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

Hybrid Meeting of the
Advisory Council for the Elimination of Tuberculosis
June 25-26, 2024

Record of the Proceedings

TABLE OF CONTENTS

Table of Contents

Minutes of the Meeting 3

June 25, 2024 Opening Session 4

NCHHSTP Director's Report 5

DTBE Director's Update 10

Current ACET Recommendations Update 15

Panel 1: Tuberculosis (TB) in New Arrivals 17

Panel 2: Regulations of Laboratory Developed Tests (LDTs) and the Impact on Tuberculosis (TB) Testing in the United States (US) 27

National Tuberculosis Controllers Association (NTCA) Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary TB in Community Settings 40

Workgroup (WG) Updates 49

Day 1 Wrap-Up and Adjourn 53

June 26, 2024 Opening Session 54

Public Comment 54

Business Session 56

Closing & Adjourn 62

Chair's Certification 63

Attachment 1: Participant Directory 3

Attachment 2: Glossary of Acronyms 6

Attachment 3: Written Public Comments 10

Attachment 4: Workgroup Slides 12

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

ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
June 25-26, 2024

Minutes of the 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 hybrid meeting of the Advisory Council for the Elimination of Tuberculosis (ACET). The proceedings were held on June 25-26, 2024 beginning at 9:38 AM Eastern Time (ET) on June 25, 2024 and 10:00 AM on June 26, 2024.

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 hybrid 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 25, 2024 Opening Session

Lynn Sosa, MD
Director of Infectious Disease and State Epidemiologist
Connecticut Department of Public Health
ACET Chair

Carla Winston, PhD, MA
Associate Director for Science
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
ACET Designated Federal Officer

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

Dr. Sosa called the meeting to order at 9:30 AM ET on June 25, 2024. Marah Condit provided meeting ground rules. She noted that members of the public would have an opportunity to provide comments during the second day of the meeting at 10:15 AM ET. Dr. Winston welcomed participants and conducted a roll call to confirm the attendance of ACET voting members, *ex-officio* members, and liaison representatives. She explained that ACET meetings are open to the public and all comments made during the proceedings are a matter of public record. She 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
Rajita Bhavaraju, PhD, CHES Rutgers, The State University of New Jersey	No conflicts
Lisa Chen, MD University of California, San Francisco	No conflicts
William Glover, PhD, D(ABMM), MT(ASCP) North Carolina State Laboratory of Public Health	No conflicts
Kelly John Holland, MD Lynn Community Health Center	No conflicts
Ann Loeffler, MD TB Controller County of Santa Clara, California	No conflicts
Kathleen A. Ritger, MD, MPH Chicago West Side Center for Disease Control	No Conflicts
Lynn Sosa, MD Connecticut Department of Public Health	No conflicts
Jason Stout, MD, MHS Duke University Medical Center	No conflicts

The roll call confirmed that the 21 voting and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on June 25, 2024. The roll was called subsequent to each break and lunch, with a quorum established each time throughout the day. Dr. Winston welcomed the following new members:

- ❑ Rajita Bhavaraju, PhD, CHES: Deputy Director, Global Tuberculosis Institute Instructor, School of Public Health Rutgers, The State University of New Jersey

- ❑ Kelly John Holland, MD: Primary Care Family Physician, Lynn Community Health Center, Massachusetts

Dr. Winston expressed gratitude to Drs. Ahmed and Loeffler for agreeing to extend their terms for 180 days. In addition, she announced that the next ACET meeting would be convened on December 3-4, 2024.

Dr. Sosa, the new ACET Chair, welcomed everyone and thanked them for attending this ACET meeting.

NCHHSTP Director's Report

Jonathan Mermin, MD, MPH
Director, National Center for HIV, Viral Hepatitis, STD and TB Prevention
Centers for Disease Control & Prevention

Dr. Mermin provided the NCHHSTP Director's Report, beginning with leadership updates. Dr. Renata Ellington is now the NCHHSTP Deputy Director for Management, Operations, Communications, and Policy. Dr. Kirk Henny is serving as the Acting Associate Director for Health Equity. Dr. Robyn Neblett Fanfair is the new Director of the Division of HIV Prevention (DHP). Dr. Bradley Stoner was selected as the Director of Division of STD Prevention (DSTDP), starting on July 28, 2024.

Last year, NCHHSTP awarded a new cooperative agreement to support our policy as a public health intervention initiative through two distinct but integrated components: (1) conducting in-depth law and policy surveillance and research to better understand the association between laws and health outcomes and disparities, and (2) a robust technical assistance center to aide state and local public health leaders in navigating complex law and policy environments. As part of this work, our funded recipient the National Network of Public Health Institutes (NNPHI) recently launched the Policy Innovation Exchange (PIX) for HIV, Viral Hepatitis, STD, and TB Prevention, or PIX for short. PIX is a collaborative effort between CDC, NNPHI, and five technical assistance partners: Morehouse School of Medicine, NASTAD, National Viral Hepatitis Roundtable, NACCHO, and the Network for Public Health Law. Our online PIX portal serves as a "one stop shop" where state and local public health leaders can request individualized TA on law and policy issues tailored to the unique needs of their specific jurisdictions. We are proud to offer this new first-of-its-kind national resource to support leaders looking to improve public health outcomes for HIV, viral hepatitis, STDs, and TB in their local communities.

NCHHSTP continues to support a wide range of modeling activities including the assessment of morbidity and mortality projections, the burden and costs of diseases, costs and cost-effectiveness of interventions, population-level program impact, and optimized resource allocation. On April 8, 2024, applications closed for the new 5-year cycle of the NCHHSTP Epidemiologic and Economic Modeling Agreement (NEEMA) CDC-RFA-PS-24-00281,[1] which is set to begin September 30, 2024. The Program and Performance Improvement Office, in collaboration with experts across NCHHSTP, has supported the American Medical Association (AMA) to develop and release an online toolkit[2] to help physicians and other health care professionals increase routine screenings for HIV, sexually transmitted infections (STIs), viral hepatitis, and latent tuberculosis infection (LTBI). The toolkit shares best practices and strategies for screening programs, specific to community health centers (CHCs) and emergency departments (EDs).

DSTDP released 2 new reports. The first was "*Vital Signs*: Missed Opportunities for Preventing Congenital Syphilis — United States, 2022."[3] There was nearly a 1000-fold increase in congenital syphilis over the past decade in the US, which has been coincidental with an increase in syphilis in women of childbearing age. A worldwide increase has occurred in syphilis and gonorrhea, the US has been particularly hard-hit. This publication highlights, about 40% of congenital syphilis occurs because women are not receiving prenatal care. The other 60% of cases are essentially due to failings within the system, such as receiving either no or non-timely testing or no, or inadequate treatment during pregnancy. Models, which were used for HIV perinatal transmission prevention, treat these cases as sentinel events, but some of the issues are bigger than the healthcare setting. With over 3,700 cases last year, it is a major challenge to treat every case as a sentinel event.

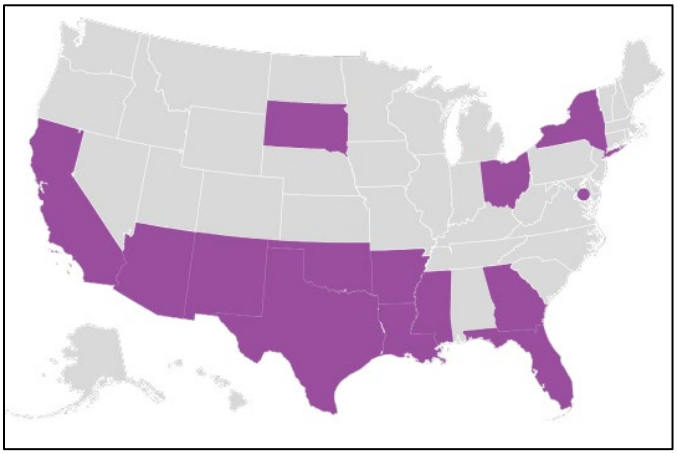
The second new report released was "Sexually Transmitted Infections Surveillance, 2022."[4] This annual report showed STIs continue to climb in 2022. In 2022, more than 2.5 million cases of syphilis, gonorrhea, and chlamydia were reported in the United States. While chlamydia and gonorrhea saw 10-year increases of 18% and 95%, syphilis and congenital syphilis saw staggering increases of 267% and 937%. Chlamydia trends are dependent on routine screening, which changed with the COVID-19 pandemic. Cases appear to be leveling off, but monitoring continues. Gonorrhea cases decreased by approximately 9% from 2021 to 2022, with 2023 data being analyzed to determine whether this is consistent. The syphilis and congenital syphilis epidemics signal an urgent need for swift innovation and collaboration from all STI prevention partners.

In an effort to address this, the HHS Assistant Secretary for Health (ASH) established the multi-agency National Syphilis and Congenital Syphilis Syndemic (NSCSS) Federal Task Force. The goals of the NSCSS Federal Task Force are to: 1) reduce rates of primary and secondary syphilis and congenital syphilis; and 2) reduce syphilis health disparities across race, ethnicity, and other factors. The task force first met in August 2023 and has established the goals of act quickly and strategically to reduce rates of primary and secondary syphilis and congenital syphilis in the United States. To do this the task force has identified and engaged 14 priority jurisdictions (shown in purple on the map). These jurisdictions cover nearly 75% of congenital syphilis cases and 55% of primary and secondary syphilis cases nationwide to focus on targeted

---

[1] https://www.cdc.gov/nchhstp/neema/funding -opp-announcement.html
[2] https://www.ama-assn.org/delivering-care/public-health/routinely-screen-hiv-stis-viral-hepatitis-and-latent-tb-infection
[3] https://www.cdc.gov/mmwr/volumes/72/wr/mm7246e1.htm
[4] https://www.cdc.gov/std/statistics/2022/default.htm

interventions. To date, some of the task force actions have included: 1) Conducting briefings with external partners, including the American College of Obstetricians and Gynecologists, the Associations of State and Territorial Health Officials, the National Alliance of State & Territorial AIDS Directors, the National Coalition of STD Directors, and the National Association of County and City Health Officials to explore collaboration opportunities; 2) Supporting a temporary import of Extencilline, (benzathine benzylpenicillin) to address the ongoing shortages of Bicillin® L-A in the United States; 3) Convening multiple workshops to address disparities, interconnected health issues, and research gaps; and 4) Working with agencies to issue funding flexibility letters to grantees for syphilis care.



DSTDP issued 2 sets of guidelines: "CDC Laboratory Recommendations for Syphilis Testing, United States, 2024"[5] and "CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024."[6] Doxy PEP has proven to reduce the risk of getting a bacterial STI for gay, bisexual, and other men who have sex with men and transgender women at increased risk for these infections (specifically, syphilis, chlamydia, and gonorrhea). According to the guidelines, 200 mg taken once within 72 hours after sex has been shown to reduce syphilis and chlamydia infections by over 70% and gonococcal infections by approximately 50%. This inexpensive, readily available intervention could be used at home. Doxy PEP represents the first new STI prevention tool in decades, at a time when innovation in the nation's fight against STIs is desperately needed.

DHP issued a new Notice of Funding Opportunity (NOFO), PS24-0020: Capacity Building Assistance (CBA) for HIV Prevention Programs to End the HIV Epidemic (EHE) in the United States. This NOFO, funded at $127,500,000 anticipated over 5 years, supports the network of funded providers, established and referenced as the CBA Provider Network (CPN), to implement the following 6 inter-related program components:

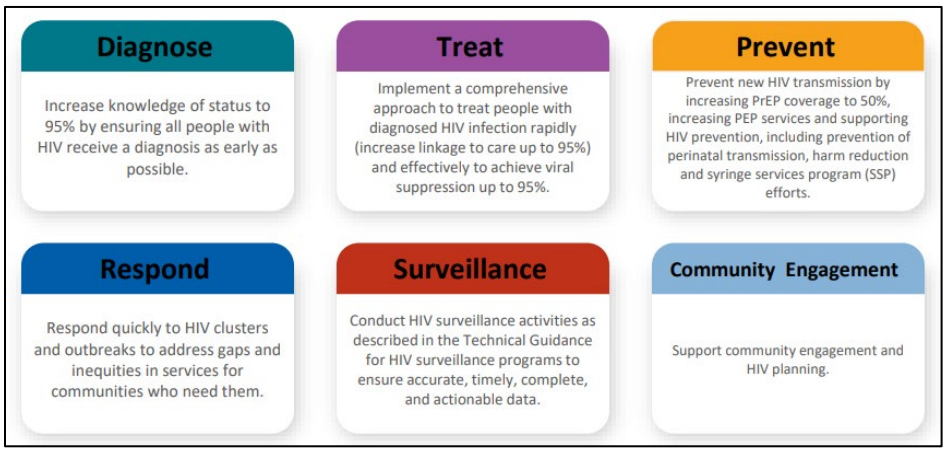
- ❑ Component A: Technical Assistance to Enhance Integrated HIV Activities for Health Department Jurisdiction
- ❑ Component B: Instructor-led Training for High-Impact HIV Prevention Programs
- ❑ Component C: eLearning Training for High-Impact HIV Prevention Programs
- ❑ Component D: Technical Assistance for High-Impact HIV Prevention Programs

[5] https://www.cdc.gov/mmwr/volumes/73/rr/rr7301a1.htm
[6] https://www.cdc.gov/mmwr/volumes/73/rr/rr7302a1.htm

- ❑ Component E: Organization/Workforce Development and Management for Community-Based Organizations
- ❑ Component F: CPN Resource and Coordination Center

In addition, DHP issued PS24-0047: High-Impact HIV Prevention and Surveillance Programs for Health Departments. In this new NOFO for health departments, the division is integrating 2 funding streams to better align the work in health departments on that goal. While we do not have the funding or mandate to expand EHE funding to the entire nation, we can and will be applying lessons learned through EHE across the country. NOFO – 0047 will run for 5 years to align with our sister agency's NOFOs and ending in the 2029 fiscal year. Sixty Health Departments will be eligible for funding which translates to, anticipating level funding, a yearly investment of $485M and a total 5-year investment of around $2.4 billion.

The core strategies remain the same as shown here:



Approximately 87% of people with HIV in the US are estimated to know their status. The hope is to increase that percentage with routine screening and efforts such as free internet-order home-based HIV tests. The major obstacle for expansion of home-based testing is the high cost of the only Food and Drug Administration (FDA) HIV self-test approved in the US. The goal of the treatment strategy is intended to prevent HIV transmission to others, help those with HIV avoid opportunistic infections, and prevent mortality. There is a larger framework of social determinants of health (SDOH) and viral suppression, which requires considerable effort from healthcare and the public health system. The pillar for prevention seeks to prevent new HIV transmission by increasing Pre-Exposure Prophylaxis (PrEP) coverage to 50% and increasing post-exposure prophylaxis (PEP) services such as syringe services program (SSP) efforts. After 2 decades of decreases HIV incidence among people who inject drugs (PWID), one of the greatest successes of the epidemic is the leveling off of injection drug use-associated HIV for about 6 to 7 years. In terms of the response pillar, the DHP now has a branch that is targeted toward outbreaks that is in some ways modeled after what TB has in terms of surveillance and community engagement. Using this strategy, people in the communities most affected by HIV are part of the solution and guide the processes at the local level.

There are changes in this NOFO to improve impact and apply EHE concepts to our whole Health Department portfolio. DHP has significantly increased the flexibility of health departments to determine the HIV prevention activities that will best fit the community needs and achieve the goals. Funding recipients will have the freedom to build tailored and comprehensive HIV prevention and surveillance programs designed based on specific local needs, policies, and

resources. To account of increased cost of operations, the funding floor was increased from $1M to $1.2M to ensure all jurisdictions can continue providing essential HIV prevention and surveillance activities. This NOFO has added ability for CDC to fund other organizations to ensure continuity of critical programs if HD is unable or unwilling to receive CDC funding. This NOFO reflects National, HHS, and CDC strategic priorities – including community engagement, health equity, syndemics, and whole person approaches to HIV prevention. Combining this NOFO will reduce reporting burden and also move the start of the NOFO further into the fiscal year in the hopes of avoiding funding delays due to continuing resolutions. This NOFO encourages whole person care approaches allowing tailored interventions that can help dismantle structural barriers to accessing care, eliminate stigma, and optimize the health of people with HIV and people who can benefit from prevention services. Part of this is an investment in HIV-related syndemics such as STIs and viral hepatitis and allowing up to 10% of funding to be used for these syndemic issues. EHE results from CDC-funded programs between 2021 and 2023 show approximately 600,000 free HIV self-test kits were distributed; among 831,000 HIV tests, 3,000 people were newly diagnosed; over 55,000 persons were prescribed PrEP; there were 261 SSPs, more than 60% of which were mobile; and over 200 clusters were detected.

Between March 2022-March 2023, CDC collaborated with HRSA to hold 15 community engagement sessions across 10 regions. In these engagement sessions with diverse partners and community leaders we discussed community-driven solutions to ending the HIV epidemic – identifying local challenges and innovative solutions as it relates to PrEP. These sessions engaged 1,684 people through 16 in-person meetings across 10 regions, including an in-person Spanish language session. CDC also convened community engagement sessions in collaboration with DSTDP, DHP, NACCHO, SAC, and regional community conveners to host in-person engagement sessions with community-led and community-serving organizations in the Southeast. The aim of these sessions was to discuss barriers and opportunities to promote health equity, expand community engagement, and understand local programming around syndemic and whole person approaches.

In January, CDC updated the Viral Hepatitis Surveillance and Case Management guidance to align with the updated hepatitis B case definition approved by the Council of State and Territorial Epidemiologists for 2024. The Division of Viral Hepatitis (DVH) released the *Viral Hepatitis Surveillance Report – United States, 2022*[7] and the *2024 Viral Hepatitis National Progress Report*[8] in April 2024. Data from this report shows the multi-year, multi-jurisdiction, massive outbreak of hepatitis A primarily among people experiencing homelessness or using drugs has been declared over by most states. This outbreak required an enormous amount of outreach and vaccination by health departments and community organizations. A cohort remains of people who were not vaccinated as children who are still vulnerable to hepatitis A. After annual increases during 2015–2019, the rate of hepatitis A decreased 88% between 2019 and 2022. The rate of acute hepatitis B remained stable between 2021 and 2022 following annual decreases during 2020–2021. This likely reflects successful vaccination efforts, including the childhood hepatitis B immunization recommendation which is an unsung public health success story. While there were massive increases in acute hepatitis C coincident with the opioid epidemic, the rate of acute hepatitis C decreased 6.3% between 2021 and 2022 after annual increases during 2015–2021. The decline likely occurred, in part, due to prevention initiatives like syringe services programs and changes in drug use patterns, including a transition from injection

[7] https://www.cdc.gov/hepatitis/statistics/2022surveillance/index.htm
[8] https://www.cdc.gov/hepatitis/policy/npr/2024/index.htm

to smoking. Over 1 million people who know they have hepatitis C have not been able to access treatment/cure, primarily due to insurance obstacles. Hepatitis C deaths have decreased, which is thought to be due to people who are older and experiencing severe disease receiving treatment. This does not address people who have acquired hepatitis C in the last 10 to 20 years. Although jurisdictional support for viral hepatitis is improving, great needs remain. CDC's partnerships with jurisdictional viral hepatitis programs have been strengthened through the Integrated Viral Hepatitis Surveillance and Prevention Funding[9] which began in May 2021, which is in Year 3 of the 5-year funding cycle. With technical assistance from CDC and NASTAD, the jurisdictions are building comprehensive surveillance programs, outbreak response protocols, expanding testing partnerships to reach the most impacted communities, establishing elimination plans, and providing comprehensive services to people who inject drugs through demonstration projects in 18 jurisdictions. Information is collected from grantees, which is reported back to them through a summarized presentation document that allows each health department to see how they are doing compared to their own goals and to other jurisdictions. There has been an ongoing effort to establish a national hepatitis C elimination program[10] in the US led by Dr. Francis Collins, the former Director of the National Institutes of Health (NIH). Great collaboration and extensive effort among multiple agencies have been put into the development of this concept, but it remains unfunded at this point. If the proposed national hepatitis C elimination initiative is enacted, that would be a game-changer to expand hepatitis treatment, prevention, and surveillance efforts.

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 the DTBE's FY24 budget and provisional 2023 TB surveillance data. The DTBE received an appropriation of $137 million, which is level with the FY23 budget. However, there also has been increased overhead and other internal costs (e.g., salaries, benefits, supplies, equipment) compared to FY23. Even with internal division funding cuts for travel and deferred hiring, this necessitates decreases in funding of external projects by 1.8%.

Provisional TB surveillance data were published in March 2024 in the *Morbidity and Mortality Weekly Report*.[11] Dr. LoBue noted that he added an important data point that was not included in the preliminary publication that would be included in the final dataset. Regarding TB cases and incidence rates in the US from 2013-2023, case counts and rates had been slowly decreasing prior to the COVID-19 pandemic and were potentially leveling off. With the onset of the pandemic in 2020, there was an unprecedented decrease in cases and case rates of approximately 20%. There were increases in cases and case rates over the next couple of years, which appeared to be a return to the pre-pandemic trend. However, there was a substantial increase in cases and case rates in 2023 at about 15% such that the number of cases was similar to those in 2013, with a case rate slightly below that.

---

[9] Integrated Viral Hepatitis Surveillance & Prevention for Health Departments | IVHSP | CDC
[10] https://pubmed.ncbi.nlm.nih.gov/36892976/
[11] *MMWR Weekly* / March 28, 2024 / 73(12);265–270; https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7312a4-H.pdf

Similar to prior years, about half of the cases occurred in 4 states with large populations: New York (n=894 cases), California (n=2,113 cases), Texas (n=1,234 cases), and Florida (n=624 cases). Another key variable is origin of birth among persons born in the US (n=2,323) and non-US-born persons (n=7,228). While about 65% to 72% of cases occur in non-US-born persons depending upon the year, the overall cases counts tended to track but diverged in 2023. While there were increases in both US-born and non-US-born persons from 2022 to 2023, the actual numbers showed that cases in US-born persons were lower in 2023 than in 2019 pre-pandemic. Regarding the preliminary data that were not included in the March 2024 *MMWR* among cases of non-US-born persons by time in the US from 2019–2023, there were approximately 850 who had been in the US less than 1 year in 2019. The number of cases decreased with the onset of the pandemic, rose quickly in 2022, but then increased in 2023 compared to 2019 with over 1500 cases to date—almost double the cases in 2019.

Stratified by race and ethnicity among US-born persons between 2013–2023, the total number of cases was less than pre-pandemic for most race and ethnicity categories, with the exception of Hispanic or Latino US-born persons. Regarding case rates per 100,000 by race and ethnicity, it is important to note that because the denominator is small for Native Hawaiian and other Pacific Islanders, there was considerable variation from year-to-year. Nevertheless, there has been an overall upward trend in this population. This corresponds anecdotally with a number of outbreaks occurring among Pacific Islanders, which includes children who were born in the US. Cases among most of the other groups are similar to or somewhat less than they were in 2019. Regarding stratification of TB cases among non-US-born persons by race and ethnicity between 2013–2023, the number of cases compared to 2019 was higher. For a number of the racial and ethnical groups, particularly the Hispanic and Latino and Black and African American groups, the number of cases has increased compared to 2019. The number of cases among Asian groups tended to be lower than in 2019. The cases rates for TB incidence among non-US-born persons by race and ethnicity, there was variation among Native Hawaiian or other Pacific Islander groups and those of multiple races due to small denominators. Nevertheless, rates among Native Hawaiian or other Pacific Islander groups have been increasing. Rates among Hispanic and Latino groups also increased from 2019. Rates among American Indian or Alaska Native (AI/AN) appear to have increased since 2019, but these groups typically do not fall within non-US-born persons, so this may be the result of data errors and/or unusual aberrations. A similar pattern is observed when the rates are stratified by ages with decreases pre-pandemic, subsequent increases during the pandemic years, and a return to 2019 rates or slightly higher in some of the younger age groups.

In summary of the provisional data, reported TB cases and incidence rates increased from 2022 to 2023, returning to case counts last observed in 2013. Case counts and incidence have increased every year since 2020—the onset of the pandemic. Increases were observed in every age group and among both US-born and non-US-born persons. Increases in case counts compared to 2022 were widespread geographically, with increases reported by 80% of jurisdictions. With that in mind, some contextual factors probably influenced these changes. Regarding global trends and the estimated overall TB incidence, the that were somewhat similar to what was seen in the US during those years. It is unknown yet how the global 2023 data will compare.

