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

Virtual Meeting of the
Advisory Council for the Elimination of Tuberculosis
June 21-22, 2022

Record of the Proceedings

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ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
June 21-22, 2022

Minutes of the Virtual Meeting

The United States (US) Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC), National Center for HIV, Viral Hepatitis, STD, and TB Prevention (NCHHSTP, the Center), 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 21-22, 2022 beginning at 10:00 a.m. Eastern Time (ET).

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

Information for the public to attend the virtual ACET meeting via webinar or teleconference was published in the *Federal Register* in accordance with FACA regulations and rules. All sessions of the meeting were open to the public.

June 21, 2022 Opening Session

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

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

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

Ms. Condit called the meeting to order at 10:00 am ET on June 21, 2022 and provided meeting instructions. She noted that members of the public would have an opportunity to provide comment during the second day of the meeting at 11:55 AM. Dr. Burton welcomed participants and conducted a roll call to confirm the attendance of ACET voting members, *ex-officio* members, and liaison representatives. He explained that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. He reminded ACET voting members of their responsibility to disclose any potential individual and/or institutional conflicts of interest (COI) for the public record and recuse themselves from voting or participating in these matters.

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

The roll call confirmed that the 20 voting and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on June 21, 2022. Dr. Makhene was unable to attend this meeting and Dr. Irina Gelmanova served as the National Institutes of Health (NIH) representative in his stead. Ms. Tara Ross also joined the meeting as an unofficial *ex officio* representative from the Bureau of Prisons (BOP). The roll was called subsequent to each break and lunch, with quorum established each time throughout the day.

Dr. Burton welcomed the following new liaison members to ACET:

- Valerie Adelson, American Thoracic Society (ATS)
- Dr. Jonathan Golub, The International Union Against TB and Lung Disease-North America Region (The Union)
- Dr. Masahiro (Masa) Narita, The National Association of County and City Health Officials (NACCHO)
- Elizabeth Lovinger, Treatment Action Group (TAG)
- Heidi Behm, National Tuberculosis Controllers Association (NTCA)

In Addition, Dr. Burton made the following announcements:

- The response to the latent tuberculosis infection (LTBI) recommendations letter from the ACET Chair to the Secretary Becerra was sent on March 23, 2022 and was distributed in the meeting materials for this meeting.
- The ACET Charter is up for renewal this year. Dr. Burton is working closely with Dr. Belknap and Dr. LoBue to evaluate the function of the Council to ensure that its membership is in line with the scope of activities.
- Members should expect an invitation in the fall for training on Federal Advisory Committees, ACET, and the roll of members. This training is intended for new and longstanding members.

Dr. Belknap welcomed members and participants. He reminded everyone that ACET exists to provide recommendations to the Secretary and Assistant Secretary for Health (ASH) of HHS and the Director of CDC regarding TB elimination activities. Specifically, ACET is charged with making recommendations regarding policies, strategies, objectives, and priorities; addressing the development and application of new technologies; providing guidance and review on CDC's Tuberculosis Prevention Research portfolio and program priorities; and reviewing the extent to which progress has been made toward eliminating TB.

NCHHSTP Director's Report

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

Dr. Mermin welcomed everyone and presented the NCHHSTP update. The monkeypox (orthopoxvirus) outbreak has been taking up increasing amounts of time for the Center. Over 2,000 cases in 37 countries had been identified at the time of this meeting, primarily among men who have sex with men (MSM). As of the end of the previous week, the US had 99 confirmed cases of orthopoxvirus in 18 states and the District of Columbia (DC). Contacts with STI clinics, MSM organizations, MSM-focused dating applications (apps), and other outreach venues are being used to provide information to audiences who need to know about monkeypox.

NCHHSTP also is working with the response effort to ensure that sufficient vaccine is available initially as post-exposure prophylaxis (PEP) and in anticipation of a broader vaccination approach if necessary. There have been no deaths associated with this outbreak in the United States, but it can cause severe illness. There are people under 50 years of age who have not been vaccinated previously with smallpox vaccine who are susceptible. There have been some cases in persons over 50 years of age, which is likely from waning immunity or lack of cross-reactivity from the initial smallpox vaccine.

The NCHHSTP Equity Initiative is a transformational long-term strategy to help NCHHSTP achieve equity within its workplace and eliminate health disparities by addressing racism and other systems of oppression that hinder the Center's mission. This initiative was spearheaded initially by CAPT Burton when he was Director of the NCHHSTP Office of Health Equity (OHE) and is now overseen by him in many ways as the Deputy Director for the Center. Work began on this strategy in 2019-2020 and it was launched officially in 2021. The strategy's focus areas include Workplace Culture; Workplace Policies and Procedures; and Research, Programs, and Partnerships. It is important to ensure that NCHHSTP provides a diverse, equitable, and inclusive workplace and ensures that there is a focus on public health equity in the Center's external work. In February 2021, the Equity Initiative was launched to address this and other challenges—after 2 years of research and planning by a team of representatives from all 5 Divisions and the Office of the Director working closely with an organizational change consultant. Milestones to date include an analysis of workforce data to identify representation gaps, workplace culture trainings for staff, and OD- and Division-specific equity plans; future activities for 2022 include a final monitoring and evaluation plan for the Initiative and guidance on evidence-based interventions, policies, and best practices to reduce disparities. Though NCHHSTP has worked for many years to advance equity, this Initiative is breaking new ground by intentionally and systemically integrating equity into everything the Center does.

One of the fact sheets focuses on race, ethnicity, and gender of staff across divisions and General Schedule (GS) classification levels to ensure that people being employed at higher levels are a reflection of the people NCHHSTP. A fact sheet was recently completed that focuses on trends over the past decade and shows that there have been improvements in numerous, but not all, areas. An internal workforce assessment of sexual orientation and gender was completed recently as well, which determined that about 18% of NCHHSTP's staff are lesbian, gay, bisexual, and transgender (LGBT). That is equal across all GS levels. There is more work to be done, which is being addressed by particular activities regarding inclusiveness and ensuring that the workplace is supportive of all staff.

Regarding the NCHHSTP Equity Dashboard, each division has selected multiple measures to assess specific goals for specific indicators, such as reducing the complications of infections and reducing inequity. In order to monitor disparities well, it is necessary to have both absolute and relative indicators to ensure that they both change in the correct direction over time. For some of the measures where there are multiple factors within in each variable an index of disparities (e.g., multiple races and ethnicities or other variables) is required. While relative and absolute indicators of disparity are somewhat complex to understand, this is more accurate in terms of monitoring success over time. Of note, there is an indicator for reducing the percentage of TB cases among US-born persons who experience homelessness, with a goal to achieve a 14% reduction by 2025.

NCHHSTP is expanding a new generation of program coordination and service integration within a syndemic disease scope, highlighting that public health issues reflect people, place, science, and policies. The most common definition is that “syndemics are epidemics that interact with each other and by that interaction increase their adverse effects on the health of communities that face systematic, structural, and other inequities.” People often think of syndemics as positive or negative factors that affect people as part of groups and populations. However, taking a holistic approach to disease intervention, CDC can be more effective than a disease silo approach. Potential benefits include holistic service delivery; increased efficiency and cost-effectiveness; reduced stigma; support for policy and social determinants of heath (SDOH) drivers; increased flexibility by enabling partners to adapt, implement, and modify integrated services to increase responsiveness to evolving epidemics or changing contexts; and the ability to work with implementing partners with increased control and ability to provide comprehensive services.

The first consideration is that people matter in terms of what it means to have overlapping conditions or epidemics. For many of the infections under the purview of NCHHSTP, MSM are disproportionately affected. MSM represent 70% of HIV diagnoses, 42% of primary and secondary syphilis cases, 42% of gonorrhea cases, and 17% of chlamydia cases. MSM are 150 times more likely to get HIV and syphilis than heterosexual men and women. Effectively providing services for MSM will reduce incidences in all of these infections and will help that population achieve higher levels of health. Persons who inject drugs (PWID) experience the most acute hepatitis C virus (HCV) and a large proportion of hepatitis B virus (HBV) infections, 11% of HIV diagnoses, and represent a large proportion of overdose deaths. To combat the lack of comprehensive services for PWID, NCHHSTP provides a toolkit for syringe service programs (SSPs) that broadly addresses a number of infections that effect PWID such as skin infections, methicillin-resistant *Staphylococcus aureus* (MRSA), endocarditis prevention, and others not within NCHHSTP’s purview. Racial and ethnic groups are disproportionately affected. African Americans are 8 times more likely to get new HIV infections than whites, while Hispanic/Latinos are 3 times more likely. More than a third of TB and HBV occur among Asian Americans. There are excellent pilot programs through which community health centers are performing screening for HBV and LTBI among populations which is both cost-saving and effective. Justice-involved populations also experience higher incidences of all infections.

Place matters as well. Mapping out high burden areas, we can pinpoint key locations accounting for 50% of diagnoses for HIV, chlamydia, gonorrhea, syphilis, and TB to focus efforts. The place perspective offers an opportunity for service delivery in a number of venues, including HIV, STD, and Student Health Clinics; Community Health Centers; SSPs; Substance Use Disorder (SUD) Treatment Centers; Correctional Facilities; Homeless Shelters; Emergency Departments; Hospitals; Schools; and Virtual Spaces (e.g., dating sites, digital interest groups, influencers).

High impact syndemic strategies include multi-pathogen testing for more than one pathogen when blood is being drawn, policy change, prevention interventions and outbreak response, venue- and program-based multi-disease prevention, data sharing and analyses that allow for thinking more syndemically, and digital communication campaigns and interventions. Key actions to address syndemics include putting people first, focusing on equity, putting money where the pandemic is occurring, leveraging policy as a public health tool, and prioritizing innovation and allow that to occur. DTBE in general, and the TB world at large, always have been careful about ensuring that efforts are evidence-based while prioritizing innovation at the same time.

The latest data on HIV show new HIV infections fell 8% from 2015 to 2019, after a period of general stability in new infections in the US. Much of this progress was due to larger declines among young gay and bisexual men in recent years. The HIV surveillance supplemental report *Estimated HIV Incidence and Prevalence in the U.S.,* which provides data on estimated incidence, prevalence, and knowledge of status in the U.S., was not published this year because of the disruptions in HIV testing services and access to clinical services throughout 2020. This disruption resulted in a steep, single-year decline in HIV diagnoses that is mostly attributed to declines in testing caused by stay-at-home orders and redistribution of resources to address the COVID-19 pandemic. The overall number of HIV diagnoses in the United States in 2020 (30,403) was 17% lower than in 2019. The number of people living with HIV continues to rise. The better the prevention, the less the overall burden of people living with HIV. CDC maintains focus on the four pillars of EHE and continues to amplify these efforts by investing in key strategies to advance health equity. Some creative areas on which NCHHSTP has been focused for HIV prevention and advancing healthy include self-testing, syndemic approaches, community-based organization (CBO) capacity, pre-exposure prophylaxis PrEP uptake, and status neutral models of care.

The STI crisis continues in the US, incidence continuing to rise. The 2020 STD Surveillance Report shows increases in gonorrhea, syphilis, and congenital syphilis. There were increasing reporting for syphilis and congenital syphilis for 2021 as well. Chlamydia shows a 12.7% decline in cases occurred from 2019. This decline is likely due to decreases in STD screening and underdiagnosis during the pandemic, rather than a reduction in new infections, given chlamydia is usually asymptomatic. Disparities and inequities can be addressed through a syndemic approach by identifying collaboration opportunities, increasing access to healthcare, expanding partner services and DIS, improving STI diagnostics and therapeutics, and enhancing surveillance systems.

“CDC’s Strategic Plan to Reduce Infectious Diseases Among People Who Use Drugs” has been issued internally. This is an across-agency plan that intends to pull in the expertise of multiple CDC centers. The vision of the plan is to eliminate injection drug use-associated infections. The mission is to decrease morbidity, mortality, and incidence of infectious diseases associated with injection drug use, as well as stigma experienced by people who use drugs. The strategic priorities are to: 1) strengthen the syringe services program (SSP) infrastructure nationwide and further integrate SSPs into the US public health system; and 2) establish coordinated surveillance, monitoring, and program implementation. Other priorities are incorporated into the plan as well. The National Harm Reduction Technical Assistance Center (Harm Reduction TA Center)[1] is a joint activity between the National Center for Injury Prevention and Control (NCIPC), NCHHSTP, and the Substance Abuse and Mental Health Services Administration (SAMHSA). The idea is to have a group of multiple providers who will be able to provide TA and support for harm reduction not only for grantees, but also for organizations who are interested in doing a better job of harm reduction throughout the nation.

[1] harmreductionhelp.cdc.gov

Related to viral hepatitis, there are a number of new CDC recommendations. The first is updated hepatitis B vaccination recommendations published in April 2022. These recommendations make a strong move away from using risk-based and are as follows:

- All adults 19-59 years and adults ≥60 with risk factors should receive hepatitis B vaccines
- Adults ≥60 without known risk factors may receive hepatitis B vaccines

Changes have been made to the hepatitis B screening and testing recommendations as well. Federal Register comments closed on June 3, 2022.[2] The recommendation is for all adults ≥18 years to receive hepatitis B screening at least once in their lifetime.

The vision that guides NCHHSTP in all of its work is a future where all youth have the knowledge, skills and resources they need, not only during their adolescence, but to help them move into a healthy adulthood. NCHHSTP recently released data collected through its Adolescent Behaviors and Experiences survey in 2021 which highlights the challenges youth are facing, particularly related to mental health, experiences of abuse at home during the pandemic and experiences of racism in school. While all youth experienced some disruption, these data brought home the fact that that LGBTQ youth, female students, and youth of color are facing a disproportionate level of adversity. Data show 37% of students reported poor mental health during the pandemic, 25% of students who identify as lesbian, gay, or bisexual attempted suicide in the prior year, 17% of students who identify as other or questioning attempted suicide in the prior year, 55% of students experienced emotional abuse in the home, 64% of Asian students have experienced racism in school, and 55% of both Black and multiracial students have experienced racism in school.[3] Schools need support to promote recovery and resilience.

An analysis was performed of what works in schools, to inform the approach to working with local education agencies to implement programs that support students in schools. Students in schools who implemented the program were 12% less likely to have ever had sex, and 16% less likely to have more than four lifetime sexual partners, or be currently sexually active, 13% less likely to miss school because of safety concerns, 24% less likely to experience forced sex, 11% less likely to ever use marijuana, and 23% less likely to currently use marijuana compared to students who did not receive the program.[4] CDC resources provided to schools are being used well and are having a very positive effect on students. LGBTQ-specific supportive school policies and practices result in improved mental health outcomes for all students, including decreased depressive symptoms; decreased suicidal thoughts and behaviors; and decreased suicide attempts, particularly among LGBT students.[5]

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[2] https://www.federalregister.gov/d/2022-07050
[3] CDC Adolescent Behaviors and Experiences Survey (ABES), 2021
[4] Robin L, Timpe Z, Suarez NA, Li J, Barrios L, Ethier KA. Local Education Agency Impact on School Environments to Reduce Health Risk Behaviors and Experiences Among High School Students. J Adolesc Health. 2022 Feb;70(2):313-321. doi: 10.1016/j.jadohealth.2021.08.004
[5] Sources: Centers for Disease Control and Prevention, National Youth Risk Behavior Survey (YRBS), 2015 & 2017; Centers for Disease Control and Prevention, School Health Profiles (Profiles), 2014 & 2016

ACET Discussion

Dr. Belknap said he appreciated the concept around the holistic approach and wondered what the opportunities might be to integrate TB into that and what the potential risks may be for TB and TB programs being left out or left behind.

Dr. Mermin responded that both opportunities exist. There is concern that funding for less supported diseases or activities may be diverted and that less resources would be allocated to effective TB work. In terms of benefits, it tends to be a way to build on the foundation set by more well-resourced infections or activities related to those infections. NCHHSTP received some funds under the American Rescue Plan for expanding the Disease Investigation Specialist (DIS) workforce to help health departments to be able to hire more people to conduct contact tracing and other important infectious disease control activities. Those resources specifically allow NCHHSTP to build DIS workforce capacity. This is being run out of the Division of STD Prevention (DSTDP). There is potential for work within TB because it falls under the same purview as DIS. The multi-pathogen screening support could be very effective, especially when there is overlap of populations at risk. Another benefit is ease for programs to support more efficient ways of getting the job done.

Noting that monkeypox has many commonalities with HIV and the population infected, Dr. Liu inquired as to whether there were interventions that worked well for HIV or other STD outbreaks investigations that could be applied to monkeypox.

Dr. Mermin said that almost everything that worked well for HIV and other STD outbreaks could be applied to monkeypox. NCHHSTP already has 30 people deployed, is managing a lot of the communications, and is considering how to support the work of health department and CBOs in community engagement. There are 2 potential vaccines for monkeypox, which provides a unique tool. There is a limited supply of vaccine, it is not completely clear who would benefit most from that vaccine in terms of the cost-benefit ratio and potential harm, and consideration must be given to when to move beyond PEP to pre-exposure vaccination for people who are at higher risk. Stigma is another area where HIV/STD interventions could be applied to monkeypox. Work is underway to combat backlash via communication strategies. This is a natural space for people within NCHHSTP to work on monkeypox even though it is officially a virus that belongs in the Division of High Consequence Pathogens and Pathology (DHCPP).

Dr. Sosa-Bergeron called to attention the potential downsides of the syndemic approach. While it makes sense, she has observed over time that TB usually rides the coat tails as opposed to being at the forefront. She would like some thought and effort to be put into TB to be a priority where it makes sense. The name of this committee is ACET is Advisory Council for the Elimination of Tuberculosis and there are a lot of opportunities, especially with regard to LTBI elimination. Though this work was on hold during the pandemic, there are now opportunities to put TB in the lead. She recognized that part of this is a funding issue and that NCHHSTP is trying to acquire more funding for TB. She appreciates the opportunity to have funding flexibility when there are TB outbreaks that affect persons who also are infected with HIV.

