational studies conducted in programmatic settings, "Clinical, basic, epidemiologic, and observation/programmatic research should be conducted to . . ."

Progress Toward TB Elimination

- Consider separating TB and LTBI in the second sentence to read, "Addressing TB and LTBI globally is an essential component . . ."

Assistance from the HHS Secretary

- Add a bullet above "facilitate research to shorten . . ." that reads "increase funding to CDC for basic, clinical, epidemiologic, and implementation research"
- Include CDC in the bullet beginning "facilitate research to shorten . . ."
- Separate the sixth bullet beginning "strengthen HHS support for reducing TB in congregate settings . . ." into a bullet for congregate setting and a bullet for binational and transnational continuity of care

Key ACET Activities for 2019

- Change the heading to "Key ACET Activities for 2020"
- In the first bullet, change "Due to the pandemic" to "Due to the COVID-19 pandemic"
- Add a sentence to the third bullet pertaining to the Roadmap that reads, "We are hoping for prompt approval from HHS or delegation to CDC."
- Add a sentence to the fourth bullet pertaining to the Drug Supply Workgroup that states, "We are continuing to monitor this issue closely."

Last Page

- In the first paragraph beginning "The response to the current COVID-19 pandemic . . ." *strategies* is misspelled.
- It might strengthen the letter to state that "The ongoing TB pandemic has been eclipsed for the moment by COVID-19." Though the magnitude of the TB pandemic is far greater than the COVID-19 pandemic at this time, all resources are now focused on COVID-19 ignoring the ongoing TB pandemic.

Dr. Belknap motioned to approve the letter with the noted amendments. The motion was seconded. With no further discussion or changes, the motion to approve the letter with the noted amendments carried unanimously with no abstentions or opposition.

Business Item 5: Future Agenda Items

Ms. Cole noted that while the Agenda Setting Workgroup will be convened to finalize the agenda for the next meeting, they like to get a feel for topics of interest. During this meeting, the following topics of interest were suggested:

Presenter	Agenda Item
TBD	Discuss a publication focused on TB and immigrants
NTCA	The NTCA "COVID Effect" survey mentioned by Ms. Wegener that will assess the impact of COVID on NTCA's programs and obtain information about COVID-TB co-infections nationally if it is completed and the results are analyzed
TBTC	The Tuberculosis Trial Consortium's (TBTC's) vision for the next 10 years in terms of whether they will continue to try to shorten active TB treatment beyond 4 months, LTBI treatment, strengthening international TB control, et cetera
Drs. Christine Hahn and Julie Higashi are leading this effort	NTCA's the Bacillus Calmette–Guérin (BCG) vaccine guidance development
CDC / FDA	A follow-up on rifampin shortages/impurities

Public Comment Session

No public comments were provided during this meeting.

Closing Session

The proposed dates for 2021 ACET meetings are:
- ❑ June 15-16, 2021 or June 22-23, 2021
- ❑ December 14-15, 2021 (In-Person)

With no further discussion or business brought before ACET, Ms. Cole adjourned the meeting at 12:00 am on December 9, 2020.

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

Date

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

Attachment 1: Participants' Directory

ACET Members Present

Ms. Barbara Cole, Chair
Dr. Amina Ahmed
Dr. Lisa Armitige
Dr. Robert Belknap
Dr. David Horne
Dr. Robert Horsburgh, Jr.
Dr. Ann Loeffler
Dr. Lixia Liu
Ms. Kristine Steward-East
Dr. Zelalem Temesgen

ACET *Ex-Officio* Members Present

Dr. Naomi Aronson
US Department of Defense

Dr. Amy Bloom
US Agency for International Development

Dr. Karen Elkins
US Food and Drug Administration

Dr. Jonathan Iralu
Indian Health Service

Dr. Lawrence Kline
Department of Health and Human Services

Mr. Stephen Martin
National Institute for Occupational Safety and Health

Dr. Gary Roselle
US Department of Veteran Affairs

Dr. Ronald Wilcox
Health Resources and Services Administration

LTC Naomi Aspaas for 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

ACET Liaison Representatives Present

Dr. Shama Ahuja
Council of State and Territorial Epidemiologists

Dr. Robert Benjamin
Stop TB USA

Mr. David Bryden
RESULTS

Mr. Peter Dupree
National Tuberculosis Controllers Association

Mr. Surajkumar Madoori
Treatment Action Group

Nuala Moore
American Thoracic Society

Ms. Susan Rappaport
American Lung Association

Dr. Susan Ray
Infectious Disease Society of America

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. David Weber
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

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. Lornel Tompkins
National Medical Association

Dr. Daphne Ware
Association of Public Health Laboratories

Mr. Bobby Watts
National Health Care for the Homeless Council

ACET Designated Federal Officer

Dr. Deron Burton
NCHHSTP Deputy Director

CDC Representatives

Ms. Leeanna Allen
Ms. Kia Bryant
Dr. Terence Chorba
Ms. Ann Cronin
Ms. Vanessa Fong
Dr. Neela Goswami
Ms. Connie Haley
Dr. John Jereb
Ms. Stephanie Johnston
Dr. Awal Khan
Dr. Ekaterian Kurbatova
Dr. Adam Langer
Dr. Philip LoBue
Ms. Allison Maiuri
Dr. Joan Mangan
Ms. Suzanne Marks
Dr. Jonathan Mermin
Dr. Terry Miller
Dr. Sapna Morris
Dr. Lakshmi Peddareddy
Dr. Robert Pratt
Ms. Annie Rossetti
Ms. Margie Scott-Cseh
Ms. Shona Smith
Dr. Angela Starks
Ms. Rebekah Stewart
Ms. Michelle Van Handel
Dr. Andrew Vernon