Related to the increases seen among non-US-born persons, particularly among people who have been the US less than 1 year, it is important to understand immigration numbers related to pre-pandemic, pandemic, and coming out of the pandemic. As of 2022, immigration numbers

were returning to pre-pandemic levels.[12] The number of persons classified as "new arrivals" obtaining lawful permanent resident status were decreasing pre-pandemic, decreased even more dramatically during the pandemic, reached nadir in 2021, and increased substantially in 2022. The number of refugee arrivals and individuals granted asylum between 2013–2022 was not as dramatic. This includes only people who were granted asylum—not all people who were applying for asylum. The number of non-immigrant (e.g., temporary workers and families, students) admissions during that same timeframe increased through 2019, experienced a large decrease during the pandemic, and experienced a fairly sharp increase during 2022.

A number of factors could be considered as possible explanations for the rise in cases. One potential explanation is the high global TB incidence prior to the COVID-19 pandemic coupled with immigration returning to pre-pandemic levels coming out of the pandemic. Another potential reason is the diversion of resources from TB programs to address the COVID-19 pandemic, which resulted in diversion of activities such as TB contact tracing and LTBI testing and treatment for high-risk populations. There also was a disruption in healthcare access during the pandemic—especially for certain high-risk groups.

ACET Discussion on NCHHSTP & DTBE Directors' Presentations

Dr. Sosa asked whether Dr. LoBue expects funding for the new NOFO that soon will be published to be similar to what it is currently.

Dr. LoBue indicated that he could not share details of what would be included in the NOFO. In general, the highest amount of money in the DTBE budget goes to that.

Dr. Loeffler noted that TB among Pacific Islanders is a major concern and burden for that population in certain areas of the country. An observation made with regard to COVID-19 in Oregon was that there were times when more than 100% of people who were thought to be in Oregon from those places were vaccinated. The denominator is under-estimated, so she wondered if thought had been given to this. There are certain places where people can easily come and go, especially Micronesia and the Marshall Islands, making it difficult to understand who is where. In addition, she asked which populations are considered to be US-born.

Dr. LoBue said that may be true for non-US-born populations overall because the situation was so dynamic between 2019 through 2023. That raises an issue about case rates in terms of the denominators. The reality is that this is what they have to work with. Only people born in the US territories are considered to be US-born. Most of the cases are coming from the Marshall Islands and Micronesia, which are sovereign nations and are not considered US-born.

Dr. Chen recalled that there was concern globally that the breakdown in healthcare systems would result in higher transmission for people who were not receiving care, and TB is a known driver globally. Juxtaposing that with the fact that a lot of people migrating to the US contracted TB in the last couple of years and some of the initiatives made her recall a 2015 economist article in which treating TB ranked 6th as a no-brainer for most value for the amount of money or effort spent. The US is already feeling nationally what is happening globally. It is time to put TB in the forefront again. While considering funding is allocated to TB globally, more needs to be done domestically. TB has been flatline funded for about 20 years. She asked what the TB community

[12] https://ohss.dhs.gov/topics/immigration/yearbook

can do to push the TB agenda now to make a big difference early.

Dr. Mermin acknowledged that funding for TB globally has increased, particularly with the Global Fund, which began about 20 years ago. It is important to better understand why TB has been increasing globally over the past 2 years (e.g., disruption in healthcare, social and economic determinants, et cetera). Increasing resources globally is often at the level of the country and to some extent multilateral organizations that would make a difference globally and domestically. Within the US, the situation related to level funding and inflation has made it increasingly difficult for health departments to get their jobs done. In addition to increasing incidence of TB, there is also the driving factor of up to 8.5 million people with LTBI and more people entering the US. That is creating an environment in which people are being cared for, but elimination is not progressing as hoped. Momentum is needed for public health issues, but there is skepticism and distrust of the public health system as well.

Dr. Chen emphasized that globally, there has been mobilization of community and survivor voices. Excitement breeds some of this because there finally are some breakthroughs in treatment and diagnostics. Domestically, groups keep hounding Capitol Hill. However, this is a public health issue that must continue to be addressed. Cheerleading voices are needed from within and beyond CDC and beyond Congress. As an advisory group, the ACET needs to think about how to move the agenda. They are always “speaking to the choir.” On the toolkit website, TB is not highlighted with regard to linkage to care. There must be others who are making decisions and pulling levers who they need to reach domestically.

Dr. LoBue said the only thing he has heard from people about why elimination is not progressing as hoped over time pertains to disruptions due to COVID-19. For a long time, the global approach involved the Directly Observed Therapy (DOT) strategy that focused on treating people with TB disease and only those who were smear positive. Relatively recently, there has been movement beyond this. The rationale was that this was possible due to better diagnostics and more LTBI testing and treatment specifically for household contacts of persons with HIV infection. However, these efforts went to the wayside with the COVID-19 pandemic and only recently resumed.

Dr. Mermin added that public health is good at thinking about how to do its job well. Thoughtful work has led to some of the decreases in TB and other infections over the past few years, but disruptions cause trends in the opposite direction. In addition to implementation success, he believes technological success also is needed and that implementation and technology must come together. Some of the work by the Tuberculosis Trials Consortium (TBTC) has been remarkable, such as 4 months versus 6 months of treatment for drug-susceptible TB. Reducing that to 1 injection or short oral course for LTBI probably would revolutionize LTBI treatment. Even the definition of LTBI is unclear in terms of who is going to reactivate and what that means. Answering those questions could provide a new tool that undoubtedly would make a difference in combination with innovations and implementation.

Dr. LoBue indicated that there is some modeling showing that even if implementation is executed perfectly, elimination cannot be achieved with the current effectiveness of LTBI testing and treatment. Effectiveness is approximately 50% and needs to be much closer to 100%.

Dr. Chen stressed that many of the diagnostic breakthroughs that have been supported through National Institutes of Health (NIH) grants that have led to some of the greatest breakthroughs in technologies and drug formulations that have had impacts globally are still not available in the US. Despite this research being funded by US tax dollars, the US still cannot obtain what is

needed. While the FDA presented to and engaged in discussions with the ACET, there still has been no movement. There must be some way to move forward.

Dr. Ahmed asked whether the NSCSS Federal Task Force plans to extend beyond the 14 jurisdictions and, if so, when and if there will be a report or toolkits for states so they can disseminate information to hospitals and others on the ground. A lot of work is being done in regard to syphilis, but some guidelines or something in electronic health records (EHRs) would be beneficial.

Dr. Mermin clarified that the NSCSS Federal Task Force is not focused just on those 14 jurisdictions. It is a national approach that recognizes success can only be achieved if these jurisdictions are addressed. In terms of a report, the division is providing updates about activities and some communications come from the ASH's office.

As a pulmonary TB survivor, Dr. Holland thanked Dr. Chen for her points and emphasized that there are many voices who are not speaking, such as patients and TB survivors. TB is isolating and disempowering. Everyone in their individual programs can connect survivors to other survivors. Even as a US-born, educated survivor, he was disempowered and isolated. Non-US-born patients are already disempowered economically and in many other ways, such as stigma. They are not going to speak to Congress, but if connected with other survivors, there will be solidarity and more voices.

Dr. Loeffler pointed out that culture had not been raised during this discussion. There can be screening, great drugs, shortest course ever, et cetera. However, people in the community and providers must receive the information they need to accept screening and treatment for LTBI. She received a California Department of Public Health (CDPH) California Pathways into Public Health Program (Pathways) Fellows grant, whose job will focus on this for 13 months beginning in August 2024. Although 90% of people who take LTBI treatment will not benefit from it, the suffering of people with TB is incredible. Half of their TB cases are over 65 years of age who are taking 7 other medications. They have had 10 deaths in the last month. No one wants to die like that. It is imperative to reach the communities who are suffering, but stigma is a major barrier. A good model comes from the Marshall Islands and Micronesia where people and thought leaders spoke with one another one-by-one to spread the message, combined with radio programs.

Dr. Chen emphasized that everyone is trying to determine how to do more while scaling back and trying to remain afloat.

Dr. Burzynski noted that one of the interesting data points Dr. LoBue reported was the apparent increase in TB in the US-born pediatric population, and wondered whether there were any ideas about the cause (e.g., more transmission in the US, travel, et cetera). Anecdotally, there are more cases in New York surrounding the newborn period, although it is unclear whether this relates to just awareness or something else.

Dr. LoBue said he suspects that it is a combination and that it will be necessary to dig deeper into the data once the final dataset is available. There have been some outbreaks among Pacific Islanders in which the adults are from the Pacific Islands, but the children are US-born. Obviously, there is an increase in transmission. His best assessment at this point is that if children are US-born, transmission most likely occurs in the US unless they are older and most of the transmission is likely coming from non-US-born adults.

Dr. Ritger emphasized that there are not enough hours in the day for public health to address LTBI and many clinicians do not have the expertise and/or they think public health wants this job and they should refer there. She asked whether there is still a separate NOFO that includes perinatal hepatitis B funding.

Dr. Mermin indicated that DVH has fewer resources for getting their job done and spends a lot of time maintaining surveillance, dealing with outbreaks, and trying to provide guidance on policies. Due to vaccines, it is rare for infants to be born in the US with hepatitis B. Many cases are among people moving to the US.

Dr. Holland noted that Dr. LoBue reported estimated and reported global cases and wondered if he had the same data for domestic TB cases.

Dr. LoBue responded that they do not use estimated cases because they are confident that reported cases are accurate based on previous assessments that showed congruence between estimated and reported.

Dr. Sosa said she was interested to hear about PIX and wondered whether those centers are working on anything TB-related currently.

Mr. Hogan Yarbro responded that PIX was just launched in May 2024, there are many efforts in the pipeline that are planned for release within the calendar year. He will update the ACET on this soon.

Dr. Goswami pointed out that the problem may be that clinicians also see LTBI as beyond their capacity given increased demands in healthcare.

Mx. Lovinger thinks part of the solution with respect to domestic access to new technologies is to take a more front-end, upstream approach. Federal agencies wield tremendous power in the TB research and development (R&D) funding landscape and that power can be used to put funding conditionalities in place. Any federal funding should require an end product to be fully affordable and accessible to state and local programs, acceptable to domestic patients, and negotiable for FDA approval waivers. US agencies have more power than the Gates Foundation or any other funders, it just needs to be wielded.

Ms. O'Brien noted that it is okay to "preach to the choir" and say things they think the room knows. They are still problems, and they should be acknowledged and addressed as long as they are problems.

Current ACET Recommendations 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 focused on ACET recommendations from December 2022 through June 2023. During the June 2023 meeting, further discussion on the TB workforce recommendation included pursuing working with an outside organization, such as the Council of State and Territorial Epidemiologists (CSTE), to conduct an assessment; and incorporation of an assessment as part

of the next CDC TB prevention and control cooperative agreement. These recommendations have been added to the table below:

Topic	Recommendation	Actions
Topic: TB Workforce Item #: 2022-4 Date: 12/14/2022	ACET recommends that CDC define the key components of an effective public health TB workforce in the US. ACET recommends CDC: 1) Develop a standard process for evaluation and periodic assessment of the US PH TB workforce 2) Consider a cost analysis to sustain the current TB workforce to achieve TB elimination 3) Pursue working with an outside organization, such as the Council of State and Territorial Epidemiologists (CSTE), to conduct an assessment 4) Incorporate an assessment as part of the next CDC TB prevention and control cooperative agreement	• Outstanding issue is Item 3, incorporation of an assessment as part of the next CDC TB prevention and control cooperative agreement – New cooperative agreement funding opportunity anticipated to be announced in July 2024 – Any information about inclusion of TB workforce assessment in the cooperative agreement will be presented to ACET during the December 2024 meeting
Topic: DMI/PHDS Item #: 2023-4 Date: 6/21/23	ACET recommends CDC to work with partners to identify TB data modernization priorities focusing on interoperability between data sources and automating collection and sharing of high-quality data.	• Roque Miramontes presented on current efforts in this area during the December 2023 ACET meeting, with no additional ACET recommendations made • This item is closed unless ACET makes additional requests
Topic: DMI/PHDS Item #: 2023-5 Date: 6/21/23	ACET recommends CDC explore a common dataset across NCHHSTP and the specific variables that are high value for TB care that could be shared across the Center.	• Michelle Van Handel presented on current efforts in this area during the December 2023 ACET meeting, with no additional ACET recommendations made • This item is closed unless ACET makes additional requests
Topic: Establish an LDT WG Item #: 2023-6 Date: 12-13-24	ACET recommends CDC establish an ACET WG to evaluate the current landscape of laboratory developed test (LDT) development and usage in the diagnosis of TB and potential impacts from the FDA Proposed Rule.	• LDT WG was formed and has met • The agenda for the June 2024 ACET meeting included an update from this WG
Topic: Establish a Drug Shortage WG Item #: 2023-7 Date: 12-13-24	ACET recommends CDC establish an ACET WG with a charge to: 1) Review the letter submitted to HHS in May 2023 and to bring updated information for ACET to discuss. 2) Evaluate the current actions of the federal government to address and mitigate drug shortages and ensure TB medications are included in discussions and plans.	• Drug Shortages WG was formed and has met • The agenda for the June 2024 ACET meeting included an update from this WG

ACET Discussion on Current ACET Recommendations Presentation

Dr. Sosa pointed out that her state has been struggling with the issue of interoperability between data sources and automating collection and sharing of high-quality data over the last 6 months in terms of how data gets from states to CDC.

Dr. LoBue noted that a lot could change in terms of the direction the agency ultimately takes. There has long been a desire to streamline data collection and make that easier. While on the surface it seems like this should be easy, technologically it is not. CDC has struggled and failed with this a number of times in the past. There have been improvements in what is available technologically, so perhaps this time will be "the charm."

Panel 1: Tuberculosis (TB) in New Arrivals

Detection and Prevention of Tuberculosis Among New Arrivals in Chicago

Kathy Ritger, MD, MPH
Medical Director, Tuberculosis Program
Chicago Department of Public Health

Dr. Ritger presented on detection and prevention of tuberculosis among new arrivals in Chicago, including a timeline of key events in the response, TB screening procedures of new arrivals, data trends in new arrival TB cases, and open issues and questions regarding this response.

This outbreak has been ongoing for approximately 2 years. It began in New York City (NYC) with people requesting asylum, crossing the border, and then Texas bussing people North to various cities. Chicago being a Democratic-led city and Illinois being a Democratic-led state was part of the political calculus, it was anticipated that buses would be sent there from Texas. The Chicago Department of Public Health (CDPH) was watching the NYC response and began engaging in internal discussions about types of medical screenings these individuals would need. The first bus arrived on August 31, 2022. These individuals were housed at an existing Salvation Army shelter. CDPH staff organized and staffed a clinic at the shelter over Labor Day weekend, but it was not sufficient. The Office of Emergency Management & Communications served as overall lead, the Department of Family Support Services became the lead agency for housing individuals, the CDPH is the lead agency for clinical care coordination, and Cook County Health (CCH) became the lead clinical care provider. As more buses arrived between Winter 2002 and Spring 2023, the shelter system expanded to 10+ facilities that included a variety of shelters (e.g., downtown hotels, shuttered elementary school, park district field houses), each of which required different infection control practices. The CDPH moved into the Incident Command Structure (ICS) and TB case reports become more frequent.

Bus arrivals slowed down during Summer 2023, which allowed time to conduct contact investigations related to shelters and partner with a couple of Federally Qualified Health Centers (FQHC) for these investigations in terms of performing blood draws, x-rays, and TB evaluation. In Fall 2023, bus arrivals increased sharply. This led to a lack of shelter space and became a dire situation that led to new arrivals staying at police stations and O'Hare Airport. At one point, over 800 people were staying at the airport. The city-run shelter system eventually expanded to 27 locations in 2023. By the end of 2023, over 900 buses had arrived since August 2022 and over 850 planes had arrived since June 2023. There were over 43,000 new arrivals, which exceeds the population of all but 50 of Illinois' municipalities. At peak, there was a >14,000 bed

census, although police stations and airports were no longer serving as shelters by the end of 2023. The shelters were highly dispersed, so care and systems had to be coordinated across a large geographic area. While there was a designated “Landing Zone” where the buses were supposed to go, they dropped people off wherever they could. When the city implemented an ordinance to prohibit busses from dropping people off outside the designated “Landing Zone,” the buses began dropping people off in the suburbs.

Moving into Spring 2024, there was a measles outbreak in the largest shelter that was housing nearly 2000 people. While the origin was not clear, this was a highly vulnerable population. Eventually, 57 cases were linked to this shelter and a massive public health response was required to determine people’s immune status, vaccinate, isolate those who were vulnerable (e.g., young children too young to vaccinate, pregnant persons). The 2 field staff who had been detailed to the TB Program were pulled back to work on the measles response. The pace of bus arrivals slowed and increasing numbers of new arrivals began receiving support to move into rental housing. While the rental assistance is time-limited, it moved people out of the shelters. Although moving people from shelters to apartments is good, it can make them more difficult to locate and their focus is getting a job, going to work, and taking care of their families versus engaging with public health for follow-up care and treatment. Landing Zone organization was increased in order to speed up health screenings and link people to care as needed. CCH now provides dedicated staff at the Landing Zone and there is a daily bus service to transport new arrivals directly to the CCH clinic for same-day comprehensive intake screenings. About half of the new arrivals to the Landing Zone are captured that way. After shelter placement, they are offered transport again. While people can decline, this protocol captures most people quickly. The CCH services include disease control, mental health, and perinatal care. The hope is that if people stay in the area, they eventually will have a medical home.

CCH covers the entire county. Upon city and state requests, CCH agreed to serve as the primary healthcare provider (HCP) for the new arrival response. CCH adapted their newest community clinic opened in 2021, Belmont-Cragin Health Center, into a dedicated free clinic for new arrivals. The current capacity is approximately 100 visits per day, which they ramped up over time. CDPH and CCH clinicians collaborate on infectious disease screening protocols. Regarding the CCH TB care cascade, new arrival initial clinic visits include screening for signs and symptoms of TB disease, referral to the Stroger Cook County Hospital ED if the symptom screen is positive or if there is a history of incomplete TB treatment. QuantiFERON (QFT) interferon-γ release assay (IGRA) screening positivity has been approximately 14%. If the QFT test is positive, a CXR is ordered. There is a dedicated bilingual nurse who is responsible for follow-up on QFT+ tests, who also works at the Landing Zone.

Regarding the Chicago TB case count data by time since US arrival between 2014 and 2024, the TB case count of people in the U.S. <1 year typically ran between 7% in 2014 to 14% in 2019. There was a decrease in 2020 to 7% and a large increase in 2023 to 39%. Between January 1, 2024 and May 31, 2024, the TB case count has been approximately 50% among those who arrived in the US less than 1 year from the report date. Looking just at 2023 and 2024 confirmed TB cases among non-US-born persons with a US arrival of less than 1 year (n=89), the population tended to be younger with 32.6% being 15–24 years of age and 49.4% being 25–44 years of age. About 25% of the TB cases have been female and about 74% have been male. Approximately 83% have been Hispanic compared to about 49% Asian and 34% Hispanic between 2013 and 2022. In terms of severity of disease, 46.8% were cavitary, 52.5% have been smear-positive, and co-infected with HIV has been 5.7%.

In closing, Dr. Ritger shared links to the CDPH TB webpage[13] and the City of Chicago New Arrivals webpage[14] and outlined the following open questions that she has pondered that perhaps the ACET would like to ponder with her:

- ❑ What is the likelihood of TB exposure at congregate settings where large number of people at higher risk for TB have prolonged stays? Should we recommend repeat TB screening for shelter residents who initially test negative?

- ❑ Is there a TB disease rate at which we would implement chest x-ray (CXR) screening for all new arrivals? If yes, where and when during the immigration process should that occur?

- ❑ For individuals with pulmonary TB disease, what criteria should be used to determine when it is safe for them to return to a congregate setting?

- ❑ Should we treat LTBI in new arrivals with 1HP (1 month of daily isoniazid and rifapentine) to increase treatment completion?

Opportunities and Challenges in Tuberculosis Care and Prevention Among New Arrivals in New York

Joseph Burzynski, MD, MPH
Assistant Commissioner/Director, Bureau of Tuberculosis Control
NYC Department of Health and Mental Hygiene

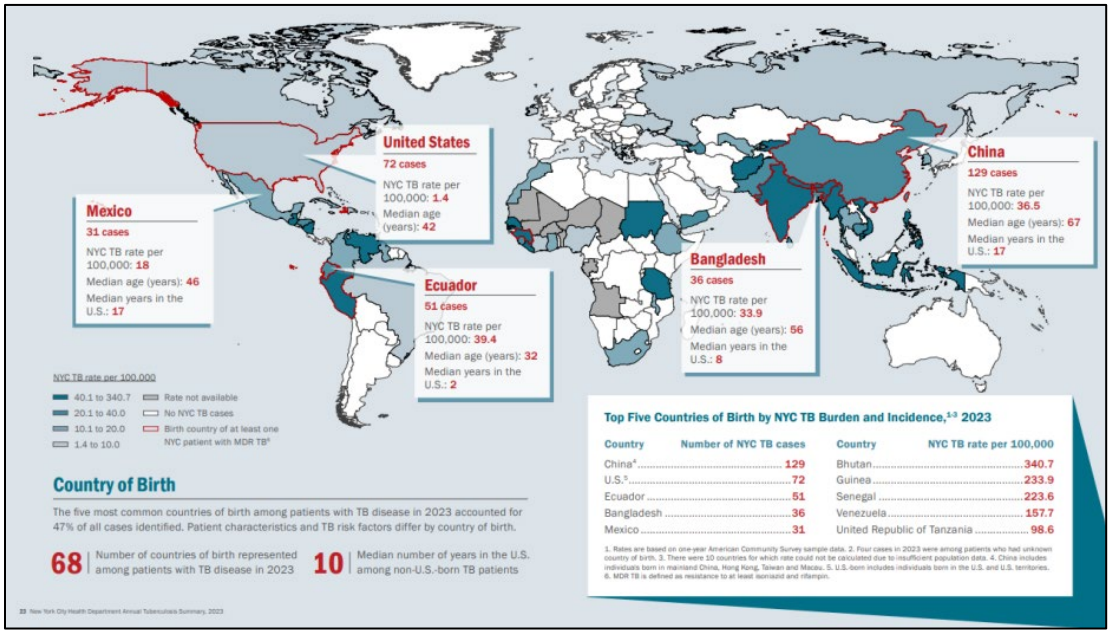
Dr. Burzynski presented an update on the opportunities and challenges in TB care and prevention among new arrivals in NYC in terms of background; the influx of newly arrived immigrants in NYC from April 2022 to date; TB detection, care, and prevention activities among newly arrived New Yorkers; and challenges, opportunities, and next steps.

Regarding background, NYC is a large city of 8.75 million people. Of these, 37% are born outside of the US, 48% speak a language other than English at home, and over 700 languages are spoken among residents. NYC has a large healthcare system that includes public hospitals and clinics, many FQHCs and community healthcare providers, private hospitals and practices, and health department clinics. Included among these are 3 TB clinics, so there is considerable potential for healthcare. The Bureau of Tuberculosis Control (BTBC) within the NYC Department of Health and Mental Hygiene (NYC Health) is an integrated program through which all core TB prevention, care, and response activities are implemented (e.g., clinical care, treatment, medical consultation, laboratory testing, case management, contact investigation, outbreak detection and response, outreach and education, strategic data use, and reporting and surveillance).

The new arrival influx has been challenging. In 2023, NYC had 684 confirmed TB cases. This represented 7.8 cases per 100,000 people, a 28% increase compared with 2022, and the highest number of TB cases in NYC since 2011. Given that this trend continues, an increase is expected in 2024 as well. Increases have been seen across multiple groups. The majority (69%) of confirmed TB cases in NYC have been among people 18-64 years of age. There have been 13 multidrug-resistant TB (MDR-TB) cases and 1 extensively drug-resistant TB (XDR-TB) case. About 13% of cases have occurred among people with a recent history of homelessness and

[13] https://www.chicago.gov/city/en/depts/cdph/provdrs/infectious_disease/svcs/tb_prog.html
[14] https://www.chicago.gov/city/en/sites/texas-new-arrivals/home.html

89% of TB cases have been among people born outside of the US. This map illustrates that although NYC's rates are influenced by this group of new arrivals to NYC, there is still core TB work to do:



Most cases in NYC in 2023 were among people born in China, Bangladesh, Mexico, Ecuador, and the US. Although these made a significant contribution to TB cases in NYC, now there is an additional number of new arrivals who have been entering across the US Southern Border from 2022 to the present. There has been an increase in individuals arriving in NYC from Ukraine, Venezuela, Haiti, Nicaragua, and Cuba through humanitarian parole programs and immigrants and refugees with overseas TB classification. While there are some requirements in these programs for TB testing, a large number of people entering NYC across the US Southern Border do not all fall within those groups. Over 200,000 people have arrived in NYC from the US Southern Border since Spring 2022, with little to no coordination of medical or other care prior to their arrival in NYC. Many new arrivals have endured long and difficult journeys to the US with no money and many do not have family or support networks in NYC. Many have increased TB risk due to high TB incidence and disrupted healthcare systems in home country, the nature of their journey to the US, and placement in congregate settings. When Dr. Burzynski has been working in the clinic, he has spoken to many people who described their journeys, including walking from Venezuela or other countries through the Darién Gap, through Mexico, and riding the bus to NYC. He is certain that the rates of TB in countries like Venezuela and Ecuador are much higher than reported because with the breakdown in government, there has been a complete breakdown of public health. Many patients have told him that after they were diagnosed, they could not find the medications needed to treat their TB.