Dr. Mermin replied that it is important to be thinking about TB in terms of requirements with certain populations, as well as with regard to spaces where it is most beneficial for the TB program to be in the lead. He generally thinks that the syndemic approach is extremely beneficial for TB over the current approach that is much more siloed, but he also understands the concern that it might be diverting in another direction. Intellectually and in practice in terms of implementation, the world of TB is often in the lead in areas such as with whole genome

sequencing (WGS) for surveillance, genetic markers for drug resistance, surveillance in general, conducting TBTC studies that have shown changes in treatment for mTBI or active TB, et cetera. There are many efforts from which the syndemic world is already benefiting from the TB world.

Dr. Chen highlighted that from the perspective of the frontlines, there needs to be an appreciation for the public health workforce needs in TB post-pandemic. Her workforce got pulled off of TB at the beginning of the COVID-19. They were small already and now are experiencing major burnout and stress because of the pandemic. She understands why the DIS funding is being orchestrated through STD and there is going to be benefit from backflow to TB, but TB was not at the table necessarily. In order for the syndemic approach to support TB, there must be equity that is inclusive of TB. Their workforce is gone in many instances. While they are seeing some overflow from the DIS efforts, but not necessarily everywhere. She suggested that this needs to be codified to benefit all groups.

Dr. Mermin emphasized that NCHHSTP is well aware of the need not only to protect some disease-specific resources that do go to TB currently, but also to be able to share program work or resources from other opportunities. Some of the venue-based and population-based opportunities from his presentation are very applicable to Dr. Chen's point.

Dr. Gordon observed that it would be good to have funding to address systems and social determinates of health (SDOH) issues and disease-specific work. If CDC does not support direct disease work like TB elimination at the program level, state health departments will lose individual disease programs. There is just too much political swing at the state level. They are not a priority and neither are the most affected communities.

Building on Dr. Sosa-Bergeron's comments, Dr. Ahuja added that the skills and expertise that are used to control TB were crucial in the COVID response, but their colleagues in other disease areas did not necessarily know that they had the skills to lead. That is because no one talks about TB, which may be what Dr. Sosa-Bergeron meant about "putting TB first."

Dr. Stout thought Dr. Chen's point was spot-on. At a higher level, they are dealing with a crisis in nursing in general and public health nursing specifically, not just in TB. Interventions to build and retain the public health nursing workforce are essential to making progress in TB control.

DTBE Director's Update

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

Dr. LoBue updated ACET on 2021 US TB provisional surveillance data, analysis of US TB incidence changes during the COVID-19 pandemic,[6] and the Think. Test. Treat TB. Campaign status. Regarding the total number of reported TB cases between 2011-2021, approximately 8,800 TB cases would have been expected in 2021 had the trend prior to COVID-19 continued. In 2020, there was an unprecedented decrease to 7,173 cases and somewhat of a rebound in

[6]Based on provisional NTSS data as of: 2.9.22

2021 to 7,860. Similarly with case rates per 100,000, there has been a very slow decline in recent years through 2019, with an unprecedented drop to 2.2/100,000 in 2020 and somewhat of a rebound to 2.4/100,000 in 2021. In terms of the relative changes in TB incidence per 100,000 across the country comparing 2021 rates to 2019 rates, most states had a lower rate in 2019 than they had before COVID-19. While there are exceptions, some locations have low cases counts to begin with so small changes make a big difference such as Wyoming. Delaware and Indiana were affected by the outbreak associated with contaminated bone allograft material.

Regarding the percent change in incidence rates by origin of birth between 2011–2021, there was a slow decrease in the case rate among non-US-born persons, followed by a large drop in 2020 of nearly 18%, with somewhat of a rebound in 2021 of 3.8%. Prior to COVID-19, the case rate was declining at a greater rate for US-born persons that was followed by a precipitous drop in 2020 of almost 21% and a somewhat larger rebound compared to non-US-born persons of nearly 11%. However, there is a bigger rebound in US-born persons of nearly 6% when the bone allograft contamination cases are excluded. This is somewhat closer to what is seen in non-US-born persons. A predominance, if not all, of the bone allograft contamination cases likely were in US-born persons.

Looking at TB case counts by race/ethnicity among non-US-born persons, there were decreases across the board by race and ethnicity from 2019-2020. There was somewhat of a rebound in 2021, with the exception of Black US-born persons. Among non-US-born persons, comprised primarily of Asian Americans and Hispanic Americans, a similar decrease is observed from 2019-2021 and something of a slight rebound from 2020-2021. The overall point is that no matter how the data are assessed, the patterns are similar across US-born, non-US-born, or race/ethnicity. Moving to incidence rates per 100,000 by age group, those 5-14 years of age did not have much change from 2019-2020 or 2020-2021. The youngest category from 0-4 years of age experienced a substantial decrease from 2019-2020, but a rebound did not occur among that group. Among adolescents/young adults 15-24 years of age, there was an almost 20% decrease and no rebound. Only among adults 25 years of age and above, the overall pattern is seen where there are substantial decreases in rates from 2019-2020 and a rebound from 2020-2021.

In terms of TB cases among non-US-born persons categorized by years since arrival in the US, the average was 16% of cases for people in the US less than a year from 2015-2019. That dropped to 10% in 2020 and to 9% in 2021. Conversely, the 2015-2019 average was 28% for those in the US over 20 years. That increased to 32% in 2020 and to 33% in 2021. The categories of less than 1 year and more than 20 years in the US had the most remarkable changes through the years. There has been a consistent downward trend in the proportion of cases with HIV at diagnosis between 2011-2021, with 4.3% infected with HIV. Most HIV infections occur in the 25-44 and 45-64 age groups. In the last couple of years, a trend has been observed for increased smear positivity in persons with TB. This differs for US-born and non-US-born persons. The proportion of smear positive cases among US-born has been fairly flat going back to at least 2014. However, increases were observed in 2020 and 2021 among non-US-born cases. One reason for that may be the possibility of decreased active case finding and detecting cases earlier, which would tend to result in an increased percentage of people with smear positivity. In recent years, the proportion of TB cases has been trended downward among persons experiencing homelessness and corrections. That trend continued through 2021. There is a known outbreak in the corrections setting that could change this trajectory.

With regard to some of the analyses of US TB incidence changes during the COVID-19 pandemic, the hypotheses for decline in reported TB are that there could be a true decline in cases, underdiagnoses leading to delays in diagnosis and reporting, or under-reporting. However, no evidence has been found of under-reporting in discussion with state and local partners. Published IQVIA outpatient pharmacy data looking at the TB-specific drugs isoniazid (INH) and pyrazinamide (PZA) suggest that under-reporting does not explain the 20% decline in reported TB in 2020, which is consistent with NTSS data. In terms of immigration-related changes in TB, there was a precipitous decrease in the percentage of cases from 2019-2020 occurring among non-US-born persons who arrived in the US less than 1 year prior to TB diagnosis. This persisted in 2021.

Looking at the number of persons entering the US by selected arrival type and year, the percentage of decreases were substantial between 2011-2020 among temporary workers and families (-37%), students (-52%), new arrival immigrants (-41%), and refugees (-45%). Consistent with that, the Division of Global Migration and Quarantine (DGMQ) assessed the number of refugees and immigrants with a TB classification by overseas exam from 2010-2020 and found that while there had been a downward trend from 2017-2019, there was a major decrease of 74% from 2019-2020. Based on country of birth, some of the trends were profound. While for Bhutan there was a decrease before COVID-19, by 2020 it had gone down to essentially 0.

Overall, fewer people were going through the overseas screening system with TB classifications. This is consistent with fewer people coming to the US across the board from these countries. There were many fewer refugees and immigrants entering the US in 2020 compared to 2019. Looking at the percentage of refugees and immigrants by post-arrival evaluation status for 2010-2020, from 2018-2019 and increasing in 2020 is that the percentage of people who did not have an evaluation initiated increased over the previous couple of years. Given that this is an active case-finding activity, the tendency is to find cases earlier in disease and therefore not smear-positive. If not found through this mechanism, it may be a while before someone becomes symptomatic, is diagnosed, and may be smear-positive. This may be one hypothesis of why an increased percentage of smear-positive cases were observed among people born outside of the US.

In terms of the next steps for Electronic Disease Notification system (EDN) and other immigration data, ongoing statistical consultation for time trend analysis will continue. Process delays pertaining to time between arrival and evaluation will continue to be assessed to determine whether not receiving evaluation or delayed evaluation could contribute to progression of TB and an increased percentage of people with smear positives. Analyses of other data sources include analyses of TB Genotyping Information Management System (GIMS) data to assess recent TB transmission pre- and during pandemic and Healthcare Cost and Utilization Project (HCUP), with preliminary analyses completed and 2020 data expected this fall. Ideas for consideration include MarketScan® healthcare-related data, OCHIN electronic health record (EHR) data, TB mortality through vital statistics data.

The “Think. Test. Treat TB Campaign” aims to reach those most at risk for LTBI and encourages LTBI testing to accelerate elimination. This is the first national multilingual communications campaign focused on TB among Asian Americans, the materials for which potentially could be used for other populations at risk. This addresses a major health disparity for TB. The campaign was rolled out in March 2022 in Los Angeles and Seattle as a pilot project, for which information related to the evaluation of this project should be available by Fall 2022. In closing, Dr. LoBue shared some examples of the campaign materials.

ACET Discussion

Dr. Belknap observed that smear positivity seems to be an issue of access, with people at greatest risk not accessing healthcare and TB services until late. With the integration of and need to address SDOH,this seems like an opportunity to place TB and TB programs in a position to connect people so that they are more likely to have knowledge within the community about public health TB programs as a resource.

Dr. LoBue responded that while this is a very important question, it also is complicated because there are probably many factors involved. Decreased active case-finding activities that occurred during the pandemic likely contributed to this. While he focused on the immigration element in the presentation, there are likely to be similar issues related to contact investigation. There also has been the issue of people being pulled from TB programs to support the pandemic response. This impacts the number of people left to perform the contact investigations, which are very important case-finding activities that have high yield. If cases are not found early, the likelihood is that they will progress to smear positives. In addition to access issues, it is possible that some people did not want to be in healthcare facilities due to COVID-19. In addition, some people presented for presumed COVID-19 who tested negative and no one thought of checking for TB.

Dr. Horne observed that non-US-born persons over 65 years of age seemed like a key population on which to focus going forward in terms of TB elimination in the US. His sense was that there is great variability across the country in terms of screening practices and recommendations. He wondered whether CDC is trying to better understand this and perhaps disseminate related best practices.

Dr. LoBue replied that while an analysis has not been done of this, it is a very interesting question that perhaps they could assess through some of the activities of the campaign and also through some of the Tuberculosis Epidemiologic Studies Consortium (TBESC) work, which will have baseline data from 4 healthcare systems. While there are substantial issues with newer treatment regimens, they are safer than INH. This does not mean everyone over 65 years of age will be able to tolerate it, but probably most can and will. Messaging is not meant to suggest that people in that age group should not be tested, but there is definitely work to do in this area.

Referring to Slide 12, Dr. Ahmed inquired as to whether there is further information about the demographics of that group and whether it was comprised of older adults.

Dr. LoBue said that while he did not immediately have the data, he would look it up to share later. His recollection was that this did tend to be among older adults rather than children who came over at a young age and are in their 20s or 30s.

Dr. Mermin noted that the greatest difference in active TB was seen among people middle-aged and older, and that this group is much more likely to reactivate LTBI and TB diseases. He wondered how much that could be the effect of middle-aged or older people who were a susceptible population for reactivation who died of COVID-19.

Dr. LoBue acknowledged that this certainly could be a possibility, but that it would be almost impossible to confirm. It has been observed that people at the highest risk of reactivation also probably were at the highest risk for dying of COVID-19 before they could reactivate.

Dr. Loeffler noted that delays also were observed among patients who were thought to have cancer for whom biopsy was delayed.

NIH-Funded Clinical Trial Groups Conducting TB Research

Irina Gelmanova, MD, MPH & Melanie Goth, MD
TB Clinical Research Branch
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National Institutes of Health

Dr. Gelmanova provided an overview of TB research conducted in cooperation with the AIDS Clinical Trials Group (ACTG) in 33 US clinical research sites and 25 international research sites in 11 countries (Haiti, South Africa, Malawi, Uganda, Kenya, Botswana, Zimbabwe, Brazil, Peru, Thailand, and India). Sites and investigators have extensive experience conducting scientifically rigorous TB research, with quality assured laboratory, pharmacy, and clinical infrastructure that supports a full range of TB interventional trials including prevention, drug-susceptible TB (DS-TB), drug-resistant (DR-TB), HIV/TB co-infection, and Phases 1, 2, and 3. This work is being performed by some of the world's leading TB investigators. A total of 709 participants were enrolled into TB trials in 2018.

The largest of these studies currently being conducted is A5300B, a Phase 3 trial titled Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (PHOENIx). The plan for this study is to enroll 3452 high-risk household contacts (HHCs) to be enrolled from households with an index case confirmed as having MDR-TB (N = ~2158 index cases). HHCs will include newborns to children <5 years old regardless of TST/IGRA or HIV status; adults and children ≥5 years of age who are HIV-infected or non-HIV immunosuppressed regardless of TST/IGRA status; and TST positive (≥5mm) and/or IGRA positive persons whose HIV status is negative, indeterminate, or unknown and who are not non-HIV immunosuppressed. The PHOENIx study is an open-label, multicenter trial with a cluster-randomized superiority design in which eligible contacts in the same household are a cluster. Households are randomized 1:1 either to Arm A comprised of high-risk HHCs who will receive Delamanid or Arm B comprised of high-risk HHCs who will receive Isoniazid+B6. Treatment will be administered for 26 weeks with follow-up at 96 weeks from Time 0. At this time, screening and enrollment included 690 index cases enrolled, 2,245 HHCs screened, and 1,199 HHCs enrolled. Among those enrolled, 8% are less than 5 years of age, 7% are HIV-positive, 0% are non-HIV immunosuppressed, and 94% are IGRA/TST-positive.

Another study that is very important is A5384: A Phase II, Randomized, Open-Label Trial of a Six-Month Regimen of High-Dose Rifampicin, High-Dose Isoniazid, Linezolid and Pyrazinamide versus a Standard Nine-Month Regimen for the Treatment of Adults and Adolescents with Tuberculous Meningitis (IMAGINE TBM). The primary objective of IMAGINE TBM is to determine if a new 6-month regimen improves functional outcomes measured by the Modified Rankin Scale (MRS) at 48 weeks compared with the 9-month World Health Organization (WHO) standard of care (SOC) for the treatment of tuberculous meningitis (TBM). Enrollment for this study is expected to start in Fall 2022 and will include approximately 330 participants with definite, probable, or possible TBM ≥15 years of age.

Study A5372, Drug-Drug Interactions Between Rifapentine (RPT) and Dolutegravir (DTG) in HIV/LTBI Co-Infected Individuals, is an open-label, 2-arm, multicenter pharmacokinetic (PK) study. Study treatment is INH 300 mg and RPT 600 mg for 4 weeks. During the treatment, DTG 50 mg is administered BID in Arm 1 and 50 mg QD in Arm 2. A maximum of 72 participants is anticipated with 36 in Arm 1 and 36 in Arm 2, to yield at least 32 evaluable participants in each arm. The first arm has been completed. DTG trough concentrations with 50 mg twice daily dosing during 1HP were higher, not lower, than those with standard dose DTG once daily alone.

Study A5406, Pharmacokinetics (PK) and Safety of Double-dose Dolutegravir (DTG) When Used with Rifapentine for HIV-Associated Tuberculosis, has a primary objective to investigate the effect of daily rifapentine 1200 mg on dolutegravir exposure in participants with HIV-associated TB. The study population is comprised of 30 participants to yield at least 20 PK-evaluable participants. The design is a 48-week, open-label, single-arm, multicenter PK study Isoniazid (H) 300 mg, Rifapentine (P) 1200 mg, Pyrazinamide (Z) at weight-based doses, Moxifloxacin (M) 400 mg QD for 2 months, followed by 2 months of HPM (2HPZM/2HPM). During the TB treatment, DTG 50 mg will be administered BID.

Study A5356, Prospective, Randomized, Multicenter Trial to Evaluate the Efficacy and Safety/Tolerability of Two Linezolid (LZD) Dosing Strategies in Combination with a Short Course Regimen for the Treatment of Drug-Resistant Pulmonary Tuberculosis (Phase II), has a study population of 132 (66 per arm) participants, HIV-infected and uninfected, aged ≥18 years, newly diagnosed drug-resistant (DR) pulmonary TB (MDR/RR-TB, pre-XDR-TB and XDR-TB. This study is planned to start this year. Arm A will receive 600 mg LZD once daily, Arm B will receive 1200 mg LZD once daily for 4 weeks and then 3 times per week during weeks 5-26. Both arms will receive BDQ, DLM, and CFZ. Follow-up will occur during weeks 27-72.

Dr. Goth presented on 3 additional ATCG trials, 2 of which are in development and the third that is underway. Study A5409, Phase 2 Randomized, Adaptive, Dose-Ranging, Open-Label 8-Week Trial of Novel Regimens for the Treatment of Pulmonary Tuberculosis (RAD-TB), is in development. This trial has an adaptive design that allows for regimens to be added during the course of the study. Participants will include adults ≥18 years of age with and without HIV, with sputum smear or Xpert-positive drug-susceptible pulmonary TB. The trial has 8 arms, 1 WHO SOC and 7 experimental arms. The planned sample size is 405 participants, with 45 participants for each of 7 experimental treatment arms + 90 participants in the SOC arm. The purpose of this study is to compare early efficacy (by liquid culture time to positivity) and safety of different new drug combinations and dosages. This trial makes use of some very sophisticated modeling work. The hope is that some of the learnings from the COVID trials can be applied to this TB trial. The overall aim of A5409/RAD-TB is to design an early phase clinical trial platform (Phase 2A+) that allows one to test and compare novel TB treatment regimens that includes:

- Dose-finding: optimization of new chemical entities (NCE) dosing while in combination
- Testing of NCEs within drug classes
- Novel platform design: flexibility to include novel combinations of NCEs in an unbiased way (most promising regimens based on preclinical data)
- Better link to the next clinical phase (Phase 2C/Phase 3)

Study A5362, Phase IIc Trial of Clofazimine and Rifapentin Containing Treatment Shortening Regimens in Drug-Susceptible Tuberculosis: The CLO-FAST Study, is currently enrolling and will study the impact of adding CFZ and substituting RPT for RIF compared with SOC combination TB therapy for DS-TB. Participants are stratified based on HIV status and the presence of advanced disease as determined by chest X-ray (CRX). The primary endpoints are to compare time to 12-week liquid culture conversion and to compare adverse events (safety) over 65 weeks. The secondary endpoint is to compare proportions of participants who experience favorable composite efficacy outcome at 65 weeks. The study status is that 9/185 participants are enrolled. The hope for this treatment shortening trial is that a 3-month treatment duration will be adequate with no further treatment. Experimental Arm 1 is a 3-month regimen with a CFZ loading dose; PHZE + CFZ 300 mg once daily for 2 weeks; then PHZE + CFZ 100 mg once daily for 6 weeks; then PHZ + CFZ 100 mg once daily for 5 weeks. Active Comparator Arm 2 is the SOC for DS TB. Participants will receive RHZE for 8 weeks, then RH for 18 weeks. Experimental Arm C is a PK only subgroup. Participants will receive PHZE + CFZ 100 mg once daily for 4 weeks; then on study, off study medications and treated according to SOC.

