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
June 15-16, 2021

Record of the Proceedings

TABLE OF CONTENTS

Table of Contents

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

ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
June 15-16, 2021

Minutes of the Virtual Meeting

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC), National Center for HIV/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 June 15-16, 2021 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*).

June 15, 2021 Opening Session

Staci Morris, MS
Public Health Advisor
Office of Policy, Planning and Partnerships
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

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

Ms. Morris called the meeting to order at 10:00 am EST on June 15, 2021 and provided instructions. Dr. Burton welcomed participants and conducted a roll call to confirm the attendance of ACET voting members, *ex-officio* members, and liaison representatives. He announced that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. He reminded ACET voting members of their responsibility to disclose any potential individual and/or institutional conflicts of interest (COI) for the public record and recuse themselves from voting or participating in these matters.

ACET Voting Member Institution/Organization	Potential Conflict of Interest
Amina Ahmed, MD Levine Children's Hospital at Carolina Medical Center	No conflicts disclosed
Lisa Armitige, MD, PhD Heartland National Tuberculosis Center	No conflicts disclosed
Robert Belknap, MD Denver Metro Tuberculosis Control Program	Institution receives funding for TBTC and TBESC work
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) Indiana Department of Health	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 June 15, 2021. The roll was called subsequent to each break and lunch, with quorum established each time throughout the day.

Dr. Burton made the following announcements:

- Dr. Lisa Armitige and Dr. Robert Horsburgh will be rotating off of ACET as of June 2021. DTBE expressed great appreciation for their contributions to ACET. Drs. Armitige and Dr. Horsburgh have brought valuable insight and expertise regarding TB elimination to ACET. Due to COVID-19, certificates of appreciation will be mailed to these parting members.
- DTBE welcomed new ACET Chair, Dr. Robert Belknap, who is the Medical Director of the Denver Metro Tuberculosis Control Program at Denver Public Health.
- At this time, DTBE is awaiting acknowledgements from HHS for two nominations who will replace Drs. Armitige and Dr. Horsburgh.
- On June 8, 2021, HHS Secretary Becerra requested agency representation to ACET from the Federal Bureau of Prisons (FOB), US Marshall Services, and the US Department of Homeland Security (DHS) to serve as *Ex Officio* agencies for ACET.
- ACET will no longer have representation from the Agency for Health Care Resources (AHRQ). The ACET current charter approved in February 2021 will be amended to reflect this change.

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 thank everyone for taking time out of their schedules to participate in ACET, especially during this busy time. He recognized that with all of the expertise needed in the time of COVID-19, one of those was people who understand prevention and treatment of respiratory disease. He thanked CAPT Burton for covering as Acting Director for NCHHSTP and continuing to support TB work during that time over the past 3 months while Dr. Mermin has been on detail with the Center for Preparedness and Response (CPR). CDC continues to be involved heavily in the COVID-19 response. While NCHHSTP has been able to deal with a lot of other issues during the pandemic, there has been a great effect of COVID-19 on both the programmatic and scientific work of the center. Some of the ways that they have been able to take advantage of some of the new technologies and surveillance actives for COVID-19 will have longer influence on and opportunities for public health in the future.

The American Rescue Plan (ARP)[1] has provided a considerable amount of increased resources for CDC for COVID-related work, primarily to support states, local health departments, territories, and tribes to be able to conduct testing and prevention work and supporting some of the treatment efforts. There is a specific set of recent resources that will be released in the next one to two weeks, which is $1.13 billion over a 5-year period for a total of approximately $200 million per year to expand work primarily under the rubric of Disease Intervention Specialists (DIS). This work is focused on contact tracing, case management, and outbreak investigations. This includes support for DIS-related training and retention to address COVID-19 and other

[1] https://www.cdc.gov/media/releases/2021/p0413-stds.html

infectious diseases. This includes related activities such as testing technologies, software, and other ways of communicating to find people who may have been exposed—all of the areas that in many ways have been at the forefront of creative work in the field of TB and others. NCHHSTP hopes to be able to increase that capacity over the next few years, focusing on COVID initially with the expectation that there will be collateral benefits and then more explicit support for other infectious diseases over time.

There has been a fair amount of disruption within all of NCHHSTP's divisions due to COVID-19. All of the divisions have assessed the effect of COVID itself and some of the response efforts on disease incidence and functions that support the center's ability to perform public health work. Major decreases were seen in testing, screening, and other activities during the first half of 2020. There also has been increasing incidence of HIV, viral hepatitis, STDs, TB over time back to the previous levels or somewhat lower in some cases. Evaluations are still being done to determine whether some of the disruptions have been related to reporting more than actual epidemiological changes, but it looks like both are probably being affected. There are more detailed data for TB than for some other infections. The ability of people in the center to do their job has been disrupted, particularly because many staff members have been high-quality and desired personnel for the response. The agency has continued to have thousands of people deployed either full-time or part-time assisting with the COVID response. Numbers specific to NCHHSTP COVID-19 deployments as of June 4, 2021 include 725 employees deployed with 1334 cumulative deployments of people who have deployed more than once, 82 employees currently deployed, and 8 staff to deploy soon.

Another cross-center activity that is related to a new budget line that began a couple of years ago is Infectious Disease Consequences of Opioids, or the IDO budget line. This focuses on the prevention of infections that occur among people who inject drugs (PWID), primarily through syringe services programs (SSPs), linkage to care, and thinking about what it means to ensure that SSPs become a normal part of the public health system the same way in which a TB or STD clinic would be expected to do that. NCHHSTP developed a partnership with the National Alliance of State and Territorial AIDS Directors (NASTAD) to develop *Syringe Services Programs: A Technical Package of Effective Strategies and Approaches for Planning, Design, and Implementation*[2] that highlights effective strategies and approaches for SSPs. Ideally, there is a varying quality to SSPs that sometimes begins with the minimum of what can be done.

Ultimately, the hope is that SSPs will be able to address multiple factors that affect PWID, such as ensuring they have access to sterile injection equipment and places for disposal and naloxone distribution, which has been shown to save lives; linkage to substance use treatment, because it has been shown that those who participate in an SSP are more likely to stop injecting drugs; access to vaccination; and screening for infectious diseases. All of these can expand into SSPs if resources are available. This technical package highlights some of the ways that this can be done effectively, including involving people with lived experience, using a needs-based distribution approach rather than limiting the number of needles and syringes that can be distributed, providing and/or expanding core services, collecting minimal but important data at syringe services programs, and ensuring program sustainability over time. NCHHSTP has a

[2] https://t.emailupdates.cdc.gov/r/?id=h37e670f5%2C12d2e1ec%2C12d2ea97&ACSTrackingID=USCDCNPIN_162-DM45084&ACSTrackingLabel=CDC%20releases%20new%20Syringe%20Services%20Programs%20Technical%20Package&s=eZvxIJ9Lw3SLgcifj7DkBmkVt9MB1XIHhqhz6ASEoLU

collaboration for the SSPs with a variety of organizations, including the Harm Reduction TA Center, National harm Reduction Coalition, NASTAD, and the University of Washington.

In an effort to expand SSPs, NCHHSTP has been thinking about ways that they can be sustainable and continue to have outreach and delivery in the areas where needed to build the capacity and infrastructure to help the partners and through community organizations. The center had resources of $10.25 to expand SSP capacity, which is being done through partnerships with NASTAD and AIDS United.

Regarding HIV, CDC released 2019 surveillance data[3]. In some ways modeled after the way the TB is able to provide preliminary results and then ultimately confirm the results for TB in a very timely fashion, CDC has been providing surveillance data in a way that is closer to the end of the calendar year of the data collection itself. In collaboration with HHS and other agencies, CDC also has a dashboard that presents data in a much timelier fashion, understanding that there are other issues with the timeliness of reporting and other factors that related to the data being reported. In the case of the 2019 surveillance data, the information came just before the onset of COVID-19 and showed that new HIV infections fell 8% overall. Among men who have sex with men (MSM) who comprise about 70% of all new HIV infections, the decrease was 9% overall. The greatest decline was among MSM 13-24 years of age at 33%. In some ways, it is a great success in that the highest rate of new incidence of HIV has historically been in the youngest age groups, particularly among African American MSM. With some focused efforts and attention, this is the area in which there have been the greatest reductions. However, there continue to be major disparities (racial, ethnic, MSM, PWID) for HIV.

Also according to the 2019 surveillance data, there has been substantial progress in PrEP coverage. CDC estimates that a little over 1 million people in the nation at one time potentially would be eligible for PrEP. About 23% who were eligible for PrEP were prescribed it during that year period, which is not where they would like it to be. There also are some racial and ethnic differences, with whites being much more likely to be prescribed PrEP than African Americans, and Latinos. There have been some important efforts underway over the past few years to try to revere those differences, so it will be interesting to see what this looks like when there are data for 2020-2021. In the US, about 66% of people with HIV are virally suppressed and about 81% linked to care within one month of diagnosis. There are many efforts to ensure that people who are newly diagnosed are placed on treatment.

For the Ending the HIV Epidemic (EHE), jurisdictional plans[4] have been received from all jurisdictions. Over 50% of the jurisdictions plan to implement testing programs. In terms of prevention, over 50% plan to implement tele-PrEP and over 70% included PrEP navigation and expanding SSPs. With regard to treatment, 75% of the plans include rapid linkage to care and 63% include implementation or expansion of telemedicine. Regarding response, 50% include enhancing partner services. NCHHSTP has continued to improve and expand on its ability to respond to clusters of HIV, which has continued to be extremely challenging in terms of what that entails for the state and local response, the community ability to maintain services, and for CDC itself to be able to support this.

From a communications standpoint, the Let's Stop HIV Together campaign launched the "Take Me Home" HIV self-testing program. This is an area in which researcher already had been

[3] https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html
[4] https://www.cdc.gov/endhiv/action/local-ehe-plans.html

conducted through randomized controlled trials (RCTs) to show that sending people HIV tests through the internet is highly effective in identifying HIV infections, getting people linked to care, and is cost-effective. COVID moved this on even faster. The plan is to distribute about 100,000 HIV rapid self-tests in creative ways to accelerate the identification of undiagnosed infections. Through this communication campaign, CDC is partnering with the Building Healthy Online Communities and Insignia Federal Group to develop the web-based ordering portal.[5] This will help to get tests to people who live in rural areas, who might not be presenting to a clinic regularly, or who may not be visiting a community-based organization (CBO).

The longstanding effort to revise HIV transmission criminalization laws continues. *The Lancet HIV* published a commentary by CDC/NCHHSTP titled "HIV Criminalization Laws and Ending the HIV Epidemic in the United States."[6] There continue to be 37 states with these laws or with application of non-HIV-specific criminalization laws in ways that are not based on science. This commentary makes recommendations to align HIV criminalization laws and application of general statutes with current science. Some states have been re-examining and revising their laws (e.g., Virginia and Nevada), but generally this is only 1 to 3 per year. The hope is that there will be more momentum to support these changes over time.

CDC/NCHHSTP also published a report [7] that focused specifically on transgender women who are disproportionately affected by HIV, poverty, and homelessness. This analysis was in the National HIV Behavioral Surveillance (NHBS). While it is not nationally representative, it is representative of multiple urban settings that are participating in NHBS. This analysis showed very high rates of prevalence of HIV infection among transgender women, as well as racial disparities. Among participants, 62% Black/African Americans, 35% of Hispanic/Latinas, and 17% whites tested positive. A little over half (63%) had visited a health care provider (HCP) within 1 month after diagnosis and 90% were currently taking antiretroviral therapies. Prevalence is very high, but so is access to treatment. The analysis reflected that numerous underlying factors affect transgender women that make their lives particularly challenging, including that 63% lived at or below the federal poverty level, 42% experienced homelessness in the past 12 months, and 34% received drugs in exchange for sex. A number of efforts are underway to help transgender women to leverage experience and interest in the social determinants of health (SDOH) to enable people to get services and to work with HIV prevention, and NCHHSTP continues to see ways to do a better job for what is a highly affected group that often experiences a lot of stigma.

Within the Division of Viral Hepatitis (DVH), a new cooperative agreement has been issued that supports integrated viral hepatitis programs, Integrated Viral Hepatitis Surveillance and Prevention Funding for Health Departments (CDC-RFA-PS21-2103).[8] Previously, there were separate surveillance and prevention cooperative agreements. This had caused difficulties in implementing comprehensive programs in state and local health departments. The amount available for this new announcement for Year 1 funding in 2021 is about $22 million, which is at a scale that is much less than for TB. Component 1 focuses on core outbreak and comprehensive surveillance activities, Component 2 focuses on comprehensive prevention activities, and Component 3 is an area for creative implementation science and pilot programs

[5] https://together.takemehome.org/
[6] https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30333-7/fulltext
[7] https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-special-report-number-27.pdf
[8] https://www.cdc.gov/hepatitis/policy/2103_CoAg.htm

that focus primarily on the infectious disease consequences of drug use. This cooperative agreement also supports core viral hepatitis outbreak response, surveillance, and prevention activities and special projects.

The 2.5-year series of outbreaks of hepatitis A primarily among PWID started in 2017 but took off in 2018. Until dealing with the numbers involved with COVID, these were very large numbers of tens of thousands of people affected, tens of thousands of hospitalizations, and hundreds of deaths. This was difficult to tackle, but dramatic reductions occurred at the end of 2019 and have continued through 2020. The rates appear to be much more similar to what was experienced previously in terms of hepatitis A incidence in the nation. It is unclear what exactly the effects of COVID and its response have been, but the ability to rapidly implement vaccine to the people who need it, particularly stigmatized populations, is a challenge that was met with hepatitis A and is being met with COVID. The costs have been considerable in terms of human lives, morbidity, and financially. One example is reflected in a cost analysis of hepatitis A-related clinical costs among West Virginia Medicaid beneficiaries[9], in which Medicaid beneficiary costs alone ranged from $1.4 million to $5.6 million for the time period of January 2018–July 2019. Obviously, that would be much higher for the states in which more people were infected.

A report issued by CDC related to viral hepatitis[10] shows that there remains a struggle to reverse the trends in hepatitis B and C. This is particularly true for hepatitis C, which has experienced increasing incidence due to the opioid crisis. Incidence is generally stable for hepatitis B, which hopefully will continue to be reduced through infant vaccination and ultimately adult vaccination for people at high risk. Hepatitis C is going to require a 2-pronged approach of prevention among PWID where the vast majority of new infections are occurring and diagnosis and curing people of all ages.

In terms of the Division of Adolescent and School Health (DASH) update, there have been major impacts from COVID-19 on the lives of children and students. A recently published *Morbidity and Mortality Weekly Report* (*MMWR*)[11] showed that in general, the efforts to slow SARS-CoV-2 transmission resulted in widespread school closures, shifts to virtual educational models with mixed effects, modifications to school-based services, and disruptions in the educational and social experiences of youth. These stresses have resulted in changing mental health for students. An *MMWR* published on June 11, 2021[12] showed that there have been increased visits to emergency departments (EDs) for female adolescents of about 50% related to suicide attempts. It has been tough for adolescents over the past year and a half.

Through DASH, CDC has been able to support a lot of mental health efforts through expanded care and connectedness of students, families, and schools.[13] The agency provided over $12 million to 22 current CDC-funded school districts for: 1) implementation of policies and practices that create healthy, affirming learning in-person and virtual environments for students; and 2) implementation of positive behavior support practices and social-emotional learning. CDC also has provided funding to 7 non-governmental organizations (NGOs). The idea is to take a more comprehensive approach to improving the wellbeing of students.

---

[9] https://www.cdc.gov/mmwr/volumes/70/wr/mm7008a2.htm
[10] https://www.cdc.gov/hepatitis/statistics/2019surveillance/Appendix.htm
[11] https://www.cdc.gov/mmwr/volumes/70/wr/mm7011a1.htm
[12] https://www.cdc.gov/mmwr/volumes/70/wr/mm7024e1.htm?s_cid=mm7024e1_w
[13] https://www.cdc.gov/healthyyouth/data/yrbs/yrbs_data_summary_and_trends.htm

In terms of the STD prevention update, 2019 marked the 6th consecutive year of record-breaking STD cases with 2.6 million cases of chlamydia, gonorrhea, and syphilis alone.[14] This is the largest increase among congenital syphilis cases that has been experienced, with nearly a quadrupling between 2015 and 2019. Racial and ethnic minority groups, gay and bisexual men, and youth continue to be disproportionately affected. STDs affect an even younger population than HIV does and are a continuing challenge. The hope is to reverse this over time with both the expanded resources for DIS and with the momentum of a new Division Director who will soon be announced. In addition, CDC has issued new gonorrhea treatment guidance[15]. This involves monotherapy with 500 mg ceftriaxone for uncomplicated gonorrhea. If Chlamydia infection has not been excluded, treatment with doxycycline is also recommended. There are implications for public health practice, including continuing to monitor for emergence of ceftriaxone resistance to ensure continued efficacy of recommended regimens. TB has set the standard for what it would mean to have rapid assessment for resistant infection, ideally at the time someone is diagnosed. Dual therapy was initially recommended for gonorrhea, but monotherapy ceftriaxone is now recommended primarily for antibiotic stewardship. The idea of personalized care at the time of diagnosis could greatly benefit STD treatment and ultimately prevention.

ACET Discussion: NCHHSTP Director's Report

Dr. Belknap inquired as to whether there are planned activities to integrate hepatitis C treatment.

Dr. Mermin indicated that there are programs in some jurisdictions to screen, treat, and cure people of hepatitis C through clinically savvy SSPs, which work very well. Studies have shown that if hepatitis C treatment is combined with SSPs, there are reductions in hepatitis C incidence over years and that it is cost-saving to do this. The majority of SSPs are operating on very small budgets with a couple of staff and focus primarily on provision and disposal of injection equipment, linking people to substance use treatment, and maybe some naloxone distribution. While the vision is there to integrate hepatitis C treatment, the reality is that many SSPs struggle to continue to exist for financial reasons and/or complex political environments in their jurisdiction. There have been times when SSPs have become topics of discussion in the political partisan world when people are running for office. When that happens, it becomes extra challenging to expand SSPs in a purely public health manner.

Dr. Liu inquired as to how gonorrhea resistance is currently being monitored.

Dr. Mermin indicated that CDC has a gonorrhea surveillance system with multiple sites that perform molecular diagnoses and collect samples that are tested for phenotypic and genotypic resistance. Ceftriaxone resistance remains at a very low level. There is resistance to other antimicrobial agents that have increased beyond the level to recommend that agent, but the majority of gonorrhea isolates are susceptible. For instance, ciprofloxacin should not be used if 20% of isolates are resistant to ciprofloxacin. On the other hand, 80% are sensitive. If that is known at the time, they could be treated. Some technologies are becoming available to do this, but it has not been possible to implement that point-of-care resistance testing on a large scale.