To address the need for numerous services, over 200 new temporary housing sites were established in NYC, including sanctuary shelters, Humanitarian Emergency Response and Relief Centers (HERRC), respite centers, houses of worship, and overflow sites. Multiple city agencies have been involved in shelter operations. The sites are administered by contracted vendors, social service organizations, National Guard, and city staff. There are limited and fragmented onsite clinical and social services. While there is a "Right to Shelter" law in NYC that has been in place for a long time that mandates the city to provide temporary housing to anyone who is

homeless and seeks shelter, 30- to 60-day limits eventually were instituted on shelter stays. Initially, new arrivals are given shelter. Single individuals are allotted 30 days and families are given 60 days. City officials have tried to remove the “Right to Shelter” law, which has resulted in people scrambling to find a place to live. In addition to TB screening and medication, people arriving in NYC have a list of many other concerns as well (e.g., where their children will attend school, obtaining health insurance, getting immunizations, et cetera). NYC also experienced a measles outbreak in its shelters.

In addition to establishing temporary housing sites, surveillance has been increased to ensure that patients are not being missed. Case Managers have been placed in the shelters so that they get to know the people staying there and they are administering DOT. Many patients do not have phones and those who do rarely have a data plan, making daily DOT difficult. Having Case Managers on-site who are able to perform daily DOT has been helpful. Contact investigation processes have been adapted, given how difficult this has been due to people moving around, not knowing who they have exposed, and so forth. Given that many of the new arrivals are working, clinical services have been expanded to include monthly Saturday clinics at health department chest centers. NYC Health has worked with clinical vendors to set up testing and CXRs and Patient Navigators have been added who speak various languages. The first year was comprised of mostly Spanish-speaking new arrivals, but this has changed over the last 6 to 9 months to be primarily West African immigrants.

Outreach and TB education have been expanded through collaboration with colleagues across other disease areas and jurisdictions, community-based health events and education, and the NYC TB Coalition. Temporary staff with language skills have been onboarded and existing materials and forms have been translated and adapted. Use of WhatsApp is now available on work phones, which is great because many new arrivals with phones have WhatsApp. The ability to communicate through this medium has been helpful, though it is still challenging to find people who do not have phones and or people who have phones but no data plans. Regarding policy and advocacy, medical accommodations and extended stays in shelter sites have been established, along with enhanced hospital discharge coordination and institutional transfers. TB screening, testing, and evaluation have been expanded.

Regarding shelter-based TB screening, testing, and evaluation, NYC Department of Homeless Services (DHS) routinely performs TB testing and evaluation at intake among single adults before placement in dorm-style shelter settings. All individuals coming through the Arrival Center at the Roosevelt Hotel in Midtown Manhattan, which was opened in May 2023, are screened for TB symptoms and history. However, testing has not been set up there due to the volume of people arriving there and the need to move them through to shelters quickly. NYC Health implemented integrated on-site TB testing, vaccination, and other services in sites with high proportions of newly arrived migrants. From December 2022 through March 2024, over 4,500 people were tested for TB in over 65 shelters. A collaboration was established between NYC Health, NYC Health + Hospitals, and New York State (NYS) to conduct site-based TB testing in dorm-style HERRCs. There is a combination of intake testing and serial weekly testing along with referrals to public hospitals and health department clinics for follow-up evaluation, CXR, and treatment. From July 2023 through June 2024, over 14,000 people have been tested for TB in 5 HERRC sites. The QFT-positive rate has been about 30%, which is much higher than in the general population or even in the population of non-US-born persons. In some places, the positivity rate is very high. For instance, the positivity rate of people from Guinea has been 49%.

All of this has been challenging. The shelter system has been complex and quickly evolving, which was almost daily in the beginning, in terms of communication, varying rules among shelters, and sharing information. The transience of the new arrivals has been challenging, with frequent movement of people into and through shelter sites and movement into and out of NYC. Medical and social service needs are complex. New arrivals experience a lack of access to telecommunications, face many barriers (e.g., language, cultural, distrust/lack of knowledge of US medical system), and have competing priorities (e.g., work, school, other needs). For the BTBC, this has led to increased work due to many more cases and suspected cases of TB. Case Managers, who already had a tough job managing their cases, now have almost double the number of people to manage. Shelter exposures are very difficult to address and there has been an increase in state referrals. Clinics have been bombarded with an increased need for providing x-rays and patient care services. Most of the visits are complicated with cultural and language differences. Doctors are overloading the hotline system from throughout the city asking what to do about people with TB who want to return to their shelters. Data management and data coordination needs are complicated. There is not a consistent definition or terminology for this population across agencies. The scale of need and related resource constraints across multiple systems are complex.

Despite these challenges, there have been some successes. Expanding shelter-based case management and DOT has been beneficial. NYC Health has been working with shelter operators and has gotten a public health exemption, which has been a major step. While this is not codified in the health code, shelter operators have worked with NYC Health to get everyone diagnosed with active TB into 2 shelters. NYC Health is working with shelter managers to allow these individuals to remain in the shelter until they complete their TB treatment, along with their close contacts until the evaluation is completed. Now that all new arrivals are going through a central location at the Arrival Center, the hope is to garner funding to implement mobile CXRs for everyone in order to identify patients who are symptomatic or minimally symptomatic before they go into a shelter and have the opportunity to spread TB. While this would be an added operational component for those who run the Arrival Center, they realize the importance and are ready to work with NYC Health to implement this.

The Coalition for a TB-Free NYC has a mission to prevent and eliminate TB in NYC through community engagement, public-private partnership, and innovation and research and is guided by a patient-centered, human rights-, social justice- and gender-based approach. The Coalition for a TB-Free NYC has 40+ partners, including NYC Health, NYS DOH TB Control Program, healthcare providers, academic partners, community-based organizations (CBOs), and advocates. They meet quarterly to disseminate TB information, share resources, and help develop a NYC TB elimination strategic plan. The Coalition for a TB-Free NYC currently has 3 workgroups dedicated to efforts for recent arrivals to NYC. By June 2025, the Coalition for a TB-Free NYC will create 3 deliverables addressing the increased demand for TB detection, care, and prevention among newly arrived New Yorkers, which are to: 1) develop targeted educational materials with a focus on visuals; 2) distributing testing and treatment recommendations for HCP; and 3) developing a pilot care coordination model to link patients to TB care.

ACET Discussion on Panel 1: Tuberculosis (TB) in New Arrivals Presentations

Dr. Burzynski thought the new migrant health clinic in Chicago sounded great and that it would have been beneficial if NYC had such a clinic, because their situation is still somewhat of a mess.

Dr. Bhavaraju thanked Drs. Ritger and Burzynski for presenting the dire situation and the creative strategies they have been using to provide care for this very important group of people, especially with regard to transmission. This added a different layer to the question Dr. Chen posed earlier about who else to talk to about dealing with these efforts. Although funding is decreasing, this is a different situation that requires a new layer and more resources. While these types of stories can be used to obtain more resources, they also can create a logjam.

Dr. Burzynski indicated that they have been very careful with their messaging and being careful to ensure that they do not promote the idea that TB is a danger to the general public because some of the new arrivals are infected with TB. While the message is that this is a problem, but there are tools available to address it. With more support, it could be addressed even better. There has been no evidence to date indicating that there have been outbreaks and clusters in the city. Dr. Burzynski and Dr. Mermin met with the Commissioner to explain the desire to address this before it got worse, who was receptive and understands that TB differs from other diseases in that it occurs very slowly and that there must be immediate and long-term plans to address it. NYC Health has been fortunate to receive additional resources from the city because of this recognition.

Dr. Ritger pointed out that there have been other outbreaks and infectious disease concerns, such as measles and scabies, but talking about TB is a lot harder. The willingness to talk about it publicly is risky because of the related stigma. If they cannot obtain additional funding locally, she is not sure what might make a difference.

Dr. Narita reported that Seattle-King County is having similar issues. Implementing x-rays is expensive and difficult to coordinate. He asked whether federal agencies could support local agencies, given that this seems more like a nationwide issue.

Dr. Sosa added that TB anywhere is TB everywhere, which has been seen internationally. Just because it is occurring in large cities does not mean that other places are not feeling the impact. Connecticut is definitely feeling it. While they do not have thousands of people arriving in one location, people are arriving there. Thought must be given to how to address this as an “everywhere” problem.

Dr. Burzynski said that while he did not have a specific answer for Dr. Narita, people going through the parole asylum-seeker process are supposed to have a TB test. That is one way through which there is a structure for a group of people to be tested.

Dr. Ritger added that with the normal refugee process, there are resettlement agencies and panels performing the screening pre-departure. The influx is basically putting the role of all of that work on the receiving jurisdictions. The pressure on the border is huge as well, and there is no place to hold people. Operation Allies Welcome (OAW) placed people in Army barracks for weeks to months, which was not a great process either.

Dr. LoBue pointed out that the problem is that there is no federal structure for this at all. The difference with permanent immigrants and refugees is that CXR screening is required before people arrive in the US. Immigrants pay for CXR screening as part of their visa fees and for refugees, the State Department pays for this. A structure and resources do not exist in the situation of the influx of new arrivals that is occurring. If they come into contact with federal officials, they are typically immediately released versus going to a facility where they could be screened. OAW was rushed and probably not ideal. The Ukrainian situation was better at least because specific resources were provided that could be distributed to TB programs based on the

number of people who were going to their jurisdictions. There has been nothing like that for any other groups. It is not just about TB. There is a list of many other needs for which Dr. LoBue was not aware of any support.

Dr. Ritger said that anecdotally, because of the number of people between Chicago and NYC, there are not enough staff to keep up with Interjurisdictional TB Notification (IJN). People are going to places where the cost of living is going to be less over time and non-urban areas eventually.

CDR Rhodes shared her perspective on congregate settings in the context of her work with immigration and the Bureau of Prisons (BOP) for 19 years. As a Public Health Officer, she has deployed to the borders with Border Control and has seen the influx and the capabilities available at the border, which is nil. Regarding the questions posed by Dr. Ritger, when people enter congregate settings, the BOP performs the initial screening and x-rays for any positive screenings. Immigration implements CXRs on all new intakes. The BOP's facility in California receives many active TB cases and implements CXRs immediately upon intake. With 50% IGRA and positive smears, she would suggest that Cook County implement x-rays upon initial screening. In this population, they also see a lot of culture-negative TB cases and are finding TB disease early among people who are asymptomatic. While finding more TB is not good for the workload, it is good for catching people before they become symptomatic and infectious. The BOP does not repeat TB screening unless someone returns with symptoms, but if there has been repeated exposure, repeating screening after 8 to 10 weeks might be a good idea. For individuals with pulmonary TB disease, the BOP uses the criteria of negative smears, 5 days of medications for non-cavitary disease, 14 days of medication for cavitary disease, and symptom improvement. Immigration uses a similar protocol, which works well in the congregate setting. Cases and contact investigations stem from someone being there and reactivating or before they receive their CXR. The 5- and 14-day protocol works well with negative smears. Those with positive smears must have 3 negative smears before release.

Dr. Burzynski noted that regarding negative smears, Dr. Shah would present later in the afternoon about why re-entry decisions should not be based on sputum smear status.

Mr. Watts, who is with the National Health Care for the Homeless Council (NHCHC), indicated that the NHCHC works with several FQHCs in Chicago and NYC. He emphasized that homelessness and immigration issues are the results of failures at the federal policy level that are felt locally. He asked what proportion of new arrivals in Chicago and NYC have been families with children versus single adults and whether a difference was observed in TB in terms of prevalence and engagement in treatment between the 2 groups.

Dr. Burzynski recalled that families with children comprised about 40% of the new arrivals, while the rest were mostly single adult men. Families and children were probably better at engaging in screening, treatment, and contact tracing. He did not recall that there was any difference in prevalence.

Dr. Ritger added that this was about the same for Chicago, including a large proportion of young men and very young families of 20 to 21 years of age with infants, toddlers, and pregnant moms. Even though it has been extremely challenging and screening has not reached the preferred level, cases are being identified. Organic immigrations results in thousands of people entering Chicago and hundreds of thousands entering New York annually who are not in congregate settings, whose whereabouts often are unknown, and who are not being screened. In some

ways, more case finding is being done with new arrivals than is being done with other immigrants.

Dr. Burzynski reported that NYC was able to perform QFT on about 20,000 new arrivals and get CXRs for most of those individuals. A considerable number of asymptomatic TB was identified, with abnormal CXRs and positive sputum and most not complaining with any symptoms.

Dr. Stout noted that what struck him about both the Chicago and NYC presentations were that they were addressed from the public health perspective, yet public health is starved for funds. This is expensive, but it seemed that Chicago and NYC have done an incredible job of dealing with mass migration, integrated screening, and fundamentally investing resources in people who are going to go on to live healthy lives, work, and be productive members of society. With that perspective, he wondered what efforts the 2 cities are making to determine the costs and outcomes and whether CDC has provided assistance in the form of Epidemic Intelligence Service (EIS) Officers or other support to collect those data. This is a huge natural experiment in how this can be done well, and the money being spent on this seems trivial compared to the amount spent on people who have terrible outcomes.

Dr. Ritger replied that the cost is opaque and at her level, she does not know how the arrangements are made. State-, county-, city-, Governor-, Mayor-, and county-level conversations determine this. Chicago has a safety net hospital that is used to providing uncompensated care, which is covered by county funds that are supplemented through state and city funds. Federal appeals and Mayors traveling to the White House have not resulted in much funding.

Dr. Burzynski agreed that cost is important to consider. NYC is performing a return on investment (ROI) assessment now specific to contact investigations. It is not easy to hear how much various components of the approach cost. Experts are needed to assess the costs and measure effectiveness, for which NYC would need support. This is a great idea that he hopes someone will pursue.

Dr. Ahmed emphasized that with 40% of people with refugee status being families, this means a large bolus of children. She asked whether with contact investigations repeat testing is being done, including with children.

Dr. Burzynski indicated that they do better with families who have children. They are identifying cases in children, and children are receiving treatment for LTBI or window prophylaxis. In general, families with children are in a better situation because they typically are in rooms versus the large congregate bed situation. If a case is detected, the family is permitted to remain in the shelter for a longer period of time and contact investigations can be done more easily. On the contrary, they are lucky to get a single test in the dorm style settings for single adult men who tend to move all over the place. While an effort is made to conduct follow-up testing, it is very difficult to keep track of someone for a long period of time in this setting.

Dr. Ahmed suggested that a potential practical solution might be to treat younger children for LTBI and leave it at that.

Dr. Ritger indicated that Chicago has been able to conduct contact investigations by considering people who arrived together to be households in terms of who they came with, traveled with, are staying with et cetera. The larger exposures occurring in the congregate setting are harder to

keep up with operationally. She pointed out that the first question she posed for consideration about repeat testing was almost theoretical.

Dr. Ahmed recalled that when she was in the United Kingdom (UK), CXRs were being done on arrivals at the airport.

Dr. Goswami asked what state, federal, and/or other resources there currently are to arrange baseline CXR for any new arrival from a high-TB burden country similar to what happens for US applicants abroad, what this would cost to arrange and conduct with the current volume of new arrivals, and how long operationally they have been able to keep track of new arrivals after contact.

Dr. Loeffler asked whether anyone is considering a screening TB nucleic acid amplification test (NAAT) project, noting that the Santa Clara County Public Health Department laboratory performs XPert MTB RIF and has capacity. She would love to study sputum for TB NAAT serially, given that it is cheaper than X-ray and sputum acid-fast bacilli (AFB) smear and CXS.

Dr. Chen asked when the California prison site started the 5- and 14-day isolation policy.

CDR Rhodes indicated that it has been in their clinical guidance for at least as long as she has been in this position for 12 years. They have a low rate of transmission with the practices that have been used for years. San Diego does not have any working isolation cells, so they complete the work-up in the local hospital.

Ms. O'Brien reminded everyone that We Are TB is a Spanish-speaking group. Somos TB has biweekly, free, and confidential Spanish language support groups on Zoom. Those with a cell phone can access the calls. A computer is not needed. Somos TB has built a great community of compassionate people who are helping each other through TB diagnosis and treatment.

Recognizing the need for investments and support for programs, Dr. Chen asked whether there would be consideration for operational research support to study best practice solutions that could guide programs. She imagines that this is a long-term issue with which ACET will grapple. In addition, she asked whether there is any information on best practice solutions that may inform practice, particularly from border cities that have been dealing with these volumes for longer.

CDR Rhodes indicated that the San Diego Health Department is very involved with TB cases and immigrant populations. While she could not speak for their local policies, based on the BOP's experience with them, she would assume that they have a very organized system. Texas border cities, such as Laredo where there is a binational program, are very experienced in tracking patients who move between Mexico and Texas and may have helpful information.

Dr. Chen clarified that she knows there have been strong responses along the border, but her comments were targeted toward those in the room to consider as they ponder whether there are actionable recommendations the ACET could make to better address the specific TB overloads that were raised by the NYC and Chicago presentations.

Panel 2: Regulations of Laboratory Developed Tests (LDTs) and the Impact on Tuberculosis (TB) Testing in the United States (US)

Initial Summary: LDT Final Rule

Peter Kyriacopoulos
Chief Policy Officer
Association of Public Health Laboratories

Mr. Kyriacopoulos noted that he was presenting the work of Amanda Cosser, who is the Manager of Regulatory and Public Policy with the Association of Public Health Laboratories (APHL). APHL is currently gathering feedback from all APHL members. Several APHL members and other organizations that have shared interests with public health laboratories (PHLs) have submitted comments to the FDA on the Final Rule under Docket FDA-2023-N-2177-0001, including the following:

- ❑ San Francisco Department of Public Health Population Health Division (PHD)
- ❑ Connecticut Department of Public Health (CT DPH) State Public Health Laboratory
- ❑ Tennessee Public Health Laboratory
- ❑ Washington State Department of Health
- ❑ Oregon State Public Health Laboratory (OSPHL)
- ❑ Utah Public Health Laboratory (UPHL)
- ❑ Texas Department of State Health Services (DSHS)
- ❑ Wisconsin Department of Health Services (WisDHS)
- ❑ NYS-DOH-Wadsworth Center
- ❑ Washington State Public Health Laboratories
- ❑ Monterey County Public Health Laboratory
- ❑ Sonoma County Public Health Laboratory
- ❑ Missouri State Public Health Laboratory
- ❑ Contra Costa Public Health Laboratory
- ❑ California Department of Public Health Center for Laboratory Sciences
- ❑ County of San Luis Obispo Public Health Laboratory
- ❑ Minnesota Department of Health Laboratory
- ❑ Debbie Gibson, Montana PHL
- ❑ Allen Bateman, Wisconsin State Laboratory of Hygiene (WSLH)
- ❑ National Coalition of STD Directors (NCSD)
- ❑ WA State Department of Health (NBS Program Director)
- ❑ Big Cities Health Coalition (BCHC)
- ❑ Council of State and Territorial Epidemiologists (CSTE)
- ❑ National Association of County and City Health Officials (NACCHO)
- ❑ Infectious Diseases Society of America (IDSA)
- ❑ American Society for Clinical Pathology (ASCP)
- ❑ National Alliance of State and Territorial AIDS Directors (NASTAD)
- ❑ Muscular Dystrophy Association (MDA)

APHL also has submitted comments,[15] created a guide for comments,[16] and has been engaged in an ongoing dialogue with the FDA as they engage with all of their federal partners on the activities that are affecting PHLs and how. APHL has stressed to its FDA colleagues that APHLs member laboratories need to continue the very important work they perform on a daily basis. APHL specifically highlighted in their comments, which were resonated by many others who submitted comments, that this is public health and limited resources are dedicated to public health. They also went into some specificity about how LDTs are used, why, and how there are not alternatives that make good sense. APHL made some recommendations because APHL traditionally will not only identify problems, but also will propose solutions. The recommendations to FDA that APHL thought would be helpful as they move forward on the Final Rule were to:

- ❑ Expand the scope of enforcement discretion for:
  - Public health surveillance (results can be returned).
  - PHL LDTs used for at least 2 years.
  - PHL assays that are LDTs due to certain modifications to FDA-approved tests.
  - Public health emergencies to include assays needed for outbreaks of any size (before and during).

- ❑ Provide a less burdensome pathway for PHL LDTs.

- ❑ Stratify the phaseout period for LDTs and provide more information/guidance on submitting applications.

Regarding the APHL's understanding of the current status of the Final Rule, if a test has been approved by the New York State (NYS) Clinical Laboratory Evaluation Program (CLEP) that is good. These are for testing work that was done on people who lived in NYS, but are now exploring the possibility that with the Final Rule, FDA is suggesting that if a test passes the NYS requirements, it could be good for people who do not live in NYS. APHL is working on clarity in that space. LDTs currently marketed and not modified following issuance of the Final Rule as of May 6, 2024, the date the Final Rule was printed, are acceptable provided that no changes are made to these tests. It is anticipated that in many cases, adjustments will be made that will not cause FDA any concern. There is an exception for LDTs for unmet needs manufactured and performed by a laboratory integrated with a healthcare system for patients receiving care at that healthcare system (hospital laboratories, most academic medical centers). One aspect of the unmet need exception is that there must be a liability connection between the laboratory and the healthcare system. With PHLs, there is not a similar potential liability connection between them and the various medical advisors to the work that they perform. There are exceptions for LDTs manufactured and performed within the Veterans Health Administration (VHA) or Department of Defense (DoD). There also is an exemption for non-molecular antisera LDTs for rare blood cell antigens when there is no alternative to meet patient's need for a compatible blood transfusion.

[15] https://www.aphl.org/policy/Advocacy_Documents/2023%20LDT%20Proposed%20Rule_APHL%20Comments.pdf
[16] https://www.aphl.org/policy/Advocacy_Documents/2023%20LDT%20Proposed%20Rule_Template%20for%20comments.pdf

There are some new draft guidance policies that the APHL finds to be highly informative and thinks it is also clear that much of the information the APHL communicated to the FDA is represented in the way these guidance documents have been developed:

- ❑ *Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration under Section 564*[17]
- ❑ *Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency*[18]

That said, the APHL will submit comments on the guidance documents and will seek some clarity for both of those as well. APHL has encouraged its members and encourages others who are so inclined to submit comments on the guidance documents. These are not the only guidance documents that FDA is going to produce in pursuit of the implementation of the Final Rule. A lot of the information APHL is seeking and the questions it is asking are intended to inform the future guidance documents that FDA is going to produce.

Regarding Final Rule communication and next steps, the APHL has posted updates about the Final Rule to its Laboratory Directors' listservs and eUpdates and has organized focus groups comprised of APHL members to help APHL better understand what questions require more clarity from the FDA and how that clarity should be structured so that all APHL members are best able to proceed with implementation of the Final Rule. APHL is also sharing everything that has been done with partner organizations and federal agencies and has posted its comments and concerns on the APHL website. APHL produced a summary document and plans to respond to the draft guidance documents that are available.

The effective data of the Final Rule is approximately July 5, 2024, which is 60 days after the Final Rule was printed. Comments for the draft policies are also due by July 5, 2024.

Diagnostics for *Mycobacterium Tuberculosis*: Implications with Regulation of LDTs

Marie-Claire Rowlinson, PhD, D(ABMM)
Bureau Chief, Bureau of Public Health Laboratories
Division Disease Control and Health Protection
Florida Department of Health

Dr. Rowlinson provided the state PHL perspective from the Florida Bureau of Public Health Laboratories (BPHL) on the implications of the regulation of LDTs. There are 3 laboratories that comprise the state PHL in Florida that are located in Jacksonville, Tampa, and Miami. Florida is a large state of 22 million people, the 3rd most populous in the US, and is 4th in the number of TB cases. In 2023, there were 624 TB cases in Florida (2.8/100,000 persons). That represented an increase from 2022 of 535 cases (2.4/100,000 persons). Public health testing for TB is performed only in the Jacksonville facility, which has a Biosafety Level-3 (BSL-3) suite and 18 staff. This is a high-volume laboratory with nearly 17,000 specimens received every year. Perhaps different from other state TB PHLs, Florida receives a number of primary clinical specimens and isolates that may be referred from other hospitals. The laboratory supports Florida and the Southeastern

[17] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-enforcement-policies-tests-during-section-564-declared-emergency?utm_medium=email&utm_source=govdelivery
[18] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-enforcement-policies-tests-during-section-564-declared-emergency?utm_medium=email&utm_source=govdelivery

National TB Center (SNTC) for complex cases, and will provide support to other states within the SNTC Region.