Study A5397/HVTN 603, a Phase 2A/2B Study Evaluating Safety and Immunogenicity of Therapeutic ID93 + GLA-SE Vaccination in Participants with Rifampicin-susceptible Pulmonary TB, is in development. Participants include adults 18-60 years of age with or without HIV with rifampicin-susceptible pulmonary TB at the start of TB treatment who are receiving locally provided SOC TB treatment. This is a blinded, placebo-controlled study with 2 components. The Phase 2a component will evaluate the safety and immunogenicity of different vaccination schedules (Groups 1-4) and the Phase 2B component will evaluate the clinical efficacy of one of the vaccination schedules (Group 5). The key objectives of the study are to: 1) evaluate the safety of a vaccine regimen administered 56 days apart with TB treatment when administered at varying months after the start of TB treatment; 2) determine if therapeutic vaccination with ID93 + GLA-SE will increase the magnitude of vaccine-specific cellular and humoral responses compared to placebo; 3) evaluate the proportion with bacteriologically-confirmed unfavorable outcomes (treatment failure, TB recurrence, or death due to TB) at 18 months after start of TB treatment; and 4) compare therapeutic vaccination with ID93 + GLA-SE to placebo with respect to lung function, as measured by lung function tests and the St. George's Respiratory Questionnaire (SGRQ).

ACET Discussion

For this discussion, ACET was asked to consider the following question:

1. *Does ACET have any recommendations on potential collaborations between CDC TBTC and NIH TB clinical trials groups?*

Dr. Ahmed inquired as to why participants are adults ≥18 years of age instead of going down to 14 or 15 years of age in Study A5409.

Dr. Goth indicated that a lot of the drugs being used in the studies are new and there are no PK data in pediatrics.

Dr. Ahmed said she would expect the PK to be the same in a 15-year-old as in an 18-year-old. The PK cutoff in the pediatric world is 15 years of age anyway, so she wondered whether they could be included instead of trying to extrapolate, with sequential drop down to younger ages.

Dr. Gelmanova added that they have had these discussions. For some of the early studies, they have data for only 4 weeks of treatment. Therefore, they did not feel this to be safe enough to move below adults ≥18 years of age. They have had a lot of discussions about children and will perhaps include them in later stages. There are regulatory considerations as well.

Dr. Horne observed that most of the ACTG studies seemed to be not specifically focused on TB prevention in people with HIV or on TB/HIV treatment. That may be a slight departure from 5 to 10 years ago. He asked at what level they coordinate with other groups like Tuberculosis Trials Consortium (TBTC) to leverage each other and plan out studies going forward. The target population is people with HIV and without HIV, which seems to have some overlap with TBTC's main foci as well as TB treatment. He wondered since ACTG and TBTC are both federally funded groups if there are efforts at a higher level to coordinate studies or combine efforts as was done with Study 31 to have a more comprehensive approach.

Dr. Gelmanova replied that A5300B/PHOENIx is looking at latent TB infection treatment in people living with HIV, who are contacts of MDR-TB, which is a huge problem in several parts of the world. Every research protocol includes people living with HIV. DAIDS is always open to collaboration with TBTC and others. They are also trying to expand collaboration with European networks. Collaboration helps to use limited TB funds more efficiently.

Dr. Loeffler noted that it would be great for TB trials to be good role models in including children and implored the investigators not to be timid in this regard.

Dr. Benjamin asked whether NIH is considering looking at bacteriophage as it appears to be successful in treating mycobacterium TB (MTB).

Dr Benjamin asked whether NIH is considering looking at bacteriophage treatment as it appears to be successful in treating *MDR Mycobacterium abscessus*.

Dr. Gelmanova indicated that they do not look at bacteriophage, but other TB research branches at NIH, for example, NIH's Division of Microbiology and Infectious Diseases (DMID), may do this work.

Dr. Belknap said he had some recent conversations with Bill Burman, former Director for Denver Public Health, who has been raising the question about whether TB research has paid enough attention to safety and tolerability as an issue. Studies often look at whether treatment is at least as safe and tolerable as the control regimen, which most would agree is not acceptably safe and tolerated. Perhaps they should be looking at a higher bar in terms of shortening treatment and for safer and more well-tolerated treatments, and he wondered whether that has been a topic of discussion around designing trials at NIH.

Dr. Gelmanova indicated that the main goal of the A5409 study Dr. Goth presented is to identify a safer regimen. In addition, the drug pipeline looks great now.

Dr. Mermin found the studies presented to be impressive and expressed appreciation for the thoughtfulness that went into selections in each of the studies from an outcomes and tools perspective. He asked Dr. Gelmanova to talk about the selection process for the short-course regiment study in terms of whether consideration has been given to using the comparison regimen from Study 31 and even shorter than 4 months (e.g., use Study 31 as a control).

Dr. Gelmanova said that Study 31 was a Phase 3 trial. A5409 is a 2A/2B trial looking at 9 different combinations which are only given for 2 months to compare culture conversion rates, followed by a standard INH/RIF combination for 16 weeks. The reason for not using Study 31 as a control is because it is a complete 4-month regimen. The best combinations from A5409 will move to Phase 2c and 3 where comparison with Study 31 regimen is appropriate.

Dr. Chen noted her enthusiasm that the trials are investing in adaptive/stratified design strategies.

Dr. Loeffler noted that in addition to safety and tolerability, it will be nice to have drugs that are accessible/affordable to US patients and programs. Bedaquiline (BDQ) is great and takes weeks to procure.

Pediatric Tuberculosis in the United States, 1993-2021

Erin Lee Miller, PhD, Epidemiologist
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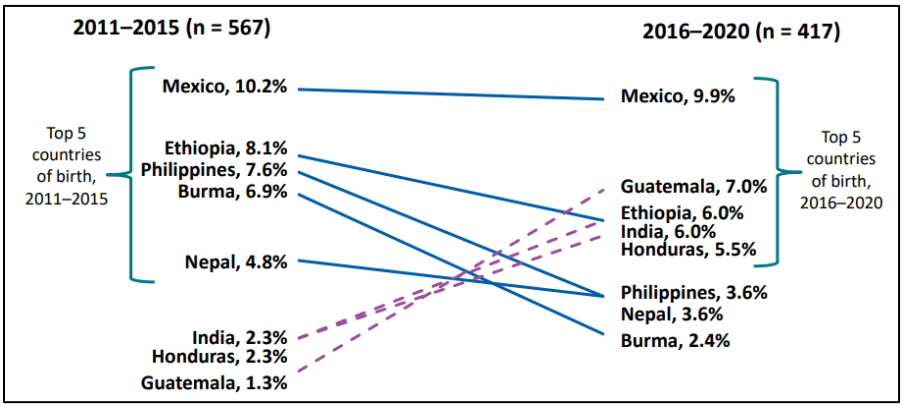
Centers for Disease Control and Prevention

Dr. Miller provided an overview of pediatric TB in the US from 1993-2021, with 2020 data as of June 14, 2021 unless otherwise noted and 2021 estimates are based on provisional NTSS data as of February 9, 2022. In 2020, the US reported the lowest number of TB cases and the lowest TB incidence rates on record at a rate of 2.2 cases/100,000 persons. This represented a substantial decline in TB incidence of 19.7%. However, the incidence rate for 2021 increased to 2.5 cases/100,000 persons. For the purpose of understanding the context of this presentation, pediatric TB is defined as a case of TB disease in a person less than 15 years of age. Pediatric TB often indicates recent infection. Infants and young children are at greater risk of developing life-threatening forms of TB disease (e.g., disseminated TB, TB meningitis). However, TB in children 10-14 years of age presents more like TB in adults compared to other pediatric age groups.

Both pediatric and non-pediatric cases have declined since 1993. Pediatric cases account for 4% to 4.7% of TB cases reported each year since 2016. Non-pediatric cases or cases in persons 15 years of age or older experienced a nearly 25% decline between 2019-2020, with a 9.2% increase in 2021. In contrast, pediatric TB cases experienced only a 15.5% decline in 2020 and declined by a further 1.9% in 2021. The distribution of TB by age group in 2020 remained similar to past years, with the plurality of cases occurring among persons 25 years of age and older. Only 317 cases occurred among children under 15 years of age in 2020, declining to 311 cases in 2021. TB incidence rates differ by age group and generally decrease with decreasing age. The youngest age group, 0-4 years of age, had a rate approximately twice that of the second lowest cases among children 5-14 years of age. The data from 2020 and 2021 can be compared to the context of an average of the TB cases from 2015-2019. Most notably, this stratification of the data showed a decline in all age groups in 2020. This was followed by a partial rebound in 2021 for adults 25 years of age and older. However, that rebound was not observed in the pediatric and 15–24-year age groups, which was slightly lower than 2021.

Focusing on the pediatric age groups, case counts in the two pediatric age groups of 0-4 and 5-14 years of age showed a 24.7% and 15% decline in 2020, respectively. When compared to the previous 5 years these were 3.6% and 7% lower in 2021, respectively. Further investigation of the pediatric data highlighted disparities in the distribution of cases among race and ethnic groups. Among the cases, 42% of cases identified as Hispanic/Latino compared to only 29.2% of pediatric cases. It also is notable that Asian persons made up a larger percentage of non-pediatric TB cases, although 17.7% of children under 15 years of age were identified as Asian. Hispanic and Latino persons represent 42% of children with TB in terms of burden. However, the incidence rate is 3 times higher for American Indian/Alaskan Native (AI/AN) children and more than 19 times higher for Native Hawaiian and Pacific Islander (NH/PI) children when the population size of each within the US is taken into account. It is important to note that the pediatric case count for persons identified as AI/AN, white, or multiple race were less than 20 cases/per group.

On average, 2/3 of overall US TB cases were among non-US-born persons. However, less than a quarter of pediatric cases were among non-US-born children. The number of both US-born and non-US-born children with TB have decreased at similar rates over time. The percentage of non-US-born cases has remained approximately the same. The proportion of non-US-born children with TB increased with age unsurprisingly. The older a child was when they were diagnosed with TB, the more likely it was that the child was non-US-born. The majority of children with TB had at least 1 non-US-born guardian. Although there have been overall declines in the number of children with TB, the proportion of children who have one-US-born guardian has remained consistent at between 60% and 72%. The top 5 countries of birth representing the highest percentages of non-US-born pediatric TB cases include Mexico (10.2%) and Nepal (4.8) from 2011-2022 and Ethiopia (8.1%), Philippines (7.6%), and Burma (6.9%) from 2011-2015. The top 5 countries from 2015-2020 were Mexico (9.9%), Guatemala (7.0%), Ethiopia (6.0%), India (6.0%), and Honduras (5.5%). In the following diagram, the blue lines showed the countries that decreased and the percentage of the total between the timeframes, while the purple hashed lines show countries that increased:



There was considerable variability in which countries of birth were most represented by pediatric cases over time. For instance, Mexico continues to be the country of birth with the highest percentage of pediatric cases among non-US-born persons in the US. In the last 5 years, India, Honduras, and Guatemala increased to be in the top 5 countries of birth for pediatric cases, while fewer cases have been reported for the Philippines, Nepal, and Myanmar. This likely reflects changing immigration trends.

Looking at trends and data related to verification criteria related to verification of TB in children under 15 years of age, the distribution of verification criteria is very different for children under 15 years of age. For persons of all ages diagnosed with TB since the year 2000, each year more than 85% were confirmed through a laboratory result. In contrast, laboratory-confirmed cases account for 40% of pediatric cases at most from 2010-2020. In children, a much larger percentage of cases has been verified by provider diagnosis. However, that percentage of cases has declined since 2009. The percentage of pediatric cases confirmed by provider diagnosis declines as age increases. Verification by clinical definition is the most prevalent in ages 1-4 and 5-9 years. If a higher percentage of laboratory-confirmed cases is expected in children 10-14 years of age, it is interesting that over 50% of infants have a laboratory-confirmed case of TB. By laboratory specimen type by each pediatric age group, for any pediatric age groups, less than 2% of laboratory verification was by sputum smear only. Of the 53% of infants with a laboratory verification, 89.4% had a laboratory result from a non-sputum culture of tissue or other body fluids. In contrast, laboratory results for children 10-14 years of age were largely split between sputum culture specimens at 45.7% and non-sputum culture at 49.2%. For children under 1 year of age, 118 had a laboratory result from a non-sputum culture of tissue or other body fluid, with 57.6% of the culture specimens coming from the gastrointestinal system. For nearly all gastrointestinal laboratory results, the sample was identified as gastric aspirate. As age increases, the percentage of samples from the gastric system decreases.

The remainder of this presentation highlighted variables of interest related to pediatric TB such as the reason evaluated, site of disease, and the occurrence of drug resistance. Most children under 15 years of age are identified as having TB through either contact investigation or by investigation of symptoms or illness consistent with TB disease. Among children less than 10 years of age, 40% to 50% were initially evaluated through a contact investigation between 2016-2020. In contrast, less than 5% of overall TB cases are initially evaluated because of contact investigations. Because the distribution of disease site was so similar between infants and children ages 1-4 years and also between children 5-9 and 10-14, these ages were combined in to 5-14 years of age for easier comparison. In all age groups, more than half of all cases have pulmonary disease only. The percentage of extrapulmonary involvement is greater in children 5-14 years of age at 30.8% compared with 17.4% in children less than 5 years of age. In terms of extrapulmonary sites of disease among children with TB from 2015-2020, any person under 15 years of age with any mention of meningeal TB was included in the meningeal category regardless of other reported sites of disease. The lymphatic, bone, and pleural categories are grouped differently. For instance, a child with lymphatic and peritoneal site with TB would be included in the lymphatic category. A child with both lymphatic and bone and joint sites would be included in the 2 or more sites category. Among pediatric cases, lymphatic TB is the most common site of extrapulmonary TB with the exception of the infancy age group where meningeal TB is the most common at 48.1%. Meningeal TB declined with age while cases of pleural TB increased with age. Only 34.8% of pediatric cases had drug-susceptibility testing results for both INH and RPT. Of those, 7.9% of pediatric cases who had INH susceptibility test results were INH-resistant. Non-US-born children had a slightly higher occurrence of 9%. In comparison, 7.7% of US-born children were INH-resistant. Fewer than 5 pediatric cases were multi-drug resistant or susceptible to INH and RPT.

In summary, pediatric cases declined by 15.5% in 2020 and a further 1.9% in 2021. Children 0-4 years of age had a TB incidence rate double that of children 5-14 years of age. Hispanic and Latino children comprised 44.8% of pediatric cases compared to 29.6% of non-pediatric cases. Less than 25% of pediatric cases occurred among non-US-born persons; however, the proportion of cases that had at least 1 non-US-born guardian remained consistent between 60%

and 70% of pediatric cases. The high proportion of infants with TB verified by laboratory result is due to the use of non-sputum cultures, primarily gastric aspirate. Most pediatric cases were identified through either contact investigations or investigations of symptoms and illness consistent with TB. The proportion of extrapulmonary involvement was greater in children ages 5-14 compared to ages 0-4. Lymphatic TB is the most common extrapulmonary site among all pediatric cases. Isoniazid drug resistance is low among children at 2.8% with less than 0.2% of pediatric cases being recorded as multidrug resistant.

ACET Discussion

For this discussion, ACET was asked to consider the following questions:

1. *Does ACET have any recommendations related to domestic pediatric TB surveillance, prevention, and response?*
2. *Are there any suggestions for additional analyses that ACET members think would be useful in the treatment and control of pediatric TB?*

Dr. Ahmed asked whether the laboratory diagnoses percentages were of the children who underwent testing without the children who never underwent any testing included, or just children who were tested. It seems that efforts to increase laboratory testing would be beneficial rather than resorting to just clinical diagnosis. The yield on infants has always been known, partly because they tend to have a higher relative burden of disease because they have more symptomatic disease. They cough and wheeze and they are a captive audience. It is a lot easier to get a gastric aspirate out of a baby who sleeps several times a day than a squirming 3-year-old. In terms of a campaign to treat LTBI, she wondered who the focus should be on and when (e.g., contacts and/or non-US-born, before/after non-US-born arrive in the US).

Dr. Miller indicated that the denominator was comprised of all pediatric cases from 2016-2020. It is possible that some children never had any testing. From 2016-2020, there were 249 children total <1 year of age. Among these children 132 had some type of laboratory diagnosis. In terms of LTBI, Dr. Miller said that while it was not her place to make a recommendation on focus, the data show that most children are found because they are symptomatic in some way either incidentally or through contact investigation. Since the data are showing that they are being identified largely through contact investigation and illness, so those would be places to focus, but they also could be found through targeted testing.