[14] https://www.cdc.gov/media/releases/2021/p0413-stds.html
[15] https://www.cdc.gov/mmwr/volumes/69/wr/mm6950a6.htm

It seemed to Dr. Belknap that commonalities with all of the various diseases and the overlap with TB has to do with stigma and the racial/ethnic disparities. He wondered if enough is being done to try to address those and if working together as opposed to individually there are opportunities to work more collectively to address stigma and other disparities more broadly.

Dr. Mermin said he thought this was a major area of opportunity and discussion. He noted that there is some work in this area. Dr. Burton has been spending a lot of time thinking about how to apply health equity interventions in the most effective and cost-effective way, and what has been learned across various experiences. The benefit of any organizational structure being in a center is that everyone can learn from each other. The TB world has piloted a tremendous number of interventions. While there is still some stigma, TB used to be much more stigmatized than it is now. With TB, xenophobia must be dealt with in a major way and it is still not entirely clear how to raise attention and implement programs without necessarily causing more stigma for either people born outside the US or who are homeless. The same issue occurs with syphilis being 150 times more common among gay and bisexual men, or viral hepatitis for which the vast majority of new hepatitis C infections occurring among PWID. Drug use is still very stigmatized. Communication, programs, and taking services to people where they are can break down many barriers and empower people in ways that makes a difference for their lives and the diseases of focus. CDC's Director, Dr. Walensky, has made health equity one of her top priorities and is spending a lot of time making sure that the agency as a whole is spending a lot more time on this through measurable results. That will benefit centers like NCHHSTP that have spent time thinking about health equity and having the support at the highest levels to be able to accelerate responses.

Dr. Burton echoed the importance of this issue and the importance of NCHHSTP's work as a center to develop a strategic approach to addressing the issues that focuses on crosscutting opportunities. The support from center and agency leadership to take action is exciting.

Dr. Temesgen inquired as to whether there was any impact from the COVID-19 pandemic on the hepatitis A outbreak or the response to it.

Dr. Mermin pointed out that certainly a lot of people who were spending their time trying to engage in outreach with vaccination had been diverted to COVID-19. Some of the public health response was reduced. Conversely, hepatitis A is transmitted through fecal/oral routes primarily which was probably reduced if people were reducing contact. There also is the potential for transmission through injection of shared needles, which would not have been changed unless people were having more access to sterile injection equipment. It does look like some of the decline that was seen at the end of 2019 accelerated during 2020. That could have been that it is an infectious disease and by reducing a little, there is going to be a trend toward reducing more. It could have been that a lot of people who were susceptible did get infected, so the susceptible population is reduced. However, when that is calculated, it still does not reach the numbers of people anticipated to have been susceptible. While it is not known for sure, it is probably a combination of a variety of epidemiological and environmental factors that affected the situation. They are monitoring whether there will be increases now that there is reopening. Hopefully, the reduction in hepatitis A incidence over time also will maintain itself because some precautions are still in place and there are fewer people who have a prevalent infection that can be transmitted.

Ms. Cole asked whether there are planned studies for more rapid identification of resistance for TB.

Dr. LoBue responded that this is why they have the molecular service. Finding ways to speed up identification is more about systems processing of samples and getting things done efficiently. The results are very quick in that their laboratory turns results around within 24 hours. It is a matter of getting the specimens to the laboratory.

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 Rifamycins, guidance on BPal (Bedaquiline, Pretomanid, and Linezolid) and a new short-course regimen for drug-susceptible TB, a new Tuberculosis Epidemiologic Studies Consortium (TBESC) contract announcement, Molecular Detection of Drug Resistance (MDDR) service and the transition to the Targeted Next Generation Sequencing (tNGS) assay, Whole Genome Multi-Locus Sequence Typing (wgMLST) transition, and Report of Verified Case of Tuberculosis (RVCT) 2020 implementation.

In terms of BPal, rifampin is no longer in shortage. There have been a lot of concerns over rifamycins as there have been some dropouts of manufacturers, particularly for Rifapentine. According to the Food and Drug Administration (FDA) and in terms of interruption of supply, there is not currently a shortage of Rifapentine. While there is a supply available that should be adequate, that does not mean that individual issues will not occur with the supply chain. The rifapentine shortage began in March 2020, which initially had to do with increasing global demand and the single US manufacturer not being able to keep up with it. According to what they have heard from the FDA and indirectly from the company, this shortage should be resolving fairly soon if not already. The company expects that they will be able to produce adequate amounts of Rifapentine for anticipated US demand.

The questions pertaining to supply have complicated issues that ACET discussed during the last meeting, which had to do with nitrosamine impurities in both rifampin and rifapentine. A call was held in April 2021 with FDA, CDC, and the National Tuberculosis Controllers Association (NTCA). FDA provided written and oral responses to questions posed by CDC and NTCA ahead of that call. The FDA placed no restrictions on Dr. LoBue sharing the response, so he reviewed 2 of the approximately 10 questions and responses that offer a reasonable flavor of where things stand, which were as follows:

Question 1

- Has it been demonstrated from a chemistry and engineering standpoint that it is possible to manufacture rifampin and rifapentine with the final permissible levels of impurity promulgated by FDA?
    - If no, how long will FDA allow for this to be determined?
    - If yes, how long will FDA allow release of product at interim levels?
    - If no or yes (but not economically feasible from the manufacturers' perspective), will FDA permit long-term use of these drugs with higher levels of impurity?

FDA Response

- The question of whether rifampin or rifapentine can be manufactured with acceptable levels of MNP (1-methyl-4-nitrosopiperazine) or CPNP (1-cyclopentyl4-nitrosopiperazine), respectively, has not yet been answered.
- FDA identifies a recommended timeline for manufacturers to control nitrosamine impurities in FDA's Guidance for Industry: "Control of Nitrosamine Impurities in Human Drugs."
- FDA will permit exposures above lifetime acceptable intakes and will continue to revisit the interim limits for nitrosamines in rifampin and rifapentine on a case-by-case basis to maintain patient access to these medically necessary drugs. FDA physicians and scientists make these case-by-case decisions based on the severity of disease, the potential impact of a drug shortage for the medication, and discussions with a manufacturer as to their ability to reduce or eliminate these impurities.

Question 2

Does FDA have a contingency plan for maintaining supply of these drugs if a shortage results from manufacturers either not being able to or deciding it is not economically feasible to meet final permissible levels?

FDA Response

a) We are very much aware of the criticality of these drugs and are continuing to work with the manufacturers to ensure safe and adequate supply.

Little has changed since this was addressed during the last ACET meeting. There is still a lot that is unknown and a fair amount of uncertainty. At this time, the drugs are available.

Moving on to guidance development, guidance on BPal for treatment of extensively drug-resistant TB (XDR-TB) or difficult-to-treat multidrug-resistant tuberculosis (MDR-TB) was drafted by CDC authors, reviewed by external experts, and presented for public comment at ACET December 2020. A web supplement was completed May 2021. This guidance is currently awaiting final review and approval by the CDC Office of Science. DTBE will publish this guidance on the DTBE public-facing internet site, given that there are a number of ongoing studies related to these drugs. It is likely that this guidance will need to be update based on those studies reasonably soon and perhaps several times, so they wanted to take a living document approach to this particular guidance.

The other guidance under development is on the 4-month rifapentine-moxifloxacin regimen for the treatment of drug-susceptible pulmonary TB, which comes out of TBTC Study 31/ACTG A5349 that was recently published in the *New England Journal of Medicine* (*NEJM*). The guidance was drafted by CDC authors, with external expert review approved for Summer 2021 and presentation for public comment and ACET review and approval during the December 2021 ACET meeting. The revised document will then go through the CDC clearance process. After review and approval by the CDC Office of Science, DTBE will then seek to publish the guidance in the *MMWR*. CDC staff also already contributed to the World Health Organization (WHO) TB treatment guidelines review.

The announcement for requests for proposals for the new TBESC contract has been announced by the Office of Acquisition Services and DTBE is in the process of waiting to receive proposals based on that funding announcement.

Regarding laboratory updates, the MDDR service is in the process of transitioning to primary use of tNGS sequencing. This allows more genetic loci to be examined per test run and offers the ability to add genetic loci for bedaquiline, clofazimine, and linezolid and an expanded region for isoniazid. The change in technology also enhances the ability to detect heteroresistance (i.e., mixture of resistant and susceptible populations). The laboratory anticipates implementation of this new technology by late Summer 2021.

There also has been discussion about the transition to whole genome sequencing (WGS) for cluster detection during previous ACET meetings. There are two parts to this, one of which is the change to GENtype that is based on spoligotyping and mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR) to whole genome multi-locus sequence typing (wgMLST) for cluster detection. The validation for the naming algorithm of that has been completed. The next version of the TB Genotyping Information Management System (TB GIMS) will add the ability for state and local partners to view wgMLSType information. Release of the new version of TB GIMS is expected to be live in July and training will be provided once the new version is released. In addition to moving over to the different typing systems for cluster detection, they are working on transitioning the cluster alerting algorithm from being GENtype-based to using wgMLSType. That transition is anticipated in mid-2022.

There was a plan before the COVID-19 pandemic to have a new version of the RVCT to occur in 2020. Because of the serious impact on TB programs, the deadline for implementation was initially pushed back to 2021. In assessing the situation this year, it is clear that this will not be feasible to implement fully until 2022. There are 3 categories of programs in terms of how DTBE receives data from states. The first is that DTBE has a web application version of the case reporting form, which used to be called the eRVCT and is now known as the National Tuberculosis Surveillance System Case Report (NTSS CR). That is already available and multiple states are using that in submitting with the new 2020 RVCT. Another group uses the CDC multi-disease reporting application, National Electronic Disease Surveillance System (NEDSS) base system (NBS). This is somewhat more difficult because they also are pushing back their implementation of the new version to Summer 2022 because of the pandemic. This may be one of the more complicated aspects of this. Because it is being pushed back that far, some states are already considering use of the DTBE-developed application, the NTSS CR, in the interim. The third group of states use either commercial or their own proprietary systems, and DTBE is working with them. It depends on how badly a state is impacted by COVID-19 in terms of their TB program and their IT services. Some are moving things along, with Oregon being the first program to fully transition to the new 2020 RVCT.

ACET Discussion: DTBE Director's Update

Dr. Bloom asked whether the new CDC guidance on BPal is consistent with the WHO's guidance or if there will be some kind of back and forth.

Dr. LoBue said that he had not compared them head-to-head, but the CDC guidance has not changed since it was presented to ACET and is consistent with the FDA indication. CDC has to take that into account more than WHO would have to, with the understanding that people may choose to use it more broadly. It is up to clinicians to decide on a case-by-case basis and there are certainly perfectly good reasons to do that. This guidance is likely to change soon and potentially multiple times, given that numerous international studies are underway that have different regimens, such as different dosing of linezolid, that are likely to impact this.

Dr. Ritger asked whether the addition of bedaquiline, linezolid, and clofazimine to the MDDR extends to the growth-based susceptibility testing as well, which would be a welcomed addition.

Dr. LoBue replied that those are genetic loci. He said he would have to defer the question to DTBE's laboratory. They are working on those to the extent that can be done, though he did not know the current status in terms of general availability. Some of that may take longer because they actually are looking at minimum inhibitory concentration (MICs), which is not traditionally done for other drugs.

Ms. Cole reminded everyone that during the last ACET meeting, specific questions were posed for FDA to which they said they would respond. She asked whether all of those issues were addressed during the call with CDC and NTCA within the approximate 10 questions. She noted that on the "Advice Requested from ACET" she included a bullet reading, "Monitor for FDA response to the follow-up questions." She suggested that perhaps they could review Dr. LoBue's document to determine whether everything was addressed, and perhaps would be able to consider it resolved.

Dr. LoBue indicated that he thought they were and that he would provide them all to Ms. Morris to distribute to the ACET members. It was just too long to review during this session. He emphasized that questions were largely answered, it did not result in much advancement from 6 months ago. The issue is not really resolved, so ACET may want to continue to monitor it for some time.

Dr. Belknap wondered whether any change is expected in the FDA's acceptable limit for nitrosamine based on the new Study 31 results. The levels that they determined were based on the maximum daily dose, which prior to Study 31 was 900 mg one time per week. Now there is a higher daily dose. His concern is that their acceptable limit might even go lower, because the original calculation was using 900 mg per day of rifapentine and now there is a 1200 mg dose.

Dr. LoBue confirmed that a few questions were raised on that topic in terms of whether FDA would be consistent with the Canadian level, which is substantially higher, and if they would adjust things based on the actual dosages versus the daily/lifetime. FDA's response was basically "no." It is very low as it is, with the next unit on the scale being zero pretty much.

Dr. Ahuja wondered whether there has been any discussion about the new definition of XDR.

Dr. LoBue indicated that WHO is implementing a new definition of XDR, which takes the injectables out based on oral drugs and the various drug classes. DTBE has been discussing this. His initial impression and that of people he has talked to in the division is that WHO's approach makes sense in terms of having a definition on drugs that are not recommended for use. Moving the definition to drugs that are recommended makes sense. It is more about determining the timing of how and when to implementing this because there are a few issues, one of which is availability of susceptibility testing for the new drugs that are part of the definition. There also is confusion in terms of the literature with regard to what one and what paper means when it say "XDR" compared to another paper. DTBE is considering this and is likely to change the definition, but has to figure out what makes sense in terms of timing for the US on how to do that. He wishes they had given it some kind of annotation, which would have made it easier in terms of the literature.

2020 TB Provisional Surveillance Data

Julie L. Self, PhD, MPH
Surveillance Team Lead
Surveillance, Epidemiology, and Outbreak Investigations Branch
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Self provided an update on 2020 TB provision surveillance data reported in an *MMWR* published on March 26, 2021 in conjunction with World TB Day. In that publication, a 20% decline in TB incidence was reported based on provisional data as of February 17, 2021 reported to NTSS compared with the previous year. Before delving into the data, Dr. Self shared some of the hypotheses the Surveillance, Epidemiology, and Outbreak Investigations Branch (SEOIB) developed as they began monitoring the number of TB cases reported throughout 2020.

First, they hypothesized that there might be a true decline in the number of TB cases in the US. One possible reason for a true decline is the reduction in international travel and immigration. Another possible explanation is improved TB control unrelated to the pandemic, such as the effects of new technical instructions for overseas screening that went into effect in late 2018. Improved detection and rapid treatment of TB cases is also a possibility. Finally, the effects of COVID-19 disease or the public health interventions that might have an effect on TB incidence are of interest. For example, public health measures to control COVID-19 such as mask wearing and social distancing might also have affected TB transmission. It is also possible that increased COVID-related mortality among people at risk for TB reduced the number of TB cases.

Underdiagnosis is another hypothesis for the decline in TB. Possible explanations for underdiagnosis include patient hesitancy to seek care because of concerns about COVID-19, low suspicion for TB by healthcare workers, and missed or delayed TB diagnosis due to the focus on COVID-19. For example, anecdotal reports have been received for individuals presenting to healthcare facilities who test negative for COVID-19 multiple times and are only diagnosed with TB at a later time, including some instances in which the person passed away before being diagnosed with TB. Finally, TB cases might have been underdiagnosed or experienced delayed diagnoses because of reduced public health capacity to conduct active TB case findings, such as TB contact investigations and targeted testing. A third hypothesis is underreporting of diagnosed TB because of staffing and other public health resource constraints. Anecdotally, it is known that there were initially some reporting lags occurring at the local and state levels, but all of the partners were able to meet the provisional data deadline and indicated that they reported all cases that remained to public health.

Dr. Self pointed out that most of the data she would review during this session would include cases reported to NTSS from the 50 US states and the District of Columbia (DC). In terms of the number of TB cases per year during 2010-2020, based on recent trends they would have expected see about 8800 cases in 2020. However, there were only 7163 provisionally reported cases—a 20% decline from 2019. Reported incident rates for the same period also showed a decrease in 2020. Based on recent trends, an incidence rate of 2.6 cases per 100,000 persons would have been expected. However, the observed rate was 2.2 case per 100,000 persons in

2020. There is a wide range in the relative changes of incidence rates compared with 2019. Most states had a large decline in incidence, while some states showed an increase in incidence. Most of these were relatively low-burden TB states. For example, Wyoming reported no cases in 2020. This is why they had a relative reduction of 100%.

In terms of incidence rates by origin of birth for 2010-2020, TB incidence rates have been declining in both US-born and non-US-born populations over the past 10 years. Greater reductions were observed in 2020 for both groups, which were relatively similar in magnitude of reduction at a decrease of 20% for US-born and 19% for non-US-born groups. Regarding incidence rates by race/ethnicity among US-born persons during the same timeframe, TB incidence declined among all race/ethnicity groups for US-born persons except Native Hawaiians and Pacific Islander populations, for whom the small population size also leads to year-to-year variability in incidence rates. Similarly, TB incidence rates declined among non-US-born persons for all racial and ethnic groups except Native Hawaiians and Pacific Islander persons. Comparing the number of years since first arrival in the US in 2020 to 2015-2019 among non-US-born persons, there is a shift of a higher percentage of cases among individuals who arrived in the US more than 20 years ago. Not surprising, a drop is observed in the proportion of individuals diagnosed within 1 year of arrival in the US. As of 2019, the top 5 countries of birth among non-US-born persons were Mexico, Philippines, India, Vietnam, and China. Also, no substantial changes were noted in the percentage of cases by age or in the reason for TB evaluations for US-born compared to non-US-born persons. In a recent assessment, a substantial change was not seen in seropositivity or cavitary disease in the percentage of changes in either of those indicators of more infectious disease.

Overall, a steep decline was seen in reported TB cases and incidence rates in 2020 compared to previous years. Little difference was observed in several of the key demographic variables included in the provisional datasets. The age distribution and the primary reason for evaluation were all relatively similar in 2020 compared to the previous 5 years. The decline in TB incidence was similar across origin of birth and most racial/ethnic groups. While racial and ethnic minorities continue to have the highest rates of TB, the pattern of decline in 2020 is not substantially different by race and ethnicity overall. However, a shift was seen in the patterns of new arrivals in the US.