Guest Presenters

CAPT Christine Bina, RPh, MPH
Food and Drug Administration

Joseph Burzynski, MD, MPH
New York City Department of Health & Mental Hygiene

Owen G. McMaster, PhD
Food and Drug Administration

Ms. Evelyn Moua
Association of Asian Pacific Community
Health Organizations

Members of the Public

Dr. David Ashkin
Dr. John Bernardo
Dr. A. Chang
Dr. Yi-Ning Cheng
Dr. Dan Everitt
Ms. Diana Fortune
Ms. Anne Gaynor
Ms. S. Dasgupta-Tsinikas
Ms. Amanda Holt
Mr. Ed Lee
Ms. Dee Pritschet
Ms. Donna Wegener

Attachment 2: Glossary of Acronyms

Acronym	Definition
AAPCHO	Association of Asian Pacific Community Health Organizations
ACET	Advisory Council for the Elimination of Tuberculosis
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AFB	Acid-Fast Bacilli
AI/AN	American Indian/Alaska Native
AJPH	*American Journal of Public Health*
APIAHF	Asian and Pacific Islander American Health Forum
BCG	Bacillus Calmette–Guérin
BDQ	Bedaquiline
BPaL	Bedaquiline, Pretomanid, and Linezolid
BTBC	Bureau of Tuberculosis Control
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CDPH	Chicago Department of Public Health
CfZ	Clofazimine
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CDER	Center for Drug Evaluation and Research
CDPHE	Colorado Department of Public Health and Environment
CPDB	Carcinogenic Potency Database
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-Ray
DASH	Division of Adolescent and School Health
DFO	Designated Federal Officer
DHAP	Division of HIV/AIDS Prevention
DOT	Directly Observed Therapy
DSMB	Data Safety Monitoring Board
DSS	Drug Shortage Staff
DTBE	Division of Tuberculosis Elimination

Acronym	Definition
DVH	Division of Viral Hepatitis
EDN	Electronic Disease Notification
eDOT	Electronic Directly Observed Therapy
EHR	Electronic Health Record
EMA	European Medicines Agency
ESRD	End-Stage Renal Disease
FACA	Federal Advisory Committee Act
FAERS	FDA Adverse Event Reporting System
FDA	(United States) Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FQHC	Federally Qualified Health Centers
FY	Fiscal Year
GI	Gastrointestinal
GSK	GlaxoSmithKline
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCP	Healthcare Providers/Professionals
HCV	Hepatitis C Virus
HHS	(United States) Department of Health and Human Services
HNTC	Heartland National Tuberculosis Center
HRSA	Health Resources and Services
IDU	Injection Drug Use
IHS	Indian Health Service
ipDOT	In-Person Directly Observed Therapy
IT	Information Technology
ITT	Intention To Treat
IUATLD	International Union Against Tuberculosis and Lung Disease
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
LTBI	Latent Tuberculosis Infection
MDD	maximum daily dose
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MIC	Minimum Inhibitory Concentration
MMWR	*Morbidity and Mortality Weekly Report*
MTB	Mycobacterium Tuberculosis
NASTAD	National Alliance of State and Territorial AIDS Directors
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
NCI	National Cancer Institute
NDBA	N-nitrosodibutylamine
NDEA	N-nitrosodiethylamine

Acronym	Definition
NDIPA	N-nitrosodiisopropylamine
NDMA	N-Nitrosodimethylamine
NIH	National Institutes of Health
NIPEA	N-nitrosoisopropylethyl amine
NMBA	N-nitroso-N-methyl-4-aminobutanoic acid
NMPA	Nnitrosomethylphenylamine
NP	Nurse Practitioner
NTCA	National Tuberculosis Controllers Association
NTCH	National Commission on Correctional Health
NTSS	National Tuberculosis Surveillance System
NYC	New York City
OASH	Office of the Assistant Secretary for Health
PA	Physician's Assistant
PaMZ	Pretomanid, Moxifloxacin, and Pyrazinamide
PSA	Public Service Announcements
PWID	People Who Inject Drugs
PZA	Pyrazinamide
RCT	Randomized Controlled Trial
RIDH	Rhode Island Department of Health
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SAT	Self-Administered Therapy
SEOIB	Surveillance, Epidemiology, and Outbreak Investigations Branch
SFDPH	San Francisco Department of Health
SHAE	Society for Healthcare Epidemiology of America
SME	Subject-Matter Expert
SNP	Single-Nucleotide Polymorphism
SSP	Syringe Services Program
STD	Sexually Transmitted Disease
TA	Technical Assistance
TB	Tuberculosis
TB CEN's	TB Community Engagement Network's
TBESC	Tuberculosis Epidemiologic Studies Consortium
TB GIMS	TB Genotyping Information Management System
TBTC	Tuberculosis Trials Consortium
TTD	Time To Detect
UNC	University of North Carolina
US	United States
USPSTF	US Preventive Services Task Force
WG	Working Group

Acronym	Definition
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB
YRBS	Youth Risk Behavior Survey