Dr. Loeffler added that the good news is that since the 1990s, people are gradually and more consistently looking for more culture evidence in pediatrics. The number of patients who are culturally proven has gradually ticked up, given that people are looking more often. The data show that for almost half of children, obtaining culture evidence is never attempted. Part of that is because the yield is suboptimal across all age groups in pediatrics. Many people rely on the source case data to make their microbiologic susceptibility data, so that is part of the issue. She tries to encourage people to collect at least 1 specimen for microbiology. She has been in situations where there is discordance with the source cases. When she first heard about the phenomenon during COVID-19 of having decreased cases, she worried that people were sitting at home or in their pods of community still being contagious with TB. Not seeing an uptick in pediatric cases in the last year has been an amazing relief and very reassuring. Regarding characterization of cases as pulmonary versus extrapulmonary, she thinks that many clinicians are not aware that it is important when communicating with public health to convey whether a patient has intrathoracic lymph node enlargement in addition to their pulmonary disease. She thinks that a lot of cases of lymph node disease are undercounted because of the way clinicians

report and the way the Report of Verified Case of Tuberculosis (RVCT) is filled out. When presenting these data, she encouraged not thinking of the gastric aspirate as a gastrointestinal source. It is really just a bystander of sputum sitting in the stomach that can be collected. At least on the West Coast, a lot of pediatric cases are in Pacific Islanders. Guam and American Samoa are territories, so those children would be considered US-born. The Marshall Islands and Micronesia have a special relationship with the US and very high TB rates. They are not territories or protectorates anymore, so she asked for confirmation about whether adults or children from those areas are considered non-US-born.

Dr. Miller indicated that CDC's definition of US-born and non-US-born is based on how the Census Bureau classifies these, which has to do with the population data and the denominator. CDC's definition of non-US-born individual is a person born outside of the US, its territories, or a person not born to a US citizen.

Dr. LoBue added that it is different in terms of their ability to enter the US, but those are sovereign countries that by US Census definition are not part of the US.

Dr. Burton asked Dr. Miller to comment further on the status of trends in disparities by race and ethnicity in terms of pediatric TB overall and for US-born cases.

Dr. Miller explained that the data she showed was from a single year and she did not run trends. One problem with pediatric TB is that the numbers are so small. When creating a rate with groups of under 20 individuals, that creates an unstable rate. When looking at rates, it is important to be careful with trends. For this presentation, she could not answer that specifically since she did not look at trends. They will be happy to share trends in disparities by race and ethnicity in future presentations.

Dr. Liu asked why drug susceptibility testing was so low for pediatric persons and what the denominator was.

Dr. Miller responded that most likely it had to do with being able to get a sample that could be tested. Her sense looking at the data was that given the very small percentage of infants (53%) having a laboratory-confirmed result, she was guessing that the ability to get samples for susceptibility testing could have been a large part of that. The denominator for the 34% of drug-susceptibility testing was all pediatric cases in that time period.

Dr. Belknap asked whether any assessment had been done related to the use of molecular tests in pediatrics and if there has been any change.

Dr. Miller indicated that they have not looked at the molecular data for pediatric TB, but if that is of interest, they can look into it and present additional data on that.

Dr. Ahmed thought that would be helpful but noted that 90% or more would be smear negative, which limits the Xpert® evaluation. There is a place in North Carolina that will run a sample for her even if it is smear-negative, but a lot of places will not. Getting someone to do gastric aspirates has been a challenge.

Dr. Loeffler reported that work on the updated Curry guide is underway, which will include an enhanced section about molecular use in children. None of the molecular tests are more sensitive than culture. Stool is about 61%, which is helpful if it is positive and if RPT resistance is detected. Gastric aspirate is better at about 80%. The value is really in getting rapid results,

so it is worth doing. It is heartbreaking that even the newer Xpert® MTB/RIF assay, which is not available in the US, is not more sensitive than culture. However, the results are rapidly available. She asked whether children who have their disease confirmed by Xpert® would be included in the "no susceptibility" category, noting that her laboratory will now do Xpert® on gastric aspirates and Mayo will do polymerase chain reaction (PCR) on stool. This needs to be studied and dispersible tabs are needed. She thought it would be helpful to know among confirmed cases how many were diagnosed by Xpert®. She always tries to do at least one Xpert® just for more rapid diagnosis of something else.

Dr. Miller indicated that molecular drug susceptibility testing is not on CDC's RVCT until the new implementation for 2020. For pediatric TB molecular diagnostic tests and the use of Xpert®, CDC is working to implement the 2020 RVCT, which will enable them to include molecular drug susceptibility testing in the future. At this time, Xpert® would not be included in drug susceptibility results because those have only been growth-based.

Dr. Chen observed that these discussions were starting to bring up topics that ACET might consider for prioritization. In terms of pediatrics, there are instructions globally on best practices for testing stool and processing it in the field for Xpert®. How to bring these practices on board in the US so that people can implement what is more readily available overseas seems like something ACET could consider. There are promising early data on investment in diagnostics like face mask sample collecting showing that TB could be identified even earlier than with smear, which seems like it would be beneficial across the population. There are early data from ATS showing specifically that oral swabs in children and older adults are easier to collect and have some efficiency in getting a diagnosis. She thinks about the great innovations that TBTC and other groups have pushed forward, yet the programs that need them do not have access.

Dr. Belknap agreed that the US should have access to the best testing. Access, cost, and having laboratories that will not run tests for various reason are certainly limitations in the US. Overcoming barriers that are not going to reverse spontaneously and are not being incentivized in other ways need to be addressed in the US. GeneXpert® Ultra is an example of that in that there is not a great incentive for the manufacturer to go through the hurdles required. He suggested that they discuss this further during the business section of the meeting.

Bringing New TB Drugs to Market: A Regulatory Perspective

Ramya Gopinath, MD
Medical Officer, Division of Anti-Infectives
Center for Drug Evaluation and Research
Food and Drug Administration

Dr. Gopinath provided a brief overview of currently approved drugs for treatment of pulmonary TB, detailed the regulatory pathways and designations FDA uses in general to expedite drug development for serious and life-threatening conditions, and focused on clinical trial design considerations for pulmonary tuberculosis (TB) in particular. This table offers an overview of FDA-approved drugs for TB treatment:

FDA-Approved Drugs	Approval Year
Streptomycin	1946
PAS	1950
Isoniazid	1953
Capreomycin	1971
Pyrazinamide	1959
Cycloserine	1964
Ethionamide	1965
Ethambutol	1967
Rifampin	1971
Rifapentine	1998
Bedaquiline	2012
Pretomanid (with bedaquiline and linezolid)	2019

Following approvals of drugs for TB treatment in the 1950s, 1960s, and 1970s, there was a gap of 27 years until the approval of rifapentine in 1998. After that, there was a 14-year gap until bedaquiline was approved in 2012 and then another 7 years elapsed until pretomanid was approved as part of the BPaL (Bedaquiline, Pretomanid, and Linezolid) regimen in 2019. In addition, other FDA-approved drugs are used off-label for TB treatment including rifabutin, levofloxacin, moxifloxacin, and amikacin. Thus, development of drugs for TB treatment is clearly an area of great unmet need.

In the general timeline of drug development,[7] a pre-Investigational New Drug (IND) application is often submitted at the preclinical or phase 1 stages with a focus on drug safety. Phase 2 is generally focused on dose-finding and efficacy; end of phase 2 meetings are designed to discuss results from earlier studies and to agree on design for phase 3 trials. The pre-New Drug Application (NDA) or pre-Biologics Licensing Application (BLA) meeting may occur midway through phase 3 or at any other time prior to NDA or BLA filing. The traditional NDA/BLA review timeline at FDA is 10 months. If the safety database is small or there are other safety considerations, additional studies may be conducted in Phase IV post-approval.

The traditional drug approval pathway is based on clinical endpoints that measure how a patient feels, functions, or survives. The accelerated approval pathway is an expedited pathway based on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM; 21 CFR 314.500, Subpart H). In addition, other programs and designations have been developed in order to expedite development and review of new drugs[8] that address unmet medical need in the treatment of a serious or life-threatening condition. Subpart E regulations (21 CFR 312, Subpart E),[9] on which the FDA expedited program pathways and designations are based, specifically recognizes that patients and their healthcare providers (HCP) are generally willing to

[7] "Overview of the Sequence of Drug Development Activities: PDUFA Activities in Drug Development" https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/new-drug-development-and-review-process
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics
[9] Treatment of a serious condition is a qualifying criterion for all expedited programs

accept greater risk and side effects from treatments for life-threatening or debilitating diseases than they would for other diseases.

Aside from the accelerated approval pathway, other expedited programs include fast track designation, breakthrough therapy designation, and priority review designation. All of these designations can be applied to either the traditional or accelerated approval pathways. The Qualified Infectious Disease Product (QIDP) designation and Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) are additional programs designed to expedite development of drugs for serious or life-threatening conditions.

An investigational drug may be eligible for fast track designation when there are non-clinical or clinical data, a mechanistic rationale, or pharmacologic data demonstrating the potential for that drug to address unmet need for treatment of a serious or life-threatening condition or if the drug has a QIDP designation. The request for fast-track designation must be made at the time of IND submission or after, but no later than the pre-NDA meeting. Once granted, this designation includes a rolling review of the NDA or BLA application and other actions to expedite development and review.

Breakthrough therapy designation may be granted when there is preliminary clinical evidence, often from phase 1 or 2 studies, that indicates that the drug under development may show substantial improvement over current therapies on a clinically significant endpoint. Clinically significant endpoint for a breakthrough therapy designation refers to an endpoint that measures an effect on IMM or on symptoms that represent serious consequences of disease, including effects on an established surrogate endpoint that could support traditional approval, or an effect on an endpoint that is considered reasonably likely to predict clinical benefit (accelerated approval standard), or on a significantly improved safety profile. This request should be made along with the IND submission or later, but ideally, no later than the end of Phase II meeting. Breakthrough therapy designation includes intensive guidance on efficient drug development, rolling review and other actions to expedite review. Of note, both fast track and breakthrough therapy designations may be rescinded if the drug and development program no longer meet qualifying criteria.

The accelerated approval pathway is for a drug that provides meaningful advantages over available therapies and demonstrates an effect on a surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than IMM, but that predicts an effect on IMM. The request for this approval pathway can be made at various timepoints during development, and the product must meet statutory standards for safety and effectiveness. In this approval pathway, confirmatory trials are needed to verify and describe the anticipated effect on IMM or other clinical benefit; these should be underway or at least in advanced stages of planning at the time of drug approval. If the clinical benefit is not confirmed, FDA can mandate that a drug approved under the accelerated approval pathway be withdrawn from the market.

Priority review designation can be granted to a drug that would provide a significant improvement in safety and effectiveness, for a supplement for a labeling change based on pediatric studies, for a drug with QIDP designation, or for a drug application with a priority review voucher. This designation shortens the review time clock from 10 months to 6 months. The timelines for FDA response to sponsor requests for these designations are within 60 days of receipt of request for fast track and breakthrough therapy designations and within 60 days of receipt of the original NDA, BLA or efficacy supplement for priority review designations.

QIDP designation[10] is for an antibacterial or antifungal drug for human use intended to diagnose, prevent, or treat serious or life-threatening infections including those caused by antimicrobial-resistant pathogens, novel or emerging infectious pathogens, or qualifying pathogens (21 CFR 317.2). QIDP designation applies to a specific drug product (not drug substance, biologic, or device) from a specific sponsor for a specific use and can be requested at the pre-IND or IND stage. QIDP designation provides the following incentives: a) additional 5 years of marketing exclusivity for certain drugs, b) priority review for the first application for a QIDP, and c) eligibility for fast-track designation.

LPAD[11] is for drugs that are intended to treat a serious or life-threatening infection in a limited population of patients with unmet need (FD&C Act, section 506(h)(8)). A streamlined clinical development program for a limited population may involve smaller, shorter, or fewer clinical trials, but statutory standards for safety and effectiveness must still be met. FDA may conclude that there is a positive risk-benefit balance in a limited population even though there are insufficient data to conclude this positive risk-benefit balance in a larger population. Seeking approval under LPAD does not preclude seeking other designations (fast track, breakthrough therapy, priority review, and QIDP designations), or the accelerated approval pathway. Requests for approval under LPAD must be submitted along with the original NDA, BLA, or efficacy supplement submission. This pathway should not be used to manage a known or potential serious risk associated with a drug that may be better addressed in another way and should not be used to salvage a trial that fails to demonstrate its objective. Drug approval under LPAD also carries implications for patient labeling and promotional materials so that healthcare providers clearly understand that the drug is approved for a limited indication in a limited population. Thus far, inhaled amikacin (2018) and pretomanid (2019) are the only two drugs that have been approved under LPAD.

In TB drug development programs,[12], [14] the activity of antimycobacterial drugs can be evaluated in trials of early bactericidal activity (EBA) and/or in phase 2 trials with microbiological evaluations at early time points. In general, the contribution of each drug to the treatment effect should be evaluated. EBA trials measure quantitative counts of viable tubercle bacilli from daily collections of sputum and can provide information on the bactericidal activity of single drugs or a new regimen in clearing *M. tuberculosis* from the sputum of patients with newly diagnosed pulmonary TB. These trials are not intended to provide definitive treatment for patients but rather are to evaluate antimycobacterial activity for a brief duration (7 to 14 days). Patients who could be enrolled in such trials would be immunocompetent, treatment-naïve adults at low risk of drug resistance or extrapulmonary disease, who can begin standard-of-care treatment for pulmonary TB at the completion of the EBA trial.

Phase 2 trials designed to assess antimycobacterial activity of the investigational drug(s) in a combination regimen with other antimycobacterial drugs can be useful for evaluation of dose regimens before initiating phase 3 trials. Long-term follow-up should be conducted with evaluation of clinical endpoints in addition to earlier microbiological endpoints.

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[10] GAIN Provision (Title VIII of FDASIA under section 505E of the FD&C Act): https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/limited-population-pathway-antibacterial-and-antifungal-drugs-guidance-industry; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-therapies-patients-unmet-medical-need-treatment-serious-bacterial-diseases

[12] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

Two adequate and well-controlled trials to support the effectiveness and safety of the investigational drug would be optimal. However, at least one adequate and well-controlled trial demonstrating clinically meaningful and statistically robust treatment effect in subjects with pulmonary TB may suffice if there is also confirmatory evidence from non-clinical in vitro and in vivo studies, EBA studies and early phase trials, along with evidence of drug safety with an adequate safety database.

Clinical trials for treatment of pulmonary tuberculosis may utilize a noninferiority (NI) or a superiority design.[13] A NI trial design evaluates whether the investigational regimen performs within a prespecified margin of performance of the standard regimen. A data-driven justification of the NI margin must be provided, based in part, on historical evidence of sensitivity to drug effects (HESDE). Examples of trials with a NI design might be those in which an investigational drug replaces one of the drugs in a standard multi-drug combination and the investigational regimen performs within a prespecified NI margin based on the quantitative contribution of the new drug to the standard regimen, or a treatment shortening trial in which an investigational drug or regimen administered for a time period less than a standard regimen is compared to the standard regimen administered for standard duration. In this case, noninferiority would be demonstrated by showing that the treatment-shortening regimen containing the investigational drug(s) performed within a prespecified NI margin of the performance of the standard duration regimen; this margin is based on the known decrement in the performance of the standard duration regimen when administered for a shorter time period.

Superiority trials are designed to show superiority of an investigational regimen compared to a standard regimen. This study design may be employed when an investigational drug plus optimized background regimen (OBR) is compared to placebo plus OBR. Alternatively, this design may also apply when a regimen of 1 or more investigational drugs is compared to a standard regimen, with efficacy demonstrated by showing superiority of the investigational regimen over the standard.

Study populations for TB trials should include adult and adolescent subjects whenever possible, as well as those with co-existing HIV infection. Pediatric populations should be included as early as possible in the development program. Depending upon the target indication for the drug or regimen under study, subjects with drug-susceptible (DS) TB or drug-resistant (DR) TB should be enrolled. As noted earlier, the clinical design considerations discussed during this presentation are for pulmonary TB. Sponsors developing drugs for extra-pulmonary TB should discuss their development program as soon as possible with FDA so that there is agreement on trial endpoints and pharmacokinetic considerations, among others. Enrichment strategies for trials focused on DR TB could include enrollment of contacts of subjects with DR TB if the contact has active disease, of subjects who come from areas with high prevalence of drug resistance who have relapsed after previous treatment, or those whose disease has progressed on a standard regimen.

Trial endpoints should be well-defined and reliable. A traditional clinical endpoint directly measures the therapeutic effect of a drug on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives. A surrogate endpoint is a marker (e.g., a laboratory measurement, radiographic image, physical sign, or other measure such as serology) that is

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pulmonary-tuberculosis-developing-drugs-treatment

known to or reasonably likely to predict clinical benefit but is not itself a measure of clinical benefit. For TB, sputum culture conversion (SCC) from positive to negative during treatment, either as a time-to-conversion analysis or at a fixed time point (e.g., at 2 months from randomization), is considered a surrogate endpoint reasonably likely to predict clinical benefit.

The suggested primary clinical efficacy endpoint would be comprised of survival and evaluation of *M. Tb* growth on serial sputum samples evaluated at a fixed time point following randomization for all treatment arms and a period of follow-up after completion of the planned treatment period. Clinical success would therefore mean that a patient is alive, has achieved *M. Tb* culture negativity on serial sputum samples, and has had no relapse or recurrence during the period of follow-up after treatment completion. Clinical failure would encompass progression of pulmonary disease on treatment, a necessary switch in therapy due to intolerance or clinical progression, recurrent signs/symptoms of TB during follow-up, growth of *M. Tb* on sputum culture indicating failure to achieve culture negativity during treatment or to maintain culture negative status after a specific time point in the trial or during follow-up, or death during treatment or follow-up.

Adequate safety data[14] supporting the safety of the investigational drug(s) is critically important. Based on potential safety signals from non-clinical studies, appropriate safety safeguards should be included in clinical trials through safety monitoring or formulation of specific inclusion/exclusion criteria. Hepatotoxicity and QT interval prolongation are common with some commonly used TB drugs, in addition to other adverse events (AEs); drug development programs should address these and other potential toxicities early in development. For assessment of risks and benefits in subjects with unmet medical need, a safety database of 300 participants who received the same dose and duration of the investigational drug(s) intended for approval may suffice. Depending upon the circumstance, FDA may require additional safety data through post-market study(ies) or enhanced pharmacovigilance.