DTBE has additional plans to further investigate the effects of the pandemic on TB surveillance. In addition to the annual report that should be available later in the fall, DTBE plans to conduct more detailed analyses of NTSS data to assess changes in demographic, risk factor, reason evaluated, clinical characteristics, disease severity, and the association between change in TB incidence and COVID incidence by state. Another DTBE data source is TB GIMS, which combines surveillance and genotyping data to detect genotypic clusters. There are plans to assess changes in the frequency of cluster alerts, characteristics of clustered cases, and estimates of recent transmission. Monitoring of 2021 case reports also will continue and that work is already underway. Based on a summary of cumulative cases reported to NTSS by month from January-May 2016-2021, the 2021 data are tracking somewhat lower than 2020 for the early months of the year. Although 2020 did not diverge from previous years until about April. It will be interesting to continue monitoring these data each month moving forward through 2021.

DTBE also has pursued several external data sources to help understand the effects of the pandemic on TB. Access to retail pharmacy data were obtained through IQVIA and assessed patterns in drugs used for TB treatment. Immigrant and refugee screening data will be reviewed from the Division of Global Migration and Quarantine (DGMQ) Electronic Disease Notification

system (EDN) to better understand changes in health screening for immigrants and refugees who are considered to be at risk for TB. Hospital administration data will be accessed from the Healthcare Cost and Utilization Project (HCUP) for primary and secondary diagnosis of TB once these data become available. DTBE is also exploring the possibility of analyzing electronic health record (EHR) data, for example from OCHIN, to assess for changes in TB-related diagnosis and services. Finally, they eventually would like to assess TB-related mortality using vital statistics data from the National Center for Health Statistics (NCHS) when those data become available. DTBE thinks that each of these external data sources can help them better understand the changes they observe in TB diagnosis reporting in 2020.

While DTBE is still waiting for 2020 data from several of the external data sources, Kathryn Winglee from this division has made considerable progress with the outpatient pharmacy data from IQVIA. IQVIA contains prescription data from retail, mail, and long-term care pharmacies and is updated monthly. Using pyrazinamide and isoniazid as proxies for active TB treatment, DTBE found that the volume of TB medication prescriptions is highly correlated with the number of cases reported to NTSS during 2006-2019 when trends were explored in anti-TB medications. Looking at each of the metrics over time, NTSS data aggregated by the month treatment began since 2006. There are some seasonal year-to-year fluctuations seen, but in general the line gradually trended down as expected. When the number of cases were aggregated by treatment start data in a given year and the percent difference was calculated from the previous year, with the exception of 2007 and 2014, there have been fewer cases every year than in the preceding year. There was a large dip in 2009 related to the recession. By far, the largest decrease was in 2020. When a line was added for the project patient counts by dispense data, there were still fluctuations occurring from year-to-year, with a general decrease over time and a large drop in 2020. While more variability was seen with the pyrazinamide data than NTSS, there was still a substantial drop in 2020 with 13.7 fewer projected patients taking pyrazinamide in the IQVIA database compared with 2019. IQVIA projected patients counts by isoniazid show the same pattern in seasonal variation, while also decreasing over time with a larger drop in 2020. The percent difference in isoniazid also had the largest drop in patient counts in 2020, with 29.7% fewer projected patients taking isoniazid in the IQVIA database in 2020 compared to 2019. The percentage decrease was similar to what is seen with NTSS data. DTBE is still conducting additional analyses, but so far they have found that there is a strong correlation between TB surveillance and TB prescriptions over approximately 15 years. TB prescriptions for pyrazinamide and isoniazid experienced a similar decrease in 2020.

In conclusion, state and local TB programs successfully met the provisional TB reporting deadline in spite of staffing and resource challenges that occurred throughout 2020 and have continued in 2021. Analyses of the effects of the pandemic on TB epidemiology are ongoing and will proceed as 2020 data become available from multiple other internal and external data sources. DTBE also will continue to monitor TB reporting in 2021. One reason they will be keeping a close watch on 2020 reporting is that there is a concern that the 20% decline observed for TB in 2020 will not be sustained if it is largely the result of underdiagnosis or reduced immigration rather than a true decline in TB incidence.

ACET Discussion: 2020 TB Provisional Surveillance Data

Ms. Cole asked whether anyone is tracking co-infection with COVID and TB in cases where patients were being seen for COVID but subsequently were diagnosed with TB or vice versa. She suggested that this be bookmarked for future review and discussion.

Dr. Self said that there are a couple of ways DTBE is looking into this. The primary way is to allow people to list COVID as an “other risk factor” in the open field where additional risk factors can be listed that are not already identified on the case report form. Programs are encouraged to list COVID as an “other risk factor” when they report a case that has had coinfection. However, there is not an opportunity to provide a lot of detail there in terms of timing or the nature of the coinfection (active infections simultaneously, one before the other, which order). They can track the number of coinfections, but lose some information. There are efforts underway in the division to attempt to provide a more detailed look and collect additional information.

In terms of complete reporting for local health jurisdictions, Dr. Higashi indicated that it was a challenge and that one of the more time-consuming activities is reporting and confirming culture-negative cases. Her usual benchmark for having done a good job of completely reporting is approximately 15% culturing of cases. For the first time in a very long time, Los Angeles was able to meet that benchmark. On a national basis, it would be interesting to see if it departed from the usual percentage. This requires a lot of clinical time, coordination back and forth, and asking providers for exams like computed tomography (CT) scans and magnetic resonance images (MRIs). It can take a lot of effort, so it is easy to see how this might have contributed to some of the reduction.

Dr. Self indicated that DTBE looked at this and did not see a large difference in 2020. She was expecting to see more differences overall in 2020 than what they did find, other than just the overall drop between some of the variables that she mentioned earlier. They had hypothesized that they would see changes in culture positivity as well as indicators of infectiousness and different distributions demographically and in some of the risk factors. But overall, changes have not been very dramatic in the provisional data. For instance, culture positivity was very close in the provisional data. DTBE is working to finalize the final dataset for the 2020 cases, but there are usually not dramatic changes between the provision and the final data. This will be reported out in the annual report.

Dr. Horsburgh wondered whether they have had a chance to assess the clustering percentage. If cases exist that have not been reported, there might be more clustering because they are transmitting even if there is not complete reporting.

Dr. Self indicated that they have not looked at this in-depth yet, but that is something that they are definitely planning to review. Looking at the clustering of recent transmission is another way to approach this. One of the challenges of assessing clustering is that any cluster that is detected through the automated cluster detection methods is that it includes cases from several previous years. Trying to figure out the right timeframe and how long to follow it is challenging, but they are working through it and plan to provide an update on those data as well.

Dr. Loeffler asked whether DTBE assessed pediatric data as a surrogate for transmission. In 2020, her county had essentially no pediatric cases and now they are starting to see more secondary cases and a delay in diagnosis.

Dr. Self said that they have not specifically explored pediatric cases and a surrogate for transmission so to speak, but overall they were surprised to find little difference in pediatric cases in general in 2020 compared with previous years. They found approximately the same percentage in children 0-4 years of age and 5 to 14 years of age. They will look into this in more depth. There are plans to look at clustering and explore some other variables in relations to age, but so far the initial analyses have not shown a difference by age. Overall, the number of cases among children did not change very much in 2020.

Dr. Reves noted that perhaps 15% of reported cases were among several million non-US-born persons on non-immigrant visas (work, student, exchange), and he wondered if it was known how these visas changed in recent years.

Dr. Self said that while they do not have reliable information on visa status, they do capture US-born versus non-US-born, country of birth, and time of arrival in the US. Therefore, they really cannot draw any conclusions or provide summary information about visas. There are a variety of ways that people come to the US, but there is not a lot of information in DTBE's surveillance about that.

Dr. Belknap asked whether DTBE has assessed diagnoses stratified by pulmonary and extrapulmonary. Denver had about a 20% reduction in diagnosis and found that it was mostly in pulmonary TB diagnosed among people living in the US for more than 5 years relative to recent prior years. They hypothesized that the overlapping symptoms of COVID and pulmonary TB may be a driver of missed diagnoses, which would not have the same impact on extrapulmonary TB diagnoses.

Dr. Self said that they looked at this and while she did not have the data handy, she did not think they saw changes nationally. They did hear about a lot of things anecdotally that are different in 2020, but when they look across the board nationally they do not see those same things happening. Even in terms of how the different areas and programs were impacted by the pandemic, it seems like there is quite a lot of variability in terms of one local area's experience. Many interesting observations are occurring locally, but it seems varied enough that it is not being seen at a national level.

Following up on Dr. Reves' question, Dr. LoBue said that DTBE cannot look at TB cases and say something about the country. What is known is that for a long part of the year, pretty much no one was entering the US. People were not allowed in. At some point, it will be possible to look at overall categories such as how many refugees actually entered the country compared to previous years, how many different visa holders entered the country during previous years. It is likely that there was a huge drop-off for all of the categories. They will need to get these data from external sources that should be publicly available. These data may be ready now and DTBE will be looking at this.

Mr. Watts asked whether DTBE has had a chance to stratify by congregate settings such as prisons and/or homeless shelters where, based on some excellent guidance by CDC, several shelters decompressed their census by placing people in motels, especially those who were vulnerable.

Dr. Self said this was another thing they were somewhat surprised to find that did not differ substantially in 2020 compared to other years. From 2015-2019, they pulled an average. The percentage of cases who had experienced homelessness in the year before diagnosis was 5%

average over those years and 4% in 2020. For correctional facilities, it was 3% each year. It has been variable from year-to-year, so they can explore this further in more depth to ascertain whether there are specific states, situations, or demographics characteristics that are more related to that change. However, the change is pretty small.

Ms. Marx wondered about long-term care facility (LTCF) diagnoses.

Dr. Self indicated that LTCFs were similar. The average in 2015-2019 was about 2% and it was still about 2% in 2020.

Tuberculosis Trials Consortium Updates

Andrew Vernon, MD, MHS
Chief, Clinical Research Branch
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

Dr. Vernon provided an update on behalf of the Clinical Research Branch (CRB) on the current activities and recent work of the TBTC. He emphasized that the interest and support of ACET over many years has been very much appreciated. The past year and a half has been an eventful period for the Clinical Research Branch as they transitioned the TBTC from the prior decade to the line-up that will be in place for the next decade. The US TBTC sites from 2013-2019 included San Francisco, Denver, Northern Texas, San Antonio, Houston, Southern Texas, Nashville, New York, and CDC Atlanta. International sites included Lima, Barcelona, Kampala, Kisumu, Soweto, Stellenbosch, Hanoi, and Hong Kong. The awardees for the upcoming decade are shown in the following table:

CDC Contract Sites	VA Medical Center (VAMC) Sites
Case Western-Kampala	Washington DC VA/GWU + DCH
Medical University of South Carolina (MUSC)-University of Cape Town	NYC HHS + NYC BOT
Cornell-GHESKIO	San Antonio VAMC
McGill University CAB V: Canada, Australia, Benin, Vietnam	Minneapolis VA + Hennepin City
Denver Public Health	Stellenbosch - Pediatric
Seattle-King County	

The 47th TBTC meeting was convened on June 7-8, 2021. This was the Consortium's third virtual meeting. The meeting was used as a primary opportunity to introduce all of the new sites and to review ongoing TBTC work. Dr. Vernon provided a brief update the studies. Study 26 is related to Study 37. This study is reviewing the experience with latent tuberculosis infection (LTBI) treatment in foreign-born individuals, who represented about 70% of that study so there is a lot of experience with these persons.

Study 31 is the 4-month TB treatment study. The primary results were presented during the International Union Against Tuberculosis and Lung Disease (IUATLD) World Lung Health (WLH) conference in October 2020 and were discussed during the North American Region meeting of IUATLD. Additional materials were presented at the recent ATS meeting. They also were presented at the AIDS Clinical Trials Group (ACTG) Network meeting that just took place, and in

the ACET virtual meeting. The report was published in the *NEJM* on May 7, 2021 that was accompanied by a very helpful editorial. In addition, reports on the design of the trial, quality assurance (QA) measures, and management already have been published. There is a long list of publications that will be pursued over the next couple of years. Another symposium focused particularly on the pharmacokinetic/pharmacodynamic (PK/PD) results has been submitted for consideration for the IUATLD WLH conference in 2021. The PK/PD analyses are well underway. A substantial part of that work has been completed, but there is a lot still remaining. This is the largest trial that has every provided PK data. There are PK data on virtually every one of the nearly 2500 patients in the trial. This is a remarkable opportunity to assess the role of PK on outcomes. Risk factor analyses are underway. Many of the traditional risk factors will be challenging to consider because many of them interact with the amount of drug exposure. One could expect, for example, that 2-month culture conversion as just a single example would be heavily influenced by the level of exposures to key drugs. An additional sub-study addresses sputum transcriptomics. Known as Study 36A, this study is being conducted with National Institute of Allergy and Infectious Diseases (NIAID) which has funded the basic science elements of that work. That will address application of the ribosomal ribonucleic acid (RNA) synthesis ratio, a novel biomarker that may have great utility in predicting outcomes in the future. Study 31B focuses on quantitative Xpert indications of outcome, as well as MICs of organisms in the subgroup nested within the trial. The hope is that Study 31A will have results to report later in 2021 and Study 31B results probably will be ready in 2022.

As mentioned earlier, WHO is considering the 4-month TB treatment regimen used in Study 31. They announced on June 14, 2021 that they are approving it as a possible alternative for use in drug-susceptible patients. The real value of that trial in Dr. Vernon's view is that these multiple opportunities to learn about what worked and what did not work will provide a roadmap for further treatment shortening in the future. That is probably a more valuable output than a particular regimen at this time.

Study 32 aimed to optimize levofloxacin dosing. This study has struggled with a variety of logistical challenges over its performance, but it is close to the end of these. The MICs are now being performed in the CDC laboratory. The hope is to be able to report primary outcomes from that study later in the summer.

Study 33 compared self-administered therapy (SAT) to directly observed therapy (DOT) for 3HP and was the basis for the approval of SAT for use of 3HP. There are two manuscripts in process, one of which will address the experience in Study 33 with adverse events (AE) and hypersensitivity findings in particular. The second will comment in more detail on the assessments of the three adherence measures: patient self-report, pill counts, and microelectronic monitoring systems (MEMS) caps recordings.

Study 35 assesses the novel water dispersible child-friendly formulation of rifapentine (Ped RPT). This is a Phase I/II PK and safety study aimed at children up to 12 years of age. The initial first two cohorts contributed 8 patients each and the first interim analysis has been completed. Final confirmation is awaited from the manufacturer regarding the dosing plan, which was based on the findings of that interim analysis to apply to the younger cohorts. The study had been paused for some time due to COVID, but will hopefully resume shortly. The consent form has been adjusted in response to the nitrosamine issue, which is likely to be a continuing challenge.

Study 36/36A is essentially paused. This was the observational platform that was initiated prior to Study 31 getting started. It also contributed specimens to the biobank of the TB Alliance. The Study Officer on that study retired a number of months ago, and the effort to replace that individual is underway.

Study 37 is the current leading study from the Consortium assessing 6 weeks of rifapentine alone for the treatment of LTBI. This study was paused in March2020 due to the pandemic at a time when 92 patients were enrolled. This has been the platform upon which much of the understanding has been acquired about how to manage trials in the context of a pandemic. The hope is that activities for this trial will be reinitiated shortly. Efforts to complete closeouts or transfers are underway and new sites are being on-boarded. While onboarding is primarily being done for new domestic sites, there is strong interest from some of the new high-burden sites. That discussion will be pursued over the next couple of months. The consent form for that trial also was revised and submitted to various regulatory and ethical authorities and panels. There is also a significant discussion underway surrounding the eligibility criteria for LTBI-positive immigrants in terms of what additional criteria would apply to make those individuals good candidates for Study 37. The issue is the identifiable risk of progression for individuals in that category.

Study CRUSH-TB began as a working group assessing combination regimens for shortening TB treatment and gradually came to focus on the backbone of the bedaquiline, moxifloxacin, and pyrazinamide (BMZ) plus some other novel drug. CDC has been negotiating with pharma with the TB Alliance who holds the rights to oversee use of and bedaquiline for drug-sensitive TB from J&J. Those negotiations are moving forward in a slow but very satisfactory fashion. The events and delays of the reconstitution were significantly responsible for some of the delays. That delay was utilized to support a murine study to assess the regimens being proposed. Those data are gradually becoming available. The results are in for the BALBc mice, the smaller white mice. The data are gradually coming in for the Kramnik mice, which are thought to reflect more severe TB that is very often found in humans. This has been a very successful activity and one that hopefully will provide a model moving forward for increasing use of murine data as a platform for engaging any substantial Phase III work. There is still a challenge with regard to electrocardiogram (EKG) monitoring because of the QT activity of several of the drugs. The potential to use the KardiaMobile device is currently under investigation as a means for frequently assessing QT intervals, the question being whether the device will sustain FDA concurrence with that. Award of the TBTC monitoring contract is close to being completed and announced.

In terms of other TBTC activities, the Executive Committees are being reconstituted following the re-competition. A note soon will go out to the sites about nominees for those committee positions. Once the committees are re-established, the Protocol Teams will be revised with the expectation that by September 2022, all of the Protocol Team Chairs will be from enrolling sites. An active review is underway to assess what additional expertise the TBTC may need, which will be completed this summer and any actions needed for that will be taken then. A new member to the Data Safety and Monitoring Board (DSMB) is in the process of being finalized, a new liaison position has been established with NTCA, the TBTC By Laws are being revised, and data sharing standard operating procedures (SOP) are being revisited.

Regarding CRB updates, Dr. Karlyn Beer joined as new Lead for the Data Management & Implementation Team this spring. She brings substantial capacity with systems biology workflow and as an Epidemic Intelligence Service (EIS) Officer in the Mycotic Diseases Branch (MDB) at CDC. The CRB is currently seeking to replace 3 staff members: 1) Dr. Jessica Ricaldi,

Microbiology Lead, who has moved on to work on COVID fulltime; 2) Dr. Yan Yuan, Data Analysis and Programmer/CDISC Translation, who has moved on; and 3) Dr. Jerry Mazurek, Safety Reviews/Study 36 Officer has retired. Dr. Vernon emphasized that the CRB staff is a small group doing a very large amount of work to contribute to all of these activities.

ACET Discussion: Tuberculosis Trials Consortium Updates
No questions or comments.

COVID-19 Impact on TB Programs

Donna Hope Wegener, MPH,
Katelynne Gardner Toren, MPH
National Tuberculosis Controllers Association

Ms. Wegener explained that during this session, she and Ms. Gardner Toren would provide an overview of NTCA's survey effort on the impact of COVID-19 on TB Programs, review select results and limitations from a preliminary data analysis, and engage in a discussion with ACET about some of the additional analyses that might be of interest with the datasets NTCA has.