The goals of diagnostic testing for TB are to: 1) rule-out or make a diagnosis of TB as rapidly as possible; 2) remove the patient from airborne infection isolation if TB is ruled out; and 3) determine drug resistance as rapidly as possible to ensure the patient is on appropriate therapy. There are many types of tests and complex testing algorithms in laboratories. Microscopy is still a mainstay of laboratory testing for TB, even though it is a method that has been utilized for over 100 years. Laboratories also have access to numerous genotypic and phenotypic tests. Different testing that can be performed directly on a specimen versus on an isolate. Testing is done for detection and diagnosis of TB, as well as further characterization such as testing for antimicrobial resistance (AR), transmission, and epidemiology. Consideration also must be given to test performance in terms of sensitivity, specificity, turnaround time, and cost.

Current FDA-authorized tests for TB are limited and include the following:

- Rule in or rule out TB:
  - Cepheid MTB/RIF (sputum only, rifampin (RIF) resistance); may not be good for pediatric patients

- Identification from an isolate:
  - Bruker or bioMerieux MALDI-ToF systems (IVD databases only)
  - Biochemicals/HPLC (no longer considered a best practice)

- Detection of resistance from an isolate:
  - BD BACTEC MGIT SIRE Drug Kit—RIF, isoniazid, ethambutol, streptomycin
  - Thermo Scientific VersaTREK Myco Susceptibility Kit—RIF, isoniazid, ethambutol

- Determination of exposure to TB:
  - Qiagen QuantiFERON-TB Gold Plus
  - Oxford Diagnostic laboratories T-SPOT. TB Test

When considering diagnostic tests, it also is important to think about intended use, performance, and test parameters. What FDA is saying is that tests must be used according to their intended use and when tests are not used for their intended use, this constitutes going outside of the authorization. For instance, the intended use of the Cepheid Xpert MTB/RIF is “as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings.” This limits the test to use of sputum only and not considering other specimen types. Performance also must be considered in terms of specificity/sensitivity and turnaround time (hours vs days). Rapid molecular methods that are not FDA-approved may have improved performance but may not be available in the US market, such as the improved Cepheid Xpert MTB/RIF Ultra assay. The US is the only market that currently uses the Xpert MTB/RIF assay. Test parameters must meet clinical needs as well. For instance, the BD BACTEC MGIT SIRE Drug Kit only tests for 4 drugs, one of which is rarely if ever used in the US and is not approved for other drugs.

Regarding some of the LDTs that the Florida PHL performs, this laboratory has high volume assessment and tries to use state-of-the-art diagnostic testing in order to provide the best service possible for TB patients in Florida. A lot of molecular methods are used in the Florida BPHL because of the need for accurate and rapid diagnosis. All of the BPHL’s molecular methods are

currently LDTs or modified FDA-authorized tests. These can be performed directly on the specimen or on the isolate. The initial real-time PCR is a LDT that costs a lot less than the Xpert. Sensitivity has been improved and it is automated on BD MAX, which makes it easy to automate and makes sense with a higher volume of tests performed between 20 and 40 per day. The BPHL currently performs the GenoScreen Deeplex Myc-TB, tNGS, which is targeted next generation sequencing (NGS) for the detection of AR (RUO/LDT). This is sold as part of a research use only (ROU) kit, which has been validated as a LDT in the Florida laboratory. That can be performed directly on the specimen or on an isolate.

Cepheid Xpert MTB/RIF is used as well, because sometimes a quick answer is needed on TB and RIF resistance. It has been modified for specimen types other than sputum and isolates and pediatric patients. Even the real-time PCR is validated for different specimen types because otherwise, diagnosis cannot be made of extrapulmonary TB. All of the BPHL's molecular/phenotypic tests are all LDTs or modified tests that are performed on isolates. PCR restriction analysis is used for organism identification. This LDT is the best method for identifying mycobacteria for TB and other mycobacteria. This is important in the process of ruling out TB. Gene sequencing (hsp65) is done if the organism cannot be identified in another way, which is another LDT. Gene sequencing (pncA) is another LDT used for detection of pyrazinamide (PZA) resistance. Antimicrobial susceptibility testing (AST) by Thermo Fisher Sensititre MIC broth microdilution customized plate is used for detection of resistance to 12 drugs. This is a RUO that the BPHL has validated as a LDT.

Consideration for the use of LDT diagnostics raises a number of questions in terms of the FDA rule, some of which are:

- ❑ What are the potential impacts of the rule?
- ❑ What is the risk of discontinuation of tests that cannot meet the regulation?
- ❑ What if new or updated methods are implemented?
- ❑ What happens when new drugs are brought to market for treatment of TB?

Given that diagnostics is a continually changing field, a test that is validated today does not mean that it will be good in a year if a new treatment regimen becomes available.

All of the PHLs in the Southeast decided to gather data about what LDTs are used in PHLs and what the impact would be of the FDA rule. Survey data were gathered from the Southeast Regional Consortium that includes 9 state and 1 local PHL. The survey captured all LDTs performed by these PHLs (e.g., LDT, modified FDA-authorized assay, CDC assay, EUA assay, RUO assay validated as LDT), volume of testing, potential impact if they were to be discontinued, and whether tests are authorized in the European market. The survey highlights the breadth and volume of LDTs performed for infectious diseases, chemical threat, and newborn screening. To provide an example of the survey results, the Florida BPHL in Jacksonville performs 68 different LDTs. There are 7 LDTs for TB that are ranked as either "medium" or "high" in terms of priority, with none of these tests being determined as being eligible for discontinuation because patient care would be impacted if discontinued. For instance, the real-time PCR test used for MTB by the Florida BPHL in Jacksonville was modified for non-respiratory sources and requires TB Medical Director approval. The LDT testing components must be purchased separately; the annual test volume is 5,600; and the test is high priority (e.g., public health necessity, high consequence result, testing mandated in statute, no testing capacity outside of public health) and could not be discontinued without patient impact.

State PHLs continue to make quality improvements to LDTs by testing performance and accuracy; monitoring performance; updating or changing if performance can be enhanced; determining whether there are alternatives (especially FDA-authorized alternatives); testing efficacy, including turnaround time and cost; and determining whether a test continues to meet clinical testing needs. Few manufacturers are developing TB tests, getting them FDA-approved, and bringing them to market. The FDA has indicated that cost cannot be a factor for deciding to allow LDTs. The BPHL focuses on partnerships, working with its TB Program and TB Medical Director very closely on all of the tests that they perform, clinical outcomes, and ensuring that the tests they develop and perform are appropriate.

Use of LDT for TB at DTBE's Reference Laboratory and in US PHLs

Angela Starks, PhD
Chief, Laboratory Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

Dr. Starks described the use of LDTs within DTBE's TB Reference Laboratory, discussed the availability of LDTs in US PHLs supported by CDC's TB cooperative agreement, and identified considerations for meeting LDT requirements and potential impacts on TB testing. DTBE also thinks about what is driving decision-making in terms of specific tests. CDC tries to look across the landscape to determine whether there are specific gaps in services, such as susceptibility testing, and is actively trying to fill those gaps. Other elements driving decision-making for TB laboratory services include introduction of new treatment regimens, new technologies (e.g., NGS), changes in platform/instrumentation availability, advances in scientific understanding, changes in test algorithms for improved efficiencies, challenges in product availability, fluctuations in personnel or fiscal resources, and limited commercial options that are FDA cleared/approved to meet needs and service gaps.

Regarding supporting and strengthening testing capacity, Dr. Starks described CDC's TB Reference Laboratory services, Specialty Testing Centers, TB Elimination and Laboratory Cooperative Agreement, and partnerships to enhance capacity. This table provides a listing of the Clinical Laboratory Improvement Amendment (CLIA)-compliant testing that is performed in CDC's TB Reference Laboratory to aid in clinical decision-making that is either currently approved for testing or for which there are plans or pending validation to incorporate that test:

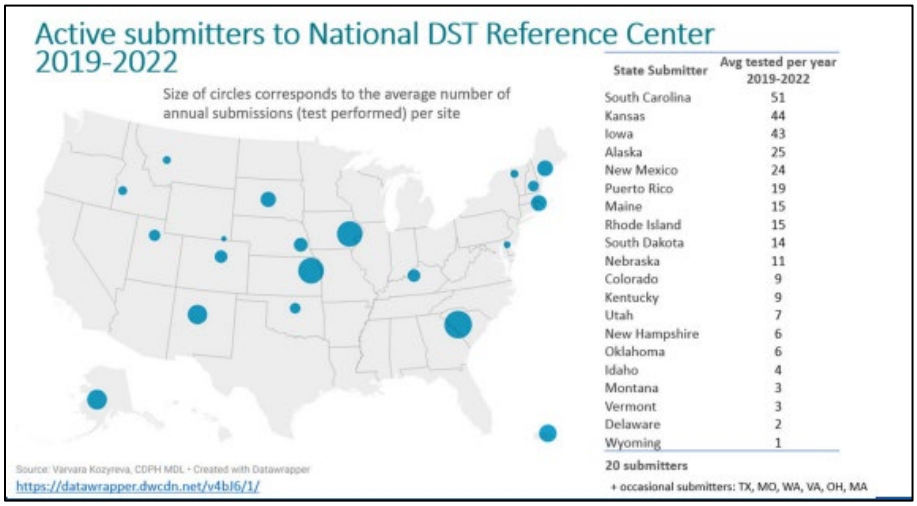
Test	LDT	Available prior to 5/6/24?
Sanger sequencing	Yes	Yes & No
Targeted next generation sequencing (tNGS)	Yes	Yes
Molecular identification (real-time PCR)*	Yes	No
Agar proportion (susceptibility testing)*	Yes	Yes & No
PZA susceptibility testing (MGIT)	No	Yes
Broth microdilution (MIC^ for new drugs)*	Yes	No
Pretomanid MIC^ testing (MGIT)*	Yes	No
Whole genome sequencing*	Yes	No

* Validation planned or completed ^Minimum inhibitory concentration

CDC validated some of the LDTs as a LDT, as shown in the second column above. Some of these may be designated for RUO, but have been validated or will be validated as a LDT. The last column indicates whether CDC was marketing the test as available for testing prior to the publication of the Final Rule on May 6, 2024. Notably in the second column, most of what CDC uses are LDTs. The only exception for CDC is PZA susceptibility testing in the BD MGIT system. In the last column, the tests indicating “yes and no” had to do with the service enhancements CDC hopes to put in place.

In terms of what the phase out of general enforcement discretion means for CDC’s TB Reference Laboratory, tests marketed prior to the Final Rule publication on May 6, 2024 that are not modified or that have limited allowable modifications would still fall under enforcement discretion. However, CDC would need to comply with other requirements (e.g., medical device reporting, quality system requirements including complaints and records, registration, and labeling). Hence, it is not saying that there is no responsibility related to these tests that were marketed prior to the publication of the rule. Currently for CDC, that would include targeted NGS (tNGS) assay and agar proportion testing as they exist now. CDC has service enhancements that they would like to make relative to those tests. Once that is done, the tests would fall under enforcement rules. Many of the tests that CDC has in the plan/validation pipeline will fall under the same enforcement approach as other in vitro diagnostics (IVDs). The good news is that disruption to current testing is not anticipated, as CDC will be working diligently to comply with the new requirements.

Regarding some of the Specialty Testing Center, the National PHL Drug Susceptibility Testing (DST) Reference Center for *Mycobacterium tuberculosis* (MTBC) is a collaboration with the APHL. This center is currently awarded to the California Microbial Diseases Laboratory (MDL) and is located on the Richmond Campus of the CDPH. The MDL offers comprehensive molecular and phenotypic DST for low-volume public health laboratories and currently serves 19 states and 1 US territory. Once isolates from those areas are identified as MTBC, they are then referred to the California MDL for phenotypic and molecular testing. Fortunately, the services that are offered by this particular specialty center were marketed before the FDA Final Rule was published. Currently, they are performing tNGS and universal whole genome sequencing (WGS) for submissions there and have a comprehensive phenotypic susceptibility testing panel as well. The following map shows the 20 active submitters to the National DST Reference Center for 2019-2022:

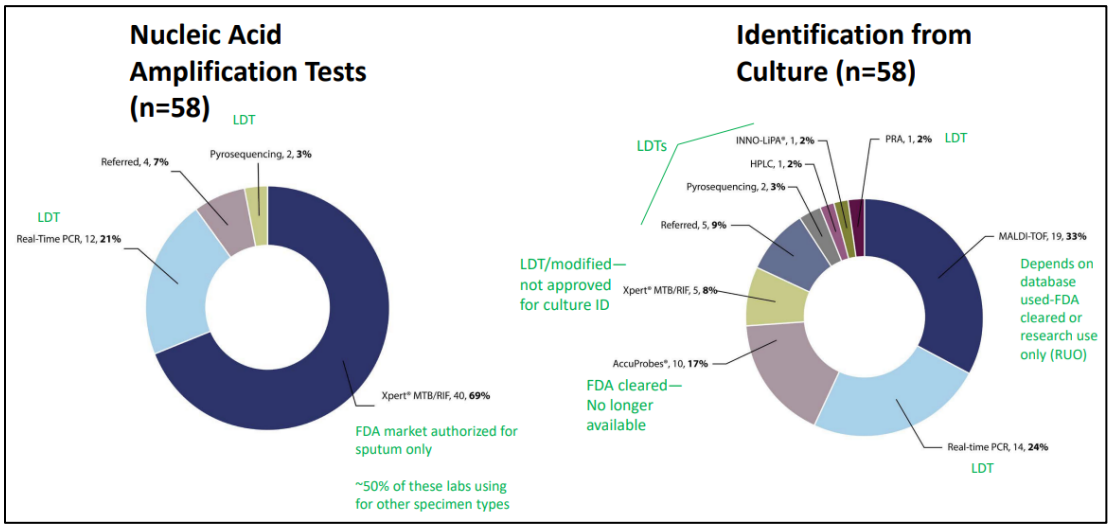


State Submitter	Avg tested per year 2019-2022
South Carolina	51
Kansas	44
Iowa	43
Alaska	25
New Mexico	24
Puerto Rico	19
Maine	15
Rhode Island	15
South Dakota	14
Nebraska	11
Colorado	9
Kentucky	9
Utah	7
New Hampshire	6
Oklahoma	6
Idaho	4
Montana	3
Vermont	3
Delaware	2
Wyoming	1

20 submitters
+ occasional submitters: TX, MO, WA, VA, OH, MA

The National Tuberculosis Molecular Surveillance Center (NTMSC) is currently awarded to the Michigan Bureau of Laboratories (BOL) for WGS for national molecular surveillance. Given that the work that is done by this specialty center is currently offered exclusively for public health surveillance, it should not be impacted by the Final Rule. However, if the approach changes to include CLIA clinical evaluation to report these same WGS results for clinical use, it would fall under same device requirements for pre-market approval.

The CDC TB Cooperative Agreement, which includes focus on strengthening public health laboratory services and activities at state and local levels, currently funds 58 awardees comprised of 50 state PHLs, 7 large cities (San Francisco, Los Angeles, San Diego, Houston, NYC, Washington DC, and Philadelphia) and Puerto Rico. CDC recently released the *2024 Tuberculosis Laboratory Aggregate Report: Seventh Edition,*[19] which is publicly available. This report provides information about workload and turnaround time indicators for all of the PHLs that are supported under this cooperative agreement. In 2022, these 58 awardees processed 161,772 (5–17,214) clinical specimens for a total of 65,049 (3–9,952) patients. Even across the PHLs, there is considerable use of LDTs. A couple of specific examples of the methods these PHLs are using in terms of LDTs follow:



For phenotypic susceptibility testing, CDC administers the Model Performance Evaluation Program (MPEP). Using this model, CDC sends out a panel of 5 isolates of MTBC for voluntary assessment of the ability to detect resistance in *M. tuberculosis*. A total of 56 laboratories participated in the 2023 panel,[20] most of which were performing testing for rifampin, isoniazid, ethambutol, pyrazinamide, and streptomycin using the FDA-cleared BD MGIT system. However, the number of laboratories performing testing for new and repurposed drugs is limited and there are currently no FDA-approved assays for testing these anti-TB drugs. Participants in that program also were asked about their molecular methods for susceptibility testing. All of their tests were developed as LDTs because there are no FDA-approved methods for this purpose.

[19] https://stacks.cdc.gov/view/cdc/157294
[20] https://stacks.cdc.gov/view/cdc/152102

To implement plans to decentralize WGS over the next few years, CDC has been working in collaboration with the Antimicrobial Resistance Laboratory Network (AR Lab Network) to expand the use of WGS data for clinical testing for drug resistance and surveillance through direct funding and has provided support through APHL and Epidemiology and Laboratory Capacity (ELC) cooperative agreements to a number of states to increase capacity for WGS for *M. tuberculosis* for surveillance and clinical purposes. Currently, 4 states have implemented either WGS or tNGS for clinical use whose services were marketed prior to publication of the Final Rule. Another 18 state or local PHLs that were in some phase of validation for clinical use of NGS prior to the publication of the Final Rule. Again, there are no FDA-approved assays approved for this purpose. Newly marketed tests and tests with applicable technical modifications prior to the Final Rule would need to meet full FDA IVD requirements.

CDC also has worked closely with the APHL to provide a funding opportunity to support 2 efforts. The first is to evaluate the revised critical concentration for rifampin. The World Health Organization (WHO) made a recommendation to revise the critical concentration that is used for testing rifampin to lower it to cover isolates with mutations resulting in low-level rifampin resistance. The second is to evaluate the addition of fluoroquinolones to be part of the first-line test panel. This funding opportunity with the APHL was awarded to 13 PHLs. All of them are still in the process of validating and evaluating this, so none of them have implemented this yet. Again, there is no FDA-cleared assay with the lower concentration of rifampin or for fluoroquinolone testing.

With regard to the way forward, everyone shares the objective to ensure safety and effectiveness of LDTs and that is not up for debate. The FDA regulation includes new requirements and new language to learn in the regulatory environment, so the implementation guidance will be key for laboratories. CDC is also working to gather information to better understand some of the decision-making in terms of the best path forward. The phased approach is helpful and also will not be disruptive to current testing, but considerable strategic planning will be needed, and it will be necessary to balance available resources with needs. If PHLs make a decision to stop some of the testing that they are doing, DTBE will have to think about shifting volumes within the PHL system in terms of how that might impact centers that the division supports and DTBE's own test volumes.

There is an exciting opportunity globally outside the US with a number of phenotypic and molecular assays that are in development, evaluation, or have been endorsed by the WHO.[21] It would be wonderful if some of these would be regulatory approved for use in the US, given that it would eliminate some of the current concerns regarding use of LDTs. This table provides an overview of the global pipeline for phenotypic and molecular tests:

[21] https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-research-and-innovation

Technologies in development	On the market (Not yet evaluated by WHO)	Technologies under evaluation by WHO	Technologies endorsed by WHO
Molecular detection of TB disease and drug resistance detection • Gendrive MTB/RIF ID, Epistem, UK • TruDiagnosis, Akonni, USA • INFINITIMTB Assay, AutoGenomics, USA • FluoroType XDR-TB assay, Hain Lifescience, Germany • MeltPro TB assay, Zeesan Biotech, China • Q-POC, QuantuMDx, UK • Truenat MTB-INH/MTB-FQ/MTB-BDQ, Molbio, India • IRON qPCR Q-RFIA (preXDR-TB RT PCR), Bioneer, Republic of Korea • STANDARD M MDR-TB; MTB/NTM; XDR-TB, SD Biosensor, Republic of Korea • Mycobacterium Tuberculosis Rapid NAT Test Kit, Bao Ruiyuan Biotech (Beijing) Co., Ltd. China • MTB qSTAR test, LumiraDx, UK • Genedrive system, Genedrive, UK	**Molecular detection of TB disease and/or drug resistance detection** • iCubate System, iCubate, USA • Genechip MDR test, Capital Bio, China • EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China • AccuPower TB&MDR Real Time PCR Kit, Bioneer, Republic of Korea • AccuPower XDR-TB Real-Time PCR Kit-A, Bioneer, Republic of Korea • AccuPower XDR-TB Real-Time PCR Kit-B, Bioneer, Republic of Korea • MDR/MTB ELITe MGB® Kit / ELITe InGenius® platform, ELITech Group, Italy • mfloDx MDR-TB, EMPE Diagnostics, Sweden • Erythra-TB-KIT, Erythra, USA	**Culture-based drug susceptibility testing** • SensititreTM MYCOTBI plate; ThermoFisher Scientific Inc., USA **Culture-free, targeted-sequencing solutions for detection of TB drug resistance** • Deeplex® Myc-TB, GenoScreen Innovative Genomic, France • DeepChek® TB, Advanced Biological Laboratories, France • NanoTB, Oxford Nanopore Technologies, UK **Biomarker based assays for TB disease detection** • Fujifilm SILVAMP TB LAM Assay, Fujifilm, Japan	**Molecular detection of TB disease and/or drug resistance** • Xpert MTB/RIF, MTB/RIF Ultra and MTB/XDR, Cepheid, USA • GenoType® MTBDRplus, Hain Lifescience/Bruker, Germany • Genoscholar® NTM+MDRTB II; Nipro, Japan • GenoType® MTBDRsl, Hain Lifescience/Bruker, Germany • TB LAMP, Eiken, Japan • Truenat MTB, MTB Plus and MTB-RIF Dx assays, Molbio Diagnostics, India • FluoroType MTB and MTBDR assays Hain Lifescience, Germany • Abbott RealTime MTB and MTB RIF/INH on m2000sp and m2000rt systems, Abbott, USA • BD Max MDR-TB, Becton Dickinson, USA • Roche cobas® MTB and MTB-RIF/INH on Cobas 6800/880 systems, Roche Diagnostics, Switzerland • Genoscholar PZA TB II, Nipro, Japan

ACET Discussion on Panel 2: Regulations of LDTs and the Impact on TB Testing in the US Presentations

CDR Rhodes asked whether there is a timeline for when diagnostic testing used outside of the US could be approved for US use and which step in the FDA approval process is causing a delay or challenges with this.

Dr. Rowlinson said she did not anticipate any of those tests coming to the US market. In addition, tests are being removed from the market because manufacturers in this country do not want to continue to support those products. Reflecting on Dr. Chen's question earlier, she is not sure what more can be done. The limiting factor for manufacturers is probably going to be cost and potential financial losses. Manufacturers do not appear to have any plans to submit additional TB diagnostics to the FDA for approval.

Regarding the cost perspective, Dr. Starks added that another issue is the risk-based classification for the specific diagnostic device. On a recent webinar, FDA said they are working to move most devices into a Class 2 risk category, which is good in terms of the amount of data that would be required for submission, but it remains a question.

Dr. Thanassi said she is getting many questions about the LTBI test regarding the difference between an FDA-cleared test and an FDA-cleared process and whether, if a process is approved on one machine and someone uses a different machine or analyzer, that makes it a LDT.

Dr. Rowlinson responded that it does not make it an LDT, but this would be out of compliance with Good Laboratory Practice (GLP) to use another instrument and washer not previously used and for which the performance is unknown. Even if a test is implemented in the laboratory that is FDA-authorized, verification still must be done to ensure that the test is performing as expected. That is about CLIA compliance rather than LDT.

Dr. Starks added that Dr. Thanassi's question also pertained to certain modifications that might be made in terms of what still may be acceptable and what may trigger revisiting the regulatory process.

Dr. Owens agreed and added that it depends upon the guidance that FDA publishes about the technical modification. With other diseases, a test becomes an LDT if the platform is changed.

Dr. Thanassi asked if a test is approved on a particular enzyme-linked immunosorbent assay (ELISA) machine, it could be used on any of the other competing ELISA machines—assuming GLP and good validations.

Dr. Rowlinson said that probably would be related more to the manufacturer's instructions in terms of listing the instruments that have been authorized for use with a particular test. Most FDA-cleared IVDs are prescriptive and usually involve 1 instrument. Using a different instrument would be considered a modification of what the manufacturer prescribes.