Bedaquiline in 2012 and pretomanid in 2019 were the most recent approvals of TB drugs by FDA. Bedaquiline was approved under the accelerated approval pathway using a surrogate endpoint of time to SCC and underwent priority review. The two phase 2 trials on which the approval was based were randomized, double-blind, placebo-controlled trials in which newly diagnosed patients with pulmonary MDR-TB received either bedaquiline + OBR or placebo + OBR. The approved indication is for adults with pulmonary MDR-TB. A confirmatory phase 3 trial was required as a post-marketing commitment and is expected to be completed in the next year. Pretomanid was approved in combination with bedaquiline and linezolid (BPaL regimen) under LPAD for a limited population of adults with pulmonary extensively-resistant (XDR) TB or treatment-intolerant or nonresponsive MDR-TB. The approval was based on a single-arm phase 3 trial as there were no defined effective comparator regimens for this patient population. The endpoint was bacteriologic failure, clinical relapse, or clinical failure at 6 months after end of treatment. Because pretomanid was approved under LPAD, no confirmatory trials were required.

FDA is committed to working with industry, academia, and other partners to further the development of new drugs for TB and/or explore innovative treatment regimens, including shortened regimens. Early engagement with FDA during the drug development program is encouraged.

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[14] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/antibacterial-therapies-patients-unmet-medical-need-treatment-serious-bacterial-diseases

ACET Discussion

For this discussion, ACET was asked to consider the following questions:

1. *Does ACET have any recommendations to HHS regarding bringing new TB drugs to market?*
2. *What are the various Food and Drug Administration (FDA) designations and regulatory pathways available to facilitate drug development for areas of unmet need, such as pulmonary TB?*
3. *What are the requirements for each designation or pathway?*
4. *How can a surrogate endpoint in pulmonary TB be used for accelerated approval?*

Dr. Belknap asked Dr. Gopinath to comment on dispersible formulations. Medications are being developed internationally in dispersible forms and may be approved in the US in a different form. He wondered whether there is a process, how to get access, and what the barriers are to getting this in the US. In addition, he asked whether FDA actively looks to incentivize sponsors beyond the items mentioned in the presentations that would entice them to get their medications approved and available so that they are accessible in the US. For instance, he could not imagine that market exclusivity for 5 years would be a big incentive for anyone developing medications for TB.

Dr. Gopinath indicated that the inclusion of pediatric populations as soon as possible in TB programs is encouraged by FDA. As part of the pediatric development program, the sponsor would be expected to submit their plans for a pediatric formulation which could be dispersible. Regarding incentives, Dr. Gopinath indicated that LPAD is specifically geared to addressing unmet needs in limited patient populations. Some of the advantages of that pathway are that there may be fewer or shorter trials required as the drug would be intended for use in a limited population, and there would be active engagement from FDA to try to further this development.

Dr. Elkins added that FDA follows the statutory regulations established by Congress, and therefore, does not otherwise incentivize. Similarly, FDA responds to what sponsors submit to them and does not have control over where sponsors wish to market their products or what indications they wish to pursue.

Dr. Belknap asked whether there is any federal entity that would be able to engage with manufacturers to discuss barriers to marketing their product in the US and to guide them on the procedures to overcome these barriers.

Dr. Gopinath responded that the manufacturing portion of drug development is critically important and FDA certainly will work with sponsors on this. At the pre-IND (PIND) or IND stage, there are often questions about manufacturing and other aspects of drug development. FDA utilizes multi-disciplinary teams that work to provide clear and specific guidance on questions from the sponsor to further all aspects of drug development and to help the sponsor navigate potential barriers.

Dr. Temesgen asked whether the pathways described in this presentation applied to vaccine development as well.

Dr. Gopinath deferred the question to Dr. Elkins (CBER) who commented that the accelerated approval pathway outlined in the presentation does apply to biologics, but the QIDP designation

or LPAD do not apply to vaccine development.

Dr. Gelmanova inquired as to what stage FDA would expect pediatric participants to be included.

Dr. Gopinath said that from FDA's perspective, the pediatric population is viewed as a very critical segment of the population which should be included as early as possible in drug development. Traditionally, evidence of safety and efficacy in adults is sought prior to embarking on trials in children. For an indication like MDR-TB where there is a critical need and very limited treatment options, FDA allows some flexibility in the timing of inclusion of pediatric participants. depending on the characteristics of the drug, the indication, its safety profile, and degree of unmet need.

Dr. LoBue and CAPT Burton asked whether any of FDA's authorities allow for waiving or discounting of the fees that are associated with the approval process.

Dr. Elkins replied in the affirmative and shared the link to the FDA Guidance for waiver and reductions of various user fees. Those decisions are handled separately from the scientific review process: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/prescription-drug-user-fee-act-waivers-reductions-and-refunds-drug-and-biological-products-guidance

Dr. Loeffler asked whether it would take legislative action to allow for review of drug formulations that are approved by the Global Drug Facility (GDF). He observed that there will never be financial benefit for manufacturers of drugs that have been on the market for decades.

Dr. Gopinath said that much depends upon the drug in question. For example, certain drugs for tropical diseases have been on the international market for decades. FDA has taken different approaches to bringing them to the US market, depending on the drug, the unmet need, type of data available, and other factors. For instance, FDA may be able to use some flexibility for a drug that has activity against DR-TB as opposed to other areas.

Dr. Lovinger asked whether it would be possible to offer any flexibilities on packaging approval. Manufacturers might not even have an incentive to create FDA-compliant packaging for medicines that would have a significantly positive impact if they were allowed to be procured within the US from GDF. Since these medicines are administered via directly observed therapy (DOT) or electronic DOT (eDOT), packaging is somewhat moot for patients anyway.

Dr. Gopinath responded that because TB medications are administered as DOT or eDOT in the US, the packaging is of less relevance for those medications.

Dr. Belknap said he appreciated that it is difficult to answer in generalities when there are so many differing and unique circumstances for drugs. He asked whether FDA could comment on any specifics with regard to clofazimine as an example of a drug that has been available for decades yet is difficult to obtain for either DR TB or in the treatment of leprosy.

Dr. Gopinath stated that FDA enables the use of clofazimine for TB under single patient INDs, and understands that the process can be somewhat cumbersome. There are ongoing discussions on potential options to address this situation, but further details cannot be shared at this time.

Dr. Goswami asked how the recent change in definitions for DR-TB terms (XDR-TB) impacted any drug approvals if at all.

Dr. Gopinath noted that the changes in definitions have not yet had an impact on FDA approvals for TB drugs because the last drug approval was in 2019 (pretomanid) before the definitions changed.

Acknowledging that FDA is restricted by its regulations and the laws, Dr. LoBue emphasized that it is especially burdensome for individual clinicians who have no experience to try and obtain a single patient IND for an individual drug as part of a multidrug regimen.

Dr. Gopinath emphasized that FDA definitely appreciates the input of the clinician community on this issue and noted that she has had to deal with it practically as well through her work in a county TB clinic.

Dr. Belknap concluded this session by recapping that there is a pipeline for TB drug development where there had not been for many decades as they heard from this presentation. If some of these drugs are shown to be safe and effective, patients in the US should have access to them. Anything that can be done to incentivize, reduce barriers, and make it easier for drug developers to get their medications approved and made available is of critical importance.

Panel: Immigration and TB

Management of Persons with TB Disease in ICE Health Service Corps-Staffed Facilities: Intake Screening, Disease Management in Custody, and Continuity of Care Post-Release

CAPT Edith Lederman, MD, MPH, FACP, FIDSA
Lead, Infectious Disease Program
ICE Health Service Corps

Dr. Lederman thanked everyone for giving Immigration and Customs Enforcement (ICE) Health Services Corps (IHSC) a voice, a seat at the table, and an opportunity to talk about the program for TB within their facilities. She provided an update on the complexity and uncertainty within ICE custody that impact the ability to manage patients with TB disease, patients and facilities within ICE's direct purview, TB incidence and clinical characteristics among ICE detainees, TB disease management programs ICE has developed to support its patients, and key partnerships for post-release and continuity of care.

Custody is highly complicated from the time that an individual enters, which may be directly from the border after just entering the US or after decades of being in the US through some other system such as the jail system of DOT. How long the individual will remain with the ICE system and immigration is quite variable and can be days, months, or years for a few exceptional individuals. Some individuals may transfer to and from other custodies during that stay, which also is variable. Where they are physically located at any point, even if within the ICE system, they might be at a dedicated ICE facility or another facility. This illustrates some of the many variables that must be considered when trying to track and help manage patients with TB disease.

In terms of detainee medical care, the complexity continues.[15] IHSC has 21 detention and staging facilities that are directly responsible for the medical care of detainees. In FY21, there were approximately 90,000 detainees for whom ICE was responsible. Compared directly to custody-contracted medical services, there are over 150 jails and other detention facilities that in FY21 were responsible for nearly 170,000 detainees. ICE and contracted facilities may rely to a varying degree on community resources for specialty referrals and hospitalizations. Each facility has a limited number of respiratory isolation cells, so community hospitals in partnership with local health departments are critical partners in evaluating and managing detainees. The average length of stay for detainees was just 37 days in FY 21, which is critical in terms of managing a long-term infection like TB.

IHSC takes TB very seriously. Immigrant detention is a high-risk setting. Detainees are housed in congregate settings with 200 of their "closest strangers." The population within any housing unit has a transient population and can shift from day-to-day and from facility-to-facility. Detainees may be there for just a few days or for many weeks or months. This is a highly vulnerable population under significant stressors within detention who may have come from very stressful situations. The prevalence of TB infection in this population is substantial at probably 16% to 20% and the statistics for TB disease have not changed over time.[16] IHSC 2017-2019 surveillance data showed a confirmed TB disease of approximately 90/100,000 with microbiologically confirmed of 49/100,000. This is consistent with data from 2015-2017 and 2004-2005.

In terms of the clinical characteristics of TB disease patients in ICE custody, an interesting and important factor is that over 71% (N=208) of them are asymptomatic according to IHSC 2017-2022 surveillance data. This is a very important point not only for ICE, but also for the community to understand when they are comanaging patients with ICE due to lack of ICE bed space for respiratory isolation. This is a challenge for ICE when patients return to them being told they are asymptomatic and whatever is on their X-ray is chronic disease when that often is not the case. Approximately 3% (N=8) of ICE patients are HIV positive. Compared to people living with HIV who are aware of their diagnosis coming into custody, that is about a log higher. The seroprevalence rate is about 0.4% HIV positive among ICE detainees. It also is known that there is another ~0.4% who are not aware of their HIV status, (about 50% of the HIV population in custody). About a third of ICE patients are going to be test-infection negative. Facilities that may be using symptom screening and test of infection to identify patients with TB will miss an important minority of patients to evaluate. About 4% of patients entering ICE facilities with confirmed TB disease are diabetic (N=13), about 1% of detainees entering ICE facilities are diabetic and also at increased risk, and about 26% are pre-diabetic.[17]

For these reasons, especially that of the patients who are asymptomatic and negative for tests of infection, ICE feels that CXR is a best practice for disease screening in a high-risk setting like immigration detention.[18] Also for this reason, IHSC has allotted significant resources to help manage its patients who are in custody. An IHSC TB Coordination and Care Team was assembled in May 2017 that is comprised of approximately a dozen health professionals from various disciplines (e.g., nurses, physicians, pharmacists, other providers, administrators,

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[15] Sources: https://www.ice.gov/detain/ice-health-service-corps; http://www.ice.gov/detention-facilities
[16] Sources: 1. IHSC – unpublished data. 2. Boardman et al. Clin Inf Dis; 2021:73(1), 115- 120. 3. Schneider and Lobato. Am J Prev Med; 2007;33(1):9-14
[17] Source: IHSC - Unpublished data, but similar, smaller data set published in Boardman et al. Clin Inf Dis; 2021:73(1), 115-120.
[18] Source: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5509a1.htm

epidemiologists) who follow patients from the beginning in terms of their laboratory and management and provide periodic quality assurance and outreach for clinical consults as needed. A telehealth consult service is also provided through which approximately 1500 infectious disease consults are provided per year to ICE's 20 facilities. A good proportion of those consults are related to TB disease.

A fulltime pharmacist is embedded in the IHSC program and a part-time pharmacist provides help as a collateral duty and quality assurance checks on patients who are receiving TB treatment. A minimum of 1 TB training is provided per year as a webinar to the 20 facilities. There also is participation in other community webinars with Curry and others to help provide information and guidance on patients in ICE custody. ICE has a unified electronic health record (EHR) for all of its facilities and has developed EHR tools, including templates and order sets to help with primary care management of the daily needs of TB disease patients, standard operating procedures (SOPs), and clinical guidelines. In addition, they coordinate closely with their single teleradiology vendor that provides teleradiology to the facilities that are large enough to have their own in-house radiology. Those radiology reports are standardized with an impression template based on the findings as opposed to an ordinary radiology interpretation, which may or may not include TB and may lead clinicians astray recommending a CT scan or other tests as opposed to isolation and initial management.

ICE also has spent significant time developing patient education materials, which are unique and focus on asymptomatic disease and other aspects of TB management within ICE custody, including referral to continuity of care services such as CureTB. These materials have been developed alongside the NTCA's Corrections Workgroup, have been tested among some of the patients in the ICE facilities, have been vetted and cleared by the agency for inside and outside use, and have been translated into 21 languages. To accompany the patient brochure, clinic flipcharts have been developed in 21 languages for providers and nurses to use so that there is consistent messaging that the brochures contain as well.

In terms of ICE involvement with community partners who are considered extremely vital, ICE developed in 2018 and revised in 2021 a memorandum to community providers with a toolkit that includes a checklist of studies that are required to receive a patient back safely to a facility to be placed in general population. The memorandum gives background data and rationale for conservative management, including empiric treatment in many cases. It also provides a point of contact for case consultation with the CDC TB Centers of Excellence (CoE). The memo and toolkit have been endorsed by the CDC TB CoEs and NTCA and adopted by the BOP.[19] The BOP has indicated that they use the toolkit quite a lot and have found it useful in communicating some of the needs of patients to community hospitals.

IHSC co-manages complex patients with the TB CoEs. While over 90% of ICE's probable or confirmed patients are straightforward and do well, ICE collaborates with CoEs for MDR/XDR patients, serious adverse drug reactions, and significant comorbid disease. Most often this is accomplished through collaborative calls/warm line consults, but IHSC acts as the primary manager. They have rarely had admissions, but there recently has been one to the Texas Center for Infectious Disease (TCID), where TCID directly managed the patient until they were non-communicable and released to the local community.

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[19] Sources: https://www.tbcontrollers.org/resources/correcttb/infection-control/; https://youtu.be/hQeuBZtUIhk (CITC-sponsored webinar 2018)

ICE spends a lot of time thinking about release planning and coordination of care because there are so many unknowns. It is important to start thinking about release planning and continuity of care upon meeting the patient for the first time, because that potentially could be the last time for meeting with them as custody moves quickly in some cases. Delays in communication can result in treatment interruption, failure to isolate, and/or failure to link to the next care system (e.g., another custody system, the local community, or a community abroad). Since the ultimate destination of any given detainee is unknown, all patients with verified and probable TB disease are referred to CureTB. Reporting is done to health departments per local requirements. Regular and urgent updates are provided to both CureTB and local health department (LHD), including communication of information on transfers, releases, and removals and provision of medical records, labs, medical administrative records, and CDs of prior images.[20]

ACET Discussion

For this discussion, ACET was asked to consider the following items:

1. *Best practices for TB screening*
2. *Conservative management of possible TB disease*
3. *Utilization of prospective surveillance as prompts to partner with clinical teams*
4. *Critical partnerships with local/state health departments, federal custody partners, and CureTB in promoting and supporting continuity of care*

Dr. Gordon asked whether ICE would consider a temporary halt in detainee movement for those involved in contact investigations at the local level. Right now, MN DOH can only get movement stopped for actual TB patients. The continued movements of identified contacts makes their investigations nearly impossible.

Dr. Lederman indicated that ICE has lists of individuals which can be traced/tracked, assuming they remain in the US. ICE Health Service Corps has a list of POCs to help with CIs; their tour of duty usually is a minimum of 2 years so there should be some degree of stability to ensure that they are regularly contacting a Health Service Administrator and whatever Infection Control Officers are at the facility. She remains available and is fairly responsive, so if there are any cases, she will figure out who the person is and take action. The issue is that they are detaining folks for immigration processing. If they have a reason to either be released or they have a final order of deportation and they are clear of a communicable disease, ICE does not have the authority to hold them. That is an unfortunate side to ICE's custody.

Dr. Belknap asked whether the number of facilities where ICE is providing medical services is expanding, remaining the same, or decreasing in terms of the contracted versus what ICE does directly.

Dr. Lederman indicated that it does change from time to time. They have facilities close or transfer and new facilities are on the horizon, such as the one in Aurora, Colorado. That will be a fairly large facility that will be transferring sometime over the next 6 months to a year. The core group of ICE facilities has not changed for as long as she has been there, which has been over a decade.

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[20] Source: https://www.cdc.gov/usmexicohealth/curetb.html

A Pilot Project for Pre-Immigration Voluntary LTBI Testing and Treatment

Amera Khan, DrPH
Stop TB Partnership
London School of Hygiene and Tropical Medicine

Dr. Khan provided an overview of the Preventing TB Overseas Pilot Study (PTOPS), the focus of which is on implementing pre-immigration voluntary LTBI testing and 3HP treatment for US-bound immigrants in Vietnam. The lead organization is Global TB Branch, Division of Global HIV/AIDS and Tuberculosis. Implementing partners include the DGMQ at CDC, Cho Ray Hospital Visa Medical Department, University of California-San Francisco (UCSF), and the Vietnam National TB Programme (Vietnam NTP) / UCSF Research Collaboration. Rifapentine for the project was donated by Sanofi.