They heard already during the day about how TB Programs, TB data reporting, and individuals who might be impacted by TB also have been significantly impacted by the pandemic. NTCA was fortunate early in the COVID-19 pandemic to work with their colleagues at DTBE to conduct an assessment of the early impact. This assessment involved the Project Officers at DTBE conducting telephone interviews with each of the programs funded by DTBE, as well as some convenience samples that NTCA has access to based on its Community of Practice (CoP) calls. Later in the Summer to early Fall, there was a global effort including representation from NTCA's own We Are TB, which is the TB survivor movement in the US, to conduct an assessment to look at the early impact of COVID-19 on TB Programs in the community. This information was shared nationally and internationally.

The NTCA leadership recognized early that their programs were having many people pulled into COVID, some fulltime, and very little effort was being done on survey work in the TB Program. Knowing that the TB Programs were overloaded and exhausted, NTCA did not want to add additional burden early on. However, they realized early in 2021 that the timing might not ever be ideal and they really did need to get a sense of how its programs and those they were serving were impacted. Therefore, they decided to launch a survey. Three primary goals for the survey were to: 1) assess impact of COVID on TB Programs, including early evidence of TB-COVID co-infections; 2) identify strategies for addressing COVID impact on TB Programs; and 3) evaluate potential need for additional resources to TB Programs due to COVID-19. Ms. Wegener noted that some data were collected on the co-morbidities of TB and COVID that would not be presented during this session, but that NTCA is working very closely with DTBE and plans to launch an additional data collection effort targeted at the intersection of TB and COVID.

The survey was launched in January 2021 and continued with an open data collection effort through February and was ultimately closed in March 2021 after engaging in some targeted work to increase some of the response rates. Because of the population with whom NTCA works most closely, the initial distribution of the survey meant that they sent it to all of the NTCA members representing the DTBE-funded CoAg programs. Because they were hearing early on

that there were a lot of differences in the impact at state-level versus local-level programs, they thought it was very important to capture that perspective. Available to NTCA are those local health department programs that are members of NTCA, and that became the nucleus of the first sample. They also were very fortunate to work with the National Association of County and City Health Officials (NACCHO) and their colleagues there who are on the Infectious Disease Committee. Although they did not co-sponsor the survey with NTCA, they willingly distributed a link to the survey in their *HIV, STI, & Viral Hepatitis Digest.*

The survey respondents included a mix of 96 local county, city, and regional programs and 46 state, territory, and district programs. Because they had varying ways of rolling out these surveys, they did ask that to the extent possible, the jurisdictions coordinate responses and that only one survey be submitted per jurisdiction. In terms of the way the data are separated, it is important to note that some of the big city TB programs that are funded by DTBE are actually counted in the 96 programs. The 46 state and territorial programs includes the DTBE-funded programs, and once those that are DTBE-funded CoAg programs in the big cities, there were over 50 CoAG recipients responding. That represents 75% of those programs in the US base and the US Pacific Island Territories. They feel like there is great representation across the DTBE-funded programs, especially given all that was happening with the COVID response. While it is harder to assess what the response rate is from the local programs, they think they have a good number to start looking at how the pandemic was experienced at the local health department level and some differences between state and local health departments.

Ms. Gardner Toren identified a subset of categories in a series of questions that NTCA asked about impact, including staffing and service changes, service delivery changes, and diagnosis and reporting change. To highlight a few salient facts, if all respondents are included, nearly 85% of all respondents said that their TB program devoted to TB activities had been reduced. Nearly 80% said there was a reduction in clinic appointments, 64% said there was a reduction in LTBI treatment initiation, 70% said there was an increased use of telemedicine or eDOT, and 54% said there was a reduced reporting of presumptive TB from providers.

In terms of staffing and services changes, there was a high impact throughout all of 2020. It is important to note that no 2021 months were not included because that is when survey distribution occurred. Among respondents, 83 said there was an ongoing impact so this is known to have gone into 2021. They just do not know which month in 2021 may have been particularly impacted. They also asked a question about when staffing returned to normal for those that indicated that staffing had been reduced. Nearly a third of respondents marked that they did not know when staffing was going to return to normal. Therefore, there was a lot of uncertainty at the time of the survey around when staffing would return to normal levels or if that was even going to happen. Many services had not resumed normal operations, particularly at the local level. At the time of the survey, 50% of local health jurisdictions said that less than 25% of their services had resumed normal operations. At the state it was somewhat higher in that only 22% said that there was still a reduction in their services.

To illustrate what respondents were feeling, Ms. Gardner Toren shared the following selected quotes directly from the survey:

b) *COVID made priority by county administrators, no staff available for TB and they aren't allowed to work overtime*.

c) *Our office closed and still remains closed due to COVID. We all continue to telework for my department. I have been unable to see any of my LTBI clients in person. I do see my active*

cases for refills at their home for a quick switch, but my time is limited to less than 15 minutes. I am heavily relying on their monthly check ins with the Infectious Disease physician.

d) *TB Clinics in most local health depts. were shut down for a period of months; PH Nursing staff totally taken off TB -- and continue to be deployed exclusively to COVID response*.

e) *Large proportions of our staff are actively involved in the COVID-19 response, reducing time available for TB programmatic work. Potentially delayed diagnoses may mean that we see more and sicker TB patients in the coming years.*

f) *State is very diverse in program/population size and impacts on TB programs have not been distributed equally among jurisdictions*.

g) *Work toward TB elimination is not happening at this time. As a result of the reduction in capacity at the local level, we are not going to see progress toward TB elimination goals. All focus has been on the identification and treatment of active TB disease and not TB infection. The biggest challenge faced by our programs at the local and state level is available time and available staff to do program work*.

h) *We are pushed to do more and not hiring. We are told there's no money. I have gained 3 months comp time. Working 10- to 13-hour days, on call, holidays and weekend related to COVID. Need help…more funds for more positions*.

In terms of service delivery changes, one of the questions asked in the survey pertained to how programs adapted to the pandemic. There was a series of pre-filled items people could select, or they could put others. Some of the things that various programs did to try to still offer services to their clients included:

How has your program adapted to the pandemic to be able to continue to deliver services?		
	N	**%**
Working remotely when possible*	101	71.1
Changing inclusion criteria for eDOT*	53	37.3
Issuing interim TB Program operation guidance*	36	25.4
Modification in standards of care	27	19.0
Increasing the amount of medication that could be issued to a patient at any given time	34	23.9
Starting use of telemedicine	37	26.1
Changing prioritization of cases/case management	26	18.3
Changing approach to conducting contact investigations	26	18.3
Other	22	15.5
No adaptation*	16	11.3

"Other" responses included: Stopped/decreased targeted LTBI screening and treatment initiation, changed priority of B waivers, partnered more closely with PCPs, increased home visits, increased PPE use, had medications delivered by mail, conducted over the phone histories/teaching/contact investigation assessment

*Significant difference (<.05) between state and local responses

Based on looking through the data in the survey, there is a lot of variability by states and locals because of the different types of work that they do. A lot of locals have clinics on the ground, so one of the facts that was particularly illustrative of that was that 93.5% of the state programs were working remotely and only 60% of the local programs were able to do that. There was definitely a differential impact depending upon the kind of work and services being offered, which will definitely need to be taken into consideration moving forward.

One of the big successes of how programs have adapted throughout the pandemic is with telemedicine.

Of the programs, 75% said that they had used telemedicine and identified the following positive aspect:

- Is patient-centered:
  - Convenient (don't need to leave work or find childcare/transportation, flexible timing, removes travel time)
  - Increases compliance/adherence (i.e., reduces no-shows related to travel limitations and/or fear of coming in-person)
  - Not infringing on patient's private space
  - More control for the patient
- Increases patient satisfaction
- Increases flexibility and time saving for case manager/providers
- Reduces risk of infectious disease exposure to client and staff

Nearly 56% of programs said that there also were limitations to using telemedicine for case management, such as the following:

- Technology access (equipment, connectivity) and capacity (new technology) for patient, though a lot of the limitations are not inherent in the technology
- Ability to draw labs, do vital signs, and physically examine the patient
- Not same level of interaction with the patient/hard to build rapport
- Hard to use interpreter, which can also be challenging by phone

It is important to call out that the biggest limitation was around issues that might be able to be supported financially or through training that would build capacity. That represents an opportunity moving forward to potentially reduce some of those limitations. Another frequently mentioned part of the survey was that a lot of programs changed the inclusion criteria for eDOT. Prior to the pandemic, inclusion in eDOT was pretty strict and a lot of sites had people on in-person DOT for a period of time. During the pandemic, some sites allowed eDOT earlier in treatment, such as allowing for initiation when treatment started or after a decreased number of in-person doses within a few weeks. Some dropped the requirement for the intensive phase to be completed, the requirement for being out of isolation, and/or decreased the number of mandatory in-person doses. Some programs allowed for more patients to be eligible by including patients who did not speak English, patients with drug-resistant TB if approved by the clinician, children with a guardian present, and/or smear positive cases. There were very few exclusion criteria, such as inability to use technology or persistent non-adherence (on legal order). While a lot of patients really liked the option of using eDOT in a lot of instances, consideration must be given to what all of these alteration in eligibility and timing of eDOT means long-term in terms of relapse rates. There is an opportunity here to ascertain what all of

these changes mean for potentially long-term ability to use eDOT in different populations and at different times.

Moving to diagnosis and reporting changes, more than 50% of respondents said that reporting presumptive TB was down from providers. One thing likely driving that is that providers were not thinking about TB because they were thinking about COVID. There also were less opportunities for screening during the pandemic. Nearly 25% of programs said that there had been delays for clients in accessing TB screening, testing, and/or treatment through their primary care providers (PCPs). Programs reported testing delays for specific groups, such as 20% for healthcare workers, over 10% for schools, nearly 5% for daycares, and 7% for correctional facilities. This is probably an underestimate of the reduction of services that were being offered by outside entities, which certainly could lead to underreporting of TB, prevention activities and what will happen long-term. When asked whether programs were seeing any unique clinical, demographic, or outcome characteristics among cases seen in 2020, about 22% said that they were and the most common response was that they were seeing more advanced disease and an increase in TB-related deaths. This speaks to people not thinking of TB or not seeking care. The following quotes from respondents reflect why they thought there was a decrease in case counts:

- *Delayed hospitalization; fear of COVID, fear of medical profession; political unrest and distrust of science/medical/PH professions; fear of losing employment in midst of pandemic; fear of deportation in midst of political and pandemic turmoil*

- *Delayed seeking care by patients due to concerns of COVID; Misdiagnosis because clinicians think a patient had COVID; Delayed reporting*

- *The pandemic has definitely had an impact: people are not seeking medical care, TB is the diagnosis of last resort, health departments have curtailed activities to focus on COVID.*

In terms of highlights from the survey, it was frequently mentioned that there is a need to increase qualified staff and/or time dedicated to TB who have specialized knowledge in TB. These positions are not easy to backfill due to the specialized knowledge needed. In instances where TB staff were pulled to pandemic activities, those who were backfilling positions might not have the knowledge, background, or expertise to adequately fulfill TB services. People emphasized that it is not just staff—it is qualified staff who know TB. Programs called for flexible and sustained funding to expand TB program staff. While there were a lot of successes with eDOT and telemedicine, some of the barriers were financial or technological. Finding ways to sustainment, expand, and/or reimburse eDOT and telemedicine efforts is important. Getting messaging out to “Think TB” seems particularly imperative now to focus on that. TB Program staff are uniquely qualified to respond to COVID-19 and future pandemics. COVID-19 and TB are both respiratory and TB Program staff are experts in isolation procedures and contact investigations. Therefore, investing in TB Program staff is really an investment in future pandemics. Right now is an important time to invest in TB to respond to the depletion of resources and staffing that already has occurred and to build out a solid infrastructure and knowledge base for what might come. There has been a nationwide case count decrease and it is unknown what is going to happen in the future, such as a rebound.

There are a few limitations. This was a point in time survey that was conducted pre-COVID vaccine. Programs that responded could have been at a point of COVID case fluctuations or vaccine planning rollout, so it is not known what is occurring ongoing within programs. A lot of local health departments mentioned that they already had been pulled into the vaccine response, which certainly is a continued impact in 2021. Because this was a point in time survey, some programs only periodically have TB cases so they might not be feeling the impact of TB services or personnel that were reduced until a case come through. While the response rate to the survey was very high, it still is not representative of all jurisdictions' experience. The results are not broken out yet by burden of TB and COVID at this point, but certainly would impact what is occurring within programs. If one of those is low and the other is high, it might mean different adaptations or service disruptions. NTCA did their best to vet the survey through the Survey Committee and other TB experts, but interpretation of the questions might vary.

The following questions were posed for ACET's consideration, discussion, and input to NTCA:

- What are the data analyses of greatest interest?
- Would additional surveys/assessments of jurisdictions be important?

ACET Discussion: COVID-19 Impact on TB Programs
ACET made the following observations and suggestions:

- It is helpful to assess not only the negative impacts, but also the opportunities such as in eDOT and telemedicine and how they could be integrated into regular programming.

- Certain groups have been disproportionately impacted by TB and/or COVID. It would be beneficial to have more details about the differential impact on various populations, especially harder hit populations nationwide.

- It would be interesting to know more about whether/how the time to diagnosis and treatment was impacted.

- Further details about the disparities in access to/use of technology and how that could be alleviated going forward would be beneficial, particularly given that it was a common theme and that implementing telemedicine and/or eDOT on a wider scale could be an issue.

- Many eDOT programs now provide smart phones to patients if they do not have them. Recycled smart phones cost approximately $100 each.

- This report highlights the fact that public health needs to be included in the Administration's vision of "Infrastructure" as it is just as important in saving lives and maintaining the economy as are maintaining and upgrading roads and bridges.

- It would be beneficial for Xpert to be used for both COVID and TB diagnosis. This is being done internationally, but apparently not in the US. Using Xpert for both could identity both diseases BEFORE death.

- A lot depends upon whether people are looking for TB. The concern is that people may be dying of "complications of COVID" without ever being tested for TB.

- Consideration should be given to whether public health should recommend TB diagnostics for patients with COVID19 who have ongoing cough.

- This is a great demonstration that even before the pandemic, US TB systems were at a skeleton stage and stretched thin. As a result, they were overwhelmed by the pandemic. Consideration must be given to ways to generate data that will help to make the case to improve the situation.

- Advocacy for TB programs for resources within CDC at a level above DTBE is crucial and members wondered whether this is a priority for the NCHHSTP:

    - Dr. Mermin responded that there is concerted effort and strong support from the TB Program. There are many circumstances when the opportunity arises that they do talk about the importance of TB.

- Given the potential that there has been underdiagnosis, it is likely that programs will begin to see cases of TB among people who clearly would have been diagnosed sooner and may even have spread TB to more people in their families. Perhaps the survey team could reach out to all of their members to alert people to the need for documenting instances in which it is obvious that this had a harmful effect, and collect those cases as an advocacy tool to make the case that more resources are needed for this kind of work. Collecting a number of compelling cases would help to put pressure on the whole system:

    - Dr. Mermin noted that if under-diagnosis/under-reporting was a main cause of decreased reports of TB cases, it seemed like they would have begun to see increased numbers of TB-associated mortality over the past 1.5 years. If not, it seems that this would argue against under-reporting as the cause.

- In terms of whether people are looking for TB or not, one concern is that people may be dying of “complications of COVID” without ever being tested for TB:

    - Dr. Mermin concurred that this may have occurred. He also mentioned that there has been high-quality surveillance for TB and COVID. Smart people in both the COVID and TB worlds are evaluating data and he believes we will soon have a better understanding of what has happened and what will happen over time. The incidence of COVID is high enough that there could be overlap and a proportion of people who have TB could have concomitant COVID. Therefore, the idea that the TB component is missing would be even more relevant.

    - Dr. LoBue added that the problem is that precise data on TB mortality do not exist. NCHS is based on death certificates, from which the data are not particularly good. DTBE’s system is dependent upon the case being reported to them along with the outcome. Cases are going unrecognized and never being reported, so they cannot get it out of the TB surveillance. Typically if an older person dies from a respiratory disease, there is not going to be an autopsy. It is probably going to be pretty difficult to ascertain this information.

- Is the issue of “Public Charge” still of interest for TB? If so, and given the new administration, should ACET press the issue? For that matter, might it even have played a role in the disparate outcomes that we were/are seeing with COVID?

- This article of BCG and COVID-19 may be of interest: https://www.medrxiv.org/content/10.1101/2021.05.20.21257520v1

- Consider stratifying the results by program type in terms of local versus state.

- It is not clear where COVID will/should live long-term. It would be interesting to know what people are thinking about this in terms of what is appropriate and whether it might be combined with TB or if it should be its own independent entity and at what level:

    - Dr. Mermin pointed out that it is an interesting question when there is a new condition of public health importance in terms of where it is best situated within CDC, what will need to be done, and what the situation will look like in the future. Right now there is a massive CDC response to COVID in most states, with thousands of people deployed at any given time. While reduced, there are still thousands of cases and hundreds of deaths every day associated with COVID. There also is a massive need for vaccination and surveillance data. At this point, it remains unclear what the situation will be one year from now in terms of SARS-CoV-2 in terms of whether it will look more like measles with scattered outbreaks and ring vaccination being the main response or if it will be more endemic and showing up in constant numbers of cases. It is also not clear what public health prevention efforts will look like in terms of how much that will be a vaccine-focused effort or the traditional TB diagnosis and treatment-focused effort. Given that the government moves slowly with regard to organizational change, it will be important to know the answers to those questions before making organizational changes. If it is a vaccine-focused effort, a lot of the effort could be situated within the National Center for Immunization and Respiratory Diseases (NCIRD). There are some long-term consequences of COVID infection that will be affecting hundreds of thousands of people in the nation, which needs to find a place in the agency that deals comfortably with chronic diseases, perhaps the National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP), or NCIRD. The third space is the contact tracing DIS-type work that resembles partner services, and the new funding received by NCHHSTP could support COVID response and other activities like TB.

- Consideration should be given to how this could be tied to the workforce enhancement of the Rescue Plan mentioned earlier in the morning.

- Note that TB unfortunately was not mentioned in the recent rollout of funding for DIS training. Some state-level TB programs have not even been able to reach the table, based on the now aging concept of "PCSI" which some of us still embrace.

    - Dr. Mermin emphasized that NCHHSTP does still embrace program coordination and service integration. In fact, there are several spaces where they see that a lot more work would be productive. The funds have not been awarded yet, but the language l states “COVID-19 and other infectious diseases,” so there is flexibility. The question regards how to engage with state and local health departments and tribes to ensure that they see this as a potential opportunity. Other divisions are also looking at this. The initial

supplement for this year will be going out through the STD Prevention and Control for Health Departments (STD PCHD) because it was the most easily available space where the partner services work is going. Consideration will be given to how this can best be implemented in the future as well. DIS training should include TB.