Dr. Thanassi pointed out that there are centrifuges, incubators, analyzers, washers, machines, and a lot of steps and processes for some of the tests. The pipeline is slow and sometimes, machines are not even invented at the time a test is approved.

Dr. Rowlinson said the FDA is not that prescriptive about the centrifuge as long as the manufacturer's instructions are followed, so that is a good point. If going forward the enforcement discretion is removed, processes will be more scrutinized.

Dr. LoBue indicated that fluoroquinolones are not approved for TB treatment. The FDA previously had a policy that an assay would not be approved for drugs that were not approved for TB treatment. He asked whether that policy is still in place and if/how it would apply to those who want to develop a test for drug-resistance for fluoroquinolones.

Dr. Starks said that to her knowledge, that policy is still in place and DTBE is keenly interested in knowing the answer based on current needs.

Dr. Rowlinson added that intended use would be an aspect of that as well. The FDA likely would have an issue with the use of an LDT if they felt it was being done inappropriately.

Dr. Mermin emphasized that Dr. LoBue and his team have spent considerable time sharing information, recognizing that they have continuing engagement with the FDA about CDC's specific needs. He asked whether any thought had been given to what the FDA ideally would want to approve and about what it would cost to essentially pay for 510(k) approval of existing tests and the ongoing expenses for someone, ideally not CDC, to complete this pathway.

Dr. Starks said that ideally, CDC would want all tests currently available in its TB Reference Laboratory to go through the appropriate channels for approval because they build a need in terms of specific gaps that exist across the nation for molecular and phenotypic testing. While she thinks there are exemptions for federal and state government entities for the application costs for regulatory approval, she did not know how that would play out with the current processes that are in place. Beyond application fees, it is important to consider the amount of data that would be required and the time and expertise that would be necessary to assemble the various components of the requirements, which DTBE does not have in its laboratory. She expects that many PHLs also do not necessarily have that expertise in their facilities. While there

are concerns about the time, effort, personnel, and expertise that will be needed, the implementation guidance is going to be key in terms of moving forward.

Dr. Owen confirmed that federal government entities do not have to pay the fee to FDA for 510(k) applications but do pay for the costs of the clinical trials.

Dr. Rowlinson reiterated that the Florida PHL performs 68 LDTs currently and there is absolutely no way that the State of Florida could submit 68 510(k) applications. The state mandates that the PHL perform some tests, such as newborn screening, so they cannot have the tests done elsewhere. In some situations, they are “between a rock and a hard place.”

Dr. Ahmed asked whether it was better to push those concerns before or after the implementation guidance is made available, or if it was too late.

Dr. Rowlinson emphasized that several organizations submitted comments prior to July 5, 2024, such as APHL, IDSA, American Society for Microbiology (ASM), IDSA, American Clinical Laboratory Association (ACLA), and others.

Dr. Starks added that anything that can help clarify or address the concerns in advance of the implementation guidance would be beneficial. While this is a sobering topic, she reiterated that CDC is not anticipating any disruptions of current testing.

Dr. Rowlinson said that Florida is continuing to implement its LDTs. They have a new phenotypic susceptibility testing plate, which has bedaquiline and pretomanid. While it has not been validated yet, they do not plan to stop doing tests that meet the needs of patients. The Red Book states that IGRA can be used for anyone of any age, but FDA states that IGRA cannot be used for anyone under 2 years of age. Therefore, testing pediatric patients basically would be off-label use.

Dr. Sosa said she appreciated that nothing is anticipated to change in the short-term, there is a long game. An implementation plan is needed, and consideration must be given to whether there will be more regional testing services at a minimum. CDC has allocated a lot of investments and resources to state laboratories to enable them to perform frontline testing, which is so important to the work of public health. Her sense is that will be affected.

Dr. Starks reiterated that 18 states are in some phase of validation for CDC’s NGS assay. There has been a lot of excitement across the PHL system about the potential to have that capacity. She does not know what decisions are being made at this point in terms of continuing with or discontinuing those validations or considering more centralized approaches. CDC certainly needs to be aware and kept apprised of these decisions, given that it could inform long-term decision-making.

Dr. Rowlinson emphasized that the reason the Southeast Regional Consortium survey was conducted was to assess the data and think about which tests could be discontinued or regionalized. The challenge pertains to where the funds will come from to operationalize that.

Dr. Loeffler requested a summary of the status regarding tests that were vetted, internally validated, and advertised before May 5, 2024 which seemed different from the last time ACET met when it sounded like nothing would be allowed. She also wondered whether the FDA views TB differently than other diseases and posited that there must have some other disease targets about which they are concerned.

Dr. Rowlinson indicated that those tests will be grandfathered unless significant modifications are made to a test, in which case that test would become a new LDT. It is not clear yet what constitutes “significant modifications.” For instance, the Florida PHL validated a NGS assay that would be grandfathered in, but now has a second iteration looking at additional gene targets. It is not clear whether that would be considered a significant modification.

In terms of other disease targets, Dr. Owen said her understanding is that the FDA is not targeting diseases other than extremely rare diseases of less than 1,000 per year and TB is not being considered differently from other infectious diseases. There are requirements even for tests that are grandfathered in, such as implementing a system in the first year to accept complaints and file them in a certain quality format. In the second year, Instructions for Use (IFU) must be uploaded to the FDA website so that there is a database. Going through CLEP is fine in the future, but the question regards whether New York will be willing to take on looking at a lot of assays they have not looked at before.

Dr. Ahmed asked whether CDC has a plan or some sort of “blessing process” to push grandfathered tests forward.

Dr. Starks said that there are specific requirements with regard to device labeling, reporting, IFUs, et cetera that will be required for everything. With the phased approach, the requirements for Premarket Approval (PMA) are addressed in Years 3 and 4 for the assays that would not have been marketed prior to May 6, 2024.

Dr. Chen asked whether other infectious diseases could be labeled of public health significance in terms of transmission or risks that perhaps could experience a similar situation in which critical tests or LDTs will be affected in this way. Perhaps more upstream work needs to be done.

Dr. Rowlinson indicated that PHLs perform routine testing for STIs, but also test unusual specimen types. Most private clinical laboratories do not have the capacity to do that because it is off-label. A clinical laboratory might be able to tell someone they have dengue, but would not be able to identify the serotype, which could be important for those who have had previous dengue infection. PHLs perform testing for many types of infectious diseases, which is critical but for which there is no exception at the state PHLs. There is a carveout for unmet needs, within, but it only applies to a laboratory in a healthcare setting where the patient must be receiving. PHLs are reference laboratories and are not in a healthcare system. While she argues that they have a TB Medical Director who takes care of every TB case in the state, she does not know whether that argument will hold up based on how the rule is written in terms of unmet needs.

National Tuberculosis Controllers Association (NTCA) Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary TB in Community Settings

Maunank Shah MD, PhD
Professor of Medicine and Epidemiology
Johns Hopkins University

Dr. Shah provided an update on the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings*[22] for which abridged and full versions are available on the website. The abridged version will be printed. The following table summarizes the 5 NTCA recommendations:

Table 1. Recommendations for Community-Based Respiratory Isolation and Restriction for Persons With Tuberculosis

Recommendation 1: Goals of RIR	1.1. The decision to recommend TB RIR should consider the potential benefits and harm for both the community and the PWTB.
Recommendation 2: Defining RIR (Table 2)	2.1. RIR in community settings should be conceptualized as a spectrum of tailored restrictions that are individualized for specific circumstances (Table 2).
Recommendation 3: Determining infectiousness and transmission risk (Figure 1)	3.1. Prior to effective[a] ATT initiation, PWTB with higher respiratory bacterial burden (ie, sputum smear and/or NAAT positivity, cavitation on chest imaging) may be considered as relatively more infectious than those with lower bacterial burden, with individual variability. 3.2. PWTB on less than 5 days of effective ATT should be considered relatively more infectious than those on longer durations of effective[a] therapy. 3.3. PWTB on effective[a] ATT for at least 5 days should be considered noninfectious or as having a low likelihood of infectiousness, regardless of sputum bacteriologic status during ongoing ATT (ie, smear microscopy or culture status), with certain exceptions.[b] 3.4. Overall risk of transmission to others should consider both a PWTB's infectiousness, as well as other factors including the environment of potential exposures, durations of exposure, and biological susceptibility of contacts.
Recommendation 4: Determining RIR (Table 3)	4.1. RIR is not recommended for persons with noninfectious forms of TB (ie, localized extrapulmonary TB without pulmonary involvement, as confirmed by sputum bacteriologic studies and/or chest imaging). 4.2. People with pulmonary TB on effective[a] ATT and a low likelihood of infectiousness should not have restrictions in most circumstances (ie, RIR should be removed, if present),[b] with individual exceptions for situations involving higher-risk community settings and populations (eg, children <5, immunosuppressed individuals). 4.3. Community-based RIR may be considered for PWTB who have higher infectious potential in which there is judged to be higher risk of transmission to the community.
Recommendation 5: Determining level of RIR (Table 3)	5.1. When community-based RIR is indicated for a PWTB, a moderate or midlevel range of RIR (Table 2) should be considered appropriate in most circumstances, with individual exceptions. 5.2. Specific RIR levels (eg, low, moderate, or extensive; Table 2) and duration for PWTB should be reassessed routinely (at least weekly) and may be modified based on individual considerations or changing circumstances. 5.3. When RIR is implemented, support should be provided to patients to mitigate anticipated and experienced harms.

The guidelines follow a stepwise progression in which the first recommendation outlines the goals of community-based respiratory isolation and restrictions (RIR). It then defines community-based restrictions, determining risk, determining RIR, and determining level of RIR. An Invited Commentary also is available from Drs. Caitlin Reed and Neela Goswami from the CDC that accompanies the guidelines.[23] The IDSA officially endorsed the guidelines in May 2024, which has been incorporated into the Guideline Statement as well.

Before reviewing the guidelines, Dr. Shah provided some background on how the process transpired. In terms why the NTCA took this on, an accompanying article will be printed in the next month or so in the *Journal of Infectious Diseases* (*JID*) that reviews the legal aspects of public health powers as it relates to TB. Though not the primary purview of the NTCA Development Group, it is an accompany component that will provide additional context. Notably,

[22] https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae199
[23] https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciae198

the “police power” in the US in terms of it being a federalist system is fragmented and defaults to states and local governments rather than the national level. Part of what makes public health policies different from clinical practice guidelines is that they have both ethical and legal dimensions. Therefore, developing a policy statement is more complex than developing a clinical practice guideline because the decision to be made is not purely scientific and must consider the values and preferences of the community and the individuals afflicted by the disease. A number of papers have been written about all of this, including one that was published in the *New England Journal of Medicine* (*NEJM*) about a year and a half ago provided some background and the foundation about how NTCA approached this.[24] Public health has multiple dimensions (e.g., preventing disease, prolonging life, and promoting health through organized efforts of society). However, public health decisions have not always been transparent. In terms of the commentary that has been written in the aftermath of the COVID-19 pandemic, it is not that the decisions that were made were incorrect or not valid or appropriate, but that it is important that the process of making guidelines is at least transparent with a clearly articulated rationale. NTCA recognized that for burdens and sacrifices on the part of some persons, such as persons with TB, the goal is to protect the health of the public. Public health guidelines are unique because the values and preferences may differ based on the perspective. As part of this, the NTCA felt strongly that they wanted to have broad representation from a number of sectors on the panel that was set forth to purport the guidelines because the final guidelines have to reflect public health considerations and considerations of the persons with TB. The guideline group ultimately was a balanced group of clinicians, nurses, people with TB, and epidemiologists and no one group was thought to be over-represented.

Professor Lawrence Gostin, the architect of the Model State Emergency Health Powers Act (MSEHPA) and a luminary in bioethics and public health law, was commissioned in 1993 to survey all of the state statutes and laws. Some of the findings are useful in terms of the development of the NTCA guidelines. The first is that he noted that most TB control was governed by antiquated laws that pre-dated modern concepts of Constitutional Law. He thought that in actuality, most state statutes were incompatible with modern concepts on public health law. It is clear that state and local public health have the power to enforce isolation orders, but there also are rights-based limitations to this. It is not that isolation is unconstitutional, but rather that it has certain boundaries. The exercise of such powers has to be restricted to scenarios where there is deemed a significant public health risk. It is noted that the state of TB, TB epidemiology, and the tools available have changed since the late 1800s and early 1900s when some of the case law was instituted. Gostin notes that Health Officers should be acting flexibly and guided by the principle of using the least intrusive means to achieve the public health objective.

It seems like the Gostin paper is tied to the role of the ACET as well and speaks to who sets policy. Shortly after that survey and recommendations about TB law and public health policies that was put forth by Gostin, ACET published a set of recommendations later in 1993 about TB control laws to articulate aspects that state legislatures should consider in their statutes.[25] Different from clinical guidelines, a number of parties have a stake in informing public health policy. The 1993 ACET recommendations basically state that consideration can be given to restricting the activities of persons with TB for as long as they are infectious, and those restrictions should be terminated when they are no longer infectious. One of the key provisions,

---

[24] Boon et al. Challenges in applying GRADE approach in public health guidelines: a concept article from GRADE public health group, JCE 2021 Parasidis et al. Closing the public health ethics gap, *NEJM* Sept 2022

[25] https://www.cdc.gov/mmwr/PDF/rr/rr4215.pdf

particularly when enforcing involuntary confinement or detention, is that there has to be evidence that there is a substantial risk of infecting others. To be clear, this pertains to isolation orders or recommendations at the point of a person being diagnosed with TB and thinking about the overarching amount of risk to public health and the public. Dr. Shah pointed out that the 1993 ACET document was one of the first instances he could find in the literature of the notion about laboratory testing and non-infectiousness in that the person is smear-negative and asymptomatic. This is one of the instances where the concept of smear-negativity seems to enter into TB guidelines as it relates to isolation. It is not clear what evidence was reviewed by the ACET to make this determination and recommendation, so this is another area where transparency is needed since such recommendations have far-reaching consequences. This is probably one of the first statements that influenced a number of state laws and statutes.

Regarding what transpired after that, the 2002 Model State Emergency Health Powers Act (MSEHPA)[26] was enacted about a decade later. Gostin was again commissioned to update to determine how public health authority should be constructed across states. This was a non-legally binding document, but essentially all 50 states adopted laws based on this act. While this act was in response to 911 and bioterrorism threats, one of the key concepts that relates to isolation that this guidance document puts forth is that "Officials must follow specified legal standards before using isolation, which is authorized to prevent transmission of a contagious disease and must be by the least restrictive means possible." The guideline also goes on to talk about due process. Due process rights primarily come into play with regard to involuntary confinement and detention, but if voluntary measures are being asked of a person with coercive statements that if they fail to comply, they will be subject to involuntary confinement, then due process rights kick in. There is wide heterogeneity in terms of how isolation orders are actually executed by local and state public health officials in terms of whether people are informed of their rights and the level of harm to the public that is required before they can be asked to be in isolation.

All of this is that the concepts that keep coming up are that for isolation to be ethically and legally grounded, it should use the least restrictive means possible that follows due process of law and is not arbitrary. In part what is meant by arbitrary in most of these contexts is that there should be evidence that intervention itself is effective. People's Constitutional rights cannot be restricted if there is not reasonable belief or evidence that the intervention is actually going to lead to the public health outcome desired. All of that was in the backdrop and brewing as NTCA took on this task in 2022. The goal was to try to go through the process in a transparent and methodical way. The Guideline Development Group was established and everyone in the group was working from the same set of evidence. An adapted Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was used because these are not clinical practice guidelines, for which GRADE was developed.

Systematic reviews were performed of key questions that followed the standard GRADE PICO (Population, Intervention, Comparator, Outcome) format, with a goal to make recommendations about community-based respiratory isolation and restrictions. Because it was thought that determination of infectiousness was going to be a key part of this and does not follow a standard PICO format, several specific questions were set forth at the onset for the evidence to help the Guideline Development Group better understand the determinants of TB infectiousness. There was a standard process of evaluating the evidence and making Evidence to Recommendations

[26] https://jamanetwork.com/journals/jama/article-abstract/195159

(EtR) frameworks, which are all in the appendix of the guidelines for those who are interested in additional details. Within the GRADE approach, these are the types of recommendations based on the certainty of evidence as applied to this scenario:

- ❑ *Strong Recommendations:* This type of recommendation is typically based on "high certainty of evidence" that reflects values and preferences, where the action or the assessment would be the preferred choice for most people with TB, communities, clinicians and policy makers. The magnitude of benefits is expected to outweigh harm in most circumstances.

- ❑ *Conditional Recommendations*: This type of recommendation is typically based on lower certainty of evidence and reflects values and preferences where there may be important uncertainty or variability in the anticipated benefits and harms. The magnitude of benefits probably outweighs harms in most circumstances, with individual considerations or variability.

The primary PICO questions were:

- ❑ Does community-based respiratory isolation of people with TB reduce incident TB infection (i.e., prevent transmission), incident TB disease, and/or TB mortality?

- ❑ Does community-based respiratory isolation of people with TB worsen mental health, stigma, and/or costs?

The following additional questions informed recommendation building:

- ❑ Are people with TB [not on treatment] with higher bacterial burden more infectious than people with TB with lower bacterial burden based on bacteriologic tests (e.g., sputum smear-microscopy, NAAT) and/or other clinical parameters (e.g., cough, chest imaging)?

- ❑ Are people with TB [on treatment] with higher bacterial burden more infectious than people with TB with lower bacterial burden?

- ❑ What is the impact of treatment on a person with TB's infectiousness?

The Guideline Development Group knew from the outset that they would have to weigh different sets of considerations between protecting the public's health as well as the impact on the individual. There are multiple levels of uncertainty, including scientific uncertainty in terms of determinations of effectiveness and as it relates to the effectiveness of the intervention itself. Within those scenarios, there are multiple strategies that could be utilized (e.g., abstain and make no decision, exclusively prioritize public health, or exclusively prioritize the person with TB). The group's goal was to find a balance, with the understanding that different people might come to slightly different conclusions. The Guideline Development Group met many times in the course of about 6 months to work through the development and incorporation of an ethical framework to address how uncertainty would be dealt with. This table depicts the ethical framework they developed, which is described further in the NTCA guidelines as well as in an accepted publication (August 2024) in *Journal of Infectious Diseases (JID)* as part of an accompanying manuscript on "Integrating ethics into public health guideline development:"

Domain	Term	Explanation
Approaches to uncertainty Support policymakers in interpreting limited scientific data	**Abstention**	Make no recommendation, but be mindful of what will happen in the absence of guidance
	Prioritization	Default to prioritizing a single value or good
	Evidence grading	Transparently describe the limitations of scientific data
	Practical wisdom	Critically examine and interpret limited data using expertise gained through relevant training and personal experience
Ethical values Support policymakers in deciding which effects of a policy decision would be desirable and should be promoted, or undesirable and should be avoided/ minimized	**Wellbeing**	**Individual** Health – Individual health and safety outcomes Livelihood – Access to work, school, housing, food, and basic resources Social relations – Access to a stable and supportive social network Esteem – Self-esteem and dignity **Community** Public health – Community and population health and safety outcomes Economic productivity – Community level economic stability; GDP Social cohesion – Strength and stability of shared community bonds Community identity – Sense of national, regional, or group identity and esteem
	Justice	**Recognitional:** Be aware of differences in identity and experience **Distributive:** Seek a fair distribution of benefits and burdens **Procedural:** Ensure due process
	Liberty	Freedom from obstructive interference, without exclusion from beneficial or empowering resources Incorporate opportunities for choice Offer compensatory resources
Justificatory conditions Support policymakers in determining whether a compromise between values is acceptable and fair	**Necessity**	Infringement on one value to promote another must be necessary or unavoidable
	Proportionality	Infringement on one value must be balanced by at least qualitatively proportional promotion of another
	Least infringement	Refine the conditions of a proposed compromise to minimize infringement on any value
	Lines in the sand	Identify the boundaries of a pluralistic framework by defining compromises that would be unacceptable because they violate fundamental rights or obligations

Kates et al. **Integrating ethics in public health guideline development: a case-study of the NTCA guidelines on respiratory isolation for persons with TB in community settings,** in preparation JID

Moving to the recommendations, the goals of Recommendations 1 and 2 pertain to the goals of isolation and defining isolation. In the GRADE format, these are called “Good Practice Statements.” These statements are not based on a specific set of evidence, but instead are actionable statements that are deemed necessary for practice. At the beginning of the guidelines, this helps to frame the ethical and legal background and explains why these statements were made. The heart of the idea is that a decision to institute isolation has multiple dimensions. The specific recommendations follow, with Dr. Shah’s brief comments made during his presentation in italics:

<u>Recommendation 1: Goals of Respiratory Isolation and Restrictions</u>
1.1: The decision to recommend TB respiratory isolation and restriction should consider the potential benefits and harm for both the community and the PWTB.

This recommendation formalizes the ethical and legal principle that decisions about RIR must consider individual well-being and community well-being and ensure that it is rooted in justification.

<u>Recommendation 2: Defining RIR</u>
2.1 Respiratory isolation restrictions in community settings should be conceptualized as a spectrum of tailored restrictions that are individualized for specific circumstances (see Table 2 for a suggested framework).

The Guideline Development Group sought to formalize the idea of using the least infringement, which is a core concept in most Constitutional and state law as it relates to enforcing public health powers. The enforcement of isolation and interventions should be balanced. This recommendation addresses strict and extensive restrictions, moderate restrictions, and no restrictions. This is a basic acknowledgement that there are 2 halves to the transmission equation (e.g., the infectious person with TB and the frequency and duration of contact in the environment in which those contact events occur). Not all situations carry an equal community health risk. Many activities, particularly those in good and naturally ventilated environments, have a relative more modest transmission risk. Table 2 of the guidelines describes the spectrum of respiratory isolation and restrictions for persons with TB in a community-based setting.

Recommendation 3: Determining Infectiousness and Transmission Risk

3.1: Prior to effective treatment initiation, PWTB with higher respiratory bacterial burden (i.e., sputum smear and/or NAAT positivity, cavitation on chest imaging) may be considered as relatively more infectious than those with lower bacterial burden, with individual variability (Strong Recommendation, Moderate Certainty of Evidence).

3.2: PWTB on less than 5 days of effective treatment should be considered relatively more infectious than those on longer durations of effective therapy (Figure 1, chart A) (Strong Recommendation, Moderate Certainty of Evidence).

3.3: PWTB on effective treatment for at least 5 days should be considered noninfectious or with a low likelihood of infectiousness, regardless of sputum bacteriologic status during treatment (i.e., smear microscopy, NAAT, or culture status), with certain exceptions (Conditional Recommendation, Moderate Certainty of Evidence).

3.4: Overall risk of transmission to others should consider both a PWTB's infectiousness, as well as other factors including the environment of potential exposures, proximity, frequency, and durations of exposure, and biological susceptibility of contacts (Figure 1, chart B).

Before even getting to whether respiratory isolation should be considered, there is an intermediate recommendation that involves the synthesis of data regarding infectiousness. This is the prerequisite to determining whether to isolate an individual. Individuals who are non-infectious should not be considered for isolation and isolation can be considered for individuals who are infectious.

For 3.3, "effective treatment" is defined as a recommended multi-drug regimen to which the organism is susceptible or anticipated to be susceptible. No single test or treatment duration universally predicts non-infectiousness. Available evidence suggests that most PWTB are unlikely to transmit to others within the first few days (24-72 hours) after treatment initiation. Other factors to consider may include pre-treatment bacterial load, adequacy and adherence to treatment regimen, and/or adherence and clinical response to treatment. Given the data showing that treatment effect is relatively rapid in almost all circumstances, 5 days was chosen as a more pragmatic time period than 24, 48, or 72 hours. This recommendation sets the floor for how long a person should be considered infectious. The Guideline Development Group considered whether to put forth an endpoint, but decided to put forth a recommendation that applies to most circumstances and also allows for individual consideration in instances where there is more uncertainty.

Recommendation 4: Determining Whether Community-Based RIR is Indicated (Table 3)

4.1: RIR is not recommended for persons with noninfectious forms of TB (i.e., localized extrapulmonary TB without pulmonary involvement, as confirmed by sputum bacteriologic studies and/or chest imaging).

4.2: People with pulmonary TB on effective treatment and with a low likelihood of infectiousness should not have restrictions in most circumstances (i.e., RIR should be removed, if present), with individual exceptions for situations involving higher-risk community settings and populations (e.g., children <5 years, immunosuppressed individuals) (Conditional Recommendation, Moderate Certainty of Evidence).

4.3: Community-based RIR may be considered for PWTB who have higher infectious potential in which there is judged to be higher risk of transmission to the community (Conditional Recommendation, Low Certainty of Evidence).

The first part of this recommendation, 4.1, is the foundational principle that restrictions should not be recommended for people with non-infectious forms of TB. The Guideline Development Group conducted an extensive literature review and concluded that there was moderate certainty of evidence that bacterial burden measured by bacteriologic studies are associated with infectiousness prior to treatment. In addition, the group concluded that there was moderate certainty of evidence that bacteriologic studies after effective treatment initiation are not reliably associated with transmissibility of M. tuberculosis from PWTB to others. In terms of whether treatment reduces transmissibility of MTB to others, the group felt that there was moderate certainty of evidence that effective treatment appears to rapidly and steadily reduce infectiousness, irrespective of bacteriologic studies conducted during ongoing treatment. However, not all time points have been uniformly evaluated. Transmissibility declines rapidly. The data reviewed and discussed stemmed from a number of studies. Laboratory studies have shown a 90% decline in viable bacteria within the first 48 hours. Human-to-guinea pig studies have shown that the treatment effect is prompt (24-72 hours). Effect in some studies appears almost immediate (24-48 hours). Transcriptomic/gene-expression studies have shown that the treatment effect changes in 1-4 days of treatment. The majority of observational/epidemiologic studies have evaluated transmission after 1-2 weeks of treatment. The Madras randomized controlled trial (RCT) showed no difference comparing those in isolation with those with home-based treatment and ongoing exposure. Ultimately, the best type of study for this would be a human challenge study. However, that has not and never will be done.

Transmission depends on more than infectiousness of a person with pulmonary TB. Different environments and activities are anticipated to have different transmission risk, independent of infectiousness of PWTB. Studies suggest that the risk of transmission is lower with outdoor activities and those with natural ventilation, compared to shared ventilation indoors. There is no minimum duration of exposure that is required for infection, but studies suggest that longer durations have greater risk than shorter. While 120 contact hours per month has been used to stratify risk in prior contact investigation guidelines, 8 hours of close exposure in closed space has been used (derived from limited evidence related to air travel). Individual circumstances and community context are important for assessing the expected benefits from isolation decisions. This is why Recommendation 3.4 states that overall risk of transmission should consider a PWTB's infectiousness and other factors (e.g., environment in which exposures occur, duration of exposures, and biological susceptibility of contacts).

In terms of the question regarding whether individuals with pulmonary TB in the community should be isolated, the evidence was modest. The only clinical trial did not show treatment to have much effect on incident TB infection disease or mortality. The evidence that isolation actually reduces community levels of transmission perhaps stems from modeling studies, but even these have limitations because they have many assumptions, including other preventive measures. There are data from healthcare settings,[27] but that is a different systematic review, and these were almost always studied in conjunction with other infection control measures. Even in a high-risk scenario, the findings were that isolation led to a 1% increase to a 20.5% decrease in LTBI in the healthcare setting. The evidence that package measures were effective was

[27] Karat et al. CID 2021

indirect and of low quality. The healthcare setting is not necessarily extrapolatable to a community-based setting, but even there, the data on isolation is uncertain. This led to a scenario with which the Guideline Development Group had to wrestle, because they did not want to make recommendations that were arbitrary or lacking in evidence that they are effective. They also acknowledged that measuring these outcomes is challenging, and absence of data may not reflect absence of benefit (Very low certainty of evidence regarding magnitude of benefits).

Regarding the other PICO questions about harms, there was moderate certainty of evidence about harms or undesirable outcomes to the individual with TB from various isolation interventions. The caveat is that most of the data came from hospital-based isolation, with limited data from community-based isolation, but all of the data was in the same direction in terms of directionality effect or dose effect. Ultimately, this led to Recommendation 4.1 stating that "RIR is not recommended for persons with non-infectious forms of TB (i.e., localized extrapulmonary TB without pulmonary involvement, as confirmed by sputum bacteriologic studies and/ or chest imaging).

In terms of 4.3 pertaining to whether community-based RIR is indicated, higher infectious potential is based on assessment of pre-treatment bacterial burden and duration of effective treatment. Community assessment includes considerations of the environment, duration, proximity, and frequency of new exposures within school, employment, and other activities. This recommendation is based on considerations of weighing values and preferences related to community and individual well-being and harm. The Guideline Development Group felt that the desirable consequences of RIR in this scenario probably outweigh undesirable consequences in most situations. For 4.2, community assessment includes considerations of the environment, duration, proximity, and frequency of new exposures within school, employment, and other activities. The Guideline Development Group determined that the undesirable consequences outweigh desirable consequences in most situations at longer durations of the intervention.

<u>Recommendation 5: Determining Level of RIR</u>
5.1: When considering restrictions for PWTB, a moderate or midlevel range of RIR should be considered appropriate (Table 2) in most circumstances, with individual exceptions.

5.2: Specific RIR levels (e.g., low, moderate, or extensive) (Table 2) and duration for PWTB should be reassessed routinely (at least weekly) and may be modified based on individual considerations or changing circumstances.

5.3: When RIR is implemented, support should be provided to patients to mitigate anticipated and experienced harms.

Regarding 5.1, determination of RIR is based on weighing benefits and harms to the community and the individual and incorporates the principle of "least restrictive means" to achieve the desired public health goals. Moderate restrictions allow for some outdoor activities where there is a lower transmission risk. Extensive restrictions may be considered in circumstances with higher infectious potential (e.g., prior to treatment initiation) and high community transmission risks or consequences (e.g., concern for transmission of drug-resistant TB).

In terms of 5.2, the highest risk of transmission to others is anticipated to be prior to treatment initiation. Community benefits and individual impact should be assessed. While longer durations of treatment may lead to greater certainty in the assessment of infectiousness, longer durations of RIR are anticipated to lead to increased harms to PWTB. Implementation of RIR of PWTB

involves sacrifices and potential harms to PWTB for public health benefit. Concerns for financial, food, and housing security should be assessed and supported as resources allow.

The following decision schematic is provided in the guidelines that synthesizes all of these concepts together and basically boils down to say that before treatment is initiated, smear-negative and smear-positive individuals probably deserve an extensive or extensive to moderate level of restrictions that continues as treatment is initiated. However, as treatment becomes longer than 5 days, smear-negative and smear-positive individuals can be moved off of restrictions and isolations:

Table 3. Integrated Schematic and Decision Aid to Support Community-Based Respiratory Isolation and Restriction Recommendations for Individuals With Pulmonary Tuberculosis

Recommendation 3: Determining Infectiousness			Recommendation 4: Determining RIR	Recommendation 5: Level of RIR	Notes
ATT status	Pretreatment respiratory bacterial burden[a]	Assessment of individual infectiousness[a,b]	Is RIR indicated?[c]	What level of RIR to choose? (Rec 2; Table 2)	Specific recommendations should balance community and patient risks and benefits (Rec 1)
Pretreatment	High	Highest (Rec 3.1)	Yes (Rec 4.3)	Extensive	Support should be provided to mitigate harm to PWTB (Rec 5.3)
	Low	Moderate (Rec 3.1)	Yes (Rec 4.3)	Extensive or moderate (Rec 5.1)	
Treatment ≤5 d	High	Moderate (Rec 3.2)	Yes (Rec 4.3)	Moderate (Rec 5.1)	
	Low	Moderate/low (Rec 3.2)	Yes (Rec 4.3)	Moderate (Rec 5.1)	
Treatment >5 d	High	Low (Rec 3.3)[b]	Not indicated in most situations (Rec 4.2)[d]	None	Individual exceptions to continue RIR may be considered (Rec 5.2)[d]
	Low	Lowest (Rec 3.3)		None	

Abbreviations: ATT, anti-tuberculosis therapy; NAAT, nucleic acid amplification test; PWTB, person or persons with tuberculosis; Rec, Recommendation (from Table 1); RIR, respiratory isolation and restriction; TB, tuberculosis.

[a]Prior to treatment, assessment of respiratory bacterial burden may include sputum smear microscopy testing (smear positivity and grade), NAAT (lower cycle thresholds may indicate higher bacterial burden), and/or cavitation. Before ATT initiation, higher bacterial burden (and strength of aerosolization) may be associated with greater infectious potential (see Figure 1, chart A, *y*-axis).

[b]There is individual variability in the rate of decline of infectiousness following ATT initiation, but available evidence suggests rapid decline in infectiousness after treatment initiation. Most individuals should be considered to have a low likelihood of infectiousness after 5 days of effective ATT, defined as a multidrug treatment regimen to which the organism is susceptible or anticipated to be susceptible (see Figure 1, chart A, *x*-axis). Factors that may be associated with a longer duration of infectiousness may include high pretreatment respiratory bacterial burden (eg, cavitation, based on initial sputum smear and/or NAAT status), bactericidal and sterilizing activity of the treatment regimen, and adherence and tolerance of treatment. Final decisions on RIR should also include an assessment of net transmission risk to others in the community (see Figure 1, chart B).

[c]The decision to recommend TB RIR should consider the potential benefits and harm for both the community and the PWTB (Rec 1.1).

[d]Additional restrictions or longer duration may be considered in some scenarios of known or suspected drug-resistant TB, higher-risk community settings (eg, longer duration, frequency, and increased proximity of previously unexposed contacts in indoor settings with poor ventilation), potential exposure to vulnerable contacts (eg, children <5, immunosuppressed individuals), slow or inadequate clinical response to ATT, or inadequate adherence to daily ATT. Specific recommendations should balance community well-being and patient impact. Additional review or expert consultation is warranted when RIR is extended beyond 14 days.

In summary, it is not a trivial decision to restrict people's movement. Such decisions should consider both community and individual benefits and harms. That is not always easy from a public health implementation standpoint, but it is worth considering that to be grounded in ethical and legal principles, consideration should be given to the nuanced aspects. Respiratory isolation and restrictions should be conceptualized as a spectrum of tailored interventions, which is meant to empower health officials and health officers to operationalize the ideas of least restrictive means and understand that there are situations in which a person with TB could go for a jog outside or go to outdoor spaces where they are not in contact with others. Isolation should not be thought of as "one size fits all." Treatment rapidly reduces infectiousness among PWTB, irrespective of bacteriologic studies (i.e., smear) collected during treatment. Of all of the aspects of the guidelines, this is probably the biggest change as it represents a departure from even the 1993 ACET recommendations pertaining to smear-negativity as a requirement. Effective treatment duration is probably the key determinant of infectiousness. The Guideline Development Group felt that in most circumstances, isolation could be removed after 5 days of effective treatment, with exceptions for higher risk scenarios (e.g., very high pre-treatment bacterial burden, and anticipated exposure to vulnerable populations). From a practical standpoint, this may include scenarios with very high pre-treatment bacterial burden for which some variability might be anticipated in the rate of decline of bacteria. Moderate restrictions are appropriate when community-based RIR is indicated, and PWTB should be offered support to mitigate harms of RIR.

A series of manuscripts are anticipated to be published soon in *JID* and *CID* that complement the NTCA guidelines and help explain the process, including the following:

- ❑ Review article on determinants of infectiousness
- ❑ Systematic review of the impact of isolation on population and patient outcomes
- ❑ Building an ethics-informed framework for public health guidelines, based on a presentation at the Oxford Global Health and Bioethics International Conference
- ❑ Legal considerations for tuberculosis restrictions
- ❑ History of TB isolation practices

ACET Discussion on NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary TB in Community Settings Presentation

Dr. Sosa expressed appreciation for this work and recognized that it is a paradigm shift for thinking about TB isolation, which can have a major impact on TB programs in terms of implementing care of TB patients.

CDR Rhodes expressed appreciation for the presentation and the evidence collected by NTCA to develop the recommendations. Prison is a complicated scenario in which to try to apply these recommendations, given that people with TB, when released, may be housed with others in an immunocompromised state. In addition to their housing status, her system encounters issues with inmates and employees not having a set timeframe or standard to follow when dealing with isolation. They are in the process of updating their guidance and would be interested in having a discussion with Dr. Shah about updated evidence.

Workgroup (WG) Updates

Laboratory Developed Test WG

William Glover, Ph.D., D(ABMM), MT(ASCP)
Chair, Laboratory Developed Test WG

Dr. Glover reported that the Laboratory Developed Test WG (LDT WG) has 5 members. The LDT WG has convened 3 meetings to date and invited guest speakers, Ms. Susan McClure and Dr. Michele Owen, from CDC to provide preliminary interpretation of the LDT FDA Proposed Rule and provide their overview and assessment of that rule.

The scope and charge of the LDT WG are to: 1) gather information in order to provide individual input, exchange ideas or information, or analyze relevant issues and facts in preparation for deliberation by the ACET; 2) provide input to ACET to address current and emerging issues related to TB diagnostic testing availability and access in the context of the FDA proposed rule regarding LDTs; and 3) evaluate the current landscape of LDTs development and usage in the diagnosis of TB and potential impacts of the FDA Proposed Rule.

Dr. Glover observed that there is considerable overlap with what the LDT WG has been working on and addressing with the ACET discussions throughout the day. To date, the LDT WG has been wrestling with several questions, including the following:

- ❑ How are LDTs currently being used in the diagnosis of tuberculosis?
- ❑ In what settings are LDTs being used?
- ❑ For which part of TB diagnosis are LDTs being used?
- ❑ How often are LDTs used (e.g., what percentage of laboratories use an LDT in the diagnosis of TB)?
- ❑ What will be the impact of the FDA-proposed rule on the ability to rapidly and efficiently diagnose TB?
- ❑ Will this impact be disproportionate (e.g., specific healthcare settings, regionally, specific communities)?
- ❑ What impact will the rule have on patients?

Regarding how LDTs are currently being used in the diagnosis of tuberculosis, LDTs are integrated into laboratory diagnostic testing services and are used to detect the presence of MTB-complex in patients and identify patients who have drug-resistant TB. LDTs are widely used. While there was a focus on PHLs during the day's discussion, LDTs are also utilized by clinical laboratories in hospitals and medical centers, commercial laboratories (Quest, LabCorp, ARUP, Mayo), specialty laboratories within academia, PHLs, and CDC's TB Reference Laboratory. LDTs are being used for initial diagnosis of TB patients, treatment decisions, therapeutic drug monitoring, and ongoing patient management.

The LDT WG is still in the process of locating and identifying what specific data are available regarding how often LDTs are used and the percentage of laboratories using an LDT in the diagnosis of TB. While comprehensive data appear to be lacking, the LDT WG can make some inferred assumptions based on limited but informative data provided to them. LDTs are known to be utilized by many laboratories to aid in the identification of TB. Laboratories performing molecular methods other than Xpert MTB/RIF are known to utilize LDTs, such as PCR and sequencing. Many laboratories are known to utilize the Xpert MTB/RIF on specimens other than the approved specimen type of sputum. Laboratories are also known to be providing drug susceptibility/MIC broth microdilution for drugs other than IRE or PZA.

Regarding the potential impact of the FDA Proposed Rule on the ability to rapidly and efficiently diagnose TB, the possibility exists that laboratories that are unable to bring on LDTs utilizing modern molecular methods will have slower turnaround times due to reliance on limited FDA-approved tests. For example, the diagnosis of patients with extrapulmonary TB may be delayed due to lack of FDA-approved tests for alternate specimen types. Impacts are anticipated to healthcare providers' ability to choose appropriate TB treatment for patients due to fewer laboratories being able to provide non-IRE and PZA phenotypic DST/MIC and/or molecular results to aid in decision-making.

In terms of whether this impact will be disproportionate in specific healthcare settings, regionally, and in specific communities, the full impact remains unknown. The majority of laboratories providing TB testing services are likely to be impacted in some manner, because laboratories that have legacy assays still will be required to comply with FDA reporting requirements and other requirements that will be dictated by the guidance. Further evaluation is needed as this depends on the details that FDA provides within the guidance document, which will be critical in determining the full impacts of the FDA LDT rule and how to respond. Regarding perceived impact thus far based on initial review of Rule and webinars, reference level testing provided by PHLs will be impacted. Patients seen in local health department clinics supported by PHLs will be impacted as the Rule has not deemed PHLs part of an integrated healthcare system despite

the fact that many TB programs have Medical Directors and consultants from academic medical centers to mitigate perceived risks.

The Rule's full impact on patients remains unknown as well. However, potential impacts will become clearer as FDA provides further guidance details. There are some examples of clinician concerns based on initial review thus far. For instance, patients with concerns for MDR-TB greatly benefit from the LDTs that have been developed for mutations that confer drug resistance. Without access to this information provided by these LDTs, HCP will have to "guess" at the best regimen for their patients and await confirmation of drug resistance for weeks to months.

Some of the outstanding questions that have emerged thus far following initial review of the Proposed Rule including the following:

- ❑ Are fees waived on FDA submissions that relate only to pediatric patients?
- ❑ Mycobacteria isolate identification methods include methods such as real-time PCR, *rpo B* sequencing, and MALDI TOF methods, many of which are not FDA-approved, as well as available databases utilized. Will FDA provide guidance for laboratories utilizing these isolate identification methods?
- ❑ For LDTs under enforcement discretion before May 6, 2024, what constitutes a major change versus a minor change (e.g., new mastermix, new sequencing chemistry in kits, new instrument upgrade)?
- ❑ Will laboratories that have LDTs approved by NYS CLEP be able to test patient samples other than New York patients?

Drug Shortages WG

Ann Loeffler, MD
Chair, Drug Shortages WG

Dr. Loeffler reminded everyone that the Drug Shortages WG (DSWG) was established to provide input to ACET to review the June 27, 2023 Drug Shortages letter addressed to HHS requesting assistance, as well as to bring updated information to ACET to discuss, deliberate, and develop recommendations as needed. The focus of the DSWG is to evaluate the current actions of the federal government to address and mitigate drug shortages and ensure TB medications are included in discussions and plans. The WG has met 3 times and heard from special CDC guest, Ms. Susan McClure. The DSWG also attended the Duke-Margolis Virtual Seminar on June 12, 2024 titled "ReVAMPing the Pharmaceutical Supply Chain: Implementing Policy to Prevent Drug Shortages."[28]

Drug shortages have been an issue for over 20 years and seemed to have peaked in the early 2010s. Shortages increased during the COVID-19 pandemic, with a 30% increase of new drug shortages occurring between 2021 and 2022 and 55 new drug shortages in 2023 compared to 251 in 2011. Generic drugs account for 84% of drugs in shortage, which is in part because generic drugs have a much narrower profit margin. Injectable drugs used in hospital settings have been particularly problematic, including sterile saline. Drugs made outside the US are more problematic due to irregular supply chains. Rifapentine and rifampin have led the TB drug

[28] https://healthpolicy.duke.edu/events/revamping-pharmaceutical-supply-chain-implementing-policy-prevent-drugshortages?ct=t(2024.06.07)

shortages. Other first- and second-line drugs have been in shortage over the last 10 years or so. In an effort to help address shortages, CDC DTBE established a TB medication stockpile. Advice has been provided to reach out to distributors, explore drop shipments, and borrow from other institutions. CDC also distributed a Tuberculosis Drug Supply Interruptions and Shortages Dear Colleague letter.[29] In addition, a letter was sent from ACET to HHS in May 2023 that asked HHS to: 1) prioritize working with appropriate stakeholders, including the Centers for Medicare and Medicaid Services (CMS), the pharmaceutical industry, and others involved in contracting practices to address the root causes of drug shortages, as outlined in the 2019 FDA Report; and 2) work with FDA to review and update the essential medications list which currently does not include all first-line medications for treating drug-sensitive and drug-resistant TB.

As the DSWG began to delve into the issues, they found that much attention is being paid to drug shortages as demonstrated by the following:

- ❑ Senate white paper
- ❑ White House Fact Sheet
- ❑ HHS establishment of a new Supply Chain Resilience and Shortage Coordinator
- ❑ FDA efforts to prevent shortages, which has averted many issues and requires reporting of supply issues or increased demand
- ❑ Proposed new Manufacturer and Hospital Resilient Supply Programs
- ❑ Support for hospital-based stockpiles (controversial)
- ❑ Effort to keep more production in the US
- ❑ ASPE and ASPR work
- ❑ Duke Margolis ReVAMP Drug Supply Consortium

In the context of what the ACET was hoping for with its letter to HHS, the first request is occurring and the second has not yet been successful. TB drug supplies are somewhat different from other drugs people are considering to be high priority in this area. Less than 0.1% of the TB cases in the world annually are in the US. Therefore, TB drug manufacturers do not have a lot of motivation to pass through FDA and maintain supply chains for a drug that serves a lot of underserved and uninsured people with TB. There are drugs and diagnostic resources that the US cannot access because the US case numbers do not make it profitable for manufacturers to go through the FDA approval process.

With all of this in mind, the DSWG proposed the following for consideration and discussion and emphasized the need to be clever and vocal in order to benefit TB populations:

- ❑ Working with the Supply Chain Resilience and Shortage Coordinator to ensure that this individual hears the story of patients and communities served.

- ❑ Propose the exploration of procuring drugs through the Global Drug Facility (GDF) or a different vetted process such as WHO approval.

- ❑ Propose a test case of exploring the purchase of pediatric formulations and expanding the process over time, which could serve as a pilot to explore what in the FDA process is going to exacerbate the problem of continued TB drug shortages.

---

[29] https://www.cdc.gov/tb/php/dear-colleague-letters/2023-tb-drug-shortages.html

ACET Discussion on WG Update Presentations

Dr. Chen thanked the WGs for this work. She recalled an “Aha” moment during the meeting in Baltimore when the representative from the GDF said that they would love to share drugs and diagnostics with the US but need to find a vehicle through which to do so.

Dr. Loeffler recently told this story in Minnesota where she was reminded that Senator Amy Klobuchar has a line that she, “Will always keep fighting to get Americans the medications they need.”

Ms. O’Brien agreed that the GDF would be a game changer.

Day 1 Wrap-Up and Adjourn

With no further business posed, the meeting was adjourned at 4:25 PM ET. The ACET stood in recess until 10:00 am ET on June 26, 2024.

June 26, 2024 Opening Session

Lynn Sosa, MD
Director of Infectious Disease and State Epidemiologist
Connecticut Department of Public Health
ACET Chair

Carla Winston, PhD, MA
Associate Director for Science
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
ACET Designated Federal Officer

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

Dr. Sosa called the meeting to order at 10:00 AM ET on June 26, 2024 and provided meeting instructions. Dr. Winston conducted a roll call to confirm attendance of the ACET voting members, *ex-officio* members, and liaison representatives. She reminded everyone that ACET meetings are open to the public and that all comments made during proceedings are a matter of public record. She also reminded 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 21 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on June 26, 2024. No new COIs were declared, and quorum was maintained throughout the meeting. Dr. Sosa reviewed the agenda for the day and provided instructions for discussion, voting, and the Public Comment session.

Public Comment

Priya Shete, MD, MPH
Assistant Professor of Medicine
University of California San Francisco

Thank you very much for the opportunity to speak to ACET this morning. My name is Priya Shete, and I'm an Associate Professor in Medicine and Epidemiology at the University of California, San Francisco and presenting on behalf of myself and Matthew Murrill who is unable to join today. I'm part of a coalition of over 20 organizations who in January 2024 formally requested the CMS to make a National Coverage Determination (NCD) in favor of latent TB screening using IGRAs for Medicare recipients.

The distribution of TB in the US reveals striking disparities, particularly for immigrant communities who bear the disproportionate burden of this disease. Addressing TB in the US from a health equity framework is an essential element of the CDC's Goals for Health Equity in

Tuberculosis Prevention and Control and is in keeping with the Federal government's Executive Order on Advancing Racial Equity and Support for Underserved Communities. Because of the intersecting social and structural determinants of health that drive TB disease, these marginalized communities often rely on Medicare or Medicaid to facilitate access to basic preventive health services. The lack of a CMS NCD for a disease that affects minoritized and marginalized communities disproportionately creates additional barriers to quality preventive care, further perpetuating health inequities.

A National Coverage Determination for latent TB screening would benefit many Medicare recipients who have multiple risk factors for TB infection as well as poor TB outcomes. Upwards of 15% of Medicare recipients are born outside of the US, the most important risk factor for TB disease. Furthermore, over 25% of incident TB occurs among persons over the age of 65, who suffer an increased risk of death. These statistics are grim for a preventable and curable disease, yet we allow it to impose substantial financial costs on individuals, communities, health systems, and insurers, including Medicare.