In 1989, CDC and ACET published a goal of TB elimination by 2010,[21] with elimination being defined as <1 case per million. In terms of reported TB cases in the US between 1993-2020, over 7100 new cases of TB disease were reported in 2020 or 2.2 cases/100,000 persons. The case rate was 22/million, which is far from <1/million goal. Although there has been a decline in TB cases over the years, the rate of the decline has been slowing with the exception of the last year. Looking deeper into the data, about 71.5% of reported TB cases in the US in 2020 occurred among non-US-born persons.[22] Additional genotyping studies suggest that over 80% of TB disease cases result from reactivated LTBI, not recent transmission.[23] This further suggests that TB in non-US-born persons is most likely attributed to TB infection acquired before immigrating to the US.[24] To make progress toward TB elimination, US efforts must be strengthened to address LTBI in non-US-born persons.

There are increased domestic efforts to address LTBI; however, the diagnosis, treatment initiation, adherence, and completion rates of LTBI remain suboptimal for high-risk groups.[25] There have been improvements in these rates with availability of shorter treatment regimens, but still efforts to reach the estimated 13 million people with LTBI in the US need to be strengthened in order to make progress. A DGMQ analysis of newly arriving immigrants and refugees at risk for TB suggested that 35.5% did not complete a US post-arrival evaluation. Among those who did and were recommended for LTBI treatment, 69.0% initiated treatment and only 40.0% completed treatment.[26] There are many reasons for this throughout the LTBI care cascade with this approach, such as barriers and challenges on behalf of newly arrived immigrants in seeking care, staffing and resources shortages in health departments trying to follow-up with newly arrived immigrants. To address this, there is a need to implement new innovative strategies to address LTBI in non-US-born persons from high-TB incidence countries. With that in mind, the PTOPS was designed to determine whether it would be possible to offer and deliver voluntary 3HP (3 months weekly doses of isoniazid and rifapentine) TB preventive treatment (TPT) to US-bound immigrants prior to their arrival in the US using the overseas medical exam platform at the Panel Sites.

Overseas medical examinations are conducted at Panel Sites. All US-bound visa applicants for

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[21] CDC, MMWR, 1989; 38, 1-25
[22] CDC, Report Cases of TB, 2020 https://www.cdc.gov/tb/statistics/surv/surv2020/default.htm#
[23] Yuen, Kammerer, Marks et al, Plos One 2016
[24] Ricks, Cain, Oeltmann et al, PLoS ONE 2011; e27405
[25] Systematic review of LTBI completion varies from 4-99% (Sandgern et al, BMC Infect Dis. 2016)
[26] Liu et al. Tuberculosis among Newly Arrived Immigrants and Refugees in the United States. Ann Am Thorac Soc. 2020 Jul 30

permanent residency in the US must undergo this medical exam as part of their immigration application to enter the US. A major focus of the exam is to screen for "inadmissible conditions." These include communicable diseases of public health significance which includes active TB disease. Since LTBI is non-infectious, detecting and treating LTBI is not required as part of the exam for US immigration. As a component of screening for active TB disease, an interferon-gamma release assay (IGRA) is required for children 2-14 years of age as part of their TB disease work-up and known contacts to those with TB disease may be given an IGRA as part of their overseas medical examination.

Use of Panel Sites to implement voluntary TB preventative treatment offers an opportunity to test and treat large numbers of immigrants prior to arrival. These sites already have been shown to successfully contribute to the halting of importation of TB disease by detecting and treating TB disease among applicants prior to their arrival. Approximately 1/2 million immigrants and refugees move to the US every year. There are about 350 US Panel Sites in 160 countries. In addition, over 600 Panel Physicians are already trained to diagnose TB and can rule out active TB disease, which is an important step before starting TPT treatment.

Vietnam was selected for the pilot study because it has been in the top 5 countries of birth of non-US-born persons with TB in the US. Additionally, the Vietnam NTP was interested in scaling up their TB preventative treatment activities to meet their End TB Strategy Goals and they were particularly interested in using the 3HP regimen in their country for the first time.[27] The aims of the pilot study were to: 1) assess initiation and completion of voluntary 3HP TB infection treatment when offered during the overseas immigrant medical screening exam; 2) use findings to inform US TB elimination strategy; and 3) help build Vietnam NTP's capacity to treat LTBI using the 3HP regimen to meet their END TB Goals. At each step of the LTBI care cascade (testing, treatment initiation, treatment completion), they wanted to capture each applicant's reasons for declining or accepting testing or treatment with 3HP.

In terms of study implementation, a protocol was developed that was based primarily on CDC guidelines at the time of the study for LTBI testing by IGRA and treatment by 3HP implemented in routine medical exam process after active TB disease is ruled out.[28],[29] Medical eligibility for treatment was based on the clinical findings through the routine physical and medical exam conducted at the Panel Site. As part of the exam, LFT, HepB, and HepC testing were added. These are not necessarily needed to initiate treatment based on the CDC guidelines, but they were added as a more conservative approach because this was the first time using 3HP in Vietnam and there was a potential that applicants may be traveling during their treatment. In this study, the 3HP was given by DOT at Cho Ray Hospital Visa Medical Department (CRH-VMD) for at least 8 doses. If participants completed at least 8 doses and needed to immigrate to US in the middle of treatment, they were allowed to take the remaining 4 doses by self-administered therapy (SAT) in the US with a follow-up call by a US Study Coordinator.

Dr. Khan reviewed how LTBI testing and treatment was implemented at the sites to provide a brief idea of how it was incorporated into the routine operations of the overseas medical examination. This image shows the flow of the visa applicant through the exam at the Cho Ray

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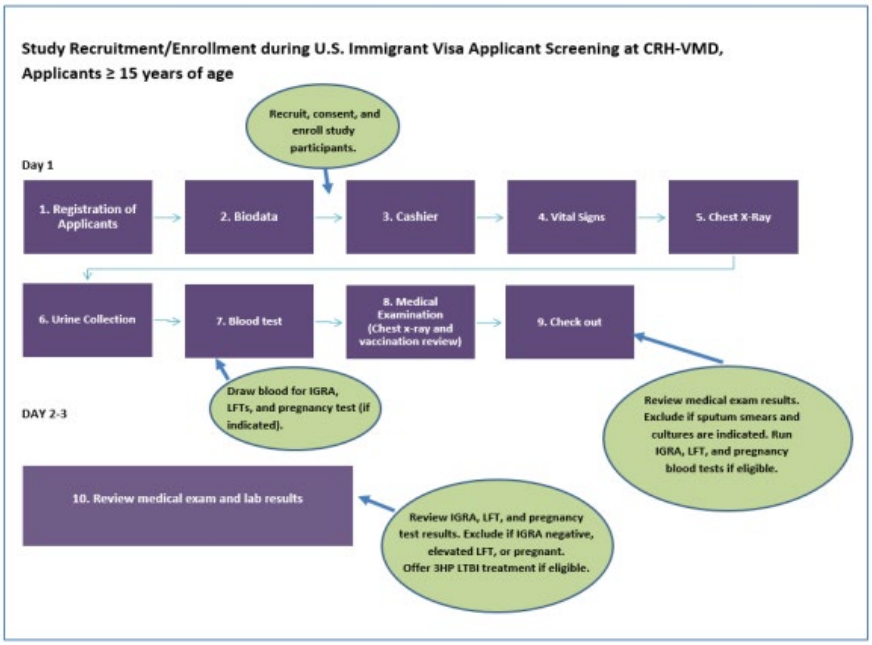
[27] CDC, Report Cases of TB, 2020 https://www.cdc.gov/tb/statistics/surv/surv2020/default.htm#

[28] Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection — United States, 2010; MMWR 2010; 59 (RR-5); 1-25

[29] Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection MMWR 2011;60:1650–1653

Clinic. The purple squares indicate what occurs routinely and the green circles indicate the steps at which the study components of LTBI testing were incorporated:



The overseas medical exams generally take 1 day, with the results available within the next couple of days. The study was implemented from September 2018-October 2019. Recruitment was of eligible visa applicants undergoing a required medical exam ≥12 years of age living in Ho Chi Minh City province who were not pregnant. Those who consented to participate received an IGRA, the additional blood tests, a pregnancy test, and required full TB workup to determine eligibility for preventative treatment in this study. Those who were IGRA-positive and eligible for this study after medical exam were offered 3HP. Those who accepted and initiated treatment had the option of taking 12 doses of 3HP by DOT in Vietnam at CRH-VMD or ≥8 dose 3HP by DOT in Vietnam at CRH-VMD and up to 4 doses of SAT in the US with weekly phone follow-up by a US Study Coordinator.

In this study, 5,311 eligible visa applicants were identified upon initial screen who were recruited to participate among whom 2,873 (54%) declined and 2,438 (46%) consented. IGRA tests were performed on 2,276 (93%), with 1,789 negative, 3 (<1%) intermediate, 484 (21%) positive, and 452 (93%) eligible for treatment based on blood test and medical exam results. Among the 452 who were eligible, 148 (33%) declined treatment and 304 (67%) accepted. Among the 304 who accepted treatment, 36 (12%) did not complete treatment with 3/36 reporting Grade 3 side effects due to 3HP and 268 (88%) completed treatment. Of those who completed treatment, 192 (72%) completed treatment in Vietnam by DOT and 76 (28%) completed treatment in the US with ≤ 4 SAT doses.

At each point of the cascade, those who declined were asked to provide reasons to help understand why there were drops in the cascade and determine whether there was any room for improving the intervention. The top reasons for declining PTOPS participation and IGRA (N=2873), 881 (31%) said that they were too busy or stressed to participate, 723 (25%) said the study and the IGRA were not required for the visa, and 641 (22%) said they did not believe they were infected. It is difficult to discern whether the majority of people who declined this first step of the cascade did so because they did not want to participate in the study or they were truly not

interested in learning about their LTBI status. The top reasons for declining the next step of the cascade, the 3HP Treatment (N=148), 99 (67%) said they declined because they did not feel that they had enough time to tale treatment by DOT as they were planning to leave for the US immediately after receiving their visa, 23 (16%) expressed a preference to take treatment after arriving in the US, 22 (15%) thought that DOT at the clinic was inconvenient because of time or distance. The top reasons for 3HP treatment discontinuation (N=148) were that 18 (50%) participants decided on their own to stop due to Grade 1 or 2 side effects, 5 (14%) applicants decided to stop on their own because they were too busy with their move to the US, 5 (14%) people were identified as a contact to a person with MDR or INH resistant TB, 5 (14%) people had either a Grade 3 side effect or elevated liver function tests, and 3 (8%) people were lost to follow-up in the US. Among the top reasons for accepting 3HP treatment among those completing treatment (N=270), 161 (60%) said preventing TB was good for their health, 57 (21%) said it was more convenient or easier to take treatment in Vietnam than the US due to a variety of reasons (language, navigating the health system, transportation), and 22 (8%) mentioned that they wanted to protect their family and community.

In conclusion, this study showed that IGRA implementation is feasible at the overseas Panel Sites. Positive results were found in 21% of study participants screened. Feasibility of incorporating voluntary 3HP treatment as part of required medical screening was demonstrated. Acceptance of treatment and initiation among eligible participants (67%) was similar to prior post-arrival studies conducted in the US. Retention of study participants initiating 3HP treatment was high, with 100% in Vietnam and 96% in the US. Overall treatment completion rates were higher than post-arrival efforts at 88% versus 40%. Scale-up of routine offering IGRA testing and options to offer TPT should be considered during the overseas medical exam to support US TB elimination efforts. PTOPS II is currently underway in Tanzania with US-bound Congolese refugees.

ACET Discussion

For this discussion, ACET was asked to consider the following questions:

1. *Does ACET have any recommendations for follow up of this pilot project?*
2. *Should pre-arrival offering of latent TB testing and treatment to visa applicants be considered as a potential strategy for further US TB elimination efforts?*
3. *What are some additional considerations for such a strategy?*

Dr. Loeffler inquired as to why children 2-12 years of age were not enrolled, emphasizing the importance of enrolling children in research trials. In addition, she asked how many doses were missed at Cho Ray and emphasized that 3HP should still be given by DOT—especially for this population.

Dr. Khan indicated that at the time, they were following the CDC guidelines. When the protocol was written in 2016-2017, the guideline was for only 12 years and older. If participants were not able to make it to their scheduled time for DOT, the Cho Ray staff promptly followed up with them to reschedule their DOT dose within the weekly time frame. As such, all participants completing treatment in Vietnam (n=192) and in USA (n= 76) did not “miss” a dose and took all weekly doses.

Dr. Horne asked whether there was much difference between those who took all of their doses before departing for the US and those who took at least 8 doses and complete the other 4 in the US. In addition, he inquired as to how the decision was made that participants had to take 8 of

the 12 doses before leaving.

Dr. Khan responded that the decision for the 8 doses was made in consultation with the study medical advisors at UCSF. Studies show that side effects tend to occur between the third and fifth dose, so they wanted to make sure they were passed that point. In addition, they looked at the average time people spend in Vietnam from when they received their medical exam to when they actually left the country. This was not necessarily pre-determined because people do not always know their move date up front. No differences were observed in the completion rates between those who took all doses before departing for the US and those who completed 8 before leaving and 4 after arrival.

Dr. Belknap asked whether children 12 years of age and younger would be enrolled in the pilot study in Tanzania.

Dr. Khan indicated that children 5 years of age and older would be included in the Tanzania study. The Vietnam pilot study was conducted during a time when 3HP was recommended to be given completely by DOT. Now that this has changed, people who opted out of the study who did not want to go to the clinic every week or who were too busy might be better retained by being permitted to have at least part of their treatment through SAT.

Dr. Horne thought that was an interesting point because SAT was not shown to be as good in Sub-Saharan, Africa or outside the US. If implemented overseas, he wondered whether they would feel comfortable using SAT.

Dr. Khan said she thought getting someone through the first 4 doses of treatment at the very least with some support is quite important. There are studies that show that if people get through the first part where they tend to experience side effects, with additional supports they are more likely to complete treatment. This may vary among different populations and the investigators are well aware that they may not be able to replicate these results elsewhere.

Dr. Belknap added that DOT is ideal in terms of documenting treatment and results in the highest completion. If a large proportion of people are not accepting to start treatment because DOT is a barrier, then the ability to offer eDOT that is increasingly available globally or SAT is a good strategy. He agreed with an approach that would allow observation with the first 4 doses, which is when treatment-related side effects occur, might get people through those side effects. Some can continue if they have frequent support through that time period. If the pilot in Tanzania demonstrates success in replicating the results, he asked what the next steps would be to more broadly implement this strategy as a standard approach.

Dr. Khan agreed that while this was a very important question, it was one for CDC to answer. Certainly, it seemed to her that understanding the costs associated with this approach would be an important next step to evaluate as well.

Dr. Liu inquired as to whether the study results would be likely to change the practice of pre-immigration screening.

Dr. Khan said she hoped it would inform some sort of implementation change, but there is more to understand about this approach before it could inform any pre-immigration screening changes.

Day 1 Recap

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

Dr. Belknap said he would like to hear from ACET members about the key takeaways from the day, topics they thought might require more discussion and might lead to recommendations they may want to discuss further the next day.

Discussion Summary

- Access to drugs and diagnostics that have an evidence base and global distribution. TB is not an orphan disease, but there are no incentives in the US to bring these programs to bear. Perhaps a working group should be formed to consider these issues that includes members from ACET, FDA, industry, users, et cetera to brainstorm about the barriers and how access to these drug formulations and diagnostics that are supported by US investigators available to domestic programs.

- Some of the issue seems to have to do with profit for private industries. Otherwise, why would manufacturers not be bringing their diagnostics and drugs to the US market? Why are US laboratories not able to make the effort to validate the test that would allow them to be able to offer Xpert® for stool or gastric? For example, the federal government was able to fund expensive COVID-19 therapeutics.

- Treatment in the immigration process. There is likely to be economic gain in prevention of cases, spread, and reactivated cases in the US. Perhaps economic modeling could be done to demonstrate this.

- There was disruption of TB services and care due to the COVID-19 pandemic that led to a variety of alternative strategies. It is important to apply the lessons learned from the pandemic to engage in more intensive collaborations, utilize accelerated pathways, conduct overlapping clinical trials, and embrace technology.

- There is a need for coordination between various groups that are testing TB drugs and leveraging each other's efforts.

- It would be beneficial to establish electronic medical records where information can be accessed about people's medical information such as TB tests, treatment, and images. Through the FDA and Ukrainian process, it is shocking how hard it is to see those images even from the US's own military bases. It is not clear why this is hard. The numbers cannot even be seen for the QuantiFERON level. There are many successful efforts to get vaccine records into EHRs. While it is important for people immigrating to the US not to feel coerced, it would be nice to be able to access their information about TB tests, treatment, and images—especially since as many as 90% of cases come from LTBI, most of which comes from being outside of the US. Perhaps there is a way to incentivize people instead. It has to be easy for people to do what is in their best interest for their health and what is best for the

community at large. Systems within the US do not talk to each other, so perhaps there are data modernization efforts that could be leveraged to have access to screening.

With no further business posed, the meeting was adjourned at 4:06 pm ET. ACET stood in recess until 10:00 am ET on June 22, 2022.

June 22, 2022 Opening Session

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

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

Ms. Condit called the meeting to order at 10:00 am ET on June 22, 2022 and provided meeting instructions. Dr. Burton welcomed participants to the second day of the ACET meeting. He then conducted a roll call to confirm attendance of the ACET voting members, *ex-officio* members, and liaison representatives. He reminded everyone that ACET meetings are open to the public and that all comments made during proceedings are a matter of public record. He informed the ACET members to be mindful of their responsibility to disclose any potential COI, as identified by the CDC Committee Management Office, and to recuse themselves from voting or participating in discussions for which they have a conflict. The roll call confirmed that the 17 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on June 22, 2022. No additional COIs were declared and quorum was maintained throughout the meeting.