- More information about pediatric cases would be beneficial, given the bump in cases, severe disease, and a couple of pediatric cases in low-burden areas.

- Autopsy studies are needed. TB-related mortality in hospitals may be under-reported since autopsies are rarely done, particularly for indigent patients. Medical Examiners (MEs) were/are overwhelmed with certifying and counting COVID deaths, so very few autopsies are taking place.

- Bill Stead surprised the community by reporting on unrecognized TB in nursing homes some 35 years ago.

- There is concern that TB diagnoses may be delayed (or never happen) for incarcerated persons who have COVID-19 diagnosed but then have ongoing cough, et cetera.

- Ms. Wegener noted that the NTCA national conference would include 3 sessions that would focus on the impact of COVID on TB. There will be a clinically-relevant session, another that will involve NTCA's programmatic partners that focuses on the impact on program services, and the third will be a reprise of what Ms. Gardner Toren presented during this ACET session with some more expanded analyses specific to this survey. She requested that if ACET members thought of other considerations after this ACET meeting that they submit them via email to her or Ms. Gardner Toren. They will continue to analyze the existing data and to think about various ways to disseminate the results either through peer-reviewed journals or in the advocacy space in an effort to impact funding decisions.

Link Between Country of Birth and TB Risk

Katharine Tatum, PhD
Peraton Contractor
Surveillance, Epidemiology, and Outbreak Investigations Branch in Partnership with 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

Dr. Tatum presented findings from the LTBI message testing project, which was funded and led by DTBE's Communications, Education, and Behavioral Studies Branch (CEBSB). In terms of background, TB cases have been steadily declining in the US for decades. Despite this immense progress, the US has not yet reached the elimination threshold for TB. The main driver of TB cases in the US is not from recent transmission of active disease, but from longstanding untreated LTBI. More than 80% of TB cases in the US are due to untreated LTBI rather than from recent transmission, and an estimate 5% to 10% of persons with untreated LTBI will

progress to active TB disease at some point in their lives.[16] In addition, the majority of TB cases now occur among non-US-born persons who likely have been exposed to TB in their countries of origin, but show no symptoms. While cases among US-born persons have been steadily declining over the past 3 years, cases among the non-US-born have remained steady. In 2019, 71.4% of all reported TB cases in the US were among non-US-born persons.

In response to these trends, CDC, the American Thoracic Society (ATS), and the US Preventive Services Task Force (USPSTF) have all issued recommendations for targeted testing and treatment of LTBI among non-US-born persons. Implementing these recommendations requires buy-in from non-US-born persons who can proactively seek testing if they perceive themselves as "at risk."[17] One way to do this is through public health campaigns and messaging, which can help to communicate who is at risk and encourage proactive health behaviors. However, a recurring pattern documented in the health risk literature finds that people who are at increased risk of a condition are often the least receptive to relevant health information. Instead of being receptive to the information when they see a health risk message, people may become defensive. This happens because an at risk status can be seen as a threat to an individual's positive self-concept. The types of responses include counter-arguing, self-exemption, disengagement, and avoiding risk information all together.[18]

This framework was used to understand how non-US-born persons respond to being told they are at risk for TB due to their country of birth. Specifically, the focus of the research was to understand perceptions of non-US-born persons to health risk messages describing the link between country of birth and TB risk. To answer this question, the data were used from the LTBI Message Testing Project, which Dr. Tatum reviewed briefly. LTBI Message Testing Project was comprised of 15 in-person focus group discussions with non-US-born persons living in the US. Data collection occurred in April and May of 2019. The sample was stratified by two variables, country of origin and location of focus group. The project team focused on the 6 countries with the highest TB case count among non-US-born persons: Guatemala, Mexico, Vietnam, the Philippines, India, and China. To ensure geographic diversity, participants were recruited from 5 US metropolitan cities: Miami, Chicago, Houston, San Francisco, and New York. Within each focus group, variety was also sought on other attributes such as education, years in the US, gender, and age. Participants were recruited through a market research company. English literacy was a requirement for participation, which is a limitation of the study. Importantly, participants were not told that the discussion would be about TB—only that it would be a health-related discussion. This was done to prevent participants from studying the topic in advance of the conversation. Focus groups were limited to 9 participants and all participants who showed up were given $40 to thank them for their time. A professional moderator conducted all focus groups using a discussion guide. All discussions were recorded for later transcription. There were 4 major sections of discussion:

- ❑ Section 1: Top of Mind Health Concerns
- ❑ Section 2: Prior TB Knowledge
- ❑ Section 3: Review Messages
- ❑ Section 4: Health Information Source

---

[16] Yuen et al. 2016
[17] LoBue and Mermin 2017; Menzies et al. 2018
[18] Kessels, Ruiter and Jansma 2010, Liberman and Chaiken 1992, Sherman, McQueen, Vernon and Swank 2013, Nelson and Steele 2000, Zhou and Shapiro 2017

The majority of the conversations focused on reviewing messages related to TB and LTBI. A selection of some of the messages participants read that described a link between country of birth and TB risk included the following:

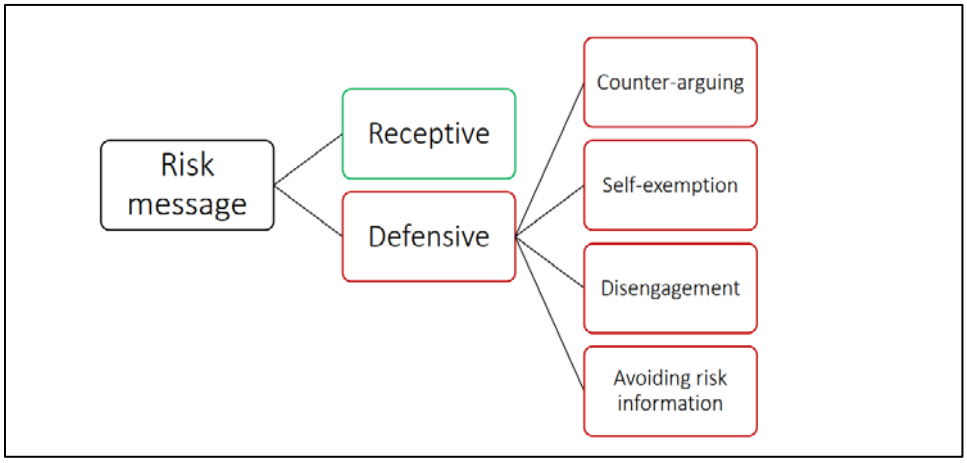
> Statement G:
> "TB disease in the United States is most common among people born in countries where TB disease is more common."
>
> Statement YY:
> "CDC and the US Preventive Services Task Force recommend testing populations that are at increased risk for latent TB infection including people born in countries where TB disease is common regardless of how long they've been in the United States."
>
> Statement YZ:
> "People born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala, or other countries with high rates of TB disease."

To analyze the data, all audio files were transcribed verbatim and reviewed for accuracy. The transcripts were then imported into a qualitative database for analysis. The basic analytic process include the combined 3 steps: 1) creating a codebook on a sample of the transcripts; 2) coding of all of the transcripts using that code book; and 3) conducting queries on codes and documented patterns in relation to the research question.

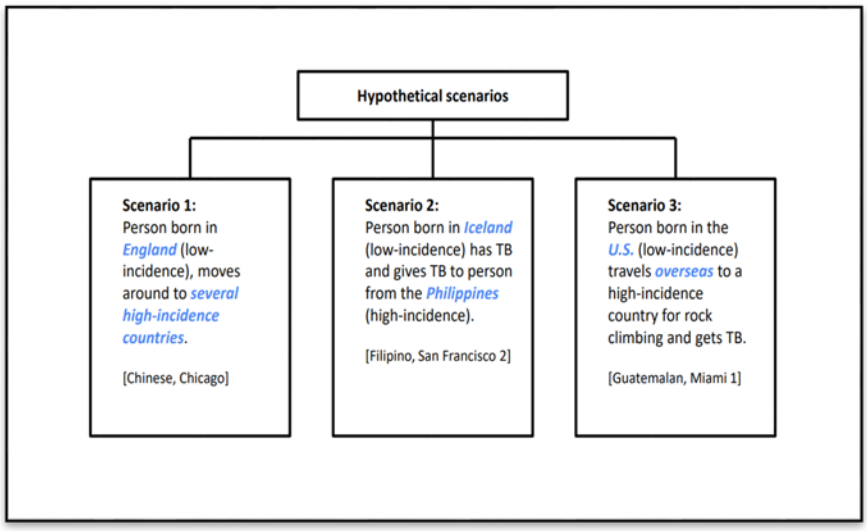
In terms of some background on the participants, in 10 of 15 focus groups over half of participants had at least a college degree. Among the Hispanic focus groups, proportions of participants with their college degree ranged from 0% to 38% and was lower than the overall average of 61%. There also was a wide range of ages among participants. The youngest participant was 18 years of age and the oldest was 80 years of age. Most participants had lived in the US for more than 10 years. Participants' prior TB experience and knowledge also was assessed. In all 15 groups, at least 1 participant reported receiving a TB test. In 6 groups, a participant revealed information that appeared to indicate a prior LTBI diagnosis. In 5 of those 6 groups, a person also reported taking treatment. In 14 groups, at least 1 participant reported knowing someone diagnosed with TB or LTBI. This include family members like parents and cousins, co-workers, nannies, and neighbors. In 7 groups, a participant mentioned TB as a health concern unprompted. This was in response to a question at the beginning of the focus group that asked participants about what health conditions they were most worried about. Looking only at Asian groups, 6 out of 10 participants mentioned TB unprompted. By contrast, only 1 in 5 Hispanic groups mentioned TB unprompted. Taken as a whole, no Hispanic group had all 4 variables present suggesting lower TB experience and knowledge. By contrast, both Vietnamese and 1 Filipino group had all 4 variables present.

The framework presented at the beginning of this presentation was used to categorize participant responses to the messages. First, it was important to understand general reactions to the messages in terms of whether the messages make sense. In 8 of the 15 groups, participants engaged in defensive responses, arguing that the general message was problematic. Participants challenged the logic of the message and raised concerns about potentially stigmatizing messaging implications. In all 15 groups, at least 1 participant indicated that they were generally receptive to the messages. The first defensive strategy observed was that some participants challenged the logic of the messages by questioning how country of birth

could be a relevant risk factor for TB given that anyone could get TB. One quote from a participant was, “If it is not genetic, then why does it matter if someone is born there?”



One way in which participants challenged the logic of the link between country of birth and TB risk was to make up hypothetical scenarios in which the definition of risk would miss a source of infection. This diagram shows 3 hypothetical scenarios that participants invented to challenge the messages:



By presenting a case of an alternative lifestyle in Scenario 1, participants called attention to exposure rather than country of birth. In Scenarios 2 and 3, participants described scenarios in which people born in low-incidence countries such as Iceland and the US also can have and spread TB germs. This further called into question the link between country of birth and TB risk.

Another strategy focused on the stigmatizing consequence with a TB country link. While this argument did not always invalidate the link between country of birth and TB link, it refuted the message by suggesting that the message itself was problematic as illustrated by this quote:

> *Just say other countries, don’t say ‘born,’ because that just means you're triggering or attacking foreigners. Like just say ‘if you were to visit or go to other countries,’ keep it simple like that. Because it could be from anybody.*

(Guatemalan, Miami #1)

Other concerns participants raised regarding possible negative messaging implications, such as being worried about being singled out and that the messages were blaming immigrants for bringing in TB.

By contrast, at least 1 participant and often multiple participants in all 15 groups felt that the link between country of birth and TB made sense. Here is a sample quote:

> *No I wouldn't be offended if it singled out. I mean I feel like they actually care because they made an effort to translate it into your own language and it's based on a scientific fact that we are prevalent with TB and it's just a preventative process.*

(Filipino, San Francisco, Group #1)

In terms of why some people accepted the link between country of birth and TB risk, some participants could think of other health outcomes that differed by country (e.g., Tapeworm in Guatemala, Hepatitis and Lupus among Chinese). Some participants already knew that TB incidence differed by country. Some participants identified structural reasons to explain the link (e.g., "Third world" countries, historical reason, disease control), which helped to avoid feeling prejudice or blame expressed by those who rejected the messages.

Some participants occasionally tried to convince others that using country of birth made sense and did not have to be prejudicial. Here is a quote from a Guatemalan participant in Miami who tried to assuage the concerns by a fellow participant who suggested that messages describing the link between country of birth and TB risk are offensive:

> *P1: So I don't find it offensive, I find it informative. They're not attacking one country per se. It boils down to –unfortunately—third world countries where medicine or information and education to the people in those countries is not up to par where we're at, for whatever reason. So it's just letting you know, "Look, these other countries that have the highest percentage of this particular disease. So if you are planning on visiting any of these countries, be aware and be on the lookout and take your precautions, basically."*
>
> *P2: Oh. See that's better.*

(Guatemalan, Miami #1)

Questions also were asked to assess whether participants thought the messages were personally relevant. While many participants accepted the link between country of birth and TB risk, those same participants did not feel the messages were personally relevant to them. Instead, participants in 13 of 15 groups engaged in defensive strategies arguing that they were exempt from these messages. Participants claimed to having passed mandatory TB tests as immigrants and they saw themselves as not risky but at risk, downplaying the possibility of current infection and instead worrying about future infection from others. However, some participants in 4 groups said they were motivated to get tested because they were born in a high-risk country.

One of the most common defensive strategies observed was that many participants claimed to having passed medical exams for immigration, school, or work that included TB tests as evidence that they did not have LTBI and were therefore exempt from these risk messages. Participants did not appear to be aware that TB screening conducted overseas by family physicians only screen for active TB disease and does not prevent someone with LTBI from immigrating to the US. Here are some exemplary quotes:

> *When people come from China to the United States, they must do their TB test. If they find something wrong, they don't allow you to come to United States because of all the germs.*
>
> (Chinese, NYC)

> *Before coming to this country, the embassy sent me to have a [TB] test.*
>
> (Guatemala, Miami #1)

> *We both came from Mexico when we were very young – so we were tested for TB when we were going to school. So everything was negative, you know?*
>
> (Mexico, Chicago)

> *When I came here for the first time, I was doing my master's. It was mandatory to do the tuberculosis skin test.*
>
> (India, Chicago)

> *When we came from India to here, before the admission for my son, you know, it's mandatory. My son had to go get the [TB] test.*
>
> (India, NYC #1)

> *When people coming from China to United States, they must do their TB test. If they find something wrong, they no [sic] allow you to come to United States.*
>
> (China, NYC)

> *Before you could actually immigrate to the United States you had to get tested for [TB] to make sure you didn't have it.*
>
> (The Philippines, SF 1)

> *Before we came, so we're in the refugee camp, everybody had to take a shot before they go to the country, United States or Canada.*
>
> (Vietnam, Houston)

Overall, relatively high levels in mandatory TB testing were observed among participants. Reasons varied for getting tested for TB across the 15 groups. In 12 groups, at least 1 participant reported receiving a TB test before their immigration to the US. In 9 groups, at least 1 participant reported receiving a TB test for a job or for volunteering. In 9 groups, at least 1 participant reported getting a TB test for admission to school. In 13 groups, at least 1 participant reported getting a TB test that was classified as "other" such as for military, jail, or contact investigations. Many times, reasons for the test were not specified. Overall, there was a fair amount of experience with mandatory TB testing, with some variation by groups.

Another type of defensive strategy involved drawing a distinction between those deemed currently risky (e.g., current infected with TB germs) and those deemed at risk of infection through transmission and selecting the more favorable between the two identities. Here is an exemplary quote:

> *MODERATOR: Does this list [of countries] motivate you to get tested for TB infection? Why or why not?*
>
> *P1: I mean I think so because all the risk and, you know, the dormant. I mean I could be sitting next to someone and they have dormant and it develops and I don't know… it scares you. So, maybe the disease is out there.*
>
> (Guatemalan, Miami #2)

Rather than acknowledge the possibility that they might be currently infected with TB germs, participants instead described concerns about future infection from others. This often came through about getting TB via international travel. This argument was particularly interesting because participants often would mention their country of origin as a place of possible infection, but would link this to travel rather than long-term infection from earlier in their lives. Here are some examples:

> *MODERATOR: Does this list motivate you personally to get tested for TB infection? Why, why not? The list of countries.*
> *P1: Yes, because I do frequently travel back home.*
> *MODERATOR: So, it would motivate you?*
> *P1: Yeah, it would motivate me.*
>
> (Filipino, San Francisco #1)

> *I think it increases my probability much more because I might not be going back to Vietnam, but I might go to Mexico for a vacation, maybe some place else to other places like China or India.*
>
> (Vietnamese, San Francisco)

> *Vietnamese people travel back to their country a lot. So like me if I didn't travel back, I didn't get the TB. And I got the TB without knowing it.*
>
> (Vietnamese, Houston)

In 4 groups, some participants did express some motivation to get tested for TB because they were going to high risk countries. Here is an exemplary quote:

> *Earlier there was a statistic one in ten. You know, you might not take it seriously because you might think 'I'm not that group.' But here, if you were born or you go to these countries you include yourself in these groups a little bit more. So it increases your level of seriousness of how you should take this recommendation.*
>
> (Vietnamese, San Francisco)

To summarize potential messaging implications that came out of this analysis, first, future messages can emphasize both country of birth and travel as risk factors for TB in order to minimize a singular focus on birth location as a risk factor. This will help to avoid defensive arguments about the logic of country of birth as a risk factor and concerns about being singled out. It might also capitalize on some of the concerns voiced by participants about getting TB due to international travel. Second, messages can frame TB exposure as one of low controllability to reduce feelings of personal responsibility or guilt. Participants appear to be more willing to accept TB risk messages when they are framed as beyond personal control, for example, due to larger structural forces such as public health infrastructure or transmission from others. Third, messages should provide more detail on what is and is not included in the immigration medical exam. Having a past medical exam was a common tactic for downstaging risk. Therefore, messages should preempt this argument. Messages can clarify that immigration exams only screen for TB disease not LTBI and that LTBI is not grounds for denying entry or legal status, but should be treated to prevent TB disease. Fourth, messages can encourage people who have only had a chest x-ray or a skin test to ask their provider to administer a TB blood test and check for LTBI. The literature shows that giving recommendations on specific actions people can take to mitigate a health risk are often persuasive. Ultimately, health risk messages need to identify ways of communicating risk while allowing at risk persons to maintain a positive self-confidence.

ACET Discussion: Link Between Country of Birth and TB Risk

Dr. Belknap inquired as to what next steps are anticipated now that all of this information has been captured.

Dr. Tatum indicated that a point that has been raised when she has presented this to other groups is that the focus is on what not to do and that it is also important to understand what should be done. Perhaps certain pitfalls can be avoided while framing messages that this will be effective. They have started to implement next steps because this work has been used in the preparation of the LTBI campaign that is being led by the CEBSB. They were able to parlay some of these results into how they tested some initial concepts for the campaign. One thing they learned that was confirmed in the initial concept testing was that the reaction was negative when the focus was on country of birth as a risk factor. This prompted them to find other ways to present motivating messages.

Dr. Nick DeLuca, CEBSB Chief, added that all of this research was done with the goal of trying to guide some of the development of a campaign focused on LTBI and specific audiences. As Dr. Tatum mentioned, they used the messaging to develop and test concepts. Over the next several months, they will be trying to get those concepts cleared and tested within communities. The plan is to begin working in Seattle, Los Angeles, and perhaps a few other places.

Dr. Temesgen asked whether any questions were asked about perception of protection from Bacillus Calmette–Guérin (BCG) vaccination and if so, what was concluded from that in terms of future messaging.

Dr. Tatum indicated that some specific messages pertaining to BCG vaccine were tested. There were so many messages, they had to rotate them across groups. There was a series of messages around BCG vaccine that seemed to give participants the impression that the issues did not pertain to them because they already had the vaccine. They did see some evidence of learning during the course of reading the messages that the fact that the BCG vaccine wanes over time was new information for a lot of people. This did impact some of the defensive responses in the sense that some people thought this does not apply to them. In terms of future

messaging, providing the information was motivating for people such as clarifying that the BCG vaccine wanes over time and even if someone received the vaccine they should still get tested. Emphasizing proactive health behavior, such as getting the blood test as opposed to the skin test, is very important.

Dr. Ray said she has been thinking about the push that will be coming to encourage PCP to be engaged in the treatment of LTBI and thinking about how much of an advantage there might be if a doctor, nurse, or nurse practitioner that a person already knows is giving the advice as opposed to the health department. Sometimes there is a pretty negative reaction from families to contact investigations by health departments for a variety of reasons.

Dr. Tatum indicated that this type of language did arise, such as people stating that they had not heard their doctors talk about and so it must not have been that important or that they would prefer to receive this type of information directly from their doctor. It is important to keep in mind as both an advantage and disadvantage in the study design is that because a market research company was used, participants were not patients and were instead people from outside the clinical encounter. What is good about that is that the participants were people who may never have even gone to a doctor, do not go for physical exams, or are not concerned about risk. They captured that perspective, which was sobering information. They are conducting a patient study to look at barriers and facilitators to patients starting treatment and those considered at risk due to their country of birth. That is primarily within health clinics and health departments, so people already have that connection. In the LTBI campaign that Dr. DeLuca talked about, they are developing materials to be used by providers in conversations with their patients. The idea overall is that increased exposure to messages will be helpful.

Dr. Ahmed asked whether there was any difference on the BCG vaccine question in terms of country of origin, and if any effort was made to try to match the interview to the country of origin of the interviewees at the marketing phase.

Dr. Tatum indicated that the same moderator was used for all focus groups, which all were in-person. The moderator was bilingual Spanish-English. In her opening in which she described the procedures, she emphasized her status as an immigrant as a way to build rapport with participants. In the second round of data collection for the campaign, better matching was done because the match was to language. She did not recall if there were differences by country of origin in terms of the BCG vaccine question.

Dr. Loeffler inquired as to whether there data around messaging that are present in the vaccine-hesitancy world. Some schools of thought say that by emphasizing health, healthy outcomes, and positive benefits rather than severe outcomes from vaccine-preventable infections, people are much more likely to engage. She said she is one for sharing guilt and doom and gloom.

Dr. Tatum said she was not aware of any specific efforts to assess the vaccine advocacy literature. They reviewed some of the risk literature to think about the extent to which to emphasize some of the negative effects and increase feel versus the benefits. Her understanding is that there are people in different camps about this and was not sure whether there is clear evidence that one is clearly better. She agreed that vaccine hesitancy literature was a great point that they should look into.

Dr. Reves noted that TB risk is really not due to the birth abroad. It is really about the cumulative time lived in countries where TB exposure is likely. Country of birth is used because that is readily available for denominators for rates. There are no such data for exposure otherwise. This also relates to the travel issue in that traveling to a country for two days to a high burden country does not matter much, but if there for months working in healthcare it could be an issue. Perhaps calling this out would be helpful for interaction with the populous.

Dr. Tatum acknowledged that they know country of birth is a shortcut and there definitely should be an effort to better explain why that is used. Part of the struggle as she understands it is that it is known that people may not have a lot of time to review a message. It has come up in this project and others that people have a knee-jerk reaction to country of birth and do not understand why that is relevant, so perhaps more could be done to explain that it is not country of birth per se, but rather time of exposure.

Dr. LoBue added that country of birth is a reasonable surrogate. It is in the surveillance data and is easy to collect in the surveillance data. It is related because most people are not born one day and then in the US the next day. Most people who are born in these countries have spent a substantial amount of time in them before coming to the US. What has been revealed is that focusing on it too much causes problems. It would be beneficial to find a quick and simple way to craft a message that is broader and emphasizes being concerned about people spending long periods of time in countries where TB is more common because they have a high risk of exposure.

Dr. Mermin added that it is easier to have an electronic health record (EHR) reminder or standing order that people who are born in a country outside the US that has high TB risk automatically gets a TB test when their blood is drawn for something else. This is easy to do electronically if country of birth is used. It is very hard to do that if time in country of high TB incidence is used. He likes the idea that they have split this into a measure and a true risk. He also thinks it would be interesting to conduct some kind of case-control study that looks at people with TB to ascertain the correlation with absolute estimated time living in a country of risk. It would have to involve some form of an interview, but it could have matched controls. It may not be linear or could depend upon age, but it might help to know where the risk is.

Dr. LoBue indicated that they do know about rates in terms of whether someone arrived recently or not recently. The people who arrived recently who have the highest risk have not traveled back and forth but were born there and just arrived in the US. He did not know whether anyone had quantitated the details of risk among those who have been in the US a long time but have traveled back and forth a lot. The accuracy of information from this type of interview is probably not great, so investing a lot of time and money in this might not be the best use of resources.

Dr. Marks indicated that there are rates of TB among Peace Corps Volunteers, Americans who spend 2 years in a developing country, by country. There are two publications that are updated periodically.[19] The National Center for Biotechnology Information (NCBI) has a new database, which might be an opportunity for collaboration.

---

[19] https://pubmed.ncbi.nlm.nih.gov/26684486/ and https://pubmed.ncbi.nlm.nih.gov/18346241/

Dr. Ahuja emphasized the importance of remembering that contacts are at the highest risk, even higher than people who are born in other countries. As a caveat, country of birth is not easy to obtain and is not collected in EHRs. Most of the time, this information comes from interviewing patients. She agreed with the intervention of adding country of birth to EHRs in order to be able to include a standing order for someone who has never had a TB test. People like herself who are foreign born go back and forth to their countries of origin, so it will be difficult to quantify risk with an individual study. While country of birth is a proxy, it is not a guarantee that somebody was ever exposed to TB. This is a complex problem and this is a great first step in these analyses in obtaining this type of information, but consideration must be given to what data and groupings of people are needed to help inform public health intervention. There are many ways that this could be done. For instance, people may live in neighborhoods with other people from their country of origin where they may be exposed to TB in the US that has nothing to do with the fact that they were born in that country. Genotyping and tools such as that help to delineate all of these elements, but it also is important to remember that TB is complicated. The approach of focusing on contacts is extremely important, given that they are the group at highest risk.

Using Big Data to Understand Latent TB Care in the US

Laura Vonnahme, MPH, Epidemiologist
Surveillance, Epidemiology and Outbreak Investigation Branch (SEOIB)
Division of Tuberculosis Elimination
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention

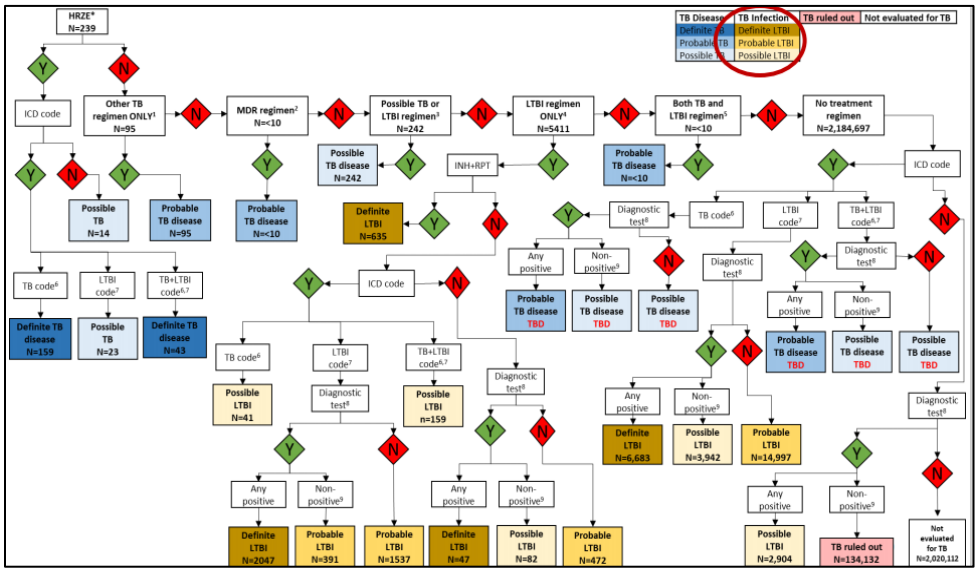
Ms. Vonnahme reminded everyone that it is estimated that 5% of the US population or 14.1 million persons has LTBI and 80% of TB cases are attributed to LTBI reactivation. Identifying and treating persons with LTBI is a critical step for achieving TB elimination in the US. Non-US-born individuals are at higher risk for TB infection. In 2018, 70% of reported TB cases in the US occurred among non-US-born with an incident rate 14 times higher than US-born persons. Additionally, it is estimated that 16% of non-US-born persons have TB infection compared to 3% among US-born persons. DTBE has done a lot of work with TB clinics and health departments to describe TB infection testing and prevalence among high risk populations. However, it is known that populations at risk receive care in other settings such as community health clinics. Therefore, DTBE has begun to explore other data sources that may provide a broader perspective and help answer questions about LTBI prevalence among higher risk populations and describe the implementation of TB screening guidelines and practices outside of health departments.

OCHIN was founded in 2000 and provides Health IT support and services to community health centers, predominantly safety-net clinics serving vulnerable and under-served populations. Currently, OCHIN is the largest network of safety-net clinics in the US. In addition, OCHIN hosts a centralized EHR on an EPIC platform for all of its clinics. Most importantly, OCHIN utilizes a common data model (CDM) to collate all EHR data from OCHIN clinics into a research database to be used for analytic and research purposes. The OCHIN EHR research database contains 3.6 million patients and is growing. The patient population is racially diverse, and approximately 33% of patients identify as Hispanic. Of the patient population, 32% are best served in a language other than English with over 132 languages represented. About 56% are at or below the federal poverty level and the majority are on Medicaid or Medicare, with almost a fourth of

the population being uninsured. Thus, the OCHIN population is relative to LTBI and for interventions to increase targeted testing and treatment.

DTBE collaborated with OCHIN to analyze an OCHIN EHR data cohort to: 1) determine the feasibility of using EHR data by developing algorithms to accurately identify patients who have been tested, diagnosed, or treated for LTBI and identify patients who meet TB screening recommendations; and 2) estimate the frequency of screening, LTBI, and LTBI treatment among persons who meet the criteria for TB testing based on screening recommendations. In terms of methods, a cohort of nearly 2.2 million patients with an OCHIN clinic encounter between 2012-2016. EHR variables were extracted related to demographics and risk factors, TB tests and test results, International Statistical Classification of Diseases and Related Health Problems (ICD) 9/10 diagnostic codes, and prescription records.

Individuals were identified who had been tested for TB infection by tuberculin skin test (TST), QuantiFERON®-TB test (QFT), or T-SPOT®. Individuals diagnosed with LTBI were identified by ICD 9/10 codes. Patients were identified who had been treated by the presence of an LTBI regimen in their EHR records. However, based on a priori knowledge, it was assumed that using only ICD codes as an indicator of LTBI diagnosis could under-estimate LTBI prevalence. Using ICD codes only to determine LTBI diagnosis is problematic because at the time of this analysis, there was no code specifying a diagnosis of LTBI. Rather, the codes indicate a positive TB infection test in the absence of TB disease. Additionally, coding can be clinic or clinician dependent. While infection test results also can identify individuals with TB infection, individuals with a prior history of TB or BCG vaccine will complicate the results of diagnostic tests. The presence of an LTBI treatment regimen would be indicative of a TB infection, but many individuals with LTBI do not initiate treatment. An algorithm was created that incorporated ICD codes, diagnostic results, and treatment prescribed to identify patients with Definite, Probable, or Possible LTBI. This is the full algorithm depicted as a flow diagram to classify all patients in the cohort in categories related to TB disease, LTBI, and TB infection ruled out or not evaluated for TB:



This presentation of the results focused specifically on the 3 LTBI categories of Definite, Probable, and Possible. The definitions of the 3 LTBI categories are summarized as follows:

- **Definite**: Documented positive test + LTBI code or treatment **OR** prescribed 3HP
- **Probable**: No positive test **BUT** LTBI code or treatment other than 3HP, including individuals who were screened outside the OCHIN network but followed up at an OCHIN clinic after a positive result
- **Possible**: LTBI code or treatment other than 3HP **BUT** conflicting evidence **OR** positive test and no other indication of TB or LTBI

To identify individuals who met TB screening recommendations criteria, patients were included from the following high-risk populations:

- Non-US-born identified by reported country of birth and patients with a non-English language preference since country of birth was largely unavailable in the EHR
- Close contacts to infectious TB cases by the presence of a specific ICD code
- Persons who were currently or ever reported experiencing homelessness and patients with an encounter in a correctional facility
- Patients with at medical risk due to immunosuppression identified by ICD codes and prescription drug records

Regarding the results, 7% (151,195) of patients were tested for TB infection with over 185,854 total diagnostic tests performed. Of the testing, 75% was performed using TST, 24% was done using QFT, and 0.4% was done using T-Spot. The 2.2 million patients in the cohort were classified using the classification algorithm. Among the entire cohort, 8% (170,574) had any indication in their EHR of having been evaluated for TB infection meaning that this 8% had a TB diagnostic test, or TB or LTBI code, or treatment for TB disease or LTBI. Among the over 170,000 patients with an indication of being evaluated for TB infection, 1% were classified as having TB, 20% were classified as having LTBI, and 79% were classified as having TB infection ruled out according to the algorithm.

Focusing for this presentation on those classified as having LTBI broken down by LTBI categories, 28% were classified as having Definite LTBI, 51% were classified as Probable LTBI, and 21% were classified as Possible LTBI. Of the patients with an LTBI classification as defined by the algorithm, 16% were prescribed a treatment regimen for LTBI. Only 30% were prescribed a short-course regimen of rifampin or 3HP. The majority were prescribed INH. Of the patient cohorts, 32% (701,467) met screening criteria. Among those who met the screening recommendations, 12% were tested for TB infection and 11% tested positive. Among the 68% (1,489,219) who did not meet screening criteria, 5% were tested for TB infection and 4% tested positive. Among those who met criteria, 3.5% were classified as having an LTBI diagnosis using the algorithm compared to 0.7% among those who did not meet screening criteria. Among those who met screening criteria and were classified as having an LTBI diagnosis, 17% were prescribed treatment. Among those who did not meet criteria, 14% were prescribed treatment. These data suggest that providers are not necessarily considering a patient's underlying risk factors for TB infection when deciding whether to prescribe treatment. Rather, roughly the same percent of LTBI cases are being prescribed treatment regardless of whether they meet screening recommendations.

In conclusion, this analysis provided insight on using EHR data as well as about what is occurring in community clinics with regard to TB testing and treatment. EHR data was found to be a valuable, unexplored resource. It was possible to determine the frequency of TB screening, LTBI prevalence, and treatment prescription. To do this, a novel algorithm was created to identify patients with LTBI. Diagnostic tests and results were extracted and the study team worked through the complexities of patients having multiple or discordant results. LTBI regimens were identified using prescription records. Data elements in the EHR identified patients at risk for TB infection. Demographic, social, and medical variables can be used to determine an at risk population. While country of birth was incomplete, it was possible to use language as a proxy.

A second finding is that the OCHIN patient population is at higher risk for TB infection. A large proportion (32%) met screening criteria for TB. In addition, there was a higher prevalence of LTBI among those who met criteria. However, this study confirmed that there is low adherence to TB screening and treatment guidelines in community health clinics. At risk populations not being screened and low risk populations are still being screened (88% not tested). The majority of screening is done by TST (75%). LTBI treatment initiation is low among those diagnosed with LTBI (16%) and recommended short-course LTBI regimens such as 3HP are not being utilized in clinics.

There were challenges related to using EHR data. Country of birth, a critical variable for determining risk for TB infection, was very incomplete in the cohort. In addition, defining LTBI diagnosis is difficult due to the fact that TB diagnostic test results are imperfect and LTBI diagnostic codes are not always appropriately used to indicate TB infection. The limitations of this study are that it likely underestimated the at risk population by using language as a proxy for country of birth because there are non-US-born English speakers. The algorithm for determining LTBI diagnosis is unvalidated. The study team did not have access to treatment completion data as dispensing data is only available for insured patients in the OCHIN EHR database. It was also not possible to analyze data by specific years. The data cohort only went through 2016.

The next steps in DTBE's collaboration with OCHIN will be focused on data validation. The intent is to determine changes in testing, prevalence, and treatment by year. The TB and LTBI classification algorithm will be validated by chart review and by comparing algorithm-identified TB cases to NTSS. There is also a plan to conduct a sensitivity analysis to determine whether language is a good proxy for country of birth. As of now, this project has been initiated since receiving an updated 2012-2019 OCHIN data cohort late last fall.

ACET Discussion: Using Big Data to Understand Latent TB Care in the US
Dr. Temesgen asked whether previous LTBI or previous treatment was accounted for in the analysis.

Ms. Vonnahme indicated that these were not accounted for this analysis. There is an ICD code for previous history of TB disease and they have done a side study looking at the care cascade specifically in which these were accounted for. People were pulled out of the cascade if they had previous LTBI or previous treatment. Determining prior history is a next step in assessing these data. Other than ICD code, which is reliant on the provider to ask and enter, it is not clear exactly how to get at this information unless there is a specific variable that the clinic itself asks about prior history of TB.