TB prevention through the testing and treatment of the estimated more than 1 million Americans on Medicare with latent TB could save millions of dollars over time and prevent untold suffering. Unfortunately, significant gaps in LTBI screening and treatment exist in the US, notably among individuals at highest risk. As you know well, the screening of high-risk individuals for LTBI has been recommended by the United States Preventive Services Task Force (USPSTF) since 1996, most recently again in 2023. The USPSTF is joined by the Centers for Disease Control and Prevention, the IDSA, the NTCA, and the American Thoracic Society (ATS) in recommending latent TB screening for those at increased risk. Evidence in support of screening and testing for LTBI is sufficient to have prompted a mandate of the Patient Protection and Affordable Care Act (ACA) of 2010 to cover LTBI screening without patient cost sharing. However, CMS does not yet have a NCD for latent TB screening, severely impeding our ability to scale up quality TB prevention for individuals and communities who need it most.

A CMS NCD would facilitate improved reimbursement, reduce patient cost-sharing, and streamline billing for risk-based LTBI screening. Reimbursement for these services through Medicare and Medicaid would also enable better monitoring, accountability, and quality standards for TB preventive care services. Most importantly, resolving these barriers to TB prevention would be an important step forward for health equity and would signify the importance of preventing a disease that disproportionately affects the most minoritized and marginalized communities in our country.

The request to CMS for a National Coverage Determination for latent TB screening is currently waitlisted and the time to review is extremely uncertain given staffing challenges. We request ACET write a letter to the Department of Health and Human Services in strong support of both a timely (i.e., this year in 2024) and favorable CMS National Coverage Determination for latent TB screening.

Cynthia Tschampl, PhD
Chair, Stop TB USA

Stop TB USA was part of the coalition that submitted the aforementioned request letter to CMS in support of a timely (i.e., in 2024) and favorable CMS National Coverage Determination for latent TB screening. We would like to request that CMS do a timely review of this. Sixteen years is too long to wait for such an essential determination for such a deadly, yet treatable disease. We stand by to assist ACET in any way and underscore the request for ACET to submit a letter

of support on this matter to HHS.

Donna Wegener, Executive Director
National Tuberculosis Coalition of America

NTCA and We are TB also were part of the group of organizations in support of this NCD and applaud the leadership of our UCSF colleagues and the entire group of organizations that participated.

Business Session

Lynn Sosa, MD
Director of Infectious Disease and State Epidemiologist
Connecticut Department of Public Health
ACET Chair

During this session, Dr. Sosa facilitated a review of 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. Chen and seconded by Dr. Loeffler to accept the minutes from the December 2023 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: NTCA Community Isolation Guidelines
Dr. Sosa recapped that the NTCA guidelines are a paradigm shift in terms of implementation of TB isolation guidelines in jurisdictions. This is likely to take some time since it is a new way of thinking for public health and HCP because it is not that easy to shift thinking on this. These guidelines are not algorithmic given the intent to put the TB patient first, while recognizing the responsibility to ensure that others in the community are not being put at risk. ACET input was as follows:

- The data upon which the guidelines are based have been available for many years and there is limited new information. The certainty of much of the data to support these recommendations is not very high. For instance, some of the studies demonstrating a lack of transmission or conversion were conducted in high endemicity areas with high background rates.
- The 5-day guidelines rely on the supposition that isoniazid-based therapy is going to be effective. The availability of rapid molecular testing to document the presence or absence of isoniazid resistance within that 5-day period is limited. In terms of a potential ACET recommendation, it is important to understand concretely how these guidelines are being implemented in various jurisdictions. CDC could be helpful in collecting the data on the timing and availability of molecular testing for isoniazid resistance, which is key to understanding whether people can achieve a lower level of contagiousness within this short period.
- Dr. Mermin indicated that there are formal comprehensive plans to evaluate the impact of the guidelines in terms public health utility; the potential for further transmission; the positive impacts; and the effects on public perception of infectiousness, stigma, and the well-being of patients who are affected by TB.

- TB survivors can describe down to the day how long they were in respiratory isolation. This is not easily forgotten, even years after treatment. The guidelines seem like an opportunity for the ACET to make a recommendation and examine the equity of how the guidelines are being implemented, particularly given how difficult the TB experience is for individuals and their families and the ACET charter requisite to address equity.
- Perhaps the CDC could have the Centers of Excellence (CoEs) develop materials, webinars, case-based guidance, and so forth. The CoEs have more leeway in terms of interpretability and making guidelines practical.
- There are models in other areas that could provide beneficial information, particularly regarding thoughtful stepwise approaches (Santa Clara, California, Washington State).
- Jurisdictions that are not well-resourced are struggling because they need these guidelines to come from CDC.
- The discordance between the old and new guidelines must be addressed, which is a huge undertaking. Each local health system has the authority to determine changes and would be grateful for official CDC commentary on this. Perhaps ACET can provide advice on this, given the importance of a centralized voice.
- Prior to the NTCA guideline, there were no guidelines on removal from isolation back into the community and people have been over-isolated in a variety of settings, which must be addressed.
- Congregate settings need guidance, particularly institutions such as prisons that do not have negative pressure rooms and have to send persons with TB to the hospital. Some congregate settings institute more stringent guidelines than a hospital that makes less stringent decisions about returning patients to congregate settings. While congregate settings can police themselves inside, problems arise in terms of which guidance is being followed when there is intersection with hospitals and/or the community.
- A topic raised for potential future ACET discussion during the last meeting was to examine the work a previous WG focused on congregate settings did around 2018-2019 to determine whether there is enough information or if that WG should be reconvened to continue to pursue this issue. Mr. Watts volunteered to connect with the ACET DFO and Chair to review the work that was done previously.
- It is important to remember that this is about people with TB's human rights being infringed upon, which is worth hard work and creative thinking.
- Something stronger is needed from CDC than the editorial accompanying the publication of the NTCA guidelines, if that is at all possible, understanding that need is different from what this current recommendation addresses. Options also are needed in case a CDC endorsement is not possible.
- Just because a document is 20 years old and would be difficult to update does not mean that it cannot or should not be updated. Either fix CDC's onerous processes or go through them. The option of not pushing for updating the 2005 recommendations is the lesser of the good options.
- Dr. LoBue emphasized that updating the CDC guidelines could take until 2035, at which time they would be irrelevant. Trying to reproduce this document as it is in the current setting is unlikely to happen. This potentially could be done by pulling out particular sections, creating separate documents, and then presenting drafts for the ACET's review/input. However, CDC would have to do this on its own.
- Perhaps it would help to fast track some support if the ACET established a WG to review and indicate the areas that need to be aligned between CDC and NTCA guidelines. Some jurisdictions are struggling to implement the NTCA guidelines without CDC's blessing.
- Dr. Mermin recapped that the tension seemed to be about how to deal with the desire to update guidelines based on additional science and experience, with the understanding that

this is a multiyear process and probably beyond the capacity of what CDC and ACET can do. With that in mind, he pointed out that it is possible to retire CDC guidelines or parts of CDC guidelines and refer readers to other guidelines that are available but not within CDC's sanctions, such as the WHO guidelines.
- Dr. LoBue thought it would be better to improve on what exists versus completely retiring guidelines, which may create more problems.
- CDC has published more rapid *Policy Notes* in the *Morbidity and Mortality Weekly Report* (*MMWR*). Perhaps this process could be considered as a way to endorse the NTCA guidance.
- Dr. LoBue indicated while he was not aware of any means by which CDC endorses guidance outside of the federal setting and was not averse to doing this, he would check with the Office of Science.
- The NTCA guidance document is in the process of being developed, and NTCA also is developing a toolkit for implementation.

Vote #1: NTCA Community Isolation Guidelines Recommendation
A motion was properly placed on the floor by Dr. Loeffler and seconded by Dr. Holland that ACET recommends CDC review the data analysis and recommendations presented in the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings* in regard to existing CDC guidelines and policy related to TB isolation. This includes, but is not limited to, the *Guidelines for Preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005* and *Prevention and Control of TB in Correctional and Detention Facilities: Recommendations from CDC* (2006) and determine the best option for updating guidelines for isolation. The motion carried unanimously with no abstentions or opposition.

Vote #2: NTCA Community Isolation Guidelines Recommendation
A motion was properly placed on the floor by Dr. Chen and seconded by Dr. Ahmed that ACET recommends CDC explore options for endorsing the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings.*

Business Item 3: Drug Shortages

Dr. Sosa recapped that the drug shortage issue is taking a more prominent role nationally in terms of being an issue not only for TB, but also other diseases drugs. There is not a Task Force assigned specifically to focus on this topic. The ACET discussion reflected the uncertainty about what actually can be done and what the priorities should be pertaining to this longstanding issue. ACET input was as follows:

- The DSWG should continue, with a shift in its focus and deliverables.
- The DSWG should continue to consider how ACET might encourage work on efforts that would help the US access drugs from the GDF. While this likely would involve legislation, perhaps the ACET could submit a letter to HHS.
- Ms. Condit reminded everyone that the ACET can provide advice to CDC through a recommendation and to HHS through a letter. A WG can wordsmith the letter, but that letter would need to be presented to the full ACET during the next meeting.
- The WG could think through the potential content of a letter that potentially could be submitted to the new HHS Supply Chain Resilience and Shortage Coordinator.

- If it is not possible to submit a letter directly to the new HHS Supply Chain Resilience and Shortage Coordinator, perhaps the letter could include an "ask" for an ongoing liaison with the Supply Chain Resilience and Shortage Coordinator.
- A new letter should reiterate the second point from the last letter to add the core TB drugs to the critical drug list and to consider the possibility of working through the GDF.

Vote #1: Drug Shortages
A motion was properly placed on the floor by Dr. Sosa and seconded by Dr. Loeffler that ACET recommends that the DSWG continue with a charge to explore a liaison with the new HHS Supply Chain Resilience and Shortage Coordinator, explore the role of the GDF, and revisit the need to add core TB drugs to the critical drug list. The deliverable would be to create a letter pertaining to these issues that would be presented to the full ACET during its next meeting. The motion carried unanimously with no abstentions or opposition.

Business Item 4: Influx of New Arrivals

Dr. Sosa recapped the presentation and discussion from the previous day regarding increases in new arrivals in large cities. In addition to ACET potentially giving advice for how to manage such situations, part of the discussion on this topic pertained to what the TB community can do to advocate about this influx and what can be done about it. The data that Dr. LoBue showed suggested that even if specific jurisdictions are not experiencing the same volume of people arriving, everyone is feeling the impact of these arrivals and the strains on the systems for preventing and controlling TB. Even though this has received media attention, it remains "under the radar" in terms of people presuming it is a problem somewhere else. ACET input was as follows:

- Given mass migration and TB screening, perhaps the ACET could make a recommendation that CDC should work with affected urban jurisdictions to understand the cost and impact of these mass screenings on TB and related health. It seems that it would be within CDC's purview to provide assistance with collecting and analyzing data to understand the impact of what is being done in terms of finding and preventing LTBI cases using these measures, and how much that costs in terms of human resources, collaborations, et cetera. These efforts are crucial for the current and future health of these future US residents.
- Acquiring these data likely will require a deep dive into local and state politics, given that this information is probably not readily available locally.
- Dr. LoBue pointed out that while the ACET was free to make a recommendation on this, it might be addressed through specific requests from the jurisdictions for technical assistance.
- Cost models are wildly onerous, and it is difficult to know what parameters to use. For example, it is difficult to put a dollar value on volunteer hours. Every one of these mass situations is different, and it is unclear whether the intent would be to evaluate something that happened in the past or to build a toolkit for support in the future.

Vote #1: Influx of New Arrivals
A motion was properly placed on the floor by Dr. Sosa and seconded by Dr. Stout that ACET recommends CDC provide support in data collection and evaluation to affected urban jurisdictions to understand the costs and impacts of mass screenings on TB and related health. There was not a second and it was agreed that perhaps the ACET was not ready to make a recommendation on this issue, so the motion was tabled to further explore ways this might be addressed otherwise. The motion to table carried unanimously with no abstentions or opposition.

Business Item 5: FDA Rule for LDTs

Dr. Sosa recapped that it was suspected and now has been confirmed that almost all tests used to diagnose TB are considered to be LDTs. While the current state of testing seems "safe" for the moment, the ability to update or improve those tests likely will be challenging in the future. Questions remain related to the implementation guidance, which is needed to truly understand the best next steps and who to work with on that.

Vote #1: FDA Rule for LDTs
A motion was properly placed on the floor by Dr. Glover that ACET recommends that the LDT WG continue with an amended charge to gather information related the FDA Proposed Rule and better understand outstanding questions once the implementation guidance is published. The motion carried unanimously with no abstentions or opposition.

Business Item 6: CMS National Coverage Determination for LTBI

Dr. Sosa recapped that requests were made during the Public Comment session that ACET write a letter to the Department of Health and Human Services in strong support of both a timely (i.e., this year in 2024) and favorable CMS National Coverage Determination for latent TB screening.

Vote #1: CMS National Coverage Determination for LTBI
A motion was properly placed on the floor by Dr. Loeffler that was seconded by Dr. Chen that ACET write a letter that recommends the Centers for Medicare and Medicaid Services (CMS) to make a National Coverage Determination (NCD) in favor of latent TB screening using interferon gamma release assays (IGRAs) for Medicare recipients and expedite off the waitlist. The motion carried unanimously with no abstentions or opposition.

June 2024 ACET Recommendations	Action
1) <u>NTCA Guidelines</u>	ACET voted unanimously on the following recommendations pertaining to the NTCA guidelines: 1. ACET recommends CDC review the data analysis and recommendations presented in the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings* in regard to existing CDC guidelines and policy related to TB isolation. This includes, but is not limited to, the *Guidelines for Preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005* and *Prevention and Control of TB in Correctional and Detention Facilities: Recommendations from CDC* (2006) and determine the best option for updating guidelines for isolation. 2. ACET recommends CDC explore options for endorsing the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings.*

2) <u>Drug Shortages</u>	ACET voted unanimously on the following recommendation pertaining to drug shortages: 1. ACET recommends that the DSWG continue with a charge to explore a liaison with the new HHS Supply Chain Resilience and Shortage Coordinator, explore the role of the GDF, and revisit the need to add core TB drugs to the critical drug list. The deliverable would be to create a letter pertaining to these issues that would be presented to the full ACET during its next meeting.
3) <u>FDA Rule for LDTs</u>	ACET voted unanimously on the following recommendation pertaining to the RDA Rule for LDTs: 1. ACET recommends that the LDT WG continue with an amended charge to gather information related the FDA Proposed Rule and better understand outstanding questions once the implementation guidance is published.
4) <u>CMS National Coverage Determination for LTBI</u>	ACET voted unanimously on the following recommendation pertaining to the CMS NCD for LTBI: 1. ACET recommends the Centers for Medicare and Medicaid Services (CMS) to make a National Coverage Determination (NCD) in favor of latent TB screening using interferon gamma release assays (IGRAs) for Medicare recipients and expedite off the waitlist.

Business Item 7: Future Agenda Items

The following topics were put forth for consideration as future ACET agenda topics:

- FDA update on whether ACET's Proposed Rule conversation might influence US access to Xpert XDR cartridges that would allow for rapid INH resistance testing
- Examination of the Congregate Settings WG
- Presentation on WGS and cluster detection in the context of the influx of migrants (perhaps updates from Cure TB, Texas, and Arizona)
- NTCA update on the implementation guidance, including clarification on remaining questions and fees for 510(k)
- Tuberculosis Epidemiologic Studies Consortium (TBESC) update on TBESC-III of the analyzed baseline data and discussion of challenges/successes in automated extraction of data from EMRs for TB public health purposes
- Presentation from Immigration and Customs Enforcement (ICE) regarding TB testing and treatment
- Pregnancy severe disease/female genital urinary TB
- How to increase the involvement of local pharmacists in the screening and treatment of TB
- Isolation experience – TB survivor dialogue
- LDT implementation guidance

Closing & Adjourn

Lynn Sosa, MD
Director of Infectious Disease and State Epidemiologist
Connecticut Department of Public Health
ACET Chair

Carla Winston, PhD, MA
Associate Director for Science
Division of Tuberculosis Elimination
National Center for HIV, Viral Hepatitis, STD, and TB Prevention
Centers for Disease Control and Prevention
ACET Designated Federal Officer

Dr. Sosa expressed appreciation to the ACET members for their contributions to the discussion during this highly productive meeting and emphasized that she was looking forward to the work of the committee over the next 6 months.

Dr. Winston thanked everyone for their participation and discussion of all of the topics presented. She reminded everyone that the next ACET meeting would be hybrid (e.g., in-person and virtual) in Atlanta, Georgia on December 3-4, 2024.

With no further discussion or business brought before ACET, the meeting was officially adjourned at 12:14 PM on June 26, 2024.

Chair's Certification

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

Date

Lynn Sosa, MD, Chair
Advisory Council for the Elimination of Tuberculosis

Attachment 1: Participant Directory

ACET Members Present

Dr. Lynn Sosa, Chair
Dr. Amina Ahmed
Dr. Rajita Bhavaraju
Dr. Lisa Chen
Dr. William Glover
Dr. Kelly John Holland
Dr. Ann Loeffler
Dr. Kathleen Ritger
Dr. Jason Stout

ACET Members Absent

Dr. Adithya Cattamanchi

ACET *Ex-Officio* Members Present

Dr. Naomi Aronson
Department of Defense

Dr. Amy Bloom
US Agency for International Development

Dr. Karen Elkins
Food and Drug Administration

Britt Gayle, MD
Health Resources and Services Administration

Dr. Sheena Harris
Agency for Healthcare Research and Quality

Dr. Jonathan Iralu
Indian Health Service

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

Dr. Mamodikoe Makhene
National Institutes of Health

ACET *Ex-Officio* Members Present (continued)

Mr. Stephen Martin
National Institute for Occupational Safety and Health

CDR Tara Rhodes
Bureau of Prisons

ACET *Ex-Officio* Members Absent

CDR Misty Carlson
Department of Homeland Security

ACET Liaison Representatives Present

Ms. Valerie Adelson
American Thoracic Society

Dr. Joseph Burzynski
National Tuberculosis Controllers Association

Mr. Jeffrey Caballero
Association of Asian Pacific Community Health Organizations

Dr. Jonathon Golub
International Union Against TB and Lung Disease

Mx. Elizabeth Lovinger
Treatment Action Group

Dr. Masahiro Narita
National Association of County and City Health Officials

ACET Liaison Representatives Present (continued)

Ms. Kate O'Brien
We are TB

Dr. Amee Patrawalla
American College of Chest Physicians

Ms. Susan Rappaport
American Lung Association

Dr. Susan Ray
Infectious Disease Society of America

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

Dr. Sylvie Stacy
National Commission on Correctional Health

Dr. Wendy Thanassi
American College of Occupational and Environmental Medicine

Mr. Andrew Tibbs
Council of State and Territorial Epidemiologists

Mr. Bobby Watts
National Healthcare for the Homeless Council

Dr. David Weber
Society for Healthcare Epidemiology of America

ACET Liaison Representatives Absent

Dr. Natasha Bagdasarian
Association of State and Territorial Health Officials

Dr. Robert Benjamin
Stop TB USA

Dr. Mayleen Ekiek
Pacific Island Health Officers Association

ACET Liaison Representatives Absent (continued)

Dr. Charles Daley (Alternate)
American Thoracic Society

Mr. Colin Puzo Smith
RESULTS

Dr. Lornel Tompkins
National Medical Association

Dr. Daphne Ware
Association of Public Health Laboratories

ACET Designated Federal Officer

Carla Winston, PhD, MA
Associate Director for Science
DTBE, NCHHSTP, CDC

Federal Representatives

Leeanna Allen
Martha Boisseau
Kevin Borden
Wendy Carr
Elise Caruso
Terence Chorba
Marah Condit
Kelly Curtis
Tracy Dalton
Nick Deluca
Kathleen DeRose
Kahina Djouini
Maria Galvis
Neela Goswami
Tempest Hill
Reid Hogan Yarbro
Stephanie Johnston
Megan Keaveney
Lauren Lambert
Adam Langer
Philip LoBue
Emily Maass
Suzanne Marks
Jonathan Mermin
Sophia Zavala Monzon
Meredith Moore
Cara Morrision

Federal Representatives (continued)

Michele Owen
John Parmer
Shameer Poonja
Caitlin Reed
Gary Roselle
Angela Starks
Kevin Taylor
David Weissman
Carla Winston
Keming Yuan

Guest Presenters

Joseph Burzynski, MD, MPH
Peter Kyriacopoulos, BA
Kathy Ritger, MD, MPH
Marie-Claire Rowlinson, PhD, D(ABMM)
Maunank Shah MD, PhD

Members of the Public

Jason Cummins
Ron Daria
Diane Fortune
Haimi Girma
Kimberly Gladfelter
Amy Painter
Priya Shete
Riana Tadeo
Judith Thigpen
Xavier Thompson
Michey Tovar
Cynthia Tschampl
Katie Waites
Stephanie Wallace
Shu-Hua (Sue) Wang
Donna Wegener

Attachment 2: Glossary of Acronyms

Acronym	Definition
ATS	American Thoracic Society
ACET	Advisory Council for the Elimination of Tuberculosis
ACLA	American Clinical Laboratory Association
AFB	Acid-Fast Bacillus
AMA	American Medical Association
AMR	Antimicrobial Resistance
APHL	Association of Public Health Laboratories
AR	Antimicrobial Resistance
AR Lab Network	Antimicrobial Resistance Laboratory Network
ASCP	American Society for Clinical Pathology
ASH	Assistant Secretary for Health
ASM	American Society for Microbiology
ATS	American Thoracic Society
BCHC	Big Cities Health Coalition
BDQ	Bedaquiline
BOL	Michigan Bureau of Laboratories
BOP	Bureau of Prisons
BSL-3	Biosafety Level-3
BTBC	Bureau of Tuberculosis Control
CBA	Capacity Building Assistance
CBO	Community-Based Organization
CCH	Cook County Health
CDC	Centers for Disease Control and Prevention
CDPH	Chicago Department of Public Health
CDPH	California Department of Public Health
CHC	Community Health Centers
CID	*Clinical Infectious Diseases*
CLEP	Clinical Laboratory Evaluation Program
CLIA	Clinical Laboratory Improvement Amendment
CMS	Centers for Medicare & Medicaid Services
CoE	Centers of Excellence
COI	Conflict of Interest

Acronym	Definition
CPN	CBA Provider Network
CSTE	Council of State and Territorial Epidemiologists
CT DPH	Connecticut Department of Public Health
CXR	Chest X-Ray
DFO	Designated Federal Official
DHP	Division of HIV Prevention
DHS	Department of Homeless Services
DoD	Department of Defense
DOT	Directly Observed Therapy
DSHS	Department of State Health Services
DST	Drug-Susceptibility Testing
DSTDP	Division of STD Prevention
DTBE	Division of Tuberculosis Elimination
DVH	Division of Viral Hepatitis
ED	Emergency Department
EHE	Ending the HIV Epidemic
EHR	Electronic Health Record
EIS	Epidemic Intelligence Service
ELC	Epidemiology and Laboratory Capacity
ELC	Epidemiology and Laboratory Capacity for Prevention and Control of Emerging Infectious Diseases Cooperative Agreement
ELISA	Enzyme-Linked Immunosorbent Assay
ET	Eastern Time
EtR Framework	Evidence to Recommendations Framework
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
FQHC	Federally Qualified Health Centers
GDF	Global Drug Facility
GLP	Good Laboratory Practice
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HCP	Healthcare Providers/Professionals
HCV	Hepatitis C Virus
Hep	Hepatitis
HERRC	Humanitarian Emergency Response and Relief Centers
HHS	(United States) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
ICE	(United States) Immigration and Customs Enforcement
IDSA	Infectious Diseases Society of America
IFU	Instructions for Use
IGRA	Interferon-γ Release Assay
IJN	Interjurisdictional TB Notification
INH	Isoniazid

Acronym	Definition
IVDs	In Vitro Diagnostics
JID	*Journal of Infectious Diseases*
LDT	Laboratory Developed Test
LTBI	Latent Tuberculosis Infection
MDA	Muscular Dystrophy Association
MDL	Microbial Diseases Laboratory
MDR-TB	Multidrug-Resistant Tuberculosis
MMWR	*Morbidity and Mortality Weekly Report*
MTBC	*Mycobacterium Tuberculosis*
NAAT	Nucleic-Acid Amplification Test
NACCHO	National Association of County and City Health Officials
NASTAD	National Alliance of State and Territorial AIDS Directors
NCD	National Coverage Determination
NCHHSTP, the Center	National Center for HIV, Viral Hepatitis, STD and TB Prevention
NCSD	National Coalition of STD Directors
NEEMA	NCHHSTP Epidemiologic and Economic Modeling Agreement
NEJM	*New England Journal of Medicine*
NHCHC	National Health Care for the Homeless Council
NIH	National Institutes of Health
NOFO	Notice of Funding Opportunity
NSCSS Federal Task Force	National Syphilis and Congenital Syphilis Syndemic Federal Task Force
NTCA	National Tuberculosis Coalition of America
NTMSC	National Tuberculosis Molecular Surveillance Center
NYC	New York City
NYC Health	NYC Department of Health and Mental Hygiene
NYS	New York State
OAW	Operation Allies Welcome
OSPHL	Oregon State Public Health Laboratory
PCP	Primary Care Providers
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHD	Population Health Division
PHLs	Public Health Laboratories
PICO	Population, Intervention, Comparison, Outcomes
PIX	Policy Innovation Exchange
PMA	Premarket Approval
POC	Point-of-Care
PrEP	Pre-Exposure Prophylaxis
PWID	People Who Inject Drugs
PWTB	People With TB

Acronym	Definition
PZA	Pyrazinamide
QA/QC	Quality Assurance/Quality Control
QFT	QuantiFERON
RCT	Randomized Controlled Trial
RIF	Rifampin
RNA	Ribonucleic Acid
ROI	Return on Investment
ROU	Research Use Only
RPT	Rifapentine
SDOH	Social Determinants of Health
SNTC	Southeastern National TB Center
SSP	Syringe Services Program
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infections
TA	Technical Assistance
TB	Tuberculosis
TBESC	Tuberculosis Epidemiologic Studies Consortium
TBTC	Tuberculosis Trials Consortium
tNGS	Targeted Next Generation Sequencing
UK	United Kingdom
UPHL	Utah Public Health Laboratory
US	United States
USPSTF	United States Preventive Services Task Force
VHA	Veterans Health Administration
WG	Working Group
WGS	Whole Genome Sequencing
WHO	World Health Organization
WisDHS	Wisconsin Department of Health Services
WSLH	Wisconsin State Laboratory of Hygiene
XDR-TB	Extensively Drug-Resistant TB

Attachment 3: Written Public Comments

ACET Meeting – June 26, 2024
CMS National Coverage Determination for Latent TB Screening

Thank you very much for the opportunity to speak to ACET this morning. My name is Priya Shete, and I'm an Associate Professor in Medicine and Epidemiology at the University of California, San Francisco and presenting. I'm part of a coalition of over 20 organizations who in January 2024 formally requested the Centers for Medicare and Medicaid Services (CMS) to make a National Coverage Determination (NCD) in favor of latent TB screening using interferon gamma release assays (IGRAs) for Medicare recipients.

The distribution of TB in the US reveals striking disparities, particularly for immigrant communities who bear the disproportionate burden of this disease. Addressing TB in the US from a health equity framework is an essential element of the CDC's Goals for Health Equity in Tuberculosis Prevention and Control and is in keeping with the Federal government's Executive Order on Advancing Racial Equity and Support for Underserved Communities. Because of the intersecting social and structural determinants of health that drive TB disease, these marginalized communities often rely on Medicare or Medicaid to facilitate access to basic preventive health services. The lack of a CMS NCD for a disease that affects minoritized and marginalized communities disproportionately creates additional barriers to quality preventive care, further perpetuating health inequities.

A National Coverage Determination for latent TB screening would benefit many Medicare recipients who have multiple risk factors for TB infection as well as poor TB outcomes. Upwards of 15% of Medicare recipients are born outside of the US, the most important risk factor for TB disease. Furthermore, over 25% of incident TB occurs among persons over the age of 65, who suffer an increased risk of death. These statistics are grim for a preventable and curable disease, yet we allow it to impose substantial financial costs on individuals, communities, health systems, and insurers, including Medicare.

TB prevention through the testing and treatment of the estimated more than 1 million Americans on Medicare with latent TB could save millions of dollars over time and prevent untold suffering. Unfortunately, significant gaps in LTBI screening and treatment exist in the US, notably among individuals at highest risk. As you know well, the screening of high-risk individuals for LTBI has been recommended by the United States Preventive Services Task Force (USPSTF) since 1996, most recently again in 2023. The USPSTF is joined by the Centers for Disease Control and Prevention (CDC), the Infectious Diseases Society of America (IDSA), the National Tuberculosis Coalition of America (NTCA), and the American Thoracic Society (ATS) in recommending latent TB screening for those at increased risk. Evidence in support of screening and testing for LTBI is sufficient to have prompted a mandate of the Patient Protection and Affordable Care Act of 2010 to cover LTBI screening without patient cost sharing. However, CMS does not yet have a National Coverage Determination (NCD) for latent TB screening,

severely impeding our ability to scale up quality TB prevention for individuals and communities who need it most.

A CMS NCD would facilitate improved reimbursement, reduce patient cost-sharing, and streamline billing for risk-based LTBI screening. Reimbursement for these services through Medicare and Medicaid would also enable better monitoring, accountability, and quality standards for TB preventive care services. Most importantly, resolving these barriers to TB prevention would be an important step forward for health equity and would signify the importance of preventing a disease that disproportionately affects the most minoritized and marginalized communities in our country.

The request to CMS for a National Coverage Determination for latent TB screening is currently waitlisted and time to review is extremely uncertain given staffing challenges. We request ACET write a letter to the Department of Health and Human Services in strong support of both a timely (i.e., this year in 2024) and favorable CMS National Coverage Determination for latent TB screening.

Attachment 4: Workgroup Slides

ACET Laboratory Developed Test Workgroup Update

June 25th, 2024

LDT WG Members and Meetings

Membership
William Glover, WG Chair
Adithya Cattamanchi, SGE
Lynn Sosa, SGE
Amina Ahmed, SGE
Kathy Ritger, SGE

2024 Meetings:
4/29, 5/14, 6/7

Invited Guests:
Susan McClure, MPH
Michele Owen, PhD

LDT WG Scope and Charge

The LDT WG is convened to gather information in order to provide individual input, exchange ideas or information, or analyze relevant issues and facts in preparation for deliberation by the ACET.

The LDT WG is established to provide input to ACET to address current and emerging issues related to TB diagnostic testing availability and access in the context of the Food and Drug Administration's (FDA) proposed rule regarding LDTs.

The focus of the LDT WG is to evaluate the current landscape of LDTs development and usage in the diagnosis of TB and potential impacts of the FDA proposed rule.

How are LDTs currently being used in the diagnosis of tuberculosis?

LDTs are integrated into laboratory diagnostic testing services and are used to:

Detect the presence of Mycobacterium tuberculosis complex (MTBcomplex) in patients

- Molecular testing of alternate specimen types (e.g. CSF, Gastric aspirate, Tissue, Urine)
- Molecular testing for specific patient populations (e.g. pediatric)
- Speciation of culture isolates to confirm MTB complex

Identify patients who have drug-resistant TB

- Phenotypic DST other than for IRE & PZA drugs as well as alternate concentrations
- Molecular testing for RIF resistance (along with detecting presence of MTB complex) other than for sputum Xpert MTB/RIF testing in adults
- Targeted and/or whole genome sequencing for detecting mutations associated with drug resistance and identification of MTB complex

In what settings are LDTs being used?

LDTs are widely used

Clinical Laboratories (hospitals and medical centers)

Commercial laboratories (e.g. Quest, LabCorp, ARUP, Mayo)

Speciality Labs (academic)

Public Health Laboratories

Centers for Disease Control (e.g. TB Reference Laboratory)

For which part of TB diagnosis are LDTs being used?

Initial Diagnosis of TB patients

Treatment Decisions

Therapeutic Drug Monitoring

Ongoing Patient Management

How often are LDTs used (e.g., what percentage of labs use an LDT in the diagnosis of TB?)

Still locating and identifying what specific data is available

Comprehensive data appears to be lacking

Inferred assumptions based on limited but informative data:

LDTs utilized by many labs to aid in the identification of Mycobacterium tuberculosis complex (MTB-complex) from culture

Labs performing molecular methods other than Xpert MTB/RIF utilize a LDT (e.g. PCR, Sequencing)

Many labs utilize the Xpert MTB/RIF on specimens other than the approved specimen type of sputum

Labs providing drug susceptibility/MIC broth microdilution for drugs other than IRE & PZA

What will be the impact of the FDA-proposed rule on the ability to rapidly and efficiently diagnose TB?

Possibility that laboratories unable to bring on LDTs utilizing modern molecular methods will have slower turnaround times due to reliance on limited FDA approved tests

Diagnosis of patients with extrapulmonary TB may be delayed due to lack of FDA approved tests for alternate specimen types

Impacts to healthcare providers ability to choose appropriate TB treatment for patients due to fewer labs able to provide non-IRE & PZA phenotypic DST/MIC and/or molecular results to aid in decision making

Will this impact be disproportionate e.g., specific healthcare settings, regionally, specific communities?

Full impact still unknown

Majority of labs providing TB testing services will be impacted in some manner

Further evaluation needed as it depends on further details FDA provides

Perceived impact thus far based on initial review of Rule and Webinars:

Reference level testing provided by Public Health Labs(PHLs) will be impacted

Patients seen in local health department clinics supported by PHLs will be impacted as Rule has not deemed PHLs part of a integrated healthcare system despite the fact that many TB programs have Medical Directors and consultants from Academic Medical Centers to mitigate perceived risks

Patient Impact

Full impact still not known at this point in time

Potential impacts will become clearer as FDA provides further details

Example of clinician concerns based on initial review:

Patients with concerns for MDR-TB greatly benefit from the LDTs that have been developed for mutations that confer drug resistance. Without access to this information provided by these LDTs, healthcare providers will have to "guess" at the best regimen for their patients, and await confirmation of drug resistance for weeks to months.

Outstanding Questions on the Rule

- **Examples of questions that have emerged following initial review of the rule**
- Are fees waived on FDA submissions that relate only to pediatric patients?
- Mycobacteria isolate identification methods include methods such as real -time PCR, *rpo B* sequencing, and MALDI TOF methods, many of which are not FDA approved as well as available databases utilized. Will FDA provide guidance for laboratories utilizing these isolate identification methods?
- For LDTs under enforcement discretion before May 6th, 2024 What constitutes a major change versus a minor change? (e.g new mastermix, new sequencing chemistry in kits, new instrument upgrade)
- Will laboratories that have LDTs approved by NYS CLEP be able to test patient samples other than NY patients?

Appendix: Data collection

1) Commercially marketed in vitro test systems categorized by the FDA since January 31, 2000, and tests categorized by the Centers for Disease Control and Prevention (CDC) prior to that date. These tests are from the CLIA database associated with the FDA Medical Device Database website. This database allowed for search terms by analyte name (Mycobacteria, Mycobacterium tuberculosis complex). Many of the tests contain the 510(k) summary or PMA summary. Based on these search terms this list was created, this list is not exhaustive and represents the findings from our search terms.

2) Brief list of examples of LDTs that may be performed in a commercial lab.

3) 1976-type commercially marketed in vitro test systems categorized by the FDA since January 31, 2000, and tests categorized by the Centers for Disease Control and Prevention (CDC) prior to that date. These tests are from the CLIA database associated with the FDA Medical Device Database website. This database allowed for search terms by analyte name (Mycobacteria, Mycobacterium tuberculosis complex). Many of the tests contain the 510(k) summary or PMA summary. Based on these search terms this list was created, this list is not exhaustive and represents the findings from our search terms.

4) Commercially marketed in vitro test systems categorized by the FDA since January 31, 2000, and tests categorized by the Centers for Disease Control and Prevention (CDC) prior to that date. These tests are from the CLIA database associated with the FDA Medical Device Database website. This database allowed for search terms by analyte name (Mycobacteria, Mycobacterium tuberculosis complex). Many of the tests contain the 510(k) summary or PMA summary. Based on these search terms this list was created, this list is not exhaustive and represents the findings from our search terms. **This list contains tests that we believe to be no longer available commercially due to discontinuation**

1

Name	Test Category	Test Category Notes	Method	Complexity
Becton Dickinson BACTEC 9000MB	Detection		Growth-based	HIGH
Becton Dickinson BACTEC MGIT 960 System	Detection/Drug Susceptibility Testing		Growth-based	HIGH
BECTON DICKINSON BACTEC MGIT 960 PZA KIT	Drug Susceptibility Testing	Pyrazinamide	Growth-based	HIGH
BECTON DICKINSON BACTEC MGIT 960 SIR KIT	Drug Susceptibility Testing	SIRE	Growth-based	HIGH
BIOMERIEUX BACT/ALERT {BioMerieux BACT/ALERT MP Reagent System}	Detection	K190405	Growth-based	HIGH
Organon Teknika BacT/ALERT 3D	Detection	K981736	Growth-based	HIGH
Organon Teknika MB {BacT Microbial Detection System}	Detection	K954468	Growth-based	HIGH
Becton Dickinson BACTEC TB System {NAP differentiation test}	Identification		Growth-based	HIGH
Becton Dickinson BACTEC TB System {susceptibility test}	Drug Susceptibility Testing		Growth-based	HIGH
Becton Dickinson BBL MGIT/Mycobacteria Growth Indicator	Detection/Drug Susceptibility Testing		Growth-based	HIGH
BECTON DICKINSON PROBE TEC ET {SEMI AUTO-SAMPLE EXTRACTION}	Detection/Identification (from primary sample)		NAT	HIGH
Cepheid GeneXpert System with Touchscreen {Xpert MTB/RIF}	Detection /Identification and Drug Susceptibility Testing	RIF only	Real-Time PCR	MODERATE
Cepheid Xpert MTB/RIF Assay {GeneXpert Instrument Systems}	Detection /Identification and Drug Susceptibility Testing	RIF only	Real-Time PCR	MODERATE
Cepheid Xpert MTB/RIF Assay {GeneXpert Instrument Systems} (Use of device results as an aid in the decision wh	Detection /Identification and Drug Susceptibility Testing	RIF only	Real-Time PCR	MODERATE
bioMerieux Inc. VITEK MS	Identification		MALDI-TOF	HIGH
CELLESTIS QUANTIFERON-TB {Whole Blood}	IGRA		ELISA	HIGH
CELLESTIS QUANTIFERON-TB GOLD	IGRA		ELISA	HIGH
CELLESTIS QUANTIFERON-TB GOLD {Enzyme linked immunosorbent assay} (Interferon gamma detection)	IGRA		ELISA	HIGH
T-SPOT.TB Test {Enzyme linked immunospot (ELISPOT) assay} (Interferon-gamma detection)	IGRA		ELISPOT	HIGH
QIAGEN QUANTIFERON-TB GOLD PLUS {Interferon-gamma detection} (Whole Blood)	IGRA		Other	HIGH

2

Name	Test Category	Method	Notes	Specimen types	Notes
Xpert MTB/RIF PCR	Detection /Identification and Drug Susceptibility Testing	Real-Time PCR	LDT	Resp, BAL, trach aspirates, tissue, and certain body Fluids (Non-Sputums)	CLEP Approved
MTB species level identification by PCR	Identification	Real-Time PCR	LDT		CLEP Approved
EMB gene mutation detection by Sanger sequencing	Drug Susceptibility Testing	Sequencing	LDT		CLEP Approved
MALDI-TOF for identification	Identification	MALDI-TOF	LDT	Isolates	CLEP Approved

3

All Acid-Fast Concentrated Smear Test Systems & Procedures	Mycobacteria	Mycobacteriology	HIGH	7/26/1993
All Direct Acid-Fast Smear Test Systems and Procedures	Mycobacteria	Mycobacteriology	MODERAT	7/26/1993
All Manual Antimycobacterial Susceptibility Procedures	Mycobacteria	Mycobacteriology	HIGH	7/26/1993
All Manual Nucleic Acid Analysis Test Systems & Procedures {isotopic}	Mycobacteria	Mycobacteriology	HIGH	7/26/1993
All Organism Identification from Culture	Mycobacteria	Mycobacteriology	HIGH	7/26/1993

4

							NOTES
DynaGen MycoAKT Kit for M. avium Complex {including culture}	K943049	K943049	Mycobacterium avium complex	Mycobacteriology	HIGH	9/22/1995	
DynaGen MycoAKT Kit for M. kansasii {including culture}	K943050	K943050	Mycobacterium kansasii	Mycobacteriology	HIGH	9/22/1995	
DynaGen MycoAKT Kit for M. tuberculosis Complex {including culture}	K943051	K943051	Mycobacterium tuberculosis complex	Mycobacteriology	HIGH	9/22/1995	
Remel MycoAKT Culture ID M. avium complex {including culture}	K943049	K943049	Mycobacterium avium complex	Mycobacteriology	HIGH	12/6/1996	
Remel MycoAKT Culture ID M. kansasii {including culture}	K943050	K943050	Mycobacterium kansasii	Mycobacteriology	HIGH	12/6/1996	
Remel MycoAKT Culture ID M. tuberculosis cplx {including culture}	K943051	K943051	Mycobacterium tuberculosis complex	Mycobacteriology	HIGH	12/6/1996	
Gen-Probe AccuProbe - M. avium complex {including culture}			Mycobacterium avium complex	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AccuProbe - M. avium specific {including culture}			Mycobacterium avium	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AccuProbe - M. gordonae {including culture}			Mycobacterium gordonae	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AccuProbe - M. intracellulare specific {including culture}			Mycobacterium intracellulare	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AccuProbe - M. kansasii {including culture}			Mycobacterium kansasii	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AccuProbe - M. tuberculosis complex {including culture}			Mycobacterium tuberculosis complex	Mycobacteriology	HIGH	9/22/1995	
Gen-Probe AMPLIFIED Mycobacterium Tuberculosis Direct {MTD} Test	P940034	P940034	Mycobacterium tuberculosis complex	Mycobacteriology	HIGH	1/27/2000	
Becton Dickinson BACTEC 9000MB	K946268	K946268	Mycobacteria	Mycobacteriology	HIGH	5/24/1996	
Syngene Snap Culture ID Diagnostic Kit - M. avium complex			Mycobacterium avium complex	Mycobacteriology	HIGH	9/22/1995	
Syngene Snap Culture ID Diagnostic Kit - M. tuberculosis cplx			Mycobacterium tuberculosis complex	Mycobacteriology	HIGH	9/22/1995	
Difco ESP Culture System II	K953129	K953129	Mycobacteria	Mycobacteriology	HIGH	1/27/2000	VersaTREK?

ACET Drug Shortage Workgroup

June 25, 2024

Ann Loeffler (chair)
Lynn Sosa (SGE)
Misty Carlson (ICE/DHS Ex-Officio)
Marah Condit (DFO, CDC)

Workgroup Scope and Meeting Schedule

Scope

DSWG was established to provide input to ACET to review the June 272023 Drug Shortages letter addressed to HHS requesting assistance, as well as to bring updated information to ACET to discuss, deliberate and development recommendations, as needed.The focus of the workgroup is to evaluate the current actions of the federal government to address and mitigate drug shortages and ensure tuberculosis medications are included in discussions and plans.

Meeting Schedule

4/25/2024

5/10/2024 with special guest Susan McClure, MPH, CDC

6/14/2024

The WG also attended the Duke- Margolis Virtual Seminar on 6/12/2024 "ReVAMPing the Pharmaceutical Supply Chain: Implementing Policy to Prevent Drug Shortages"[1]

1. https://healthpolicy.duke.edu/events/revamping -pharmaceutical -supply-chain-implementing -policy-prevent -drug-shortages?ct=t(2024.06.07)

National drug shortage

- Drug shortages have been an issue for ~ 20 years and seemed to have peaked in the early 2010's
- Shortages increased during the pandemic.
- 30% increase of new drug shortages between 2021 and 2022
- 55 new drug shortages in 2023 compared to 251 in 2011
- Generic drugs account of 2/3– 84% of drugs in shortage
- Injectable drugs used in hospital settings have been particularly problematic (including sterile saline)
- Drugs made outside the US are more problematic due to irregular supply chains

TB drug shortages

- Rifapentine and rifampin have led the TB drug shortages
- Other first and second line drugs have been in shortage
- CDC DTBE has established a TB med stockpile
- Advice has been provided to reach out to distributors, explore drop shipments, borrow from other institutions
- Tuberculosis Drug Supply Interruptions and Shortages Dear Colleague letter[1]
- A letter was sent from ACET to HHS May 2023

1. https://www.cdc.gov/tb/php/dear-colleague-letters/2023-tb-drug-shortages.html#:~:text=Since%20December%202021%2C%20FDA%20has,PZA%20to%20be%20in%20shortage.

ACET letter "ask" 2023

We respectfully ask that HHS:

1. **Prioritize working with appropriate stakeholders** , including CMS, the pharmaceutical industry, and others involved in contracting practices to address the root causes of drug shortages, as outlined in the 2019 FDA Report. iv
2. **Work with FDA to review and update the essential medications list** which currently does not include all first-line medications for treating drug-sensitive and drug-resistant TB

Much attention is being paid to drug shortages

- Senate white paper
- White House fact sheet
- HHS has established a new Supply Chain Resilience and Shortage Coordinator
- FDA efforts to prevent shortages has averted many issues – requires reporting of supply issues or increased demand
- Proposed new Manufacturer and Hospital Resilient Supply Programs
- Support for hospital-based stockpiles (controversial)
- Effort to keep more production in the US
- ASPE and ASPR
- Duke Margolis ReVAMP Drug Supply Consortium

A new angle

- TB drug supplies are somewhat different
- < 0.1% of TB cases / year are in the US
- There are drugs and diagnostic resources that we can not access in the US because our case numbers do not make it profitable for manufacturers to go through the FDA approval process

For consideration

- Work with the Supply Chain Resilience and Shortage Coordinator
- Propose the exploration of procuring drugs through the World Drug Facility or a different vetted process (WHO approved,etc)
- Propose test case of exploring the purchase of pediatric formulations and expand the process over time

Resources

- **FDA Report on Drug Shortages for Calendar Year 2023**
  - https://urldefense.com/v3/__https://lnks.gd/l/eyJhbGciOiJIUzI1NiJ9.eyJzdWIzY3IpYmVyX2lkIjoiMzEwMjczOTAwMCIsImJ1bGxldGluX2xpbmt faWQiOiIxMDEiLCJ1cmkiOiIcDI6ZGInZXN0IiwibGlua19pZCI6IjQ5ODU0ODY4MTMiLCJidWxsZXRpbi9pZCI6IjIwMjQwNjA2Ljk1ODY3NjMxIiwidXJsIjoiaHR0cHM6Ly93d3cuZm RhLmdvdi9tZWRpY S8xNzkxNTYvZG93bnevYWQ_YXR0YWNobWVudD0mdXRtX21lZGl1bT1lbWFpbCZ1dG1fc291cmNlPWdvdmRlbGl2ZXJ5IiwiZW1haWwiOiJoanE1QGNkYy 5nb3Y#Q.O1jmCcL7Y22PDNwfl25uAwBeIaCmPjtpZB2IC_8sqwE__;!!P4LiPV1inDXhLQfyIk9XqZ -f6zY-NIF23tW1awVI7WNUAQEJpevz_l0J9ttLqMaPkB-2iK9-oE_ymo1p30Y1yzi6za6ek5mLqa$
- **Prescription Drug Supply Chains: An Overview of Stakeholders and Relationships**
  - https://www.aspe.hhs.gov/reports/prescription-drug-supply-chains
- **White Paper Preventing Drug Shortages**
  - https://www.finance.senate.gov/imo/media/doc/white_paper_preventing_drug_shortages.pdf
- **FACT SHEET: President Biden Announces New Actions to Strengthen America's Supply Chains, Lower Costs for Families, and Secure Key Sectors**
  - https://www.whitehouse.gov/briefing-room/statements-releases/2023/11/27/fact-sheet-president-biden-announces-new-actions-to-strengthen-americas-supply-chains-lower-costs-for-families-and-secure-key-sectors/
- **Medical Product Shortages and Scarce Resources**
  - https://aspr.hhs.gov/scarce-resources
- **Drug Shortages | ISPE | International Society for Pharmaceutical Engineering**
  - https://ispe.org/topics/drug-shortages
- **Executive Order 13944 List of Essential Medicines, Medical Countermeasures, and Critical Inputs**
  - https://www.fda.gov/about-fda/reports/executive-order-13944-list-essential-medicines-medical-countermeasures-and-critical-inputs
- **HHS-White-Paper-Preventing-Shortages-Supply-Chain-Vulnerabilities**
  - https://aspe.hhs.gov/sites/default/files/documents/3a9df8acf50e7fda2e443f025d51d038/HHS-White-Paper-Preventing-Shortages-Supply-Chain-Vulnerabilities.pdf
- **HHS Releases White Paper Focused on Preventing Drug Shortages**
  - https://www.hhs.gov/about/news/2024/04/02/hhs-releases-white-paper-focused-preventing-drug-shortages.html