Operation Allies Welcome

Kimberly Skrobarcek, MD
Medical Officer
Immigrant, Refugee, and Migrant Health Branch
Division of Global Migration and Quarantine
Centers for Disease Control and Prevention

Dr. Skrobarcek presented an overview of CDC's response for Operation Allies Welcome (OAW) activities after the fall of Kabul, the OAW TB screenings that took place and the results, and lessons learned from the response. On August 29, 2021, the US Government (USG) began an airlift of US citizens, lawful permanent residents (LPRs), Afghans who held Special Immigrant Visas (SIVs), and other vulnerable Afghans. During Phase 1 of OAW, ultimately 75,000 Afghans went to 8 "Safe Havens" or military bases in the US for immigration and medical processing that normally would have been done overseas. They were resettled in 46 states. They are currently in Phase 2 where all processing is being completed overseas. Through OAW, Afghan evacuees were initially flown from Kabul to Lilypad sites, which were overseas US military bases where they were housed before entering the US at Dulles or Philadelphia airports from where they were transported to 8 Safe Havens for processing that took months. Finally, evacuees were resettled into their new communities. Resettlement was complete as of February 18, 2022. The 8 Safe Havens include: Fort McCoy, Holloman Airforce Base, Fort Pickett, Fort Bliss, Joint Base McGuire-Dix-Lakehurst, Camp Atterbury, Marine Corps Base Quantico, and Fort Lee.

OAW truly was an interagency collaboration that was led by the Department of Homeland Security (DHS) and executed by the Department of Defense (DoD) along with representatives from many federal partners, the International Organization for Migration (IOM), and multiple non-governmental organizations (NGOs) who all worked on different activities within the resettlement process. CDC negotiated with DHS to have the immigration medical exams and many other processing priorities during the fast-paced movement of evacuees through the bases to resettle in the US. CDC also deployed teams to help set up the immigration medical exams and provide public health technical assistance to Safe Havens. There were 2 types of Afghan evacuees processed at Safe Havens. SIV applicants included Afghans who were employed by or on behalf of the US government and certain translators and interpreters. SIV applicants made up only a small percentage of evacuees. Most of the population processed were humanitarian parolees who are individuals who have a compelling emergency and urgent humanitarian reason for entry to the US.

The medical screenings conducted in the Safe Havens differed by the visa type. SIV applicants underwent all components of the immigration exam under CDC's regulatory authority (history and physical exam; vaccinations; tests for TB, syphilis, gonorrhea, and leprosy; and mental health and substance abuse exams) , while parolees had only a history and physical exam, vaccinations, and TB testing. Different forms were used for different immigration medical exams based on visa type. SIVs were reported on Form I-693 that is normally used by Civil Surgeons to perform immigration exams for visa status adjustment applicants in the US. Form SF-600 was used for parolees, which is a special form created for OAW. While the forms were different, both used the same TB and vaccination worksheets from the I-693.

To better understand how processes were adapted for OAW, Dr. Skrobarcek briefly described the data systems used for the overseas immigration medical exam. Currently, only a few visa types have exam information reported on Department of State paper forms with CXR images burned onto CD-ROMs, that must be hand-carried to US ports of entry. Quarantine stations then mail them to the Electronic Disease Notification (EDN) center for data entry and upload into the EDN system. Most exams are now reported via electronic data systems with uploads of digital CXR images and are transmitted directly to the EDN center. Immigrant exams are entered into the Department of State's eMedical system, while refugee exams are entered into IOM's Migrant Management Operational Systems Application (MiMOSA) system. EDN then provides immigrant and refugee arrival notification and health information to state and local health departments. Currently, domestic immigration exams are still paper-based. Civil Surgeons give applicants completed I-693s in sealed envelopes, which the applicant then mails into the US Citizenship and Immigration Services (USCIS) with their immigration application.

Since the response was set up so quickly, electronic systems could not be used for the Safe Haven exams. Instead, the exam results were transmitted via Project ARMS (Afghan Resettlement Medical Screening), which was a DoD contractor/CDC-funded data entry project to provide selected fields from both versions of the exam forms to US health partners. The project provided nearly 60,000 completed medical exams to US health partners via 2 methods: 77% were sent through CDC's Secure Data Exchange System that included a CSV file without EDN notification and 17% were sent via EDN with notification.

The TB screenings were difficult to set up quickly, so the screening requirements were either based on the Civil Surgeon or the Panel Physician TB Technical Instructions. Everyone started with a history and physical and then followed 1 of 2 options. In the IGRA Pathway, anyone 2 years of age and older got an IGRA. If that IGRA was positive, they got a CXR. In the CXR Pathway, everyone 15 years and older got a CXR. Those with abnormal CXRs and their family

members then got IGRAs. Anyone with an abnormal CXR had sputum studies performed, which included 3 sputum specimens for smears and cultures. Finally, regardless of pathway, anyone with signs or symptoms of TB or known HIV had an IGRA, CXR, and sputum studies regardless of initial results. Of note, due to the congregate settings in the Safe Havens, people were cleared to travel before the sputum cultures were finalized. Those who were asymptomatic, had CXR findings that were not highly suspicious for TB, and had negative sputum smears were cleared for travel while cultures were pending. Those with positive smears or cultures or findings highly suspicious for TB disease began DOT and were cleared for travel after being considered non-infectious. This was different from overseas processing where all cultures and treatment needed to be completed before visas were issued for travel. Each Safe Haven was different. First, they varied greatly by capacity from less than 2,000 up to 13,000. The majority of Safe Havens followed the IGRA Pathway, but Ft. Lee and Holloman chose the CXR Pathway, while Ft. Bliss utilized both. Lastly, 5 Safe Havens had sputum samples processed by state public health laboratories, while some used LabCorp, Quest, or both.

As a reminder, the TB Classifications for the immigration medical exam are as follows:

- **No Class:** No clinical findings for TB, no known HIV, negative IGRA/CXR
- **Class A:** Active TB disease, either laboratory-confirmed or clinical diagnosis
- **Class B0:** Completed DOT under the care of panel physician or health department
- **Class B1, Pulmonary TB**: Anyone with signs/symptoms or CXR findings suggestive of TB or with known HIV, and sputum studies results negative
- **Class B1, Extrapulmonary TB:** Normal CXR, negative sputum studies
- **Class B2, Latent TB Infection (LTBI):** +IGRA, normal CXR, no signs or symptoms of TB

To outline the OAW TB screening preliminary results, a total of 73,714 Afghans received immigration medical exams in a Safe Haven. Of these, 708 (1%) had sputum specimens collected. Out of the 708, 105 people were diagnosed with Class A Active TB disease. Of these, 60 received a clinical diagnosis and 45 were laboratory-confirmed. The total Class A TB incidence was 142/100,000. The laboratory-confirmed TB incidence was 61/100,000, which is similar to the 60/100,000 rate seen at the immigration clinics in Kabul in 2019. Of the remaining 603 individuals with negative sputum studies and Class B1 TB, 593 were Class B1 TB, Pulmonary and 10 were Class B1 TB, Extrapulmonary. These data are still preliminary and Class B2, LTBI numbers were not included as those numbers were not collected directly from the Safe Haven Public Health Teams.

Of the 45 laboratory-confirmed Class A TB cases, 22 were smear-positive and 20 were smear-negative. The remaining 3 were not positive, 2 of which were smear-negative and the last was smear-negative with culture pending, but they are still unable to locate those results. Of the laboratory-confirmed cases, 5 had drug-resistance detected, of which only 1 was MDR to both INH and RPT. Of the 60 clinically diagnosed cases who were started on treatment at a Safe Haven, many traveled prior to finishing their evaluation and further follow-up is needed to confirm the final case designation.

This response created a lot of opportunities for lessons learned, some of which Dr. Skrobarcek reviewed. The biggest takeaway was how essential access to TB expertise is. There was a general lack of understanding of TB among clinicians outside of the public health or the TB community. Each Safe Haven connected to TB experts at either the local or state TB program or at a TB CoE. The Safe Havens met with these TB experts for CXR reviews and management discussions, which helped to identify those who were highly suspicious for TB and required

treatment initiation. Connecting to health departments for laboratory services greatly improved the overall quality of TB screenings. While utilizing contracting laboratories lessened the burden on public health laboratories, it led to many issues in the long-term, including loss of quality control by the health departments and difficulty tracking final culture results.

Lastly, the TB experts often helped remove people from isolation more quickly and clear those with low TB suspicion for travel while the cultures were still pending. However, finalizing exam forms and allowing people to resettle while cultures were still pending created a need for new data systems. While expedited travel improved the public health of the population, Project ARMS was unable to transmit complete TB evaluations to states because the forms were unable to be updated after being finalized. CDC worked directly with the TB Program and Public Health Teams at the Safe Havens to receive the TB screening results and created a separate database of those who had TB specimens collected or were on TB treatment. These results were then followed over time and final results were provided to the destination states by interjurisdictional notifications whenever they had access to the results. The Class A Notifications were done by the TB programs, while most of the Class B1 Notifications were done by DGMQ.

This experience highlighted that paper-based data systems are not ideal. They compromise or delay the ability to notify receiving health departments, and they compromise the ability of CDC to monitor and evaluate screening programs. It also costs more to capture information. Project ARMS cost approximately $2.3 million, required hiring approximately 50 additional staff for data entry, and incurred extra costs for travel between the Safe Havens and other data entry locations. Alternatively, using electronic data systems allows for monitoring and evaluation. The integration of electronic systems streamlines public health processes and ensures continuity of care and improved notifications via established networks. eMedical feeds directly into EDN and then to CDC. However, these systems need to be built at the ground level. They take time to build and cannot be planned on the fly. A modified eMedical system was built for the OAW parolees, but was not ready to be released until Spring 2022.

In conclusion, TB expertise is essential and should be built into the frontend of the public health response by ensuring dedicated public health staff are assigned to TB management and by creating access to TB experts, either through internal hiring or external partnerships. It takes time and resources to fully evaluate someone for TB and the screening cannot be set up overnight. In the end, allowing exceptions to the TB screening to expedite processing created more issues than solutions. Although there were many steps in the OAW resettlement process, the medicals and TB screenings were not usually the rate-limiting factor. Not every base followed the same protocol and the notifications were not up to CDC standards, but they did the best they could in this emergency response. Using established data systems instead of creating new ones would have improved notifications. Electronic data systems have many advantages, demonstrated by the overseas program. In the future, replacing the paper-based system used for the Civil Surgeon exam with an electronic one would also improve the domestic program.

ACET Discussion

For this discussion, ACET was asked to consider the following question:

1. *Does ACET have any recommendations for follow up of Operation Allies Welcome TB related activities?*

Dr. Belknap asked whether there are any activities to address some of the lessons learned, most specifically around the use of electronic systems, replacing paper, and integrating the various electric systems for data collection and transfer of information. He also wondered what would happen if faced with the same scenario today.

Dr. Skrobarcek indicated that for Phase II of OAW, everything is now back to normal processing. Everything is electronic, all of the exams are occurring overseas, and everything is being completed overseas, including sputum cultures and DOT treatment. For the domestic exam, they continue to have talks with USCIS to promote the use of potential electronic systems for the domestic immigration exams. If faced with the same scenario, they would be better equipped to handle it. The modified eMedical system was created for the parolees. Use of the electronic system, eMedical, requires someone to fill out a form and apply for an immigrant visa through the Department of State. That triggers the creation of a person's file. They did not have that for parolees because they were not applying for an immigrant visa, so they had to create a modified version of that in order to allow eMedical to be used for parolees. Now this is being done overseas for Phase II of OAW. They just were not able to get it out in time for use during Phase I.

Dr. Belknap asked whether any of these systems or changes being utilized for the Ukrainians, who have a very different situation in terms of how people are arriving compared to OAW.

Dr. Skrobarcek responded that they are not because it is not the same type of program. The USG has committed to bringing over 100,000 Ukrainians. The majority of them will be processed through the Uniting for Ukraine program, which is a parolee program. Parolees usually do not have any health requirements. For OAW, it was a special circumstance that was done to perform certain health requirements. This is also being done for the Uniting for Ukraine program in which parolees are required to receive 1 dose of COVID-19, polio, and measles vaccine overseas and then TB screening starting with an IGRA after arrival in the US. They are not applying for immigration, so there is no application or full exam that they are undergoing.

Since there is no systematic way to do the IGRA testing, Dr. Ahmed inquired as to how arriving Ukrainians would get that testing. There is concern because of the high rates of TB and drug-resistance, so there needs to be some downstream planning as well.

Dr. Skrobarcek responded that DGMQ is working with DHS along with DTBE on the components of the Uniting for Ukraine program related to TB screening. It somewhat complicated because the Ukrainians will be eligible for benefits, but not immediately because they have to apply for them. Right now, the DHS requirement is for an IGRA within 14 days of arrival. However, there are no restrictions on the IGRA meaning that they do not have to go to a Civil Surgeon or a physician. They could go to any private laboratory, health department, or TB program. There are many options for initiating that screening, and CDC is working on ways to message the different options to the beneficiaries and to let their supporters know how to access that testing. Part of the Uniting for Ukrainian program is that all Ukrainians must have a

US supporter who will be financially responsible for them within the US. Also, the program is a temporary period of a 2-year parole; so it is not a direct pathway to immigration. The thought is that once the conflict is over, most people will want to return home.

Dr. Stout said he was struck by how the US does the same things over and over and expects different results. He was drawn back to the Montagnards, which was 20 years ago when there was a similar mass migration with all paper records and a lot of chaos. He wondered what progress was being made toward having some kind of flexible web-based system that could be used for a range of migrants and refugees that would contain their medical records in a format that wherever they land it would be easy for providers to access. All of these ad hoc solutions never work well. Perhaps there could be something simple and workable that could be used for all future situations instead of trying to "reinvent the wheel" each time.

Dr. Skrobarcek said that these conversations do arise, but she is not the data systems expert of her divisions. There are some complications pertaining to Data Use Agreements (DUAs) and storing PII. Essentially, creating a national EMR for migrating populations would be rather complicated. However, the conversations do continue with thoughts of this issue and potential ways to alleviate the problems.

Dr. LoBue pointed out that while the Ukrainian parolees are potentially eligible for certain medical coverage, Medicaid or something similar, it takes time and health departments generally are not set up to get reimbursed. If people go to health departments, the health departments would bear the cost. For that reason, as part of the large package of Ukrainian assistance, there is funding coming through CDC that will go to health departments to help cover these costs. They are still in the process of working out the details of that. A "Dear Colleague" letter was sent out the previous day that explains the situation and the funding. The funding will be for screening, diagnostics work-up, and treatment. Medication for TB disease is not usually allowable under standard cooperative agreements, but they think they have a couple of options that will allow them to make an exception for LTBI and TB disease medication.

Dr. Belknap asked Dr. LoBue to explain why those are not allowed under the normal cooperative agreement and whether that was something that could be changed in the future.

Dr. LoBue responded that they are not interested in changing that. There is a long history, but when those cooperative agreements were set up in the 1990s because of the resurgence, the purpose was not to federalize TB control in the US and take over all of the costs. It was specifically to address certain deficiencies that were noted to have contributed to the resurgence, such as lack of DOT and lack of using the most modern diagnostic methods. The cooperative agreements were to act as a supplement and fill in gaps. The feeling was that state and local TB programs are constitutionally the ones who are responsible for disease control, and this was an addition to improve things not to supplant them.

Dr. Gordon asked whether the sponsoring family's income is considered when the parolee applies for assistance.

Dr. Skrobarcek indicated that this is a DHS question. Through the same Congressional award that provided funding to CDC and DTBE, funding was also provided to the Office of Refugee Resettlement (ORR) to provide refugee benefits to the Ukrainian newcomers. This is the same refugee benefit that all refugees are eligible for, except for the initial refugee reception and

placement program.[30] They are not being connected with housing through local resettlement agencies since they should be getting that through their supporter. The ORR has a nice fact sheet that explains benefits for Ukrainian humanitarian parolees.[31]

ACET Business Session

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

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

Business Item 1: Approval of Previous ACET Meeting Minutes

A motion was properly placed on the floor by Dr. Ahmed and seconded by Dr. Temesgen to accept the minutes from the December 14-15, 2021 ACET meeting. With no further discussion or changes, the motion to accept the minutes as written carried unanimously with no abstentions or opposition.

Business Item 2: Formation of a Biennial Letter Workgroup

A motion was properly placed on the floor by Dr. Belknap and seconded by Dr. Loeffler to form a workgroup whose responsibility it will be to discuss priority areas for the biennial letter to HHS on the ongoing activities to eliminate TB in the US as stipulated in the Charter. The workgroup will report on activities and recommendations in the December 2022 ACET meeting for member discussion and vote. With no further discussion or changes, the motion carried unanimously with no abstentions or opposition.

Business Item 3: Formation of a Workforce Impact Workgroup to Define COVID-19's Impact on the TB Public Health Workforce

A motion was properly placed on the floor by Dr. Belknap, for which Dr. Sosa-Bergeron made a motion that Dr. Ahmed seconded, to form a workgroup to define the questions related to the impact of COVID-19 on TB public health workforce capacity, with deliverables to: 1) define the impact of COVID-19 on the TB public health infrastructure capacity and staffing with a report in the meeting December 2022 ACET meeting; and 2) present the final letter with a summary of recommendations during the June 2023 ACET meeting for member discussion and vote. With no further discussion or changes, the motion carried unanimously with no abstentions or opposition.

[30] https://www.state.gov/refugee-admissions/reception-and-placement/
[31] https://www.acf.hhs.gov/orr/fact-sheet/benefits-ukrainian-humanitarian-parolees

ACET Discussion

Dr. Loeffler suggested the following ideas that the TB Workforce Workgroup might consider:

- Long-term support for public health infrastructure / workforce / public confidence. TB did not worsen per se during the pandemic because there was institutional memory in public health, which would not last forever, and lock downs muted spread.
- Continued work to promote consideration of TB as a diagnostic possibility in health care providers. Blinders will come back on during the next respiratory pandemic.
- Consideration of creative solutions to make drugs and technologies available to US and global patients, so that local lack of profitability does not dissuade pharma from pursuing approval.
- Support TB elimination. Study and give guidance around value of re-treatment after substantial exposure of folks who have previously been treated for TB or LTBI.

Dr. Chen recalled that NTCA is supporting a deep assessment of the COVID-19 pandemic's impact on TB.

Dr. Stout confirmed this to be accurate but pointed out that NTCA has no funding to support that effort, which is fairly ad hoc.

Dr. Behm agreed that NTCA could partner on the ACET TB Workforce Workgroup.

Regarding an inquiry about procedure, Dr. LoBue explained that any letters, recommendations, resolutions, et cetera could be developed within a workgroup but must be voted upon and approved in a public ACET meeting.