In thinking about how a clinic might use this approach to operationalize an evaluation and take steps to improve it, Dr. Belknap asked whether there is a way to adapt what the study team developed to something that could be used on a more continual basis by OCHIN or other clinics using EHR data.

Ms. Vonnahme pointed out that a lot of what they were trying to do here was to lay the groundwork for how difficult or easy it is to pull EHR data. It was fairly difficult, but having this framework for other clinics to use would be helpful, especially using the algorithm and how codes and screening recommendations were assessed. She has spoken to a few clinics who confirmed that they can pull some of the variables fairly easy from their back end, but just never thought about it that way before. This is a good framework to start with, but pulling EHR data is difficult, especially for clinics that are not TB-focused. They worked with OCHIN on more consistent reporting for clinics that are interested in doing that so that they can readily pull a report based on these variables more consistently rather than having to do it from the back end.

Mr. Watts indicated that he works for the National Health Care for the Homeless Council, Inc. with the Healthcare for the Homeless Clinics (HCH), which are a subset of Federally Qualified Health Centers (FQHCs). They are diligent because they are required to report housing status unlike other FQHCs. There is a major problem with missing data due to housing status not being captured. He asked whether it was possible with the OCHIN data they had to see the impact of housing status on TB risk.

Ms. Vonnahme indicated that the only variable that they were able to pull was a variable that OCHIN has for all of their clinics regarding homelessness status, which can mean a variety of things. OCHIN has a trigger for every year that the variable is supposed to be updated and patients can either say that they are no longer homeless or are still currently experiencing homelessness. Every person's definition of how they are experiencing homelessness is different. There is a place to enter whether someone is staying in a shelter, but that was a pretty unreliable variable. The data had to be pulled because it is not Yes/No, but rather is the name of the shelter. That is why they stuck to the bivariant homeless status. Whether people reported homeless status annually also depended upon the clinician asking that question. They were able to analyze for homelessness as a risk factor. They included anyone who had indicated ever having experienced homelessness. That was a historical variable in the data and was included as someone who met screening recommendations. As she recalled, about 14% to 18% had reported ever having a status of being homeless over the 2.2 million patients. They did not look at the correlation between homelessness and increased risk.

Dr. Higashi asked how many people had both TSTs and interferon-γ release assays (IGRAs) done and if so, how that was handled.

Ms. Vonnahme indicated that this was really tough for them because a lot of people did have multiple results. However, it was not possible to tell if TST became before or after IGRA because they were not able to assess them longitudinally. Therefore, any IGRA test superseded any TST results. If someone had an IGRA result, that is the result that was used. If someone had an invalid IGRA or no IGRA, the TST results were used. In the next round of analyses, they will be able to assess this longitudinally because they are seeing the dates of the testing this time. The TST was in the vaccination records, but pulling out IGRA testing was more difficult because of how laboratories work. For TST, there often was a qualitative and quantitative result, so they were able to verify through the qualitative result. If there was not a qualitative result, they looked to the quantitative result and made a cutoff for a positive of negative TST.

Ms. Cole noted that once the data have been validated, another presentation can be scheduled for a future ACET meeting. She noted that there was a lot of discussion about EHR standards and asked whether the standard process went forward in terms of the group who was assessing the standards.

Dr. LoBue indicated that he was not aware of anything the CDC has promulgated in that regard. There are different aspects of this, a lot of which probably focuses on reimbursement now so the Centers for Medicare and Medicaid Services (CMS) and related groups would certainly have an interest. Public health has an interest, but he did not know the amount of influence public health would have in this in terms of standardizing this clinical use and not public health.

Day 1 Recap

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

Ms. Cole recapped the information presented throughout the day and reviewed the agenda for the next day.

With no further business posed, a motion was made and seconded to adjourn the meeting for the day. The motion carried unanimously and the meeting was adjourned at 3:30 pm EST. ACET stood in recess until 10:00 am EST on June 16, 2021.

June 16, 2021 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 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 19 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on June 16, 2021. No additional COIs were declared and a quorum was maintained throughout the meeting.

Bacillus Calmette-Guerin Vaccine Guidance Development

Julie Higashi, MD, PhD
Naomi Aronson, MD
National Tuberculosis Controllers Association

Dr. Higashi began the update on BCG vaccination in the US, noting that it is seen as a niche topic. Recent events have made thinking about BCG and vaccination in general come to the forefront. It is the centennial anniversary of the BCG vaccine. An opinion piece that was published in *Clinical Infectious Disease* (*CID*) at the end of 2020 reflects this. It speaks to the immunogenicity of different strains of BCG.[20]

BCG is a live-attenuated vaccine of *Mycobacterium bovis* BCG, provided freeze dried. It is one of the oldest vaccines and has been used in billions of children worldwide. The US has the Tice® BCG vaccine, which is FDA approved for TB prevention as a vaccine and for early bladder cancer immunotherapy. The indications for use of BCG vaccination in the US are very narrow and the guidance is difficult to find. On the Advisory Committee on Immunization Practices (ACIP) website, the last joint statement between ACIP and ACET was released in 1996.[21] The ACIP site states that there has been evolution in the policies regarding TB and BCG vaccine and refers to the TB website for the current guidance. Clicking on the link provided leads to a dead-end. It is possible to get the archived history and the 1996 statement[22]. The indications in this joint ACET/ACIP statement, which both apply in general to travel overseas to endemic TB counties, are:

[20] Danchuk SN, Behr MA. Bacille Calmette-Guérin: One Hundred Years, One Hundred Questions. Clin Infect Dis. 2020 Nov 5;71(8):1894-1895. doi: 10.1093/cid/ciz1083. PMID: 31677382.
[21] https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/bcg.html
[22] https://www.cdc.gov/mmwr/PDF/rr/rr4504.pdf

- ACET/ACIP Joint Statement dated September 1995; published in 1996
  - Children < 5 contact close contact to parent or MDR index with inability to separate
  - HCW in occupational setting with high prevalence of MDR or ongoing transmission TB

There is a page on the ACET website that talks about BCG vaccine that cites the recommendations from the 1996 guidance, but that is pretty much all there is. It basically directs readers to their local TB program for guidance. The TB programs receive questions, which is what generated a request to ACIP. Dr. Christine Hahn sat on ACIP as the CSTE representative where she raised the issue of not having had updated guidance in a while and reported that NTCA requested the formulation of a workgroup. ACIP declined to formulate a workgroup and cited ACET guidance from a workgroup in 2014, "Multidrug-Resistant Tuberculosis: Recommendations for Reducing Risk During Travel for Healthcare and Humanitarian Work."[23] There is no link to these recommendations from the CDC website as ACET does not have links for any guidance. The guidance is specific to healthcare workers and is a very nice document, and BCG is one of the tools that is used to protect HCP traveling overseas or in these situations. However, there are still gaps. For instance, there needs to be clarification of groups who benefit from BCG vaccine based upon current epidemiology. A practice guide also is needed for live BCG procurement in the US and logistics of administration and clinical management.

To ascertain needs, NTCA and the International Society of Travel Medicine (ISTM) distributed a survey to their members. The NTCA survey was open for 3 weeks in April-May 2021. The ISTM went a little longer and was slightly different. A wide spectrum of individuals completed the survey (e.g., frontline workers, leadership, academia, public health, state and local). Questions were excluded about IGRA/TST test interpretation regarding BCG vaccination. Respondents were asked to identify the BCG vaccine questions they encountered in terms of whether they were from a HCW or researcher traveling to a TB endemic country concerned about TB risk and interested in BCG vaccine; parents wanting to travel with an infant to a TB endemic country concerned about TB risk and coverage for infants provided by the BCG vaccine; other travelers (other than healthcare associated) going to a TB endemic country; dissemination of BCG as a result of treatment for bladder cancer; and others. Respondents also were asked how often they encountered these questions:

- 1-2 x / week
- 1-2 x / month
- Several x per year
- About 1 x per year
- Never

[23] https://www.atsjournals.org/doi/pdf/10.1513/AnnalsATS.201309-312PS

About 75 responses were received from ISTB and about 89 responses were received from NTCA. It was possible to compile all of the NTCA and some of the ISTM. Respondents were receiving these types of questions mostly biannually and annually. The responses were categorized as follows:

HCW or researcher traveling to a TB endemic country concerned about TB risk and interested in BCG vaccine	15 (17%)
Parents wanting to travel with infant to TB endemic country concerned about TB risk and coverage for infants provided by the BCG vaccine	28 (31%)
Other travelers (other than healthcare associated) going to a TB endemic country	21 (24%)
Disseminated BCG as a result of treatment for bladder cancer	51 (51%)
Other (mostly related to IGRA/TST and BCG interpretation)	27 (30%)

The number of questions related to BCG vaccination annually in the US for NCTA only is about 100 to 200. Approximately 50% of the questions were not related to the guidance. All of the questions related to travel overseas with 25% HCP, 50% children less than 5 years of age, and 25% other.

Shifting to feasibility and access to BCG vaccine, Dr. Aronson indicated that the package insert states that ACET/ACIP recommend consideration in the following circumstances: 1) TB exposed tuberculin test negative infants and children; and 2) TB exposed health care workers in high risk settings. BCG vaccine is FDA-approved and solely manufactured/distributed by Merck in the US. However, it is currently not available. The indication and usage is quite broad, “BCG Vaccine (Tice® Strain) is indicated for the prevention of TB in persons not previously infected with *Mycobacterium tuberculosis* who are at high risk for exposure. In addition, BCG vaccination is applied with an FDA-approved 36-pronged steel applicator for percutaneous use with Merck BCG that also is not available.

Even with about 75 providers, about a third of them are international. About half say that they have never tried to find BCG vaccine and a third report that they have had great difficulty obtaining BCG. Some of the barriers to BCG access included that to access it in the US, broader cancer BCG and staff are often concerned about issues of infection control. When the question was asked differently by asking, “For US providers, if BCG USP was available in the US, would you consider using it in selected travelers?” 51% of responders said they would consider it, 30% said they were neutral or unsure, and the remainder said that they would not use it. When asked what their main concerns were about BCG, 40% said they cannot obtain it, 20% felt it did not work, 18% were concerned about the AEs, and 16% said they were not familiar with BCG vaccine.

There is an alternate strategy in the US that involves off-label use of broader cancer BCG Live, which is for infusion into the bladder. It turns out that this preparation is very similar to the Merck BCG vaccine. For example, the same number of colony-forming units (CFUs) are in the vial. While the current status of BCG is that Merck does not have any available, they do have BCG live available in limited supply. Many hospitals have only a set number of vials that they can order each week. BCG Live is FDA-approved for the treatment of muscle invasive bladder cancer (MIBC). BCG vaccination can be done with off-label intradermal administration of the BCG live product, and a process was described. However, there are a number of challenges with off-label use. As noted, there is a limited supply of BCG live. Facilities utilizing BCG Live for treatment of bladder cancer are allowed a limited inventory. One dose of BCG vaccine from one

vial wastes hundreds of doses of vaccine. There is a short window from reconstitution to administration. BCG is considered by the National Institute for Occupational Safety and Health (NIOSH) to be a hazardous drug, requiring a pharmacy biosafety cabinet and infection prevention precautions to reconstitute. In 2020, BCG was targeted to be removed from the hazardous drug list. There have been widely publicized cases in which nosocomial transmission of BCG has occurred in the pharmacy to others, so pharmacies follow the USP 800's very specific recommendations to protect workers. This generally requires the product to be unpacked in an area that is neutral or negative pressure, stored to avoid spillage or breakage if the container falls, and reconstituted in a biosafety cabinet with personal protective equipment (PPE). The biosafety cabinet has to be cleaned afterward using a sporocide like PeridoxRTU® with a 10- to 20-minute dwell time after use, then cleaned with sterile alcohol. Disposable PPE should not be reused and reusable items should be decontaminated and cleaned. All equipment, supplies, receptacles in contact with BCG should be handled as biohazardous.

There is a concern about dissemination of BCG and the worst side effect that is associated with vaccination. Clearly, in the higher dose that is used when it is instilled in the bladder with BCG Live is associated with higher rates of disseminated infection. Many of the NTCA respondents mentioned having received questions about this. For vaccination, about 1 per million doses have an association with dissemination. HCP BCG vaccine trials administered via intradermal route provides some US-based experience with toxicity and AEs. There is an ongoing clinical trial in the US using BCG Tice® intradermally to protect HCP in the COVID-19 Pandemic. Hundreds of individuals have been enrolled in that trial between Los Angeles and Houston and as of a month ago, there were no dissemination events in that trial. It is likely within 6 months to hear about some early toxicity and AEs in Americans using the preparation just mentioned. There is relatively limited experience among providers in the US giving BCG vaccine that includes one successful administration in the last several years at an academic institution. However, the recent clinical trial experience with BCG vaccine administration in HCP for COVID-19 protection shows feasibility of administration in the US.

In conclusion, BCG vaccine and the applicators are not available as licensed in the US. BCG can be prepared from live BCG used for treatment of bladder cancer and given off-label using intradermal administration. BCG is considered a biohazardous drug and has to be handled per USP 800. IGRA should be used after BCG vaccination for TB testing. BCG is not a costly vaccine. Overall, BCG vaccination is feasible using the off-label BCG Live product.

Dr. Higashi pointed out that in view of the fact that there is no practical guidance for programs, NTCA has developed a BCG Vaccination Toolkit within certain areas to include Clinical Guidance, Nursing Practice, and Program Administration. This will be available on the NTCA website. NTCA has some asks from DTBE in order to pull all of this together. In the short-term, NTCA would like to know whether the 2014 HPC ACET statement could be linked on the DTBE website. DTBE collaboration also would be beneficial to support access to BCG Live as a drug shortage for the indication of BCG vaccination. Longer-term, NTCA would like to see updated, completed information about the availability and recommended use of BCG vaccine in the US. It seems like now would be a good time to revisit the indications, which would require some technical assistance from NHHSTP/CDC in terms of assessment of risk regarding MDR TB exposure of HCP and DSW for humanitarian aid, MDR contacts < 5 in terms of the effectiveness of the window of prophylaxis and LTBI treatment, and FDA package insert recommendations—considerations for updated referenced guidance. One the NCTA vaccination toolkit is completed, it would be beneficial to have CDC links to NTCA website.

The asks for ACET are to coordinate with ACIP as necessary with regard to any sort of evolution of this guidance. It is not clear yet whether there will be a need to review and possibly update the FDA labeling, but that could be a possibility. There have been major advancements in the science with vaccines. The last time ACET made a statement on a TB vaccine was in 1998. It seems that right now would be a good time to revisit establishing an ACET TB Vaccine Workgroup to support and advance the US strategy. There has been some recent movement with a Virtual Global Forum on April 20-22, 2021 that was convened to look at a Global Roadmap for TB Vaccine and to put the tools together to advocated for resources. On the calendar is the 6th Global Forum focused on TB vaccine development that is scheduled for February 22-24, 2022.

Going back to some comments from the field gathered from the survey, one travel medicine physician said that, "As a previous TB doctor working with large numbers of patients in South Africa in Mozambique and Madagascar, I'd love there to be an effective vaccine against TB. Over 95% of all of my patients in the first two countries had a scar, but they developed active TB." In his or her opinion, "This was the least effective and least useful of all vaccines currently offered. Another vaccine that is truly effective in terms of preventing TB would be most welcomed. The BCG should be heading for the history books."

In summary, BCG vaccine in the US has saved lives. BCG vaccination in the US is achievable via off-label administration of BCG Live, though access is extremely limited currently. There is not practical guidance for public health programs and HCP working overseas who have real occupational risk. NTCA plans to develop a BCG vaccination toolkit to address the gap and requests technical assistance from DTBE and NHHSTP for focused questions related to target groups who may benefit from access to BCG vaccination. Given advancements in vaccine development for COVID-19, NTCA also requests that ACET consider convening a TB Vaccine Workgroup.

ACET Discussion: Bacillus Calmette-Guerin Vaccine Guidance Development
Ms. Cole emphasized that many people who have received BCG to protect/prevent TB have still developed active TB, and wondered whether there is new science regarding the efficacy of BCG or BCG Live.

Dr. Aronson indicated that there are some new data on a very interesting aspect of BCG vaccination to prevent infection in South Africa that involved revaccination of South African adolescents. There are a wide variety of results in BCG efficacy trials, but a recent study was published in the past year. It is clear that the data are convincing in children, there are some recent data in adult populations.

Ms. Kurtz, FDA *Ex Officio*, emphasized that the FDA stance is that they cannot condone or endorse off-label use of any product. In this case, the efficacy and safety of BCG live have not been reviewed for this application purpose. While there was mention about changing the product insert, the decisions about what goes into a product insert begin at the level of the manufacturer who submits that information to the FDA. Then there is a long back and forth process between the FDA and any given manufacturer as to the exact language that goes into a particular product insert. That information can only be changed beginning with an amendment submitted by the manufacturer to the FDA. Again, that involves a long review process back and forth with the FDA and the sponsor to think about changing a product insert. If the NTCA is really interested in pursuing increased use of BCG as a vaccine in the US, she suggested going to the manufacturer, Merck, to determine their interest in increasing or renewing their supply of

BCG vaccine in the US.

Dr. Higashi said she did not think they would anticipate that many changes in the near-term. She just did not know whether there would be some impact if this activity was assigned as a drug shortage.

Dr. LoBue indicated that there are ways to link documents, but they will have to discuss this with the CEBSB team. This is done with other external documents and there typically is a warning that states something to the effect of, “You are leaving the CDC website.” Linking does not require a lot of staff time to pursue. He did not commit to the other asks at this point, given the need to further assess the situation. It is difficult enough to work on keeping access to drugs. BCG vaccine is so niche and there is little indication in the US at this point, so it is not clear whether this will be worth DTBE staff time.

Dr. Belknap requested further explanation about what is meant by advancing the US strategy.

Dr. Higashi clarified that she meant for advocacy for the development of a TB vaccine in light of the fact that there is new messenger ribonucleic acid (mRNA) science that makes vaccine development a lot easier. The advancements made in recent years with TB vaccines in general suggests that there is an opportunity to use what has been learned from those experiences and potentially put it into the mRNA platform strategy for vaccine development. From the standpoint of new science, consideration should be given to how this could change the timeline to a real vaccine for TB.

Ms. Kurtz, FDA *Ex Officio*, reported that there are development strategies already in place to use some of the new platforms for TB vaccines. Some of the manufacturers who have had COVID vaccine development success are transitioning some of these platforms to TB vaccine development and discussed this in part during the Global Forum. There is a huge demand internationally for new and better TB vaccines, especially for protecting adults against pulmonary TB. BCG vaccine’s success globally is in protecting children against miliary TB, which is why it is still used in so many countries. There are people who are investigating the BCG revaccination strategy. The development pipelines are occurring. ACET getting involved in being a proactive member of the TB vaccine development community could help, but it is important to note that many new vaccines are being developed for use outside of the US and are not necessarily going to be driven toward US licensure. The Global Forum in 2022 is specifically a TB vaccine development forum, so every year they assemble stakeholders from manufacturing, regulatory entities, and academic research to discuss all ongoing clinical trials for existing platforms, products that are moving out of the academic pipeline into the clinical trial pipeline, and academic research related to the development of new TB vaccines. It is a conglomeration of products that are actively in the pipeline, already in Phase II/III clinical trials outside of the US, and currently being developed in academia or very early in Pre-Phase Investigational New Drug (IND).

Dr. Temesgen pointed out that it is not only the mRNA technology platform but also the transparency, collaboration, and funding that made the COVID-19 vaccine available so rapidly. Perhaps that is something ACET could advocate for TB vaccine as well.

Ms. Cole recapped that in terms of next steps for ACET, if there is interest specifically in dealing with BCG, there would have to be a motion from an ACET member to address that. However, they heard from the FDA that they do not endorse off-label use and she did not envision that ACET would take a position that is opposite of FDA and all of the issues involved in that.

However, there appears to be great interest in considering how ACET might be involved as an advocate for the development of a TB vaccine. ACET has always said that an effective TB vaccine is needed, so hopefully something positive that has come out of COVID is the development of new technology that might be applied to an effective TB vaccine. As the incoming Chair, she called upon Dr. Belknap to indicate whether they should wait to take action in terms of a TB Vaccine Workgroup until after hearing the results from the 6th Global Forum where a lot of these issues are already being addressed. Since there was a Global Forum in April 2021, Ms. Cole suggested that perhaps they could invite someone to present to ACET during its December 2021 meeting on the results of that forum.

Dr. Belknap thought it would be useful for ACET to hear from those who are working on this already, perhaps during the December 2021 ACET meeting before the 6th Global Forum or during the June 2022 ACET meeting after the forum to better understand the current landscape and then consider what ACET's role might be in supporting that. He agreed that as with most areas of TB and TB research in general, underfunding is a chronic problem. It is important to understand if they are going to state that ACET supports increased research and funding directed toward that, there must be an increase overall and not just static funding. It is probably too soon to establish a workgroup, because it is not clear that it would have a specific charge at this point.

Dr. LoBue reminded everyone that a workgroup is a time-limited group that has a specific task and charge. Before establishing a new workgroup, he thought they should have a good grasp on what they would be asked to do and what the expected outcome or product would be. It is important for new members to understand what workgroups do.

Dr. Horne said he supported all of the statements made and emphasized the incredible importance of TB vaccines globally. It would behoove the members to reach out to collect more resources. Another resource is the Collaboration for TB Vaccine Discovery (CTBVD), which has an ongoing annual meeting and is organized by the Gates Foundation. Perhaps a guest speaker could be invited from that group as well to address ACET.

Dr. Higashi emphasized that the most immediate short-term ask would be the 2014 ACET statement for HCP link for MDR TB to link to more current information than the 1996 guidelines.

Dr. LoBue responded that linking to the 2014 ACET statement should be a fairly simple request to fulfill.

Ms. Cole recapped that:

- NTCA will proceed with development of a BCG vaccination toolkit
- Dr. LoBue will seek information about a DTBE link to that toolkit and will further review and study the other NTCA asks
- ACET will not move forward with endorsing BCG Live, given that it is in contrast with the FDA's protocol for not endorsing off-label use
- Speakers will be invited from the Global Forum and CTBVD to further inform ACET on the current status of TB vaccine development

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. Horne and seconded by Dr. Armitige to accept the December 8-9, 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**
1) eDOT Study Update: a) Feedback in response to the study results and/or next steps outlined in the presentation b) Suggestions for expanding access to eDOT among programs, especially those with low TB incidence c) Recommendations for future digital health interventions to facilitate TB control activities	See Pg. 34-40	Schedule an update on eDOT for a future ACET meeting

ADVICE REQUESTED FROM ACET		
Topic	**Discussion From Minutes**	**Action**
2) Drug Supply Update a) Follow-up with the FDA Center for Drug Evaluation and Research (CDER) on these issues	See Pg. 42-47	Monitor for FDA response to follow-up questions: • Concerns expressed to NTCA by programs that there are challenges procuring ethionamide: - *There was no recollection about addressing anything other than nitrosamine, so it is not clear what this was about.* • Additional information on pediatric populations, pregnant women, and their unborn children 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: - *FDA has stated numerous times that their approach is so conservative, the single approach covers all groups. It is unlikely that additional information will be forthcoming from the FDA.* - *Perhaps it behooves ACET to at least state that there are no data so that the warnings are more clinically useful.* - *However, it is important to remember that absence of proof is not proof of absence.* • Need for information to be provided to patients about risk/benefit in the context of nitrosamine: - *Human data do not exist to quantitate the risk.* - *While messaging is important, this is not ACET's role. Perhaps ACET should encourage other groups to do so.* - *Dr. Loeffler will take this to her pediatric group on the West Coast and will report back to ACET.* • Provide information on BCG vaccine supply/availability: This was discussed during this meeting.

Business Item 3: LTBI Clinical Recommendations

Donna Wegener noted that the LTBI Clinical Recommendations document was included in the agenda to make all of the ACET members and others in this space aware that the NTCA's National Society of TB Clinicians (NSTC) released a document in February 2021 that was envisioned as a companion document to the LTBI Clinical Recommendations document and goes beyond what could be done with the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) and PICO (population, intervention, control, and outcomes) criteria.[24]

Business Item 4: Letter and Report to HHS Secretary

ACET received a letter dated November 24, 2020 signed by Dr. Burton in response to ACET's letter to the HHS Secretary. A copy of the response letter was provided to ACET members. Dr. Burton indicated that the letter was transmitted to HHS and CDC was delegated by HHS to provide a response to the letter. The response came from DTBE and for each of the points that ACET raised, there is discussion about what DTBE is doing and remains committed to do across each of the items. Dr. Burton highlighted the responses to each of the 6 points ACET raised.

A motion was properly placed on the floor by Dr. Horsburgh and seconded by Dr. Armitige to reference the November 24, 2020 letter in ACET's Semi-Annual Report to the HHS Secretary rather than restating everything that was previously approved in order to inform the new HHS Secretary without being redundant. With no further discussion or changes, the motion to accept the minutes as written carried unanimously with no abstentions or opposition.

Business Item 5: Status Report on ACET's Letter on LTBI Roadmap Document

The LTBI Roadmap Document was finalized, approved, and the letter was sent. The document will not go through the *MMWR* approval process. Instead, the plan is to post it on the website. Carla Winston reported that Staci Morris, as the ACET Committee Manager, was able to obtain permission just before this meeting to post that document on the ACET website. That involves 508-compliance as the last step, with the hope that it will be posted within the week. The plan is for DTBE to link from the Roadmap on the ACET site to the DTBE website where the LTBI resources are housed.

Business Item 6: Feedback on Revision of the 2006 *MMWR* on TB in Correctional Settings

Edith Lederman raised the issue of a potential revision to the *MMWR* publication, "Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC" that is now 15 years old.[25] This document begs for significant revisions and updating. The NTCA has established a workgroup of dedicated stakeholders from public health and corrections to put forth a revision in partnership with DTBE. They are currently working on a white paper and formalization of this effort and wanted to reach out to ACET early on to ask for technical advice and consideration of endorsement when the document has gone through CDC clearance. In terms of the timeline, the hope is to complete the revision over the next 1.5 to 2 years. ACET pointed out that if the group waits to bring it to ACET for endorsement when it is

[24] http://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/
[25] https://www.cdc.gov/mmwr/PDF/rr/rr5509.pdf

completed, they may not be able to endorse it. Therefore, it should be brought before ACET before it is completely finalized and cannot be changed.

Business Item 7: 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 for consideration:

Presenter	Agenda Item
Nick DeLuca	eDOT study update LTBI campaign messaging LTBI Clinical Recommendations Status of Study 31 and Study 37
Anne Loeffler	Follow-up on resources on nitrosamine impurities and medications, including examples of conversations practitioners are having with their patients regarding nitrosamines when prescribing rifampin, and information about nitrosamine levels in samples tested over time
Sherry Kurtz / Karen Elkins	Were involved in the Global Forum, with Karen contributing to the development of the Global Roadmap for TB vaccine development, so either could help review the topics covered at the Global Forum to help better inform the potential role ACET might play in addition to advocacy
TBTC	Update on ongoing clinical trials Newly reconstituted TBSC
Deron Burton	Social Determinants of Health, in terms of TB and other health conditions, the incredible inequities that existed but have been highlighted by COVID, and opportunities to leverage the acute awareness this raised in society and the overall agency focus on health equity
NTCA	Follow-up on additional COVID impact analysis
DTBE	Molecular Detection of Drug Resistance (MDDR) service and the transition to the Targeted Next Generation Sequencing (tNGS) assay, Whole Genome Multi-Locus Sequence Typing (wgMLST) transition
DTBE	Update on BPal status and usage in the US

Business Item 8: Addition of New ACET Chair

Ms. Cole expressed her gratitude to all ACET members and liaison representatives for all of the work that has been done over the last several years. She emphasized that it truly has been her honor to serve as ACET Chair, that they have accomplished great things, and that she values all of the input that they have received. With that said, she passed the baton to incoming ACET Chair, Dr. Robert Belknap, and invited him to share his thoughts about moving forward with ACET. She thanked everyone who provided support to make this meeting possible and successful.

Dr. Belknap said that it was an honor and pleasure to be given this opportunity to serve as Chair and recognized that there are certainly big shoes to fill. He has appreciated and learned from Ms. Cole and her leadership of the group since he has been a member. He stressed what a great meeting it had been despite not being in-person. While being in-person enhances meetings, the topics, speakers, and what was covered in the last 1.5 days was outstanding. The long list of potential items for the December 2021 meeting is equally exciting in terms of the opportunities ahead and areas for ACET to provide meaningful input and hopefully bridge some gaps in the move toward TB elimination. He expressed gratitude to those who were rotating off of ACET and welcomed new members.

Public Comment

No public comments were provided during this meeting.

Closing Session

The confirmed/proposed dates for upcoming 2021-2022 ACET meetings are:

- ❑ December 14-15, 2021 (Confirmed)
- ❑ June 14-15, 2022 or June 21-22, 2022 (Proposed), either of which works for Dr. Belknap

While the preference is for these meetings to be in-person, this will be dependent upon CDC's status and what is permitted. There is not yet a timeline for when in-person meetings may be resumed at CDC, and virtual meetings will be convened only if there is no other option.

With no further discussion or business brought before ACET, a motion was properly placed on the floor, seconded, and unanimously approved to adjourn the meeting at 12:00 pm on June 16, 2021.

CHAIR'S CERTIFICATION

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

Date

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
Dr. Zelalem Temesgen

ACET *Ex-Officio* Members Present

Dr. Naomi Aronson
US Department of Defense

Dr. Amy Bloom
US Agency for International Development

Dr. Jonathan Iralu
Indian Health Service

Dr. Lawrence Kline
Department of Health and Human Services

Sherry Kurtz
Food and Drug Administration

Dr. Mamodikoe Makhene
National Institutes of Health

Mr. Stephen Martin
National Institute for Occupational Safety and Health

Dr. John Palmieri
Substance Abuse and Mental Health Services Administration

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

Dr. Ronald Wilcox
Health Resources and Services Administration

CAPT David Wong
Office of the Assistant Secretary for Health

ACET *Ex-Officio* Members Absent

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

ACET Liaison Representatives Present

Dr. Shama Desai Ahuja
Council of State and Territorial Epidemiologists

Dr. Robert Benjamin
Stop TB USA

Mr. Peter Dupree
National Tuberculosis Controllers Association

Nuala Moore (Charles Daley in for Moore)
American Thoracic Society

Dr. Amee Patrawalla
American College of Chest Physicians

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

Mr. Bobby Watts
National Health Care for the Homeless Council

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

Mr. Surajkumar Madoori
Treatment Action Group

Dr. Howard Njoo
Public Health Agency of Canada

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

Dr. Lornel Tompkins
National Medical Association

Dr. Daphne Ware
Association of Public Health Laboratories

ACET Designated Federal Officer

Dr. Deron Burton
NCHHSTP Deputy Director

CDC Representatives

Ms. Leeanna Allen
Ms. Lauren Barna
Dr. Karlyn Beer
Ms. Martha Boisseau
Ms. Beth Bouwkamp
Dr. Deron Burton
Ms. Elise Caruso
Ms. Anne Cronin
Dr. Tracy Dalton
Mr. Justin Davis
Dr. Nick DeLuca
Dr. John Jereb
Dr. Dolly Katz
Ms. LeiAnn Keuth
Ms. Kathryn Koski
Mr. Steve Kammerer
Dr. Ekaterina Kurbatova
Ms. Lauren Lambert
Dr. Adam Langer
Dr. Edith Lederman
Dr. Joana Lively
Dr. Philip LoBue
Ms. Suzanne Marks
Ms. Allison Maiuri
Ms. Bria Marlowe
Dr. Jonathan Mermin
Ms. Staci Morris
Dr. Julie Self
Ms. Maria Sessions
Dr. Angela Starks
Dr. Thara Venkatappa
Dr. Andrew Vernon
Ms. Laura Vonnahme
Dr. David Weissman
Dr. Carla Winston

Guest Presenters

Dr. Naomi Aronson
Ms. Katelynne Gardner Toren
Dr. Julie Higashi
Ms. Donna Hope Wegener
National Tuberculosis Controllers Association

Members of the Public

Saurav Dahal
Karen Elkins, FDA
Chris Freedman, Maximus
Megan Klingler
Sherry Kurtz, FDA
Paola Mejia
Dee Pritschet, NTCA
Dr. Jon Warkentin, VUMC
Beth
BW
Lon

Attachment 2: Glossary of Acronyms

Acronym	Definition
ACET	Advisory Council for the Elimination of Tuberculosis
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
ARP	American Rescue Plan
ATS	American Thoracic Society
BCG	Bacillus Calmette–Guérin
BDQ	Bedaquiline
BMZ	Bedaquiline, Moxifloxacin, and Pyrazinamide
BPaL	Bedaquiline, Pretomanid, and Linezolid
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CDM	Common Data Model
CfZ	Clofazimine
CDER	Center for Drug Evaluation and Research
CEBSB	Communications, Education, and Behavioral Studies Branch
CFU	Colony-Forming Units
CMS	Centers for Medicare and Medicaid Services
COI	Conflict of Interest
CoP	Community of Practice
CPR	Center for Preparedness and Response
CRB	Clinical Research Branch
CT	Computed Tomography
CTBVD	Collaboration for TB Vaccine Discovery
DASH	Division of Adolescent and School Health
DFO	Designated Federal Officer
DGMQ	Division of Global Migration and Quarantine
DIS	Disease Intervention Specialists
DOT	Directly Observed Therapy
DSMB	Data Safety Monitoring Board
DTBE	Division of Tuberculosis Elimination
DVH	Division of Viral Hepatitis

Acronym	Definition
EDN	Electronic Disease Notification
eDOT	Electronic Directly Observed Therapy
EHR	Electronic Health Record
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
FQHC	Federally Qualified Health Centers
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCH	Healthcare for the Homeless Clinics
HCP	Healthcare Providers/Professionals
HCUP	Healthcare Cost and Utilization Project
HCV	Hepatitis C Virus
HHS	(United States) Department of Health and Human Services
ICD	International Statistical Classification of Diseases and Related Health Problems
IDO	Infectious Disease Consequences of Opioids
IGRA	Interferon-γ Release Assay
IND	Investigational New Drug
ipDOT	In-Person Directly Observed Therapy
ISTM	International Society of Travel Medicine
IT	Information Technology
IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	Latent Tuberculosis Infection
MDDR	Molecular Detection of Drug Resistance
MDR-TB	Multidrug-Resistant Tuberculosis
ME	Medical Examiner
MEMS	Microelectronic Monitoring Systems
MIBC	Muscle Invasive Bladder Cancer
MIC	Minimum Inhibitory Concentration
MIRU-VNTR	Mycobacterial Interspersed Repetitive Unit-Variable Number Tandem Repeat
MMWR	*Morbidity and Mortality Weekly Report*
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSM	Men who have Sex with Men
MTB	Mycobacterium Tuberculosis
NACCHO	National Association of County and City Health Officials
NASTAD	National Alliance of State and Territorial AIDS Directors
NBS	NEDSS Base System
NCBI	National Center for Biotechnology Information
NCCDPHP	National Center for Chronic Disease Prevention and Health Promotion
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention

Acronym	Definition
NCIRD	National Center for Immunization and Respiratory Diseases
NEDSS	National Electronic Disease Surveillance System
NEJM	*New England Journal of Medicine*
NHBS	National HIV Behavioral Surveillance
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIOSH	the National Institute for Occupational Safety and Health
NP	Nurse Practitioner
NSTC	National Society of TB Clinicians
NTCA	National Tuberculosis Controllers Association
NTSS	National Tuberculosis Surveillance System
NTSS CR	National Tuberculosis Surveillance System Case Report
PA	Physician's Assistant
PCP	Primary Care Providers
PK/PD	Pharmacokinetic/Pharmacodynamic
PrEP	Pre-Exposure Prophylaxis
PWID	People Who Inject Drugs
PZA	Pyrazinamide
QA	Quality Assurance
QFT	QuantiFERON®-TB Test
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid
RVCT	Report of Verified Case of Tuberculosis
SAT	Self-Administered Therapy
SDOH	Social Determinants of Health
SEOIB	Surveillance, Epidemiology, and Outbreak Investigations Branch
SOP	Standard Operating Procedures
SSP	Syringe Services Program
STD	Sexually Transmitted Disease
STD PCHD	STD Prevention and Control for Health Departments
TA	Technical Assistance
TB	Tuberculosis
TBESC	Tuberculosis Epidemiologic Studies Consortium
TB GIMS	TB Genotyping Information Management System
TBTC	Tuberculosis Trials Consortium
tNGS	Targeted Next Generation Sequencing
TST	Tuberculin Skin Test
US	United States
USPSTF	US Preventive Services Task Force
WG	Working Group
wgMLST	Whole Genome Multi-Locus Sequence Typing

Acronym	Definition
WGS	Whole Genome Sequencing
WHO	World Health Organization
WLH	World Lung Health
XDR-TB	Extensively Drug-Resistant TB