Business Item 4: Advice Requested from ACET

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

December 2021 Topics	Action
1) **Study 31** • ACET expressed interest in making sure that the guidance for the Study 31 regimen aligns with the guidance and recommendations for the standard 6-month regimen. For instance, for paucibacillary extrapulmonary disease there are no randomized studies for any regimen in lymphatic TB or pleural TB. • ACET suggests including language that is at least consistent with the 2016 guidelines pertaining to the use of the standard regimen in such scenarios.	• DTBE considered comments and made Study 31 MMWR guidance permissive consistent with 2016 recommendations; Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022 | MMWR (cdc.gov)
2) **LTBI Campaign** • ACET expressed an interest in CEBSB considering communication strategies that include and are considerate of incarcerated populations and other congregate settings such as shelters. • There is interest among ACET members in expansion of the LTBI campaign to incarcerated, shelter, ethnic, and pediatric populations.	• DTBE included more children in the LTBI campaign and will expand campaign further based on availability of resources.

December 2021 Topics	Action
• Perhaps images of children could be added to the campaign materials to express the idea of cocooning the child. • It is not clear whether the LTBI campaign is applicable to corrections and other congregate settings, given that it is trying to engage individuals and their providers. Corrections might be more about training and education among medical staff and persons in facilities versus television or media advertisements.	

June 2022 Topics	Action
1) **Global Electronic Medical Records** • A global EMR platform is needed to help track screening and treatment for TB and other disease conditions among immigrants and refugees entering the US.	• TB Branch/DGMQ should move forward on the development of a simple global EMR that allows central access to the key pieces of information needed to perform TB screening for immigrants and refugees coming into the US. • A unified platform for the electronic collection of information and transfer of data of could be used for other disease conditions as well. • Incorporate data modernization efforts.
2) **Pediatric Populations** • ACET expressed a strong interest in inclusion of the pediatric population in research.	• A strong statement is needed about inclusion of pediatric populations in trial design/research across groups. • Pediatric LTBI needs to be considered. • ACET's scope must be taken into consideration. For instance, ACET is not going to provide specific advice or comments back to NIH pertaining to the inclusion of children and trials. Instead, ACET's advice will focus on recommendations to HHS and CDC. • A letter to HHS must include only recommendations that are within ACET's purview.
3) **Diagnostics and Drug Availability** • ACET expressed a strong interest in domestic accessibility to diagnostics and treatment being used globally. • The availability of medications and diagnostics, particularly if fluoroquinolones are going to be used more regularly as a first-line regimen, given that susceptibility results will be needed quickly. The lack of access to the GeneXpert® cartridge for detecting fluroquinolone resistance is a need. • Consider ways for which the process for approval could incentivized or simplified for TB, which is many ways is an orphan disease in the US.	• Brainstorm how to incentivize manufacturers to bring their TB diagnostic products and treatments to the US market. • ACET should investigate the barriers from their perspective and what would be an acceptable incentive
4) **Isolation and Quarantine** • There is a great deal of variability outside of congregate settings and hospitals that does not align with the science. • In some cases, this is very problematic, given that smears and smear conversions are still used. • There are anecdotes of people being kept in isolation at home for extended periods of time.	• Develop more structured recommendations around isolation and quarantine of outpatients with TB, recognizing that it is a challenge with limited data.

June 2022 Items Voted Upon	Action
1) **Biennial Letter Workgroup** • Continue to work to promote consideration of TB as a diagnostic possibility among health care providers. Blinders will come back on during the next respiratory pandemic. • Consider creative solutions to make drugs and technologies available to US and global patients so that local lack of profitability does not dissuade pharma from pursuing approval. • Support TB elimination. Study and give guidance around value of re-treatment after substantial exposure of folks who have previously been treated for TB or LTBI.	• Discuss priority areas for the biennial letter to HHS on the ongoing activities to eliminate TB in the US as stipulated in the Charter. • Draft letter/recommendations and provide an update during the December 2022 ACET meeting.
2) **TB Workforce Workgroup** • ACET/NTCA could partner on the ACET TB Workforce Workgroup. • Long-term support is needed for public health infrastructure / workforce / public confidence. TB did not worsen per se during the pandemic because there was institutional memory in public health, and lock downs muted spread.	• Define questions related to the impact of COVID-19 on public health TB workforce capacity. • Draft letter/recommendations and provide an update during the December 2022 ACET meeting. • Present the final letter/summary recommendations to HHS and CDC during the June 2023 ACET meeting for ACET feedback and final edits. • Presentation on the questions defined related to the impact of COVID-19 on public health workforce capacity, with deliverables to provide an update during the December 2022 ACET meeting and present final summary recommendations.

Business Item 5: Future Agenda Items

Dr. Belknap invited members to suggest potential topics of interest for future meetings. During this session, the following topics of interest were suggested for consideration:

Presenter	Agenda Item
CDC	• A theme of this 2-day meeting was that there are a lot of interesting efforts underway by others, but ACET is supposed to evaluate and provide advice to CDC. Therefore, it would be helpful to hear more specific information about the challenges faced by CDC's TB Program and what specific advice ACET could provide that would be beneficial. • Perhaps CDC could dedicate some resources to systematically assess the challenges to public health workforce and confidence in public health. • Perhaps presentations to ACET in the future should be tailored around specific issues upon which ACET can provide concrete advice to CDC. For instance, the sessions on NIH clinical trials on TB and on the FDA were very informative, but perhaps ACET members would like to hear how that compares to what the work of CDC and TBTC. • It would be beneficial to hear about CDC's expectations for program evaluation products in the setting of shrinking funding and resources in the context of the public health workforce and everything else.
TBTC	• Discuss how TBTC engages with other entities to ensure that the research being conducted is thoughtful and not duplicative. • Discussion about barriers to efficiently conducting research, such as bottlenecks at the data center.
Approach representatives from: • TB Elimination Alliance • Diabetes Association • Migrant Clinicians Network • Stop TB USA	• Presentation regarding the pilot project for TB and hepatitis B screening, which could be used as an example in the future.
Infectious Diseases Board of Scientific Counselors (BSC)	• Determine the status of the Infectious Disease BSC and the ability of the ACET Chair to participate in the BSC meetings and update ACET on this.
	• Follow-up on nitrosamines and drug shortages.
	• Follow-up on Ukrainian evaluations and TB impact.

Presenter	Agenda Item
	• Follow-up on clofazimine.
NCTA	• Issues around pregnancy, severe disease, female genital tuberculosis (FGTB).
	• Presentation on isolation and quarantine of outpatients with TB to help ascertain what advice/recommendations ACET might be able to provide on this topic.

Business Item 6: Future ACET Meeting Dates

A motion was properly placed on the floor by Dr. Belknap, for which Dr. Sosa-Bergeron made a motion that Ms. Steward-East seconded, to approve the proposed June 6-7, 2023 and December 12-13, 2023 ACET meetings. With no further discussion or changes, the motion carried unanimously with no abstentions or opposition.

Public Comment

Wendy Thanassi MA, MD, MRO
American College of Occupational and Environmental Medicine

Good morning Dr. LoBue, DTBE, and ACET members. Thank you for allowing us this time to make a public comment. I am Dr. Wendy Thanassi. I am here today representing the American College of Occupational and Environmental Medicine (ACOEM), who are seeking a liaison position to ACET. The COVID-19 pandemic redefined the way the world sees the workforce—those who literally put their lives on the line keep this great nation afloat. Amongst others, the transportation industry, grocery, oil and gas, educational, and of course, healthcare workers (HCW). Beside all of them in every corner of the workforce and every step of the way were the medical professionals who care for them on the job—the Occupational Medicine Physicians. The US has a population of about 333 million, of which 63% or 264 million people are employed. Your grocery clerk could be 16 years old; your child's principal could be 66. The majority of hours we are awake in a day, we are at work. The majority of days during the week, we are at work. The majority of years of our lives, we are at work. The majority of people in the US are at work. Thus, ACOEM clinicians have unparalleled access to provide education and treatment to their employee patients. Who are the 264 million US workers? 45 million are non-US-born. Some work in coal mines, some work on international oil rigs, and 22 million of us are HCW. This leads us to TB. The CDC DTBE has led the nation to historically low rates of TB in the US. In 2018, we had only 9,000 active infections recorded. I chose that because it was pre-pandemic, so it may be an accurate number. However, the same year, we had an estimated 18 million cases of LTBI. That means there are approximately 14.4 million workers with LTBI. Over 11.5 million of those are foreign-born, and several million of those are HCP, which brings us back to occupational medicine. Over 3,000 MDs in ACOEM have screened and tested employees for TB for decades. We are perfectly poised to be foot soldiers in the effort to eliminate the latent TB reservoir. ACOEM physicians have unique and substantial access to these over 14 million latently infected workers. We are experts in the preventive and clinically care of infectious diseases in employees. We are also experts in employer/employee regulations, legislative, privacy, and regulatory issues of the workforce. The Occupational Physicians at ACOEM therefore respectfully request a liaison position to ACET to advise, collaborate, and explore opportunities with DTBE for treating latent TB in our workforce. This approach carries the promising potential to substantially impact our collective goal of eliminating TB in the US. Thank you for the time.

Closing Session

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

In closing, Dr. Belknap reminded everyone that the upcoming approved ACET meeting dates are as follows:

- December 13-14, 2022
- June 6-7, 2023
- December 12-13, 2023

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 transmission is below the threshold. Given that this seems unlikely, the December 2022 meeting probably will be in the Zoom format as well.

Dr. Belknap thanked everyone for their time, attention, and dedication to this topic and this group. With no further discussion or business brought before ACET, the meeting was officially adjourned at 12:04 pm on June 22, 2022.

Chair's Certification

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

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

Attachment 1: Participants' Directory

ACET Members Present

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

ACET *Ex-Officio* Members Present

Drs. Naomi Aronson
US Department of Defense

Dr. Amy Bloom
US Agency for International Development

Dr. Karen Elkins
Food and Drug Administration

Dr. Jonathan Iralu
Indian Health Service

Dr. Edith (Edie) Lederman
U.S. Immigration and Customs Enforcement

Dr. Lawrence Kline
US Section, US-Mexico Border Health Commission

Mr. Stephen Martin National Institute for Occupational Safety and Health

Dr. Gary Roselle
Department of Veteran Affairs

Dr. Ronald Wilcox
Health Resources and Services Administration

CAPT David Wong
Office of Minority Health

ACET *Ex-Officio* Members Absent

Dr. Mamodikoe Makhene
National Institutes of Health

ACET Liaison Representatives Present

Dr. Shama Desai Ahuja
Council of State and Territorial Epidemiologists

Dr. Robert Benjamin
Stop TB USA

Dr. Heidi Behm
National Tuberculosis Controllers Association

Valerie Adelson
American Thoracic Society

Ms. Susan Rappaport
American Lung Association

Dr. Jonathon Golub
International Union Against TB and Lung Disease

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

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

Dr. Sylvie Stacy
National Commission on Correctional Health

Dr. Lornel Tompkins
National Medical Association

Dr. Daphne Ware
Association of Public Health Laboratories

Dr. David Weber
Society for Healthcare Epidemiology of America

Elizabeth Lovinger
Treatment Action Group

Dr. Amee Patrawalla
American College of Chest Physicians

ACET Liaison Representatives Absent

Dr. Mayleen Ekiek
Pacific Island Health Officers Association

Dr. John Hellerstedt
Association of State and Territorial Health Officials

Dr. Ilse Levin
American Medical Association

Dr. Howard Njoo
Public Health Agency of Canada

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

Dr. Susan Ray
Infectious Disease Society of America

ACET Designated Federal Officer

CAPT Deron Burton
NCHHSTP Deputy Director

CDC Representatives

Leeanna Allen
Rebeccann Pope Alley
Martha Boisseau
Kevin Borden
Beth Bouwkamp
Terry Chorba
Marah Condit
Meredith Dixon
Maryam Haddad
Tempest Hill
John Jereb
Awal Khan
Kathryn Koski
Ekaterina Kurbatova
Gabriella Lamb
Adam Langer
Philip LoBue
Joan M. Mangan
Suzanne Marks
Susan McClure
Staci Morris
Donna Hope Wegener
Jonathan Mermin
Erin Lee Miller
Maria Sessions
Noah Schwartz
Kimberly Schildknecht
Kimberly Skrobarcek
Erin Thomas
Stephanie Thomas
Marylin Wolff

Guest Presenters

Dr. Irina Gelmanova
Dr. Melanie Goth
Dr. Erin Lee Miller
Dr. Ramya Gopinath
DrPH. Amera Khan
Dr. Kimberly Skrobarcek

Members of the Public

Lisa Armitige
Rajita Bhavaraju
Marla Clifton
Susan Cooley
Jason Cummins
Charles Daley
Garrett
Sarah Gordon, MN,
DOH
Amanda Khalil
Narita Masahiro
Alfred Lardizabal
Claire Leback
D Lee
Andrea Liptack
Patricia Miglowiec
Amy Painter
Lakshima Peddareddy
Tara Rhodes
A Sam
Brienna Sylvester
Shu Hua Wang
Bobby Watts

Attachment 2: Glossary of Acronyms

Acronym	Definition
ACET	Advisory Council for the Elimination of Tuberculosis
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AI/AN	American Indian/Alaskan Native
AIDS	Acquired Immunodeficiency Syndrome
App	Application
ASH	Assistant Secretary for Health
ATS	American Thoracic Society
BDQ	Bedaquiline
BLA	Biologics License Applications
BOP	Federal Bureau of Prisons
BPaL	Bedaquiline, Pretomanid, and Linezolid
CBER	Center for Biologics Evaluation and Research
CBO	Community-Based Organization
CDC	Centers for Disease Control and Prevention
CFZ	Clofazimine
CoE	Centers of Excellence
COI	Conflict of Interest
CRH-VMD	Cho Ray Hospital Visa Medical Department
CXR	Chest X-Ray
DC	District of Columbia
DFO	Designated Federal Official
DGMQ	Division of Global Migration and Quarantine
DHCPP	Division of High Consequence Pathogens and Pathology
DHS	Department of Homeland Security
DIS	Disease Intervention Specialists
DoD	Department of Defense
DOT	Directly Observed Therapy
DST	Drug-Susceptibility Testing
DSTDP	Division of STD Prevention
DTBE	Division of Tuberculosis Elimination

Acronym	Definition
DTG	Dolutegravir
DUA	Data Use Agreement
DVH	Division of Viral Hepatitis
EBA	Early Bactericidal Activity
EDN	Electronic Disease Notification
eDOT	Electronic Directly Observed Therapy
EHE	Ending the HIV Epidemic
EHR	Electronic Health Record
EMR	Electronic Medical Record
ET	Eastern Time
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
FGTB	Female Genital Tuberculosis
GAIN	Generating Antibiotic Incentives Now
GDF	Global Drug Facility
GIMS	Genotyping Information Management System
GS	General Schedule
HBV	Hepatitis B Virus
HCP	Healthcare Providers/Professionals
HCV	Hepatitis C Virus
HHC	Household Contact
HHS	(United States) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
ICE	Immigration and Customs Enforcement
IGRA	Interferon-γ Release Assay
IHSC	ICE Health Service Corps
IMM	Irreversible Morbidity and Mortality
IND	Investigational New Drug
INH	Isoniazid
IOM	International Organization for Migration
LGBT	Lesbian, Gay, Bisexual, and Transgender
LHD	Local Health Department
LPAD	Limited Population Pathway for Antibacterial and Antifungal Drugs
LPRs	Lawful Permanent Residents
LTBI	Latent Tuberculosis Infection
MDDR	Molecular Detection of Drug Resistance
MDR-TB	Multidrug-Resistant Tuberculosis
MiMOSA	Migrant Management Operational Systems Application
MMWR	*Morbidity and Mortality Weekly Report*
MRS	Modified Rankin Scale
MSM	Men who have Sex with Men

Acronym	Definition
MTB	Mycobacterium Tuberculosis
NACCHO	National Association of County and City Health Officials
NCE	New Chemical Entities
NCHHSTP	National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention
NCIPC	National Center for Injury Prevention and Control
NDA	New Drug Application
NGO	Non-Governmental Organizations
NH/PI	Native Hawaiian and Pacific Islander
NIH	National Institutes of Health
NTCA	National Tuberculosis Controllers Association
NTP	Vietnam National TB Programme
NTSS	National Tuberculosis Surveillance System
OAW	Operation Allies Welcome
OHE	Office of Health Equity
OMHHE	Office of Minority Health and Health Equity
ORR	Office of Refugee Resettlement
Pa	Pretomanid
PCP	Primary Care Providers
PCR	Polymerase Chain Reaction
PEP	Pre-Exposure Prophylaxis
PK	Pharmacokinetics
PrEP	Pre-Exposure Prophylaxis
Project ARMS	Project Afghan Resettlement Medical Screening
PTOPS	Preventing TB Overseas Pilot Study
PWID	Persons Who Inject Drugs
PZA	Pyrazinamide
QIPD	Qualified Infectious Product Designation
RPT	Rifapentine
RVCT	Report of Verified Case of Tuberculosis
SAMHSA	Substance Abuse and Mental Health Services Administration
SAT	Self-Administered Therapy
SCC	Sputum Culture Conversion
SDOH	Social Determinants of Health
SEOIB	Surveillance, Epidemiology, and Outbreak Investigations Branch
SGRQ	St. George's Respiratory Questionnaire
SIVs	Special Immigrant Visas
SOC	Standard of Care
SOP	Standard Operating Procedures
SSP	Syringe Service Programs
SUD	Substance Use Disorder
TA	Technical Assistance

Acronym	Definition
TAG	Treatment Action Group
TB	Tuberculosis
TB GIMS	TB Genotyping Information Management System
TBESC	Tuberculosis Epidemiologic Studies Consortium
TBM	Tuberculous Meningitis
TBTC	Tuberculosis Trials Consortium
TCID	Texas Center for Infectious Disease
The Union	International Union Against TB and Lung Disease-North America Region
TPT	TB Preventive Treatment
UCSF	University of California-San Francisco
US	United States
USCIS	US Citizenship and Immigration Services
USG	US Government
Vietnam NTP	Vietnam National TB Programme
WG	Working Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB