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

Virtual Meeting of the
Advisory Council for the Elimination of Tuberculosis
December 3-4, 2024

Record of the Proceedings

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ADVISORY COUNCIL FOR THE ELIMINATION OF TUBERCULOSIS
December 3-4, 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 December 3-4, 2024, beginning at 9:30 AM Eastern Time (ET) on December 3, 2024 and 10:00 AM on December 4, 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 virtual ACET meeting via webinar or teleconference was published in the *Federal Register* in accordance with FACA regulations and rules. All sessions of the meeting were open to the public.

December 3, 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 December 3, 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
Adithya Cattamanchi, MD University of California- Irvine	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

Dr. Winston conducted the roll call, which confirmed that the 20 voting and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 3, 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 liaison members:

- ❑ Jason Cummins, MPH, President, National Tuberculosis Coalition of America (NTCA)
- ❑ Marie-Claire Rowlinson, PhD, D(ABMM), Association of Public Health Laboratories (APHL)
- ❑ Deb Brown, MS, American Lung Association
- ❑ Naveen Patil, MD, MHSA, MA, FACP, FIDSA, Association of State and Territorial Health Officials (ASTHO)
- ❑ Tenzin Kunor, MSc, MEd, RESULTS

Drs. Winston and Sosa bid farewell to Drs. Ahmed and Loeffler who extended their terms for 180 days to allow ACET to meet quorum during this meeting, emphasizing that their service and expertise on ACET have been greatly appreciated.

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

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. Bradley Stoner was selected as the Director of Division of STD Prevention (DSTDP), who started on July 28, 2024. He has been in the field of STIs for 30 years, most recently in academia in Canada. Dr. Renata Ellington is now the NCHHSTP Deputy Director for Management, Operations, Communications, and Policy. Dr. Ellington came to this position from the Division of HIV Prevention (DHP), with extensive experience. NCHHSTP has 2 open positions that hopefully will be filled within the next month, Director of the Office of Health Equity (OHE) and Principal Deputy Director of DHP.

NCHHSTP reissued the Epidemiologic and Economic Modeling Agreement (NEEMA) Notice of Funding Opportunity (NOFO). For the past 10 years, this NOFO has engaged academic institutions to help the Center with some of its more complex modeling, especially related to changes with incidence, morbidity and mortality, and costs. NEEMA 3.0 was awarded to 2 recipients, Stanford University and Emory University. The new 5-year award (CDC-RFA-PS-24-0028) started September 30, 2024, and will continue the long-standing support for modeling activities throughout the Center. NCHHSTP is moving toward an approach that recognizes the similarly affected populations, geographic locations, and social and structural determinants of the infections we strive to prevent. At NCHHSTP, we also think of the potential positive opportunities that a syndemic approach provides, including a more holistic approach to individual and population health and improved efficiency in providing services. There is a new fact sheet on the NCHHSTP website.[1] The Center is prioritizing strategies and foundational pillars that work toward more holistic service delivery for populations affected by multiple diseases and

[1] https://www.cdc.gov/nchhstp/about/syndemic.html

conditions, with the goal of improving health and quality of life (QoL) for people with and at risk for HIV, viral hepatitis, STIs, or TB.

In June 2024, the NCHHSTP OHE launched a new bimonthly *CDC Correctional Health Newsletter* to advance and streamline partner communications. The newsletter already has over 1,000 subscribers and reaches leaders from all major corrections associations and correctional health advocates. In July 2024, the NCHHSTP OHE led the HHS CDC *Equity Challenge Taskforce* staff survey to inform agency belonging and inclusion strategies for workforce with justice involvement experience because lived experience can be helpful for ensuring that recommendations and programs are viable and practical in how they approach public health. Also in July 2024, the NCHHSTP OHE teamed up with the Department of Justice (DOJ) and the National Institute of Corrections (NIC) to develop an implementation field guide for HIV, viral hepatitis, and STDs in correctional and detention facilities. This is an extension of the continued effort to have routine screening and treatment for these infections in correctional institutions. Because TB already has this, it is not included in this particular area. However, references and connections will be included moving forward.

From January –June 2024, the NCHHSTP Science Office had over 1,000 products submitted through clearance including abstracts, presentations, peer-reviewed journal articles, and MMWR reports, were reviewed by NCHHSTP. NCHHSTP has been monitoring metrics for its clearance process and reports the median clearance time is 6 days. The Center is exploring what happens when the process takes longer than that and why (e.g., major issues needed to be addressed, delays in the number of people involved in the clearance process, et cetera). Overall, this has become an efficient and effective mechanism—even for some complex documents. NCHHSTP is also developing a Science Prioritization Framework, which will ensure that the scientific work the Center does is the most meaningful and practical that it can be. The NCHHSTP Science Prioritization Framework was developed to align with CDC Science Prioritization Framework and emphasizes strategic planning, establishing specific objectives, and formulating formal learning agendas. DTBE already has a strong process in place, and NCHHSTP is working with all of the divisions for implementation in 2025. Working with the CDC Office of Science Quality and Library Services (OSQLS), the Center is conducting a Scholarly Impact Assessment to calculate quantitative metrics for impact of NCHHSTP's scholarly publications, including citations. A data dashboard is being formulated for semi-customizable analyses of scholarly impact statistics.

NCHHSTP released the 2023 STI Surveillance data, reporting a decrease in gonorrhea for a second year by another 7%, totaling about a 15% decrease from 2021–2023. There appeared to be a turning point in syphilis, with decreases in primary and secondary syphilis in men and women of all ages. Trends in congenital syphilis cases and rates of primary and secondary syphilis closely track among women 15–44 years of age. Between 2020 and 2021, there was a 33% increase in congenital syphilis. There was another increase of 30% between 2021 and 2022, but there was only a 3% increase between 2022 and 2023. The hope is that, while there may be a delay in congenital syphilis trends, including a 9-month gestation, and the trends will continue to decrease in 2024 for syphilis. Congenital syphilis is at an unacceptably high rate of over 3,000 cases per year.

The STI Prevention Conference was convened in Atlanta, Georgia September 16–19, 2024. More than 1200 leading researchers, government experts, clinical STD care providers, and state and local public health administrators came together for four days of scientific updates and cutting-edge sessions on science, program, and policy. With more than 150 presentations and 250 posters, topics ranged from doxy PEP to tailored prevention efforts for congenital syphilis.

NOFO PS-24-0003 supports the Ending the HIV Epidemic (EHE) in the US initiative through scale-up of HIV prevention services in sexual health clinics (SHIPS). Total Year 1 funding was $9 million, with 15 awards of $600,000 per recipient. The period of performance for this award is 5 years from August 1, 2024 to July 31, 2029.

It is known that taking a single dose of doxycycline within 72 hours of having sex has been shown to decrease the acquisition of syphilis and chlamydia by about 75% and gonorrhea by about 50% among gay and bisexual men and transgender women. Guidance for doxy PEP was published in the *Morbidity and Mortality Weekly Report (MMWR*) on June 6, 2024. Doxy PEP-specific data elements were added into Cycle 5 of the STI Surveillance Network (SSuN) to assess the use of doxy PEP and the potential effects it might have on antimicrobial resistance (AR) and aspects of the microbiome. With support from CDC, the National Coalition of STD Directors (NCSD) hosted 2 Community Focus Groups. In addition, a webpage was published for healthcare providers (HCP).[2] STI medications have had shortages periodically similar to some TB medications, particularly penicillin for which there is only one US manufacturer. That occurred for several months, enough that the Food and Drug Administration (FDA) allowed the importation of a French product and then a second product to try to ensure that enough Bicillin L-A® was available for patients with syphilis. The manufacturer that has FDA approval to provide Bicillin to the US has an ample supply at this time.

From 2021-2023, CDC's EHE program successes include distributing over 600,000 free HIV self-test kits; over 4,600 people were newly diagnosed; over 60,000 people were prescribed PrEP; and connections were made to 329 syringe services programs (SSPs), more than 50% of which were mobile. In 2022 compared to the baseline in 2017,[3] HIV incidence decreased 21% in 50 EHE counties and 6% in other municipalities where resources and focus on HIV were increased. This translates to prevention of about 11,000 HIV cases and a savings of about $5.9 billion dollars, which is the clearest evidence available that EHE is working.
The *Let's Stop HIV Together* campaign includes tailored messaging for Black and Latino gay, bisexual, same gender loving, and other men who have sex with men (MSM) in the South and their providers to support expansion of PrEP use. These are the areas and populations with the lowest use of PrEP. NCHHSTP has been working with 6 jurisdictions to tailor the initiative to be responsive to community needs and resources.

Starting in August 2023, DHP partnered with the National Association of County and City Health Officials (NACCHO), the Southern AIDS Coalition (SAC), and regional community conveners to host in-person engagement sessions with community-led and community-serving organizations in the Southeast United States. We were grateful to have our colleagues from DSTDP attend some of these sessions as well. The sessions aimed to discuss barriers and opportunities to promote health equity, expand community engagement, and understand local programming around syndemic and whole-person approaches.

Hepatitis C is a chronic curable viral infection. In May 2024 new hepatitis C prevalence estimates were published by CDC's NEEMA partnership that found that an estimated 2.4 million people had hepatitis C in the United States from 2017-2020, and it could be as many as 4 million. Two models were applied to account for populations not accounted for in the National Household and Nutrition Survey (NHANES), which is a household survey that does not include non-civilian or

[2] cdc.gov/sti/hcp/doxy-pep/index.html
[3] Unpublished data.

unhoused persons. One model estimates that the US prevalence of hepatitis C remained unchanged since 2013-2016, despite an estimated 1.2 million people receiving curative hepatitis C treatment during the same period. The second model represents a newly developed model and includes an estimate of adult PWID, which is underrepresented in NHANES. This model indicates that the number of people with hepatitis C in the US may be closer to 4 million. In addition to these estimates, CDC continues to identify other models and data sources to be able to provide robust and contemporary prevalence estimates.
A recent policy analysis showed Medicaid non-expansion, fibrosis, and sobriety restrictions decreased hepatitis C treatment.[4] CDC staff published a paper in July 2024 that assessed the association of Medicaid policies that restricted access to hepatitis C treatment with overall treatment initiation numbers among Medicaid recipients. The analysis showed significant percent decreases in the number of people who were prescribed hepatitis C treatment because the state did not expand Medicaid, limited treatment to those with advanced liver disease, or required a period of sobriety before treatment initiation. As direct acting antivirals for hepatitis C treatment has decreased in cost, fibrosis restrictions have been completely removed, though some states retain substance use disorder screening or sobriety requirements. This analysis suggests that removing prior authorization requirements may increase the number of Medicaid recipients who are treated for hepatitis C.

FDA in partnership with NIH and CDC announced market availability of a hepatitis C virus ribonucleic acid (RNA) point-of-care (POC) test on June 30, 2024 using Cepheid GeneXpert® similar to the TB test approved by the FDA.[5] CDC has shared implementation considerations and a cost calculator tool to help health departments and other venues offering hepatitis C testing determine how best to incorporate this tool.[6] This is the first nucleic acid testing (NAT) POC test for HepC, which is critical in determining if a patient has active HepC infection or are cured but still have persistent antibodies.[7] Another exciting development in testing is that the CDC and NIH have collaborated to fund NIH's RadX (Rapid Acceleration of Diagnostics) Independent Test Assessment Program (ITAP) to rapidly bring a POC hepatitis B surface antigen test to market, similar to the recent effort for the POC HCV RNA test. ITAP announced a solicitation at the end of September. Further, the FDA posted their proposal to down classify HBV diagnostics on the federal register on September 25, 2024.[8] his test should be effective and very useful for diagnosing people outside of laboratory-connected clinical settings.

Lastly, Dr. Mermin shared that the early analysis from the Congressional Budget Office (CBO) regarding the budgetary impact of hepatitis C treatment in the Medicaid population, which is a focus population of the proposed hepatitis C elimination initiative, showed substantial cost savings.[9] This concurs with other models that project substantial cost savings from a national hepatitis C elimination initiative. A subsequent analysis by CBO of the budgetary impact of the proposed hepatitis C elimination initiative is underway and a CBO score is expected in October 2025. The CBO is scoring proposed Hepatitis C Elimination Initiative legislative text to assess cost savings of the larger proposed program. As other models have shown, good hepatitis C prevention and treatment are cost-saving.

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[4] Furukawa NW et al. Medicaid expansion and treatment restriction policies on hepatitis C treatment *JAMA* Net Open. 2024
[5] https://stacks.cdc.gov/view/cdc/164804
[6] https://stacks.cdc.gov/view/cdc/164804
[7] https://www.cimit.org/radx-tech-itap-for-hepatitis-b-virus-surface-antigen; https://www.federalregister.gov/public-inspection/2024-21932/microbiology-devices-reclassification-of-antigen-antibody-and-nucleic-acid-based-hepatitis-b-virus
[8] https://www.cimit.org/radx-tech-itap-for-hepatitis-b-virus-surface-antigen
[9] https://www.cbo.gov/publication/60237; https://www.hhs.gov/sites/default/files/hep-c-elimination-program-1-pager-508.pdf

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 Fiscal Year 2025 (FY25) budget, final surveillance report, updated TB treatment guideline, Tuberculosis Elimination Alliance (TEA), and the new 2025 Cooperative Agreement (CoAg) For Tuberculosis Programs and Laboratory. In terms of the 2025 budget, there is a Continuing Resolution (CR) through December 20, 2024. DTBE received a level appropriation of $137 million for the FY24 budget, which is prorated based on the annual appropriation for the duration of the CR. It will then be up to Congress and the Administration to decide what will occur next. In general, new activities cannot be started under a CR that were not previously funded by Congress. That should not be an issue for DTBE right now because nothing is planned at this time that has not been funded previously.

During the June 2024 ACET meeting, Dr. LoBue presented the provisional TB surveillance data that were published in March 2024 in the *Morbidity and Mortality Weekly Report*[10] that showed about a 16% increase in cases and a comparable increase in case rates. The final report[11] was published online on November 13, 2024. The final report contains an Executive Commentary and 36 detailed data tables of information on TB disease in the US. Dr. LoBue noted that later in the day, there would be a fairly detailed presentation on the surveillance system, where things stand, some of the challenges, and considerations for the future. In terms of comparing the final data to the provisional data, there was not major change. The final difference in case count was 18/9,600 (0.2% change). The main difference is that the preliminary report included select variables and the final report contains a lot more information in terms of other variables that were not reported on in the provisional data in March 2024.

The updated TB treatment guidelines were developed in conjunction with the American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and the European Respiratory Society (ERS). The ATS convened the guidelines group. The draft was presented by Dr. Carla Winston, who was the CDC Lead on these guidelines. The new information focuses on the Tuberculosis Trials Consortium (TBTC) Study 31 4-month regimen for drug susceptible TB, for which CDC already has published guidance in the *MMWR*; the BPaL/BPalM regimens for drug-resistant TB; and a 4-month regimen for children without severe TB, which came out of the Shorter Treatment for Minimal Tuberculosis in Children (SHINE) study. The updated guidelines have been approved by CDC and professional societies, with expected publication by the first quarter of 2025, tentatively in January.

[10] *MMWR Weekly* / March 28, 2024 / 73(12);265–270; https://www.cdc.gov/mmwr/volumes/73/wr/pdfs/mm7312a4-H.pdf
[11] https://www.cdc.gov/tb-surveillance-report-2023/index.html

TEA has presented to the ACET a number of times and the ACET has recommended continuation of support of TEA. The previous funding cycle for TEA closed out in July 2024. TEA produced an impact report for 2019-2024 that is available online.[12] This report includes program highlights and achievements from 2019-2024 and goals moving forward. In October 2024, TEA received a new award for FY25 of $610,000 from CDC to continue its work of increasing access to culturally responsive care and resources for populations disproportionately impacted by TB, primarily Asian, Asian American, Native Hawaiian, Pacific Islander, non-US born Latino American, and US born African American communities. CDC is happy to be able to continue to support this very important work in outreaching to these communities and providers who care for these communities where a lot of TB is occurring.

Regarding the new CoAg for TB programs and laboratory, the current CoAg ends December 31, 2024. The new 5-year CoAg was announced in July 2024, which is funded at over $70 million per year. This represents over 50% of DTBE spending and is the division's flagship project. Applications for this CoAg were received in September 2024. In the past, eligibility was limited to those who were previously funded. Unlike previous cycles, eligibility was not limited, and the process was competitive. When applications are submitted, they are reviewed by the CDC Office of Grants Services (OGS) to determine whether they meet the criteria for eligibility to receive funding. Then there is a merit review in which individual applications are reviewed based on how responsive they are to the criteria that were included in the funding announcement and are ranked based on those reviews. After the ranking, there is an ability to fund out of rank order based on 2 criteria that DTBE added: 1) the need for complete geographic coverage of the US; and 2) morbidity. The review process has been completed, a call has occurred with those who are to be funded, and the official award notifications are anticipated to be sent out this month.

ACET Discussion: NCHHSTP & DTBE Directors' Presentations

Dr. Sosa asked Dr. Mermin what the priorities would be for TB in terms of the modeling NOFO.

Dr. Mermin indicated that while some ideas come from the academic partners, there is a full day of engagement with DTBE to work out the top areas for which DTBE would like to collaborate.

Dr. LoBue added that this is a process that involves discussion because it is not a contract for which the recipients are directed. One of the topics in which DTBE is particularly interested, that was not included in the last 2 cycles, is the collection specific cost data. Right now, the data are fairly old or from the literature but are not so direct. It would be beneficial to have updated data on specific costs of various activities within TB prevention, control, and elimination. That may not be easy to do, but it is of interest. Another topic of interest is using this group's models for projecting incidence with interventions to projection of TB incidence and what impact various interventions or other factors may have to assess COVID. DTBE is interested in the models being recalibrated to take into account recent changes in 2023. The grantees also have some ideas, which DTBE will be discussing as well.

[12] https://tbeliminationalliance.org/wp-content/uploads/2024/08/Final-TEA-Impact-Report_August-2024.pdf

Dr. Sosa said she would be happy to hear updates on modeling of TB incidence with various strategies implemented, as well as information on any work that has been done to update the state-specific incidence and what that looks like in an individual state. That could be helpful as individual jurisdictions think about how they can ramp up different tools and show the impact or potential impact of efforts such as increased latent TB infection (LTBI) treatment.

Dr. LoBue indicated that there has been a focus on the 4-state model of the states with the largest morbidity. Tools have been made available, such as the Tabby tool,[13] which allows programs to enter inputs into the application based on their state information to assess those types of projections. He did not know whether there were plans to do additional work on that, but DTBE certainly would be interested in hearing suggestions or questions related to that.

Dr. Sosa said she was interested in the new bimonthly *CDC Correctional Health Newsletter* and wondered whether it was shared with health departments. She also expressed excitement and gratitude regarding the clearance metrics.

Dr. Mermin indicated that they would follow up to ensure that partners get access to the *CDC Correctional Health Newsletter*.

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 2024, and discussion of the 3 recommendations that are actively ongoing. One of the recommendations is from 2022 regarding defining and assessing the TB workforce in terms of needs, especially geared toward elimination, and also determining whether a cost analysis can be done related to achieving that. The recommendations from the June 2024 ACET meeting relate to respiratory isolation based on the presentation regarding the *NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings* published on June 18, 2024.[14] The 2022 and 2024 recommendations and their related actions are shown in the table below:

[13] https://ppmltools.org/tabby2/
[14] *Clinical Infectious Diseases*, ciae199, https://doi.org/10.1093/cid/ciae199

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	• 2025 program and laboratory cooperative agreement requirement, which has now been published: – By the end of year one, provide the following information to be used in a national TB workforce assessment: ▪ List of current positions with titles and percent Full Time Equivalent (FTE), both filled and vacant ▪ List of additional positions and percent FTE believed necessary to fully execute the program's elimination plan • For state and some larger local TB programs that are funded under the Coa, will provide a rough assessment in gaps in workforce needs – Potential to apply cost analysis to these gaps in 2026 after collecting the information in 2025
Topic: Isolation Guidance Item #: 2024-1 Date: 6/26/24	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.	• Workgroup formed • Includes members from DTBE, National Institute for Occupational Safety and Health (NIOSH), and Division of Healthcare Quality Promotion (DHQP) • Two members of the workgroup are attending CDC Office of Science GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) training for guideline development • Workgroup reviewing NTCA isolation guideline evidence summary and accompanying suite of published papers; World Health Organization (WHO) systematic review on isolation in healthcare settings • Next steps: discussion of methodology for guideline (previously were not GRADE-based) and PICO (Population, Intervention, Comparison, Outcomes) questions, consideration of adolopment (selective combination of adoption and adaption of • guidelines work done by others)
Topic: Isolation Guidance Item #: 2024-2 Date: 6/26/24	ACET recommends CDC explore options for endorsing the NTCA Guidelines for Respiratory Isolation and Restrictions to Reduce Transmission of Pulmonary Tuberculosis in Community Settings	• Explored with requests to CDC Office of Science (OS) and CDC Office of General Counsel (OGC) • Both indicated this is not permitted under current CDC policy

ACET Discussion: Current ACET Recommendations Presentation

In terms of congregate settings in the prison system, Ms. Rhodes asked whether the corrections group within CDC would be involved in the guidance development.

Dr. LoBue indicated that they are starting with healthcare facilities and based on what is done there, they can move on to correctional settings. If correctional settings are addressed separately, additional internal correctional experts would be brought in.

Dr. Holland asked whether the workgroup includes a person with lived experience, either in correctional or hospital settings with TB.

Dr. LoBue indicated that members of the workgroup have to be internal, but they do not know of anyone internally with lived experience. The best they will be able to do after a draft is developed will be to present for some degree of public comment through ACET or other mechanisms.

Dr. Ahmed asked what the timeline is for the workgroup to provide an assessment of the literature.

Dr. LoBue responded that the goal is to complete as much as possible in 2025, but how long the process will take is somewhat difficult to predict because there have been changes in how guidelines work at CDC. There are now 2 processes for review, including policy that did not exist previously. The goal is to develop a draft in 2025.

Dr. Loeffler wondered whether there is someone on the DTBE team who was even in the hospital for a couple of weeks. There are strong data about the impact of prolonged or unnecessary isolation impacting levels of care and "customer service" for lack of a better term.

Dr. LoBue said they certainly could look at that, but it would depend upon someone volunteering that personal information since DTBE does not have access to that information.

In terms of the workforce assessment, Dr. Sosa asked whether there are plans to use a specific instrument to collect the information outlined. Having a separate instrument could make it easier for DTBE to collect the information.

Dr. LoBue responded that there is not a specific instrument. Using data collection instruments requires going through the Paperwork Reduction Act (PRA). The information is included in the year-end report and is fairly straightforward in terms of the number of positions, type of positions, and FTE equivalent.

Amy Painter, South Carolina Department of Health and Environmental Control (SCDHEC), commented that for the TB workforce analysis, while looking at the organizational charts for states, positions need to be considered that are currently federally funded versus state funded. In South Carolina, current vacancies are state funded.

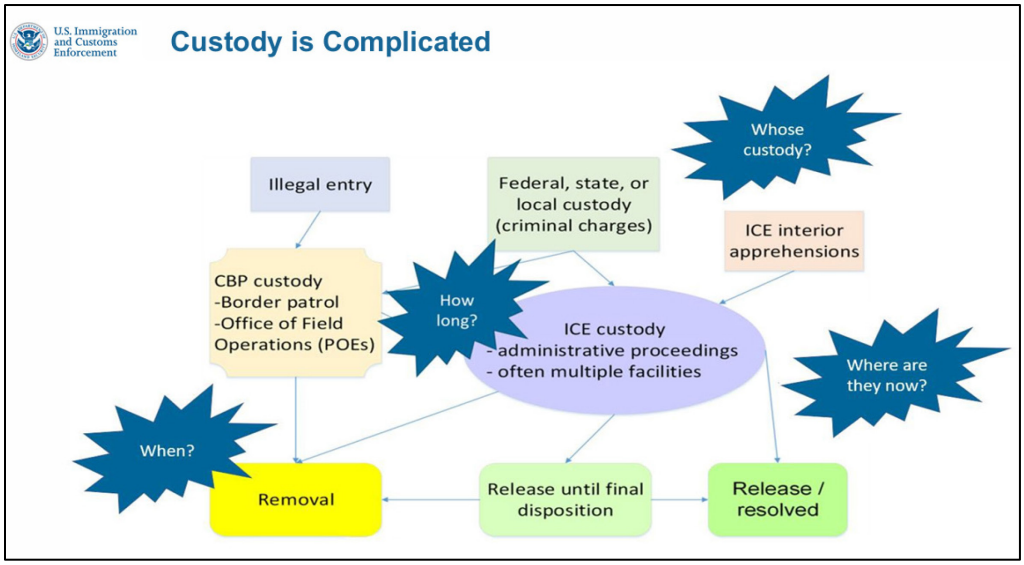
TB Management of Detained Noncitizens

CAPT Jessica Clark, MPH, BSN, RN, CCHP
Western Regional Infection Prevention Supervisor
Public Health, Safety and Preparedness Unit
US Immigration and Customs Enforcement
ICE Health Service Corps

CAPT Clark disclosed that she had no actual or potential COIs in relation to this program or presentation, that the content would not include any discussion of the unlabeled use of a product or a product under investigational use, and that no commercial support was accepted for this activity. This presentation focused on ensuring that there is an understanding of the complexity and uncertainty of medical care delivery in the Immigration and Customs Enforcement (ICE) detention setting, prevalence and clinical characteristics of TB, TB disease management

program in the ICE Health Service Corps (IHSC), and key partnerships for post-release continuity of care upon repatriation of non-citizens to their home country or release within the US.

IHSC is the medical component responsible for administrating all of the medical care within ICE facilities and works in conjunction with the ICE law enforcement side to provide the best medical care for every non-citizen held in ICE custody. Unlike many of ICE's correctional counterparts who have people in custody for some defined period of time, the detained population housed within an ICE facility throughout the country has a wide variety of ways in which non-citizens enter and leave their custody status. This pictorial is designed to illustrate the complexity of that custody:



Essentially, there are 3 main ways non-citizens make it to ICE. One way is through illegal entry and apprehension by Border Patrol, another is through ICE Office of Field Operations. Another way is for those who have served a criminal sentence in a federal, state, or county correctional jurisdiction to then go to ICE. The last way in which non-citizens reach ICE is through ICE interior apprehension which are those who have been in the US and are discovered. Once someone is in ICE custody, the administrative proceedings process is initiated through the court systems. It is common for detainees to be moved through several facilities as they make their way to their final destination where they are either removed from the US and repatriated back to their home country or released into the US while they work through their legal proceedings process awaiting their final disposition. Those who are released in the US remain until their immigration status is resolved, which means they would be allowed to stay and immigrate for various reasons or would receive a final deportation order and would be deported. The key message is that there are so many variables when non-citizens enter into custody, it is common for ICE not to have a definitive release date. Often, ICE is notified of a release date when they return from court with a release order to be released immediately.

The complexity continues in terms of detainee medical care. To further understand the medical care of non-citizens while in detention, in FY23, ICE IHSC staffed medical departments in 19 detention and staging facilities throughout the country and encountered a population of approximately 131,000 non-citizens. Additionally, there are 128 custody-contracted facilities that are non-IHSC-staffed that provide care to an additional approximately 191,000 detained non-citizens. These staffing models are outpatient ambulatory care-type settings. If non-citizens

require specialty care services, that is contracted out to community care resources. Each facility has from 2 to 14 airborne isolation rooms within the facility. For locations with limited space, the partnerships with community hospitals and local health departments are vital for evaluating and managing non-citizen workups, including initial isolation and initiation of treatment for non-citizens in custody. Another complexity is that the average length of stay for most non-citizens was 30 days in FY23.[15] A large number of non-citizens complete their workup, initiate the right treatment, and are released to communities or are repatriated back to their home country.

The risks within this population have driven the course of how ICE addresses TB. All of ICE's detention centers are congregate housing settings. Detainees are living in dormitory style housing, sometimes with hundreds of other detainees from around the world. The entire population is highly transient compared to correctional facilities where someone may live for years in the same location. Much of the population has been migrating their way through several countries enroute to the US. They are vulnerable as they make their way through unfamiliar communities and terrain and are under significant amounts of stress. It is key to point out that a majority of non-citizens come from countries with a high prevalence of TB disease.

It is known that TB infection is more common among non-citizen populations. The IHSC 2017–2019 surveillance data collected pre-pandemic reflected an incidence rate of 90/100,000 cases of confirmed TB (e.g., culture-positive). Of those cases, 49/100,000 were microbiologically or NAT-confirmed, which was consistent when compared with surveillance data collected from 2015–2017 and 2004–2005. In comparison, CDC reported 2.9/100,000 cases within the US general population in 2023. That also reflected an increase from 2.5/100,000 cases within the US general population in 2022. IHSC's preliminary 2023 surveillance data show a significant rise in confirmed TB cases at 157/100,000, with 138/100,000 of those cases being microbiologically confirmed.

The clinical characteristics of active TB patients identified while in custody, which IHSC classifies as Class 3 TB patients, includes patients with a positive sputum and/or NAAT. The vast majority of these patients originally were identified by receiving their screening chest X-ray (CXR) at intake. At all locations that have radiology technology services on-site, non-citizens are screened for TB by the use of single-view CXR and symptom screening. Those who are found to have abnormal single view x-rays or symptoms of TB complete secondary 2-view PA lateral CXR for confirmation of the 1-view findings. About 71% of those identified with active TB in our system have been self-reported as asymptomatic. It is standard practice for IHSC to then obtain tuberculin skin test (TST) and interferon-γ release assay (IGRA) for all patients with a positive CXR as part of their diagnostic workup. About 62% of those patients have been found to be TST- or IGRA-positive. That leaves a large number of patients who are not TST- or IGRA-positive but are culture-positive for mycobacterium TB (MTB). About 3% of the population were HIV-positive patients, 4% were diabetic, and 26% were pre-diabetic.[16] In terms of infectious disease management, IHSC aligns with CDC guidance.[17] Due to increased risk factors within this population, IHSC has opted to use the CDC recommendation for the more sensitive method of screening by way of CXR, and identifying TB disease. The target is to identify as much disease as possible and get people started on treatment by utilizing CXR as the initial screening method versus TST or IGRA screening for infection.

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[15] https://www.ice.gov/detain/ice-health-service-corps; http://www.ice.gov/detention-facilities/ICE Annual Report FY2023
[16] Source: IHSC - Unpublished data, but similar, smaller data set published in Boardman et al. Clin Inf Dis; 2021:73(1), 115-120.
[17] https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5509a1.htm

IHSC's medical staffing model includes nurses, advanced practice providers, pharmacists, physicians, ancillary care staff, and robust medical services for all detained non-citizens. These staff members are the "boots on the ground" who conduct the initial screenings and diagnostic workups and coordinate care for each of the detained non-citizens. IHSC also has an Infectious Disease Team stationed at various locations around the country that consists of a physician, an epidemiologist, 2 advanced practice providers, and 2 public health analysts. Their role is to consult with the field medical providers on infectious disease treatment-related issues. In addition, all IHSC facilities have Infection Prevention Officers (IPOs) who serve as the initial Case Managers and are located within the institution. They are responsible for tracking all of the TB cases within their respective facilities, and reporting all of the positive cases to local health departments along with diagnostic workup information, CXRs, sputum results, and so forth. They also provide coordination with the CureTB program where they report cases who have started on treatment and cases that are sputum-, NAAT-, or culture-positive and even cases that are culture negative if the person is in custody long enough to have a repeat CXR. In addition, the IPOs facilitate the full interview before a patient leaves ICE custody and coordinate what are referred to as "meet-and-greets" for patients returning to Mexico who are on treatment as well. There are also Regional Supervisors who oversee the whole process, ensure compliance with IHSC's standards, and serving as liaisons between IHSC facilities and headquarters staff, and local and federal public health stakeholders.

With all of these moving parts, coordination of care is required to ensure initiation of appropriate treatment, continuation of care post-release, and partnerships with community public and private counterparts. In 2021, IHSC collaborated and adopted a memorandum for all community providers that originally was established by the Bureau of Prisons (BOP) in an effort to establish congruence with the treatment of high-risk patients undergoing TB workups within the community. The document has been updated recently and will be updated again, given that IHSC is in the process of onboarding a new infectious disease physician. The document as adopted is in memorandum format that is disseminated to community providers, and it talks about why their cooperation is needed in thinking TB, and how IHSC works with CDC TB Centers for Excellence (CoEs) and the NTCA. Within the memo, contact information is listed for the various CoEs. Regarding co-management of complex cases with CoEs, the IHSC is contracting with the Mayo Clinic CoE. IHSC is the primary manager on most collaborative calls or warm line consults for IHSC facilities.

Moving to release planning and coordination of care with the ICE population, release planning is initiated with non-citizens as soon as they enter an IHSC facility because the ultimate destination or release time of the patient is usually unknown upfront. To facilitate transitions of care, IHSC staff refer all TB cases to CureTB and the local health department (LHD) where the facility is located when clinical updates are received and when non-citizens are transferred, released within the US, or repatriated to their home country. Local IPOs update CureTB and LHDs. Delays in communication with outside community partners, there is a risk that patients could have unnecessary treatment interruption, fail to be properly isolated, and/or fail to be linked to the next care system. IHSC communication with LHDs is key. If a person releases into a community but their final destination is another state. The LHDs perform the interjurisdictional transfers and ensure that the next health department is being notified of the continuity of care.

In closing, CAPT Clark shared an example of the patient education materials that are provided to non-citizens that are available in 21 languages. The "What Can You Do?" document is given to all TB patients within a facility when they are seeing a provider. It tells them what to do when

they are still being detained, what to do when they get released, and information about how to obtain medical records through a portal (not available at this time due to security issues).

ACET Discussion: TB Management of Detained Non-Citizens

Dr. Cattamanchi asked CAPT Clark whether they test for drug resistance, if they have encountered any people with drug-resistant TB, and how people with drug-resistant TB patients are or would be managed in terms of their transition of care.

CAPT Clark indicated that the IHSC does test for drug resistance and has encountered drug-resistant TB. Depending upon where in the process the person is (e.g., in ICE custody, in a facility versus a hospital, et cetera), consultation is ongoing with the CoE for care of non-citizens. The coordination of care is the same. CureTB is involved with the interview process. If someone has been released, the IHSC provides all of the contact information on file if stateside. Everything will go through the health department because the laboratories are outside of the health facility, such as LabCorp. All of the information funnels through the LHD level. If there is a multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) case, the IHSC consults immediately with the CoE regarding treatment and working with CureTB depending upon where that patient will end up going. If the patient is going back to their country, CureTB takes over to facilitate that with their Ministries of Health (MoH).

Dr. Masahiro indicated that the Seattle & King County Public Health TB Control Program has received several TB suspect cases released from ICE. Often radiographic imaging is not available or even a CT scan that was performed. He wondered whether there is any way to facilitate sharing the radiographic images.

CAPT Clark indicated that if someone has an active case that is returning to the facility in which the person was identified, they can always burn the CD. It is much harder to get direct electronic access, but there is always the capability of burning a CD that can be sent to the health department where it can be uploaded into the viewing system. CT scans are done at the local hospital, so it is the same process even if someone is received from the community.

Dr. Sosa asked how the determination is made for whether a person gets an IGRA or a skin test upon having an abnormal CXR, where in the process a person with an abnormal CXR would be triaged for a sputum, how quickly the sputum would be obtained, and what percentage of patients are getting a NAT.

CAPT Clark indicated that the test is determined based upon what is available at the facility. The majority are performing TST. In terms of sputum, people are being screened during the intake process. If they are symptomatic, they are isolated during the intake process and fast-tracked for CXR between 24 to 72 hours. If there is an abnormal result, the patient is isolated, the workup starts, and they are categorized. Sputum samples are collected every 8 hours over a 24 hour period. Category B is typically seen with old TB. If it looks like old or latent TB, only sputum will be collected. They would not meet the criteria of what is at risk to be more advanced or active disease. They are isolated, sputum samples are collected, and they are not initiated on pre-emptive treatment. Some of those people do turn out to be sputum-positive, but it is a small number of folks. People started on rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) are Category A because they have more high-risk looking radiographs (i.e. cavitary lesion). All patients are getting a NAAT, on at least one sputum sample.

Dr. Ray asked how often exposures and spread are not immediately identified within an ICE

facility but are identified say 5 days later.

CAPT Clark did not think this was a common concern. Everyone receives a physical and on average are in a facility for 30 days if in ICE custody. There are many opportunities for anyone who develops symptoms to receive medical services. Around 21 to 30 days during which they would receive a physical, depending on their underlying medical diagnoses. Those with other medical conditions would receive their physical much sooner in the process than healthy people who do not have any medical complaints, who may be a couple of weeks in the facility before a full physical.

Dr. Ahmed wondered how children fit into all of this if an adult they are with or around is identified with TB disease in terms of whether they are put on window. For instance, is consideration given to someone who crosses a border with children?

CAPT Clark indicated that no IHSCs staffed facilities have children in their custody. ICE has a process for pediatric patients, but she does not oversee any of that process and could not answer pediatric questions. The IHSCs work with the health departments to collect contact tracing information, especially when CureTB is conducting the interviews. The interviews with positive patients are very extensive and are 45 minutes to an hour long sometimes in terms of trying to identify all of someone's contacts in their own country and while they were traveling to the US. While IHSC is not specifically collecting information, they facilitate the people who are conducting contact investigation in the community to obtain that information.

Dr. Holland asked whether there are any data on patients who become culture-positive after being released or repatriated and what happens in those situations.

CAPT Clark said that while she did not have data in front of her regarding how many people have become culture-positive after release, she could speak to the process for these patients. If someone has been repatriated back to their country, that information is sent through IHSC's CureTB colleagues and counterparts so it can be related to the MoH in the country to which the person returned. If the person is stateside, the IHSC reports to the LHD where that facility was located and the LHD will make the interjurisdictional notification to provide all of the information to the location address that IHSC has for where that person was released.

Dr. Cattamanchi asked whether there are data on what proportion who start TB treatment complete treatment, including after release from custody and if she could comment on drug resistance in terms of whether it is tested for, if they have encountered any detainees with drug-resistant TB, and how those patients are managed, including transition of care. It is important to understand how effective transitions are and if individuals are completing treatment through all of the transitions people complete, particularly given that transitions are frequent in this population.

CAPT Clark said that while she did not have the overall number on hand of the proportion of patients who complete TB treatment, rarely does anyone who starts treatment complete treatment in custody with IHSC. As CureTB is closing out cases, it might be possible retrospectively to look for those numbers.

Dr. Chen asked whether individuals receive a NAAT that identifies rifampin resistance. She recently heard about a pre-XDR case who was moved to 3 different facilities before it was determined that the patient was not on effective treatment during that period. In addition, she wondered whether there is any consideration for requiring the partners that have contracts with the IHSC to use the more ideal rapid test, particularly since these are individuals who often are

moved quickly and without IHSC having the ability to predict. Early evidence for whether patients are on appropriate treatment is critical.

CAPT Clark indicated that all cases in IHSC facilities are being screened for rifampin resistance as part of their NAAT. There are cases that are worked up in the local community and local community hospitals that do not always have that ability, which is why the partnerships are so key. As a part of the IHSC's process and protocols in IHSC and non-IHSC contract facilities, that is the protocol. The memorandum is an educational and collaborative tool that serves many purposes, but she did not know offhand what is actually written into contracts and how the requirements are being implemented. She can take this back to the leadership as a suggestion that arose during this meeting. As a part of the collaborative effort, they use that memorandum for community partners such as hospitals and community locations that are completing patient workups, because they do not see these types of patients in their regular community practice.

Ms. Rhodes, BOP, added that some of the ICE and BOP facilities are in highly rural areas with small community hospitals that do not have the resources. In ideal situations, there would be rapid testing of everyone and other resources. Just getting people into a hospital in rural areas is good news.

Dr. Chen recalled that during the pandemic, many facilities had funds to at least get basic machines in most hospitals, so it is not so far-fetched now for facilities to have a GeneXpert® machine and could get a cartridge. For the other detainees' sake, the individual involved, and the staff who may be exposed to someone who may not be on complete treatment this is one safety measure to consider.

Ms. Rhodes indicated that Quest has now started incorporating that, so hopefully it is easier now that laboratories are including rifampin resistance in their NAAT testing.

CAPT Clark added that IHSC has been including it for some time when tests are run through the local laboratory. This differs when tests are run through local community hospitals that may use something different and have a different process than the IHSC. This is when the memorandum is used to try to educate and get the facilities to do what is needed to meet the IHSC criteria.

Dr. Sosa recalled CAPT Clark mentioning that when people are started on treatment in hospitals, they are released after 5 days.

CAPT Clark clarified that when people are started on treatment in the IHSC facilities, if they are acid-fast bacilli (AFB)- and NAT-negative, they can complete 5 days of RIPE and then be released into the general population. Those who are AFB- and NAAT-positive remain in isolation until they convert. They are looking for rifampin-resistant mutation in that same time period, so all 3 samples have to be collected. If all things go perfectly, 3 8-hour apart sputums would be done, the patient could be started on medication the same day, all of the results would have been returned to verify that they are smear- and NAAT-negative and asymptomatic, and those people potentially could spend 5 days on RIPE in isolation and then be released to continue directly observed therapy (DOT). Traditionally, the process takes a little longer than 5 days while waiting for results to come back prior to initiation of treatment. Before patients are released from isolation, they have to complete their CureTB interview.

Dr. Loeffler emphasized that this is great and important work. As patients who come through the Panel Physician site, she worries about the accuracy of symptom acknowledgement and the ability to get the best effort for high-quality sputum. She knows that people on the IHSC teams are good at asking open-ended questions and encouraging people to give great sputum for their own healthcare, but it is a problem in a lot of situations. Approximately 81% asymptomatic is pretty unlikely. In addition, she indicated that the correct LabCorp codes for initial diagnostic TB testing are:

- 183516 (Mycobacterium tuberculosis Complex Detection and Rifampin Resistance (PCR), Acid-fast Bacillus (AFB) Smear, and AFB Culture with Reflex to Identification and Susceptibility Testing (Sputum)) for at least one (ideally 2)
- 183764 for the third specimen or a non-sputum specimen (Acid-fast (Mycobacteria) Smear and Culture with Reflex to Identification and Susceptibility Testing)

CDC's National TB Surveillance System and Molecular Surveillance

Overview, General Landscape, Challenges, and Future Directions

CDR Rebekah Stewart, PhD, MPH, FNP
US Public Health Services
Lead, Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

CDR Stewart began by evoking the late, great Maya Angelou who said, "You can't really know where you are going until you know where you have been." Using that wisdom, CDR Stewart provided a review of the history of reporting TB case data, an overview of the current landscape, a discussion of challenges, and a summary of future directions.

Starting with an overview of the National TB Surveillance System (NTSS), TB is a nationally notifiable disease. All verified cases of TB should be reported to NTSS from all 50 states, the District of Columbia (DC), 8 US territories or affiliated islands. All jurisdictions utilize a Report of Verified Case of TB (RVCT) to report case information to CDC. The RVCT captures demographic, clinical, and risk factor data. While initial submission must be within 7 days of an initial TB case report, it can be updated as needed. Provisional data are finalized for a subset of variables by February of each year, and complete data for all variables are finalized in March–June for the previous year.

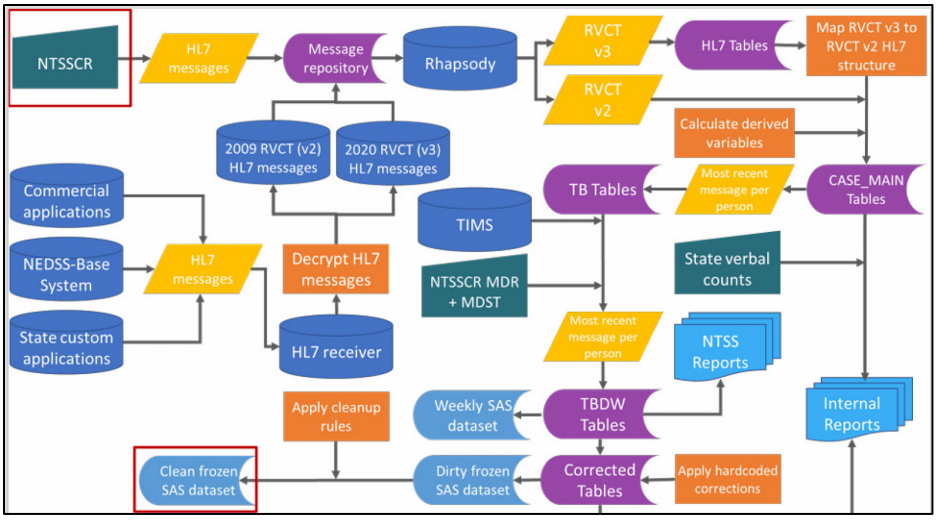
TB data are used to track progress toward TB elimination, identify and monitor risk factors for TB, conduct scientific analyses of public health importance, and detect outbreaks. TB surveillance data collection started in 1953, with individual case reporting started in 1985. By 1993, cases were reported electronically to CDC. As a result, the current dataset includes TB case data back to 1993. In 2009, the system transitioned to data collection via the Public Health Information Network (PHIN) and the National Electronic Disease Surveillance System (NEDSS). A plan was created in 2015 to revise RVCT within 5 years. The global COVID-19 pandemic in 2020 led to some delays in implementing the fully revised RVCT that was planned to be fully implemented in 2020. By 2023, all RVCTs have been submitted using the new format.

The decision was made to revise the 2009 RVCT for several reasons. Some quality assurance (QA) issues were identified with some of the questions. In addition, some new anti-TB drugs and drug-susceptibility testing (DST) methods became available. Another reason this update was pursued was that in 2015, the *National Action Plan for Combatting Multidrug-Resistant Tuberculosis*[18] was launched that had several 5-year goals that needed to be implemented by 2020, which included capturing molecular DST results for all cases, recording more detailed information on MDR-TB treatment, and storing sufficient information to distinguish primary and secondary resistance. All of those reasons gave DTBE a rationale for updating the RVCT and creating the new plan. There were many steps along the way that started with making the decision to revise the RVCT. From August 2016–Mid 2017, a workgroup was convened, and a proposal was developed for DTBE leadership. In mid-2018, a message mapping guide (MMG) draft was developed. In 2019, the RVCT received Office of Management and Budget (OMB) approval, the MMG pilot was completed, and the first reporting area started onboarding the system. CDC began accepting TB case reports in the new 2020 format in January 2020. The Surveillance Team provided a lot of technical assistance (TA) to reporting jurisdictions during this time, which included but is not limited to recorded trainings, “office hour” calls, live virtual presentations, and some live in-person training at conferences.

To highlight some of the many challenges along the way, redirection of CDC resources and focus on data modernization initiatives (DMIs) led to confusion and delay for programs using the National Notifiable Diseases Surveillance System (NNDSS) for reporting. There were objections from states to specific data elements due to privacy concerns, community perceptions of questions and unwillingness to share information with states, the burden to collect information, and incompatibility between RVCT and how local/state systems were designed. The Assurance of Confidentiality (AoC) was very helpful in navigating several tricky concerns about privacy and data security. Implementation was dependent on TB programs working closely with information technology (IT) and general health department staff, which states with good cross-communication navigated more easily. Staff turnover within state TB programs led to substantial interruptions and lack of understanding of the process and expectations. Finally, all verified cases were reported to CDC in 2023 using the 2020 RVCT and continue to be reported using that format.

Regarding the current landscape, TB case data via the 2020 RVCT are transmitted to CDC through 1 of 4 mechanisms: 1) DTBE’s homegrown National TB Surveillance System Case Report (NTSS-CR); 2) CDC’s NEDSS Base System (NBS); 3) state-developed systems; or 4) commercial systems. While the data transmission process may seem pretty simple, this comprehensive flowchart illustrates all of the steps between submission of the case report to the creation of the final dataset that is used for analysis:

[18] https://www.usaid.gov/sites/default/files/2022-05/national_action_plan_for_tuberculosis_20151204_final.pdf



There are currently 24 reporting jurisdictions that are using NTSS-CR, although some of them are working to transition to their own system or a commercial system, 17 are using the NBS, 10 are using a state-developed system, and 9 are using a commercially-developed system. The DTBE team has several regular check-in points with TB programs to facilitate delivery of high-quality TB data. These include monthly TB data users group calls that are led by the Data Management Team (DMT) and often feature trainings by people on the Surveillance Team (S-Team), as well as biannual state check-in calls that are led by S-Team members with data management assistance from the DMT. The purpose of the biannual calls is to review data quality and completeness, ask questions specific to TB surveillance, and provide technical support. There are also on-demand resources for TB programs that are updated frequently. These include an externally facing SharePoint site that includes all training materials and frequently asked questions about the RVCT. This year, there is a new Power BI platform created by the DMT that states can use to review data quality reports in real-time based on their reporting. DTBE also uses those to review data quality with its programs.

Approximately 600 variables are derived from the 2020 RVCT, several of which are new and differ from the 2009 RVCT. Some of these variables include the following:

- Smoking status
- Pregnancy status
- History of incarceration
- History of experiencing homelessness
- Hepatitis
- Date of illness/symptom onset
- Current Occupation and Industry for aligning with NIOSH codes
- Information on contact investigations
- US Census Tract
- New laboratory tests
  - Hemoglobin A1c
  - Fasting blood glucose
  - CD4 count
- Inclusion of molecular results for drug susceptibility testing
- Repeating block groups for testing results

  - Jurisdictions can report multiple results for each test type
- MDR supplemental form
- A lot more . . .

The annual TB surveillance report was published on November 13, 2024[19] that included the data submitted using the 2023 RVCT format, from which CDR Stewart shared some highlights. The surveillance report includes graphs for tracking progress toward TB elimination, such as the one showing the annual incidence rate in the US since 1983. There also are graphs for tracking progress that break down case counts and incidence rates by origin of birth, which is a key demographic risk factor. For this graph, data are provided since 1993. Another graph highlights risk factors for TB (e.g., race and ethnicity) and medical risk factors (e.g., diabetes, post-organ transplantation, viral hepatitis, et cetera) that are shown by origin of birth. There is also a graph for social and behavioral risk factors.

As mentioned earlier, NTSS can be used to detect outbreaks. TB case data for culture-confirmed cases are linked to molecular genotyping data from patient isolates in CDC's Tuberculosis Genotyping Information Management System (TB GIMS). CDC identifies genotype-matched clusters using geospatial analysis to identify unexpected clustering of TB cases within a defined time period. Clusters are evaluated based on a log-likelihood ratio statistic and concerning patient or group characteristics (e.g., HIV status, congregate setting, number of cases in cluster). CDC alerts TB programs of concerning clusters, facilitating further investigation and response. CDC tracks and reports annually on the number and size of county-based TB genotype clusters, as well as characteristics that are associated with clusters that are alerting as part of the system.

In addition to the annual report, LTBI reporting is available through CDC's the TB Latent Infection Surveillance System (TBLISS) module in NTSS-CR. This is relatively new and is optional reporting for states, with at least 9 jurisdictions that are using the TBLISS to report their LTBI cases. A TBLISS instruction manual is available for states to use.

Regarding future directions, with the new RVCT comes the need for a new data dictionary reference guide for analysts. In development is a data dictionary in an Excel format to provide comprehensive cross-walking across the 3 versions of RVCT and allow for searching and filtering based on analytic needs. This is anticipated to be available in early 2025. OMB has updated standards for race and ethnicity reporting that will change the way CDC is currently collecting race and ethnicity data. The updates are to collect data using a single combined race and ethnicity question, allowing multiple responses; add Middle Eastern or North African (MENA) as a minimum reporting category, separate and distinct from the White category; and require the collection of more detail beyond the minimum race and ethnicity reporting categories. DTBE will update its reporting in coordination with the rest of CDC's NNDSS and is awaiting further guidance for that.

Every year, multiple analyses are completed and published using NTSS data in furtherment of the strategic goals. Much of the analyses that are currently in progress focus on understanding changes in incidence and risk factors associated with the COVID-19 pandemic, but DTBE is working to develop its analytic agenda for the next body of research using NTSS data and certainly would welcome any analytic ideas from the ACET for this strategic planning moving forward. There are many ways to access NTSS data. Publicly accessible aggregate data are

[19] https://www.cdc.gov/tb-surveillance-report-2023/index.html

available through multiple routes, as well as line-level data that are restricted because NTSS is protected by an AoC. Unrestricted access is available through the TB surveillance annual report, the Online TB Information System (OTIS),[20] NCHHSTP's AtlasPlus,[21] and ad hoc aggregate data requests.[22] Restricted public access is available through DTBE's Analytic Steering Committee (ASC) with approval and a Data Use Agreement (DUA). For line-level access, investigators must submit a proposal to ASC that requires ≥1 DTBE co-investigator. The ASC reviews and makes a decision (e.g., Approved Without Revisions, Provisionally Approved Pending Revisions, or Not Approved).

To summarize, NTSS receives TB disease case data from 50 states, DC, and 8 territories or affiliated islands. In 2023, all reporting jurisdictions submitted TB case data to CDC using the revised 2020 RVCT. New items on the revised form provide additional understanding of characteristics and risk factors among persons with TB disease. The annual surveillance report was published on November 13, 2024. CDC is working on a revised data reference guide, alignment with new race/ethnicity reporting standards, and an analytic agenda. CDC has several publicly available data sources, increasing transparency and usability of NTSS data.

National Molecular Surveillance of TB

Jamie Posey, PhD
Lead, Applied Research Team, Laboratory Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

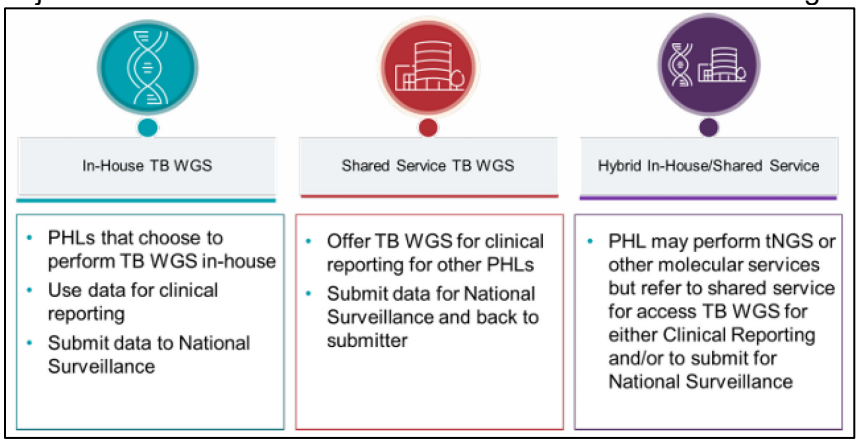
Dr. Posey described the past, present, and future in terms of leveraging the utility of universal whole genome sequencing (WGS). For molecular surveillance of TB, universal genotyping has been available since 2004. In the beginning, only PCR-based methods were being used that looked at less than 1% of the genome. In conjunction with CDC's Antimicrobial Resistance Laboratory Network (AR Lab Network), the National TB Molecular Surveillance Center (NTMSC) at the Michigan Bureau of Laboratories (BOL) was established in 2018 to perform genotyping on at least 8,000 isolates per year. In the beginning, the NTMSC was performing conventional genotyping along with WGS. Conventional genotyping was dropped in 2022, with WGS becoming the primary method for cluster detection. These data were used for detection of outbreaks, possible transmission networks, and surveillance of drug resistance. This allows for monitoring at the national level, and aids in evaluation for any potential pre-existing resistance to drugs included in new treatment regimens before they are implemented. All of the results are captured in TB-GIMS). To date, the NTMSC has sequenced over >50,000 TB isolates.

Currently, all of the data generated from the NTMSC is used only for surveillance purposes (e.g., detection of outbreaks, possible transmission networks, and drug resistance). However, a goal is to be able to leverage the utility of WGS at the national level for surveillance and clinical use. To do this, it is necessary to understand the current landscape of WGS for *M. tuberculosis*. Given that most of the data are generated at a single site, it is highly centralized with the NTMSC sequencing about 8,000 isolates per year. Those data are then sent to CDC to be analyzed and incorporated into TB-GIMS. Several state public health laboratories (PHLs) are performing in-

[20] https://wonder.cdc.gov/tb.html
[21] https://www.cdc.gov/nchhstp/atlas/index.htm
[22] https://www.cdc.gov/tb/statistics/DTBE-Data-Request.htm

house WGS. To be able to expand from surveillance to clinical use, more than 1 or 2 laboratories need to be doing this work. Sequencing, reporting, and consultation of 8,000 isolates cannot be done a single site. There is an emphasis on ensuring that the data are being used to their full potential. Because NTMSC does not perform WGS as a Clinical Laboratory Improvement Amendment (CLIA)-compliant test, the data cannot be used for clinical management. To expand the capacity for WGS and get this into multiple sites, the division partnered with the AR Lab Network/ARLN to fund 9 state PHLs (CA, GA, IA, NY, OH, TX, VA, WA, and WI) in 2022 to support validation, implementation, and/or continuation of WGS to predict resistance. Unfortunately, the funds that were supporting this strategy were rescinded. However, for Budget Period 5 of the current CoAg, it was possible to move this directive to SHARP 2.0 in 2023. At that time, 17 states submitted a workplan as a place holder, but only a few states submitted a budget specifically for mTB WGS. Therefore, it was not clear how many of these sites would use SHARP 2.0 funding specifically for TB. Several states have validated WGS as a CLIA-compliant test (CA, NY, TX, and WI), and several are in the process of validating. Some sites are routinely sending WGS files to CDC for national surveillance dataset (AZ, CA, FL, and NY). Arizona and Florida do not have this under CLIA at this time.

In terms of the future, the ability to leverage universal WGS for surveillance and clinical management of patients will require a decentralized system that includes CDC-funded WGS Centers and local jurisdictions. There are 3 models that are illustrated in the figure below:[23]



The new ELC NOFO is in the first Budget Period of a 5-year Co-Ag to maintain status quo. The data being generated are for detection of outbreaks and surveillance of drug resistance. A single site, the Michigan BOL, was funded at $1.8 million by CARB and DTBE to perform WGS for up to 8,000 isolates per year. Those data will be sent to CDC for analysis. The language is being developed for Budget Period 2, which is anticipated to be finalized and published soon.

While NTMSC is generating the majority of data, some local jurisdictions are performing their own sequencing. A lot of effort is being put into the analyses. The current bioinformatic workflows are all embedded in BioNumerics, which is a nice platform that is owned by bioMérieux. Unfortunately, they have decided not to support BioNumerics beyond 2024. For the last year and a half, DTBE has been working to identify a funding mechanism in order to build a new analytic platform to replace BioNumerics to maintain this national molecular surveillance. The new

[23] Provided by Anne Gaynor, APHL

bioinformatic workflow that is being tested will use all open-source workflows instead of the proprietary workflows that were being used previously, and it will be owned by CDC. Instead of being a local resource at CDC, it will be implemented on the new Advanced Molecular Detection (AMD) platform that is all cloud-based. Even though this has been a major challenge over the last year and a half, it is also an opportunity to make enhancements to the system, such as the ability for TB programs to interact with the data versus just having a static phylogenetic map, implement more data visualizations, use local epidemiologic data, and automate strain comparisons that have been done manually previously. These enhancements will occur throughout 2025. The new bioinformatic workflow will have a centralized pipeline into a single "mega" workflow and will be cloud-based. Inputs include a Metadata Sheet (Sample ID, Accession Number, SRSID, Optional Inputs) a Sample Sheet (Sample ID, Fastqs), and a Staged Input Fastqs. Outputs will include an output director naming convention, will be stored in AWS, and will be fed back into CDC systems and there will be a lot more automation. The intent is for this to be a future-proof and a more efficient system that will allow CDC to do more in the coming years.

Regarding some of the uses of WGS data and public health impact, 648 TB clusters were evaluated by CDC and public health partners in 2023. Surveillance of drug resistance is possible, and analysis of pre-existing resistance can be done for new drugs implemented programmatically. There is now a huge potential for universal, CLIA-compliant, comprehensive testing providing results in days versus weeks-to-months for phenotypic testing. This can be done on a national level and will add value for investment with use for clinical management.

Regarding other efforts that have been made with these data from a drug-resistance and surveillance standpoint, the "STOP_DST" project seeks to correlate the phenotypic DST (pDST) with molecular DST (mDST to assess the accuracy for first-line drugs and be able to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for predicting resistance. Fortunately, there is not a lot of drug-resistance in the US. About 90% of samples submitted to the NTMSC to be sequenced are susceptible. The first step for this project was to develop interpretation criteria. We already had a bioinformatic pipeline for identifying the variants. The CDC interpretations were harmonized with the WHO catalog, which is the "Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance."[24] Approximately 29,000 samples from 2018–2022 that also had phenotypic results were analyzed. Sensitivity and specificity were calculated for each drug. Accuracy was fairly high for rifampicin, isoniazid, ethambutol. However, sensitivity for pyrazinamide was only about 52%. Much of that was due to Lineage 1, with false resistance with pyrazinamide. Once Lineage 1 is removed, sensitivity increases. The highest probability of pyrazinamide-resistance occurs is MDR strains, for which sensitivity increased to 94%–96%. That is for predicting resistance, which raised a question regarding how accurately susceptibility is being predicted. The data were stratified by the major lineages, with Lineages 2–4 at 99.1% accuracy and Lineage 1 was 90%. Taking all of this in at the national level, about 85% of pDST can be reduced if all of them are assumed to be susceptible to these first-line drugs based on WGS data.

[24] https://www.who.int/publications/i/item/9789240028173

Another area for which work is being done is data sharing, for which there are 3 levels as follows:

- **Raw WGS data (fastq) shared with states**
  - DUA must be signed by laboratory and TB program representative
  - Be assigned a POC
  - Data shared via Basespace to receive a link to download data

- **National Center for Biotechnology Information (NCBI) Bioproject**
  - Raw de-identified data (fastq)
  - Finalized a set of data (2018–2022) cleaned using the STOP_DST Project
  - Develop a plan with SciComp and contractor
  - Goal to have this upload by June 2025

- **States share fastq files with CDC**
  - Instead of sending isolate to the NTMSC
  - Shared via Basespace or the ftp
  - Certain criteria have to be met (sequencing instrument, chemistry and quality metrics)
  - Work with CDC to discuss approach and evaluate data before halting the shipment of isolates to NTMSC

TB Molecular Surveillance in the US

CDR Jonathan Wortham, MD, FAAP
US Public Health Service
Chief, Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

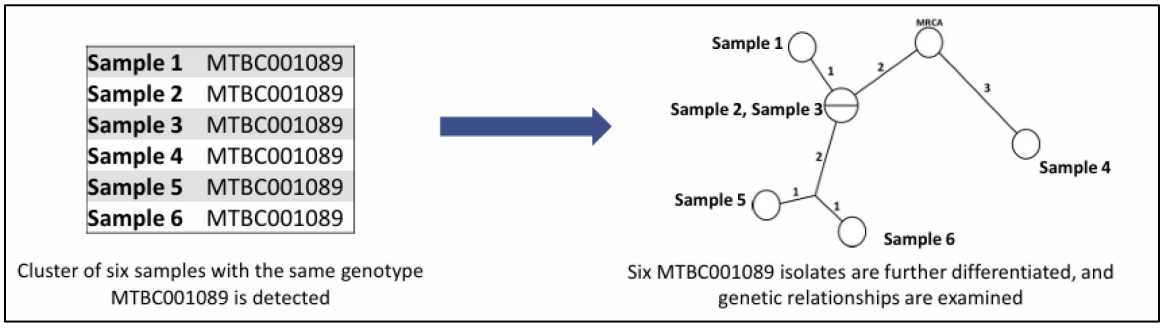
CDR Wortham presented content about TB and molecular surveillance in the US in terms of why molecular surveillance is important, how WGS data are used for molecular surveillance, and how CDC plans to improve the usability of WGS data for public health action while making some of the necessary changes Dr. Posey discussed. Increasingly, molecular surveillance is important for identifying TB outbreaks within the US. In a published analysis[25] of CDC outbreaks during a 6-year period, 16 of the 21 outbreaks during 2009-2015 were initially identified through the use of genotyping data. These outbreaks disproportionately affected different demographics than most TB cases. Most patients affected outbreaks were US-born, many had mental illness (defined in this study as Axis I disorders besides major depression), and many had experienced homelessness and reported using alcohol or illicit substances. Identifying these outbreaks and the infected people informed situation-specific response strategies to promptly diagnose and treat TB infections in at-risk people. Those outbreaks may not have been representative of TB transmission overall.

[25] Mindra G, Wortham JM, Haddad MB, Powell KM. Tuberculosis Outbreaks in the United States, 2009-2015. Public Health Rep. 2017 Mar/Apr;132(2):157-163.

In addition to outbreak detection, molecular detection has facilitated systematic surveillance for large outbreaks of TB, defined as more than 10 cases related by transmission within a 3-year period. Findings from large outbreak surveillance were first reported in a 2022 publication.[26] Compared with most people with TB, people affected by large outbreaks were more likely to be US-born, younger based on median age, more likely to have reported American Indian/Alaska Native (AI/AN), Black, or Native Hawaiian/Other Pacific Islander race, more likely to have clinical indicators of infectiousness/advanced pulmonary disease such as cavitation, and more likely to have reported substance use, experienced homelessness, or have been incarcerated at diagnosis. In addition to detecting outbreaks and facilitating large outbreak surveillance, molecular surveillance can be used to exclude genetically distant cases from outbreak investigation, saving time and resources that might be used to unnecessarily pursue epidemiologic linkages that do not exist and transmission hypotheses that are not correct.

To summarize, molecular surveillance facilitates identification of clusters and outbreaks alongside traditional epidemiologic data and facilitates prompt public health action to interrupt transmission. It also facilitates systematic descriptions of large outbreaks, which affect distinct epidemiologic groups compared to non-outbreak-related TB cases. These demographics and co-morbidities have important implications for public health action to prevent and stop outbreaks. Finally, molecular surveillance facilitates refuting outbreaks in certain situations characterized by cases with genetically diverse isolates. Public health partners have used these molecular surveillance data to redirect outbreak-specific resources and strategies for groups of cases caused by outbreaks that are closely related genetically and more likely to be related by transmission.

To achieve the goals of molecular surveillance, WGS data are used in 2 ways. The first is whole-genome multilocus sequence typing (wgMLST), which is a typing scheme used for genotyping and cluster detection. wgMLST is used to issue county-based cluster alerts that represent geospatial concentrations of cases with matching genotypes, perform large outbreak surveillance, and calculate recent transmission estimates. Second, when genotype clusters are identified using wgMLST, whole genome single nucleotide polymorphisms (wgSNPs) comparisons can be used to further differentiate the genetic relationships between isolates in a genotype cluster. This is helpful for further differentiating the genetic relationships between isolates in a genotype cluster. This is helpful for further assessing whether cases are related by recent transmission. In this example, 6 samples form a genotype cluster with the same wgMLST type and generate a phylogenetic tree like the one shown on the right:



[26] Raz KM, Talarico S, Althomsons SP, Kammerer JS, Cowan LS, Haddad MB, McDaniel CJ, Wortham JM, France AM, Powell KM, Posey JE, Silk BJ. Molecular surveillance for large outbreaks of tuberculosis in the United States, 2014-2018. Tuberculosis (Edinb). 2022 Sep;136:102232.

DTBE first began performing wgSNP comparisons and phylogenic analyses in 2012 and has been building capacity for this service continually since that time. At this point, over 1,800 clusters have been analyzed over time. Between 2012-2018, wgSNP and phylogenic analyses were provided for select clusters of concern and clusters flagged as potential large outbreaks as samples had to be sequenced retrospectively. Sequencing capacity was limited at first and wgSNP comparison was mostly a manual analysis process. In 2018, DTBE began prospective WGS for all samples submitted for genotyping. This meant that wgSNP comparison was no longer limited by sequencing capacity. At that time, the analysis process was switched to a more automated pipeline using the BioNumerics software package that Dr. Posey discussed earlier. Although there is still some hands-on time involved in the analyses when using this software, DTBE began performing wgSNP for all of the weekly cluster alerts for geospatial concentrations of genotype-matched cases to assist in the review of those clusters to determine which were most likely to represent transmission. wgSNP comparisons are available for other clusters upon request from DTBE's partners.

At this point, DTBE is performing more than 1,000 analyses per year or about 23 per week. This sounds like a lot, but that is because each cluster is repeatedly updated as new samples and new isolates are added to the cluster. While capacity has increased dramatically over the years, sometimes the demand is quite high for the number of personnel. DTBE recently heard feedback from state programs that they find these data extremely helpful. Requests from state programs for wgSNP comparisons have continued to increase over the years. Currently, just half of clustered samples are included in an analysis, meaning that many clusters do not get analyzed.

At the end of 2024, DTBE will no longer be able to use BioNumerics for wgSNP comparisons and will be switching to run these platforms on the AMD Platform. The necessity to switch the pipelines onto a new platform has provided opportunities for enhancements to the process, one of which is the opportunity to expand capacity even further by increasing automation and integration with TB GIMS. Requests for wgSNP comparisons are currently made through TB GIMS and can be made by state or CDC users. Starting in January 2025, TB GIMS will be able to send the job to the AMD Platform where it will be run. Later in the Spring, TB GIMS will be able to pull the results of the run back into the system and store them for user access. This increased automation and integration will greatly decrease the amount of hands-on time for DTBE staff who run these analyses, allowing for expanded capacity and personnel time for other activities. In the Fall of 2025, DTBE plans to expand capacity even further by implementing automatic national wgSNP comparisons for all clusters. When new genotypes results are uploaded into TB GIMS, the system will send jobs to the AMD Platform to generate new or updated wgSNP comparisons so every genotype cluster will have a phylogenetic tree available to view. These trees will be automatically updated as more samples are added to the cluster. This will decrease the need for states to do ad hoc requests for wgSNP comparisons for their cluster cases and for DTBE staff to manually process those requests. The ability to request custom comparisons will still be available. For example, a state might want a tree that includes samples just from their state.

The switch to the new platform also has allowed the opportunity to provide states access to tree visualization tools. While DTBE has been building capacity steadily and increasing the number of clusters that are analyzed by wgSNP over the years since 2012, visualization of the results for the phylogenetic trees has largely remained the same. Currently, a visual of the tree is produced in BioNumerics and a static image of the result is exported and uploaded into TB GIMS. This static image makes it very cumbersome for programs to try to color-code or relabel to aid in interpretation or facilitation of discussions with their partners about the cluster. Because some

trees are very large, users also would benefit from being able to manipulate the tree to make it easier to see or to find particular samples of interest. They cannot do this with the static image that is currently provided. Starting in Spring 2025, the tree visualization program GrapeTree will be available to states through the AMD Platform. States will be able to access the results of the wgSNP comparisons with TB GIMS and interactively visualize and edit the tree using GrapeTree in the AMD Platform. This will allow users to zoom in and out and move branches around, search for samples of interest, bring in corresponding epidemiologic data in order to select parts of the tree and see corresponding epidemiologic data for those cases in the table, and change the color coding and labeling of the tree. This will make it easier for programs to consume and interpret the wgSNP comparison results for use in cluster investigations and other programmatic activities.

In summary, molecular surveillance data are useful for public health action. Public health programs are requesting more analyses of WGS sequencing data than they have in the past. Nonetheless, changes are coming to the bioinformatic tools and pipelines, and CDC is working to improve data access and visualization alongside needed changes in bioinformatic tools and pipelines that Dr. Posey discussed earlier.

ACET Discussion: CDC's National TB Surveillance System and Molecular Surveillance

Dr. Loeffler commented that it is inspiring to see where this is all headed, and that it offers hope when things are challenging in the field. She asked what the optimistic goal is for when some of interoperability will occur, especially for results from CDC, Wadsworth, and California laboratories to be imported automatically into the RVCT system. The current expectation that teams will enter all of the molecular susceptibility results in the RVCT by hand, especially for situations in which there are results from several different laboratories, is not practical.

CDR Stewart responded that her understanding is that some of CDC's results can be entered directly into NTSS. A lot of the laboratory results that are received come from outside laboratories, so a minority of programs have the ability to receive the results from CDC's service. There is not a great path yet for when there will be a complete, seamless transfer of molecular results into NTSS. CDC has done a lot of work and some of it can be transferred already, but because there are so many different ways in which those data are received, when this will be possible is not known at this time.

CDR Wortham added that there are at least 2 steps with this to getting to electronic laboratory reporting (ELR). In his clinical realm, a number of laboratory results are still received by fax. The second step would be getting the ELRs, which is not done universally, to then be submitted to surveillance. Given the number of systems and all of the complex issues that CDR Stewart discussed earlier, it is difficult to provide a specific date. DTBE has certainly heard about the challenges from people inputting data into the RVCT and will continue to think about that as best they can.

Mr. Watts, with the National Health Care for the Homeless Council (NHCHC), recalled that there was over-representation in CDR Wortham's data of TB clusters around people experiencing homelessness. He pointed out that homelessness is often under-reported in healthcare settings because the question is not asked and wondered whether CDR Wortham knew how the people experiencing homelessness in his data were identified.

CDR Wortham indicated that the TB outbreaks in the US between 2009-2015 were CDC-investigated outbreaks, including people in his group. They used a definition of a patient either sleeping at a homeless overnight facility, meeting the local definition of experiencing

homelessness, or where they had mail sent. If a patient could not provide an address that was not the homeless overnight facility, which many of them provided, they were considered as experiencing homeless in those outbreaks.

Mr. Watts said it sounded like different jurisdictions may have had different methodologies or definitions, which was not surprising.

CDR Stewart added that the revised RVCT does ask about the history of experiencing homelessness. That question is meant to be asked of all patients having been identified as having TB by whomever is conducting the interview, which is typically a local public health nurse. There are specific instructions about what should be considered "homeless." This includes people who do not have a fixed, regular, adequate night-time residence. It goes beyond just those who are in a shelter, although they are certainly included.

CDR Wortham added that people who were considered to be "couch surfing" also were included as experiencing homelessness during those outbreaks.

Mr. Watts said that sounded appropriate and like the HHS definition, which is more expansive than the US Department of Housing and Urban Development's (HUD's) definition.

Mr. Cummins asked CDR Wortham whether the GrapeTree application would pull in the linked state case numbers in the RVCT in order to see the full picture of a cluster that includes clinical- or provider-verified cases.

CDR Wortham said that is easy with linked, culture-confirmed cases, but visualizing relationships between clinical- and provider-diagnosed can be done.
Mr. Cummins clarified that he was not seeking to add notes, but he would like to see the linked case numbers if he hovers over an individual that might include clinical- and provider-verified cases. Case numbers are another component of surveillance data on the RCVT that would be useful in GrapeTree.

Dr. Stout commented that this is a wonderful way to emphasize the importance of the whole genome data. He noted the resource of over 50,000 sequenced isolates of TB coupled to the reasonably detailed clinical data in the RVCT, given that it seems like an enormous scientific resource that could be useful for people in academia. He encouraged creative thinking about ways to make the data publicly available. While the sequences up to 2022 are going to NCBI, the sequences linked to de-identified clinical data would be a vast resource for better understanding TB. Recognizing that there are administrative hurdles, he encouraged trying to navigate those.

Dr. Sosa asked Dr. Posey what the goals and added benefit are for having the WGS data for TB in the NCBI, understanding that CDC has done a lot of this work already in terms of linking cases.

Dr. Posey indicated that CDC is being pressed to put all data the agency generates into the public domain, so the goal is to address that issue. There will be some metadata linked to this even though it is de-identified, such as DST results and anatomical results. The types of metadata were established and approved years ago and were presented to NTCA, and they are trying to get the data out to the scientific community to use it to the best ability possible without it being identifiable. Even when states have access to data, they do not necessarily know what to do with it. People have reached out to request data, so DTBE is doing the best they can to "keep the wheels on the bus" and get the data out at the same time.

Related to the data shown about the correlation of WGS drug-resistance data to phenotypic data and perhaps not needed as much phenotypic testing in the future, Dr. Sosa observed that it seemed like the ability to perform WGS on raw specimens would make that even more useful.

Dr. Posey pointed out that every sputum is different depending upon the amount of human deoxyribonucleic acid (DNA) and bacterial DNA that are there. For drug resistance, more depth of coverage equals more certainty in heteroresistance. QIAGEN has a product for sequencing directly from specimens, which DTBE has experimented with over the years to look at assays built on that type of platform and found that with enough bacterial burden, this could be done. However, the specimens do not have enough bacterial burden most of the time. Targeted sequencing can be done easily, which DTBE does now.

Regarding Mr. Cummins's question, CDR Wortham said it will facilitate looking at the NTSS variable, the linking variable, which facilitates programs' putting which cases have epidemiologic links. However, it is known that this variable is not universally used. Therefore, he will have to do more investigation programs that do not use that variable.

Dr. Loeffler asked what everyone's vision is about inevitably transitioning away from phenotypic DST. A 2% to 5% false negative has been used, but people must get to a place where they are comfortable waiting for the rare patient to have some treatment failure before the old phenotypic DST is pulled out.

Dr. Posey said he thought a lot could be learned from what New York is currently doing. Not all of their patients meet the criteria. It also depends upon whether WGS data are available, which is why they are trying to analyze the data on a national level. There is not a lot of New York State data in the analysis because they were doing their own sequencing, so DTBE is trying to get the empirical data to support it one way or the other and just base it on the phenotypic result. Anytime something is seen for which the meaning is unknown, such as finding a new variant that is not classified as resistant or susceptible, that automatically would trigger a phenotypic DST. That is what Public Health New England and New York are doing currently, from which DTBE can and build from on a national level.

Dr. Narita commented that phenotypic does not detect resistance. For example, there is discordant information and maybe there are different levels of minimum inhibitory concentrations (MIC) impacting clinical outcomes. It could be important to assess the discordant information between molecular and phenotypic and any clinical impact on those few cases.

Dr. Loeffler agreed that more MIC data might be helpful.

Dr. Ritger asked whether it would be possible to have the NTSS data divided into smaller units than states, such as for large cities. She represents Chicago and looking at all of the Illinois is not very useful to her in her specifical role in terms of any ad hoc look ups at NTSS or even in an annual report.

CDR Stewart said consideration could be given to something like large cities for the annual report. They try to be careful with what is made publicly accessible in terms of how small the data are presented. This might not be an issue for Chicago and Illinois, but there are some states with just 1 case or just a few cases. In AtlasPlus, data are provided at the county level for most states. They used to provide the Metropolitan Statistical Area (MSA) level for OTIS but have not

been doing this for the last couple of years. Ideas of ways to present the data at smaller levels than states certainly can be considered.

CDR Wortham invited Dr. Ritger to contact his team, who would be happy to get her what she needs for her public health operations.

Thinking about new arrivals who are highly mobile, Dr. Ritger recalled that when a genotypic cluster is defined, location of where the case is counted is part of the algorithm. Highly mobile people might impact the ability to cluster people if they are counted in a state that is not where their exposure occurred. For example, she has 2 people who recently arrived in Chicago from Venezuela who are a cluster. However, no linkage has been identified between them in terms of family, travel, or their stay in Chicago. It could be that they did not name each other, but it could link back to an ICE facility or a shelter at the border. DTBE has the data at a national level to look at that in a way that the local or state levels do not have. Often, migrants do not know the details of their journey in terms of the names of places where they were held, the cities, or even the states where they were.

CDR Wortham confirmed this to be accurate but noted that there are a couple of directions that situation might go. It is true that if people have a common exposure someplace else and then go to other places, the county-based, state-based, and geographically narrowly focused may not detect those. Some “national” clusters have been identified of rare genotypes. DTBE has been able to engage with programs to try to identify places where there are potential transmission hypotheses amongst these cases caused by a rare isolate nationally. Sometimes programs have informed them of a laboratory contamination issue that could represent this. A large laboratory was processing specimens from a number of places that all popped up as the same. Other hypotheses have been identified as potential exposures, though not in the US. It could be more challenging if a genotype is common. In terms of recent arrivers, DTBE has seen this and has reached out to programs. This is especially common when there are 1 or 2 cases in each jurisdiction that would not otherwise prompt programs to think about a transmission hypothesis amongst a number of cases. They recognize that in practice, patients are sometimes reticent to share the details of their journey up to being in the US, but they are asked about any commonality in their journeys since they have been in the US, thinking about the potential to engage other partners with regard to questions and ability to inform TB control measures within the US or government systems. That notwithstanding, DTBE has found it difficult to elicit specific journeys. Based on his personal experience taking care of people in clinical roles outside of CDC, there are elements of many of their journeys that could facilitate transmission that they would be unwilling to share. That has been a challenge in terms of eliciting the histories that programs have conveyed to DTBE. It is also difficult to intervene to stop those conditions.

CDR Stewart added that all of the cluster detection methods right now are county-based. While DTBE might not receive a notification through its automated detection method, they can look at it if notified in another way.

Dr. LoBue recalled that in calculating estimates of recent transmissions, DTBE excludes people based on being recent immigrants to the US within 100 days. That is an arbitrary cutoff that may need to be longer. A recent case to the US is probably a prevalent case rather than an incident case. If there are clusters among those people, it will be difficult to impossible to tell whether transmission occurred inside or outside of the US. Another consideration regards why molecular epidemiology works relatively well in the US, for which he thinks there are 2 reasons: 1) TB is relatively rare; and 2) the population is very diverse in terms of where people got their TB. When dealing with other countries, which relates to the recent immigrants, there may be highly

prevalent strains within those countries. While molecular epidemiology helps a lot, there are limitations. It is not perfect.

Dr. Ray said she loves the data this DTBE team provides. This is another useful tool for detecting and/or confirming cross-contamination. Because patients are treated using DOT, there is very high sensitivity for identifying unstably housed people.

Tuberculosis Epidemiologic Studies Consortium III

Kathryn Winglee, PhD
Lead, Epidemiology Team, Surveillance, Epidemiology, & Outbreak Investigations Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

Dr. Winglee provided an update on the Tuberculosis Epidemiologic Studies Consortium (TBESC)-III, which launched in 2021 and will end in 2026. TBESC-III's mission is to assist TB elimination efforts in the United States by designing and conducting epidemiological research studies to answer the most important questions to guide policy and practice, while its objective is to use implementation science to identify primary care interventions that increase LTBI targeted testing and treatment that are both effective and efficient. TBESC-III's specific aims are to: 1) identify primary care settings serving non-US-born persons at risk for LTBI; 2) collect retrospective and prospective electronic medical record (EMR) data; 3) design and implement clinical care-based interventions to improve performance measures across the LTBI care cascade; and 4) monitor and evaluate intervention performance over time to identify efficient and effective strategies. In accordance with the objective and aims, TBESC-III is specifically focusing on improving TB testing and treatment of non-US-born persons, although it is anticipated that the intended study outcomes will benefit all populations. The focus is primarily on non-US-born persons because in the United States, the TB incidence rate is 18 times higher among non-US-born persons compared with US-born persons.[27]

In order for a site to be eligible to participate in TBESC-III, it had to be a primary healthcare setting with an EMR and provide primary healthcare services each year to at least 10,000 non-US-born patients living in the US. There were 4 sites awarded with the initial contract, including the following:

- ❑ Denver Health and Hospital Authority (DHHA), working with community clinics
- ❑ Public Health - Seattle & King County (PHSKC) in partnership with International Community Health Services (ICHS)
- ❑ Kaiser Foundation Research Institute, specifically Kaiser Permanente of Northern California (KPNC)
- ❑ The Regents of the University of California, San Francisco (UCSF) in partnership with North East Medical Services (NEMS)

[27] Data from CDC's Reported Tuberculosis in the United States, 2023

These 4 sites provided the baseline data provided during this session. In addition, a separate contract was awarded to RTI International for cost-effectiveness analyses for which data were not provided during this session. Over the course of the TBESC-III Work Plan, sites are designing and implementing interventions that improve adoption of CDC LTBI recommendations, particularly for increasing testing of non-US-born populations at high risk for infection, use of IGRAs for TB testing, and use of rifamycin-based short course treatment regimens for LTBI. All non-US-born patients who have a primary care visit during the study period at 1 of the 4 sites collecting data are included in the analyses. Patients who are missing data on country of birth are included if they have a non-English language preference. Each site was allowed to define their study populations based on their clinic's practice. As a result, the definition of "primary care visit" varies between sites and generally includes both in-person and telehealth visits. All sites are including patients ≥18 years of age, with Site A also including patients ≥2 years of age.

The TBESC-III study period is divided into 2 time periods, the baseline and the intervention. The baseline period was required to be a minimum of 12 months before any interventions were implemented. Any patient who had a primary care visit at one of the sites during this time was included in the baseline cohort. Sites could choose their baseline period, meaning that the baseline period varies by site, with 2 sites having a 1-year period, 1 site having a 1.75 year period, and 1 site having 2 years. Although the baseline period ended in late 2022, the baseline data were closed out in December 2023 to allow 1 year for patients to complete treatment. The intervention period started the day after the baseline period ended and is also the day the first interventions were implemented. The intervention period will continue for 3.5 years until the contract ends in March 2026. Any patient who has a primary care visit at 1 of the sites during this time will be a part of the intervention cohort. Sites have an option to implement additional interventions during this time, meaning that there may multiple interventions with different starting dates occurring during this time. Dr. Winglee's presentation focused largely on the baseline period.

The main scientific question of TBESC-III is, "What are the most effective and efficient interventions?" To answer this question, line listed EMR data are being collected on patients that will be used to assess the effect of the interventions. This includes developing LTBI care cascades for baseline and intervention. Implementation, monitoring, and evaluation (IM&E) data are also being collected. These are aggregate data that will allow for assessment of how the interventions were implemented and why those effects are being identified through the EMR data. Cost data are also being collected, which will be used to assess the cost-effectiveness of the interventions. This presentation focused largely on the results from the EMR data.

In terms of the timeline, TBESC-III started in October 2021 and sites had until October 2022 to implement their interventions and initial based EMR data, with baseline cost data shortly after that. In March 2023, sites were required to start submitting their EMR and IM&E data quarterly and their cost data every 6 months. The submission in December 2023 is when the baseline period data were closed out, which allowed a year for baseline patients to complete treatment, which is the dataset Dr. Winglee presented during this session. DTBE is soon to receive the 8th quarter of post-intervention IM&E and EMR data and the 4th round of intervention cost data.

The baseline care cascade is the main tool being used to assess the TBESC-III results. The care cascade, also known as the cascade of care, is a health framework that can be used to monitor the progress of a population through testing and treatment. Patients generally have to go through the steps in order. For instance, a patient must have a positive test result to be included in the treatment bar.

To walk through the preliminary baseline care cascade, in total across the 4 sites, 3.5 million patients had a visit meeting the sites' primary care definition during baseline. Of those 3.5 million patients, 549,000 or an average of 47.9% met screening criteria, meaning that they were non-US-born or country of birth was missing, but they had a non-English language preference. Note that guidelines have additional groups recommended for screening, but since TBESC-III is specifically focusing on the non-US-born population, only that risk factor is included in the care cascade. Since the majority of non-US-born patients at these sites are from countries recommended from screening, only a binary US-born/non-US born analysis is being done.

With respect to patient demographics, the largest age group is 40 to 64 years of age, although many patients are ≥65 years of age and there were more females than males. Looking at race and ethnicity on a logarithmic scale, the most common race is Asian, but many patients are also Hispanic. Based on a linear scale for the top primary languages, the biggest bar is patients who preferred English. Among those who preferred another language, Spanish and Chinese were the top 2 most common. Looking at a map of countries of birth among patients who met screening criteria during the study period, many of the patients come from Asia. China, India, the Philippines, and Vietnam have a large number of patients. However, there also is a sizeable number of patients born in Mexico. Regarding risk factors for infection or progression to TB disease, diabetes was the biggest risk factor with about a quarter of patients living with this disease. However, it is important to note that these are largely based on International Classification of Diseases (ICD) codes, which can be unreliable and are likely an underestimate—especially for close contacts and those experiencing homelessness. Most patients have private insurance or Medicare, with the other largest category being no insurance.

With those demographics in mind, Dr. Winglee returned to the preliminary care cascade. It is important to note for this care cascade, the height of the bar and the number at the bottom indicate the sum of the patients across all 4 sites. Percentages are calculated using the previous bar as the denominator. Since the sites see a different number of patients, the percentages are averaged across the 4 sites so that a single site does not dominate the percentage outcomes. This makes the percentages more representative of how all 4 sites are doing, while the number gives the overall progress. Since the ultimate goal of TBESC-III is to assess the performance of the interventions, the next step in the care cascade is unique to TBESC-III and removes patients who would not be eligible for an intervention. This group includes all patients who have a history of TB or LTBI diagnosis or treatment, or a history of a valid TB test result. In other words, patients are excluded at this step who have already been tested and are treated for TB or LTBI. On average, 68.8% of patients are eligible for intervention.

Just over 18,000 patients or an average 14% had at least 1 IGRA test ordered during the baseline period. Recall that one of the goals of TBESC-III is to increase testing using IGRAs, so this care cascade looks only at IGRAs. However, this analysis shows that over 90% of the tests ordered during the baseline period were IGRAs with less than 10% TST, indicating that even at baseline, these sites had already shifted their testing to IGRAs and not too many patients are being lost who have only a TST. Of those IGRAs ordered, an average of 92.4% had a valid positive or negative result, indicating that most patients were getting the test if they were ordered and there were no issues with the labs. Of those with a valid test result, an average of 16.8% tested positive. This is in line with national estimates of LTBI prevalence among the non-US-born. Patients who test negative would not need to progress through the rest of the care cascade, so they were removed from subsequent steps and the scale was changed. The majority (an average of 81.8%) of those with a positive test had a chest image order, which is needed to rule out TB disease prior to starting treatment. Unfortunately, it was not possible for sites to determine systematically if the imaging was performed or what the result was. As a

result, ICD codes were used to determine whether a patient was diagnosed with LTBI. Although ICD codes have many limitations, the majority of patients (an average of 69.7%) had an LTBI diagnosis. Among those with an LTBI diagnoses, an average of 59.9% were prescribed an LTBI regimen. Among those who were prescribed treatment, an average of 85.4% filled the prescription at a pharmacy, which is used as a proxy for starting treatment. Finally, an average of only 53.5% of those who started treatment completed treatment.

There are some caveats with regard to the treatment prescribed, started, and completed. As a result of looking at prescription data, it is not possible to distinguish between 6 or 9 months of isoniazid. An algorithm was implemented to determine whether rifampin and rifabutin prescriptions were for treatment for TB or LTBI or for another condition. Treatment completion was estimated from the number of doses filled at the pharmacy within the specific regimen timeframe, with the assumption that a patient who picked up a prescription at a pharmacy took it. However, it was only possible to analyze fill data from pharmacies on the same EMR systems as the sites. This means that patients who go to external pharmacies will look like they did not pick up their prescriptions. Therefore, the numbers are likely underestimates of started and completed treatments. All sites have on-site pharmacies that are used by most of their patients. In addition, 1 site did a manual chart review for all patients, meaning that they have data on patients going to the on-site pharmacy and some data on patients using offsite pharmacies.

To break down the treatments by regimen, among the 973 people prescribed treatment in baseline, nearly 2,000 regimens were prescribed. The majority of these were for 4 months of rifampin. Overall, 91% of regimens prescribed were short course regimens. Regarding the number of prescribed regimens that were subsequently picked up at the pharmacy, used as a proxy for treatment, 1,381 regimens or 69% of regimens prescribed were started among the 860 people who started treatment within the care cascade. About 64% of the prescriptions of 6 or 9 months of isoniazid, 72% of 4 months of rifampin, 52% of 3 months of isoniazid and rifapentine, and 58% of 3 months of isoniazid and rifampin were started. A total of 506 people of the 860 who started treatment completed treatment. Just 23% of 6 or 9 months of isoniazid, 36% of 4 months of rifampin, 56% of 3 months of isoniazid and rifapentine, and 38% of 3 months of isoniazid rifampin regimens were completed.

The care cascade ends here with treatment completion. The goal is to get patients through this step which is needed to reduce the chances of patients progressing to TB disease. There are many steps to getting a patient to treatment completion and these are places where intervening could improve cascade performance. Where there are losses in every step, the losses were much smaller in getting the test, ordering test imaging, diagnosing a patient with LTBI, and starting treatment. The biggest loss is in tests ordered, with an average of 86% of cascade-eligible patients not having a test ordered. The next big loss is in treatment, with an average of 40.1% of patients diagnosed with LTBI not having a treatment prescribed. An average of 46.5% of patients who started treatment did not complete. While these are big losses, these percentages are typical of the LTBI care cascade and if anything, these sites have higher percentages of patients progressing through the entire care cascade compared with other publications. These losses are why the goal of TBESC-III is to implement interventions to improve the care cascade specific to testing and treatment.

To delve further into the interventions in TBESC-III, 3 sites are implementing interventions that will be monitored to determine which are most effective and cost-effective. These interventions probably can be grouped into 4 activities. EMR modifications are changes built into the EMR to help with LTBI management. Care navigation/case management are interventions that use task shifting to help patients navigate the care cascade. Education and trainings include developing

resources to improve provider and/or patient knowledge of TB and LTBI. All 3 sites have interventions that contain elements from these first 3 activities, while 2 sites have a few additional interventions that do not fall into these categories. Samples of activities within these interventions are as follows:

EMR Modification Interventions

- Alerts to prompt providers to order an IGRA
  - Best Practices Advisory (BPA)
  - Care gap
  - Manually flag patients by pending IGRA orders
- Improvements to the EMR to make ordering easier
  - Custom built TB screening forms
  - Smart tools to help with documentation and ordering

Care Navigation/Case Management Interventions

- Nurses to follow-up on results
- Pharmacists to assist with prescribing LTBI treatment, addressing side effects, and ensuring completion
- Patient navigators to outreach to patients with positive tests
  - Provide additional LTBI education, help with barriers, and follow-up to ensure they get chest x-ray and treatment

Education/Training Interventions

- Provider trainings, updated guidelines, and updated workflows
- Site champion
- Patient education materials

Other Interventions

- Letters sent to patients notifying them they have a standing order for an IGRA, which was replaced with an EMR alert
- Cover costs of testing, CXRs, and treatment for uninsured patients

To summarize, EMR data can be used to build an LTBI care cascade. The baseline care cascade shows that a large percentage of patients are not being tested. Of those with a positive test, many are not receiving LTBI treatment. However, the TBESC-III sites have a suite of interventions to improve testing and treatment among non-US–born patients. As the study continues, monitoring of the impact of these interventions is ongoing. By the end of the study and after the interventions are evaluated, the following long-term outcomes are anticipated from TBESC-III:

- Increased availability of policy-based screening programs
- Increased percentage of non-US–born populations screened for LTBI
- Increased treatment completion for LTBI
- Decreased progression from LTBI to TB disease
- Decreased incidence of TB disease in the US

ACET Discussion: TBESC-III

Dr. Lovinger asked what explains such low prescribing of the 3HP regimen, especially since

patients prescribed 3HP had significantly higher completion rates than patients prescribed other regimens. She wondered whether that was due to slow rollout of recommendations around 3HP, isoniazid shortages, and/or widespread isoniazid intolerance.

Dr. Winglee confirmed that 3HP had the highest of the completion rates, but there is a relatively small portion in total. In fact, it is very site-specific. Some sites are prescribing a lot of 3HP and some sites are not prescribing any, which is largely driven by cost and whether insurance covers it. While there also have been a few shortages during the study, this is largely being driven by cost and clinic practice.

Dr. Loeffler said she thought the drug shortage drove down the use of 3HP at an important time. With Kaiser data, it may be possible to comment on the pharmacy piece.

Dr. Stout commented that while this fantastic work is very helpful, he was struck with start and completion rates. Historically, completion rates for 6 to 9 months of isoniazid in health department program conditions have been in the 50% to 60% range. The clinical trials of rifampin and 3HP completion rates were 80% and over 90%, respectively. The data Dr. Winglee presented are in stark contrast to that, with some of the worst completion rates he has ever seen. While useful and interesting, he asked whether she had any explanation for why the completion rates are so terrible in this large, robust, and more health system-based data compared to what has been seen historically in program level public health data. Regarding the cost-effectiveness analyses, he will be interested to see at what threshold along the care cascade doing all of this becomes not very cost-effective.

Dr. Winglee said she thought part of it would be related to the limitation around the data to which they have access. This is pharmacy data. If a patient switches pharmacies during their treatment, they will appear not to have completed even if they actually completed. There is no DOT. This is just primary care patients going in to pick up their prescriptions. At least in baseline in particular, there is not necessarily follow-up from the physicians either unless the patient presents with side effects.

Dr. Ahmed found this to be amazing work that is likely to have great long-term impact. There was a survey recently looking at who is identifying people at risk for LTBI and testing and treating them. Pediatricians were found to be one of the better groups. She wondered whether Dr. Winglee had any information on the breakout of the 4,000 pediatric patients versus the others in terms of the cascade of care. For the system that absorbed the cost of the CXRs and treatment, she wondered whether that is sustainable. If a large healthcare system took this on, they would want to see a return on investment (ROI) as well.

Dr. Winglee indicated that because they have only 1 site looking at pediatrics, they have not necessarily broken out the pediatric group specifically. That site does intend to look more closely at that group, but how the pediatric group is doing compared to the broader population has not been assessed at this point. There are plans to assess sustainability beyond the end of the project. While sustainability is certainly a concern, this was meant to be a demonstration project to determine whether covering the cost would improve rates. If the site is able to show results, their plan would be to look for other sources when the contract ends. Given that they do not have many uninsured patients, not many patients are falling into that category.

Dr. Holland asked what DTBE anticipates doing with the findings in terms of getting them adopted, expanding funding, et cetera moving forward.

Dr. Winglee said that specifically in terms of TBESC-III, the goal for the end of the study is to describe what was done, lessons learned, challenges, and the cost-effectiveness as considerations for other sites interested in replicating this. Ultimately, the goal of TBESC-III was to determine which interventions are most effective, which ones are most cost-effective, and whether that can be used to provide some guidance for other groups trying to roll this out.

Reflecting on Dr. Stout's comment about low treatment, Dr. Cattamanchi agreed with the importance of verifying whether the rates are actually that low. Conversely, when looking at trends and comparing pre- and post-intervention, the point estimates may not be valid but as long as the data collection is the same, whether there are changes post-intervention should be valid. He asked whether there are any plans to conduct any qualitative or other analyses to interview people who did not complete treatment to understand whether that was actually the case and, if so, why. He also wondered whether time trends were assessed by month or quarter to determine whether there was improvement during the pre-intervention period, and whether consideration has been given to an interrupted time series (ITS) analysis rather than a simple pre-post analysis. A concern is secular trends in terms of whether as a result of starting to work with the sites, things are improving over time and whatever changes are seen in the post-intervention period are just a continuation of those trends. If an assessment is done collapsing the entire pre- and post-intervention periods, one result will be seen. However, looking at intervals of time across the period can help to understand whether there are trends occurring and whether any changes are beyond those trends.

Dr. Winglee indicated that in addition to the EMR data, there are also the IM&E data that includes a very large qualitative component. Some sites are interviewing their patients and some sites are interviewing their providers to get their thoughts on the interventions, and how things are going, how they feel about LTBI. In addition to the simple pre- versus post-intervention care cascade, DTBE is working with its statistics team to conduct a time series analysis to determine whether there are statistical difference over time, particularly as sites implement new interventions.

Dr. Sosa noticed that there was a high amount of missing race and ethnicity data. While that is not necessarily unusual for this type of study, she wondered what DTBE was trying to do to improve the data quality for those and any other variables that would be important for this kind of study.

Dr. Winglee stressed that these data are pulled straight from the EMR data, so they are real-world data and there is not a lot that can be done to improve the data quality, particularly for some of the demographic variables. While they do run QA/QC checks to determine whether things are changing over time or there are weird values, they do not have sites checking information that is missing.

Think. Test. Treat TB Campaign

Elise Caruso, MPH, CHES
Behavioral Scientist, Communication, Education and Behavioral Studies Branch
Division of Tuberculosis Elimination
Centers for Disease Control and Prevention

Ms. Caruso provided the results of an outcome evaluation of the *Think. Test. Treat TB Campaign.* In 2020, CDC began planning this first national LTBI health communications

campaign. This campaign aims to increase awareness of LTBI primarily among people born in the Philippines and Vietnam and other non-US-born people (referred to as consumers throughout this presentation) and among the HCPs who serve them. The concept seeks to encourage consumers and HCPs alike to think about the risk factors and talk about TB, test for LTBI, and treat LTBI to prevent the development of TB disease. The campaign focused paid media and in-person community engagement activities in Seattle, Washington and Los Angeles, California locations, as well as posting materials online that were available for use nationally. The campaign used a combination of paid, earned, and CDC DTBE media to reach audiences, which included social media and a newly developed CDC webpage for the campaign. Media channels and partners included web, social media, television, and print; in-person venues such as shopping centers and clinics; community-based organizations (CBOs); and professional medical associations.

Evaluation was performed throughout the campaign process. The Communications Team in the Communications, Education, and Behavioral Studies Branch (CEBSB) led the creation and rollout of the campaign. They conducted formative evaluation activities, which informed development of campaign materials. This included focus groups with intended campaign audiences.[28] Process evaluation activities tracked engagement of the campaign during the rollout. Ms. Caruso shared a small snapshot of the process metrics used. In the first phase of the campaign between March and September 2022, the campaign garnered over 33 million impressions (e.g., number of times the campaign was advertised), over 54,000 clicks on links within the campaign advertisements, and about 35,000 materials shipped from the CDC warehouse. Since these numbers are collected, DTBE continues to track the use of campaign materials and these numbers have grown quite a bit.

This presentation focused on the results of the outcome evaluation. The outcome evaluation had 2 primary goals, which were to: 1) assess LTBI awareness, knowledge, and behavioral intentions among consumers and HCP; and 2) inform adjustments to the campaign content and strategy. Activities for process and outcome evaluations also included publishing the results for dissemination.[29] In terms of the methods used, 4 online surveys were created based on audience type and self-reported campaign exposure. The surveys were conducted in the Seattle campaign market. DTBE had a strong relationship with both Los Angeles and Seattle, but the scope had to be limited to 1 market due to the limited budget for this evaluation. The decision was made to focus on Seattle because DTBE had some pre-campaign data on exposure to LTBI in Seattle from another project. The 2 audiences for the evaluation were HCPs and consumers, which aligned with the intended audiences of the campaign. An online panel and community outreach recruitment methods were used, with an aim to sample 25 to 50 providers and 125 to 200 consumers. To be eligible to participate, HCP were required to be internal, family, or general medical physicians; nurses, nurse practitioners, physician assistants, or associates and serve a patient population composed of at least 20% non-US-born Asian persons. Consumers were required to be persons 25 to 65 years of age who were born in the Philippines or Vietnam. The consumer surveys were available in English or Vietnamese.

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[28] Parmer J, Macario E, Tatum K, Brackett A, Allen L, Picard R, DeLuca N, Dowling M. Latent tuberculosis infection: Misperceptions among non-U.S.-born-populations from countries where tuberculosis is common. Glob Public Health. 2022 Aug;17(8):1728-1742. doi: 10.1080/17441692.2021.1947342. Epub 2021 Jul 6. PMID: 34228584; PMCID: PMC8733044.

[29] Caruso E, Parmer J, Allen L, Maiuri A, Mangan J, Bouwkamp B, DeLuca N. Process and Outcome Evaluation of the Centers for Disease Control and Prevention's Think. Test. Treat TB Health Communications Campaign, United States, March-September 2022. Public Health Rep. 2025 Jan-Feb;140(1):13-21. doi: 10.1177/00333549241268644. Epub 2024 Aug 27. PMID: 39189099; PMCID: PMC11569662.

Surveys started with questions to screen for exposure to the campaign. Participants were categorized as “exposed” to the campaign if they reported seeing any of the campaign graphics shown to them. Participants were categorized as “not exposed” if they did not report seeing the campaign graphics shown to them. Survey questions were developed based on McGuire’s Communication
Persuasion Matrix and assessed exposure to the campaign, recall of information, message comprehension, perceived risk, agreement with messages, decisions and rationale related to messages, actions taken in response to the campaign, and advising others to take action. Campaign materials also were shown to participants not exposed to the campaign toward the end of the survey for additional feedback. Ms. Caruso shared samples of some of the messages used in the survey.

Moving to a high-level review of the results, the surveys were fielded from July 28, 2022 to August 22, 2022. There was a 19.3% response rate for consumers and a 15.9% response rate for providers. Of those who were eligible and started the survey, 91.5% of consumers completed it and 100% of providers completed it. There were final samples of 123 exposed consumers and 50 non-exposed consumers for a total sample of 173 consumers. For HCP, 33 were exposed and 11 were non-exposed for a total sample of 44 providers. These reflect quotas that were set for the survey to ensure that perspectives were captured from those who were exposed to the campaign in the field. There also were 4 consumer surveys completed in Vietnamese. In terms of where people saw the campaign, among consumers who were exposed to the campaign, 61.8% reported seeing the materials in their physician’s office, 58.5% on social media, and 30.9% in a newspaper or magazine. Of providers exposed to the campaign, 54.5% reported seeing the materials in a communication from the public health department, 48.4% in their workplace, and 45.5% on the CDC website. Ms. Caruso noted that although she highlighted the top 3 results, these results indicated to DTBE the utility of having a multi-pronged dissemination approach.

Consumers reported taking the following actions most often after exposure to the campaign:

- Reading through the messages (48 of 123; 39.0%)
- Looking up more information on TB (42 of 123; 34.1%)
- Scrolling through the content (40 of 123; 32.5%)

HCP reported taking the following actions most often after exposure to the campaign:

- Looking up additional information about TB (19 of 33; 57.6%)
- Scrolling through the content (14 of 33; 42.4%)
- Reviewing the patient conversation guide (10 of 33; 30.3%)
- Reading through the messages (10 of 33; 30.3%)

Consumer knowledge was assessed with a survey item “people can have inactive TB and not know it.” A higher percentage of people exposed to the campaign correctly answered “True” at 83.7% compared with those not exposed at 30%. Of consumers exposed to the campaign, 14.6% responded “not sure” and 0.8% responded “false.” Among consumers not exposed, 54% responded “not sure” and 16% responded “false.” More than half of exposed providers felt the materials most helped expand their knowledge of incidence of progression from LTBI to active TB disease (22 of 33; 66.7%) and testing options for TB (17 of 33; 51.5%). Regarding the construct of perceived risk, consumers self-reported chances of getting TB. There were slight differences in reporting no risk, high risk, and not being sure between exposed and non-exposed consumers. Notably, no exposed consumers felt that they had no risk for TB. To assess perceived relevance of the campaign, respondents were asked if they felt the campaign materials were meant for themselves. Overall, 87.3% of consumers felt the materials were meant

for themselves. About half of providers at 54.5% did not feel that they were the intended audience of the campaign and about 16% were not sure.

While not part of McGuire's Communication Persuasion Matrix, providers were asked about their current testing practices to help contextualize their responses. Almost all providers regardless of campaign exposure reported already testing patients, with 93.9% of those exposed and 90.9% of those not exposed reporting already testing for TB. This may be why some did not feel the campaign was meant for themselves. Additionally, all providers felt the campaign materials were relevant to their patient population, 95.5% felt the materials were relevant to providers who serve patients at risk for TB, and all agreed on some level that the information was important for them to know. To assess agreement with messages among consumers, consumers were asked about the importance of the information and trustworthiness of the information. Almost all consumers (91.3%) felt the information in the campaign was important for them to know, 7.5% were not sure, and 1.2% did not feel the information was important for them to know. About 70% of consumers reported trusting the information, while 29.5% were not sure and just 0.6% did not trust the information.

Looking at decisions and rationale related to the messages, among consumers, those exposed to the campaign more often reported being very likely or likely to ask their HCP about TB during their next visit compared with those not exposed at 87.8% and 64%, respectively. When providers were asked how likely they are to talk with patients about their TB risks, 97% of providers exposed to the campaign and 90.9% of providers not exposed reported being very likely or likely to talk with patients about their TB risks. Just over half of exposed providers and just under half of non-exposed providers reported that they were very likely or likely to increase TB testing in their practice. When asked in a follow-up question about why they would not increase testing or were not sure, most said it was because they already were testing patients for TB. In terms of how likely providers were to recommend treatment for LTBI, 84.8% of exposed providers and 72.7% of non-exposed providers reported the likelihood to recommend treatment for LTBI. In all of these instances, intention to engage in TB prevention behaviors encouraged by the campaign were more often reported by those who were exposed to it. Fewer than half of healthcare providers (19 of 44; 43.2%) reported being very likely or likely to recommend to their colleagues that they test and treat patients for LTBI, 21 (47.7%) were unsure, 3 (6.8%) were not likely, and 1 did not respond. This signaled to DTBE an area that they could think about for future education or messaging efforts.

These results are subject to a few limitations. Due to the short amount of time from when the campaign was live to when the survey was fielded, participants might not have had time to engage in prevention behaviors and behavior change was not measured. Additionally, DTBE had a limited budget and limited scope, so this was a small, localized evaluation that may not reflect perspectives of other campaign audience members or the general public. Survey questions were closed-ended for the most part, so nuances of experiences may not have been captured. As with most surveys, the results are subject to biases of people wanting to answer in socially desirable ways or misremembering from the past. Other public health activities focused on TB could have influenced participants, confounding the effects. Finally, it was not feasible to test all campaign materials in this evaluation.

After these initial provider and consumer materials were disseminated, DTBE continued to fund the provider portion of the campaign for an additional year that included creating updated materials. Although there is no dedicated funding currently, CDC continues to promote aspects of the campaign through no-cost channels. This includes tracking process metrics of online materials and CDC warehouse orders, which indicate that the campaign continues to resonate with audiences. As of September 1, 2024, for example, there have been 168,103 items shipped from the CDC warehouse since campaign inception. DTBE maintains an active partnership and shares resources via social media. There are plans to develop and refresh campaign assets with

internal mechanisms, such as social media and translating materials into additional languages; maintain a roadmap for scale-up of the campaign is done in case there is future funding; and provide TA and consultation to state and local TB programs and other partners on using the campaign.

In terms of the campaign budget by breakdown of fiscal year, from October 1, 2021, to September 30, 2022, the first year of the campaign that the outcome evaluation assessed included focused campaign dissemination in Seattle and Los Angeles and national distribution of campaign resources for consumers and HCP for a total budget of about $1,260,000. The second year of the campaign included the development of supplemental materials for the HCP audience for a total budget of about $750,000. The 2021-2022 campaign evaluation budget was approximately $200,000.

To summarize, the evaluation of the first large-scale LTBI communications campaign in the US demonstrated the importance of communicating with key audiences about LTBI. Continuing engagement with providers and consumers about LTBI to encourage testing and treatment is integral to eliminate TB in the US. As mentioned earlier, these evaluation results have been published for those interested in reading them for more information.

ACET Discussion: *Think. Test. Treat TB Campaign*

Dr. Sosa said that while she was not in a state that was targeted for this campaign, they have found it very useful and helpful in talking with providers and sharing it as a resource.

Dr. Loeffler posted a link to the paper, “Process and Outcome Evaluation of the Centers for Disease Control and Prevention's *Think. Test. Treat TB* Health Communications Campaign, United States, March-September 2022”[30]

Dr. Caballero commented that TEA has found the campaign materials to be a vital supplement in its community engagement efforts.

Workgroup (WG) Updates

Laboratory Developed Test WG (LDTWG)

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

Dr. Glover provided an update on the ACET FDA LDTWG meeting in November 2024. To recap the charge of the WG, the LDTWG was 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 FDA’s Proposed Rule regarding LDTs. The focus of the LDTWG is to continue to gather and clarify information regarding the LDT Rule and understand outstanding questions once implementation guidance is published. The LDTWG met on November 22, 2024, to provide an overview of how APHL is working to provide resources to aid PHLs in meeting the new requirements regarding the FDA LDT Rule. The WG also discussed clinician engagement with laboratories as it pertains to LDTs.

[30] https://pubmed.ncbi.nlm.nih.gov/39189099/

The FDA phaseout policy also was reviewed. FDA is phasing out its general enforcement discretion approach for LDTs in stages, so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other in vitro diagnostics (IVDs). That is, FDA's expectations for compliance will generally be the same, with various milestone dates that must be met. This begins with the May 6, 2025, phaseout timeline that includes medical device reporting, correction and removal reporting, and quality system requires regarding complaint files. The phaseout timeline beginning May 6, 2026 will address requirements not covered in the other stages, including establishment of restrictions and device listing, labeling requirements, and investigational requirements. The phaseout deadline beginning May 7, 2027 will address quality system requirements. For LDTs, FDA will expect compliance with design controls under §820.30; purchasing controls (including supplier controls under §820.50; acceptance activities (receiving, in-process, and finished device acceptance) under §820.80 and §820.86; CAPA under §820.100; and records requirements under part 820, subpart M. The phaseout policy timeline beginning November 6, 2027 will include premarket review for high-risk IVDs. The phase out policy timeline that begins May 6, 2028 will include premarket review for moderate and low risk IVDs, with most low risk IVDs being exempt from premarket review.

The FDA released webinars to address the various components of phases and requirements of the LTD Rule beginning May 14, 2024. The December 3, 2024 webinar that occurred during the ACET meeting between 1:00 to 2:00 PM focused on registration and listing requirements for IVDs and LDTs. Presentations, printable slides, and a transcript will be available on the FDA webpage after the presentation.

One of the updates that was provided to the ACET LDTWG regarded the formation of the LDT Task Force by the APHL, which was approved by their Board on August 1, 2024. The LDT Task Force is composed of quality and subject matter experts (SMEs) to guide APHL staff in developing useful materials that public health laboratories can use to meet the FDA requirements. The LDT Task Force is composed of Infectious Disease (ID), Newborn Screening (NS), and Cross-Discipline (CD) subgroups. The current focus of materials being developed by the APHL LDT Task Force focus on meeting the May 6, 2024 deadlines for medical device reporting, correction and removal reporting, and quality system requirements regarding complaint files.

Some of the considerations the ACET LDTWG discussed included awaiting implementation guidelines from FDA with specific details that complement the materials that have been presented in the various FDA webinars thus far.

In terms of next steps, the ACET LDTWG will continue to touch base as more details are learned. Laboratories will continue to work to address the Phase 1 deadline beginning May 6, 2025. The WG will highlight ways in which clinicians can leverage existing avenues to communicate with leadership of laboratories whose LDTs they utilize to manage their TB patients and the importance of the testing provided by these LDTs and laboratories.

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 DSWG met on September 16, 2024 and October 7, 2024. During the October meeting, they heard from Dr. Brenda Waning, who is the Chief of the Global Drug Facility (GDF), which is an important worldwide resource that is hoped will be a resource for Americans in the future.

The DSWG researched mechanisms for accessing the GDF for procurement of TB drugs in shortage that are not available in the US. One approach as a pilot would be to focus on pediatric formulations first. Given that there are currently very few pediatric TB cases in the US, there is a very small market for palatable TB formulations of medication. Many parts of the world have access to palatable and fixed drug combinations for pediatric TB. In their conversations with the Director of the GDF, the DSWG learned about how evaluation of facilities is often done side-by-side with FDA and WHO in those places where the medications are used in both markets. There are some circumstances in other parts of the world that have successfully used regulatory pathways to access these medications supplied by the GDF for the benefit of their patients.

During the process of this research, the DSWG also learned that there is a relatively new role in HHS called the Supply Chain and Resilience Coordinator. Perhaps the ACET team would be interested in inviting this individual to attend an ACET meeting in 2025 to learn firsthand about the challenges of TB drug shortages, particularly regarding the IV fluid shortage and how important it is for specific patient populations.

With all of this in mind and given that ACET's scope in recommendations is limited to CDC and HHS, the DSWG proposed the following ACET Actions:

1. **Add Oral TB Drugs to the List**
   We suggest addition of the 4 most common oral TB drugs, specifically isoniazid, rifampin, pyrazinamide and ethambutol (including the most frequently used formulations and strengths) to the FDA Essential Medications List. This list was developed to "ensure sufficient and reliable, long-term domestic production of these products, and to minimize potential shortages." Inclusion on the list would prioritize protection of TB medications during shortages and supply chain challenges.

2. **Explore a Path Forward**
   We strongly encourage exploring a mechanism for accessing the Global Drug Facility for procurement of TB drugs in shortage or otherwise not available in the US.

3. **Discuss the Issue**
   We formally invite the HHS Supply Chain and Resilience Coordinator to attend one of our biannual ACET meetings to learn firsthand about the challenges of TB drug shortages and work with ACET to develop solutions.

ACET Discussion: WG Updates

Dr. Sosa requested that the ACET think overnight about what they would like to do with these 2 WGs, and whether the ACET would like to vote on the proposed ACET Actions put forward by Dr. Loeffler from the DSWG.

Day 1 Wrap-Up and Adjourn

With no further business posed, Dr. Winston officially adjourned the first day of the meeting at 4:30 PM ET. The ACET stood in recess until 10:00 am ET on December 4, 2024.

December 4, 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 December 4, 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 18 voting members and *ex-officio* members in attendance constituted a quorum for ACET to conduct its business on December 4, 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.

Recap of Day 1

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

Dr. Sosa recapped the first day of the meeting, recalling that the ACET heard some interesting and informative presentations. She was particularly excited to hear about the coming improvements to national TB surveillance, especially as they relate to molecular surveillance. That is an area that she has had the pleasure and privilege of working on throughout her career, so it was exciting to see how far this has come and where it is going with WGS for TB and how that affects TB outbreak investigations. She also appreciated hearing about the formation of the WG by DTBE to consider guidance related to isolation in congregate settings, which is a great step forward in terms of how patients can be helped in those settings. She also enjoyed the updates on the TBESC-III study and the *Think. Test. Treat Campaign*. Even though the *Think.*

Test. Treat Campaign was not necessarily focused for a state like Connecticut, it has been useful and is an important tool that they have used very often when they receive questions from HCP. People have enjoyed using this, so thought needs to be given to how to continue to improve and use it, especially in terms of LTBI. For this session, Dr. Sosa thought ACET should consider the work of the 2 existing WGs from whom they heard updates the previous day in terms of whether they want those WGs to continue and if so, on what they should focus. Consideration also needs to be given to how to move forward with the proposed ACET Actions from the DSWG. In addition, ACET sends a biennial letter to the HHS Secretary. That letter is due in 2025, so there should be a discussion about how ACET should approach that letter.

ACET Discussion: Recap of Day 1

In terms of the addition of the molecular data to the RVCT, Dr. Chen noted that major reference laboratories differ in how they report out some mutations. That will be reflected again in the data that are collected, so she thought it was worth discussing whether the laboratories have considered unifying their reporting process for some of these mutations. This has mostly to do with the fact that everyone is using the WHO catalogue, and some mutations are listed as "uncertain" and laboratories differ on how they report that. Perhaps during the next ACET meeting, someone from the laboratories could discuss this. Consideration needs to be given to the fact that this will affect the data collection in the long-run and there will need to be some expansion or ability to capture future mutation data as it changes over time.

Dr. Rowlinson, APHL Liaison, said this is definitely something that has been discussed and there are overlaps. The complexities of it are that people are using different testing methods and reports. Looking at a molecular report from CDC versus from her laboratory in Florida, there are definitely differences. She would be happy to take this back to APHL, which has a TB Subcommittee that works on these types of issues, to find out whether they would be interested in pulling something together for the next ACET meeting.

Dr. Glover agreed that it does relate to the different methods that are being used. The drugs and mutations and mutations that were validated also affect what can be reported back, so differences will be seen in the scope. The way that molecular testing is taking place, the laboratory is fragmented. A molecular laboratory may be doing all of the work, so the TB specimen is being deactivated and brought into a molecular laboratory outside of the TB laboratory, so those staff are actually performing the TB work and funding for that may be through various mechanisms. His concern is about how to build and ensure that the TB workforce are prepared to take on and sustain that work, and end-users outside the laboratories within the TB program staff are trained to consume those data. This is something the WG could take on.

Dr. Chen thought better understanding the compare, contrast, and rationale for the differences would be helpful. People could brainstorm on how to inform the user end better on why it is different with the different methodologies. Right now, everyone just looks at it as resistant, sensitive, and uncertain but they know that there is a difference. Many people are going to the catalogue and making decisions themselves because it is not clear from the various reports they receive.

In terms of maintaining the TB workforce, Dr. Sosa commented that it was not lost on her that the advances that were discussed in terms of moving more toward molecular work in TB laboratories instead of culture-based techniques is a shift not only in the type of work being done, but also that they need less people to do the same work. Consideration must be given to the impact to funding.

Public Comment

No public comments were provided.

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. Ahmed and seconded by Dr. Loeffler to accept the minutes from the June 2024 ACET meeting. With no further discussion or changes, the motion to accept the minutes as written carried unanimously with no abstentions or opposition.

Given that the first day of the meeting was running ahead of schedule prior to the lunch break, this business item was completed on the first day.

Business Item 2: Drug Shortages

Dr. Loeffler recapped that consideration of whether the DSWG should continue and reviewed the proposed recommendations. DSWG proposed the following ACET Actions:

1. We suggest addition of the 4 most common oral TB drugs, specifically isoniazid, rifampin, pyrazinamide and ethambutol (including the most frequently used formulations and strengths) to the FDA Essential Medications List. This list was developed to "ensure sufficient and reliable, long-term domestic production of these products, and to minimize potential shortages." Inclusion on the list would prioritize protection of TB medications during shortages and supply chain challenges.

2. We strongly encourage exploring a mechanism for accessing the GDF for procurement of TB drugs in shortage or otherwise not available in the US. One approach would be to focus on pediatric formulations first."

3. We formally invite the HHS Supply Chain and Resilience Coordinator, in whatever form is appropriate, to attend one of our biannual ACET meetings to learn firsthand about the challenges of TB drug shortages and work with ACET to develop solutions.

If approved, the ACET Actions would be submitted to HHS in the form of a letter and would be in follow-up to the letter that ACET sent in June 2023. A draft letter outlining the proposed ACET Actions was posted for discussion.

ACET Discussion: Drug Shortages

Dr. Loeffler pointed out that in the last letter, which the DSWG did not pursue again, was the idea that testing or treatment for LTBI is considered in a special category in the Centers for Medicare & Medicaid Services (CMS).

Dr. Sosa indicated that that was a separate letter that was sent to CMS.

Dr. Loeffler recalled that when FDA attended ACET meetings in the past, they articulated FDA approval is required by law. In the context of the Bicillin® shortage and the syphilis surge, there was access to drugs from France. While that is exceptional, she wondered if that might be a model for something that could be done in the future. When the DSWG met with the Director of the GDF, she mentioned that other entities have approached her from academia and advocacy to ask her about the same idea. WHO would like for all countries to be able to purchase from the GDF, which has made such an explosion of availability of affordable and safety drugs. They also have supply chain interventions to keep supplies within their expiration dates. The original idea was to have it available for low- and middle-income countries, but WHO seems to have shifted somewhat such that high-income countries are accessing it for at least specific situations that are problematic in their own countries. The GDF Director told the DSWG that in her personal opinion, it would take a full-time person who makes it their job to advocate for this.

Dr. LoBue confirmed that the ACET could direct recommendations to FDA as part of HHS.

Dr. Sosa recalled that because the recommendations touched different parts of HHS and the previous letter went to the HHS Secretary, that was the thinking for this letter as well.

Comments on the draft letter to HHS outlining the proposed ACET Actions:

- The letter is very thoughtful and the ACET should vote to move it forward.
- If the new Supply Chain Coordinator is invited, perhaps other key people should be in the room (e.g., GDF Director, FDA representative, et cetera). A WG is not needed to invite these individuals to present to ACET.
- There are some contractual components specifically written into the contracts with the GDF. Even if ACET makes some headway, there will be limitations.
- There does not seem to be any downside to asking for these actions in the letter to HHS.
- There are a few references that could be outlined.
- Instead of limiting the second action to drugs, perhaps diagnostics should be added as well. There is going to be an explosion of approved diagnostics available through the GDF over the next couple of years. The US is going to be behind in molecular tests for diagnosis and sequencing-based assays for drug resistance compared to the reset of the world.
- The ACET made the decision to keep the pediatric formulation idea, but not to include diagnostics because that might be distracting.
- The diagnostics in the pipeline for children, especially swab-based tests, are going to be huge for children who right now require induction, gastric aspirates, et cetera. Even with a focus on pediatrics, the diagnostics piece is important given what is coming out worldwide.

- One suggestion would be to address that separately. As it is, there are already 3 items in this letter. Diagnostics could be distracting, but they could address it in a separate letter or other avenue. Part of this is just getting HHS to think about this.
- Based on the cascade of care results presented on the first day, diagnostics always seem to get short-changed. It is not clear how this would be addressed separately.
- Perhaps another WG needs to be stood up to address diagnostics, and someone could be invited to talk about what is in the pipeline, the gaps, et cetera to help make the case for better diagnostics in the US that are currently being developed and studied closely by a lot of US research groups that could be beneficial to programs in the US. Diagnostics could be included in this letter, and it would not be that much more, or another letter could be written next year.
- Instead of standing up a Diagnostics WG, perhaps the DSWG could continue but shift to a Diagnostics WG.
- One suggestion to open the door to that idea would be to rephrase the second bullet to read, "We strongly encourage exploring a mechanism for accessing the GDF for procurement of TB drugs **and diagnostics** in shortage or otherwise not available in the US. One approach would be to focus on pediatric formulations **as a pilot**."
- Diagnostics also could be a topic in the Biennial Letter.
- From the patient perspective, having access to the best medicines for TB treatment is such a priority. To not be able to participate in a regimen because there is no rifapentine is a massive disadvantage for patients. The issue and need for access to medicines will not go away if the DSWG is discontinued. Perhaps the letter is enough for now versus additional interventions the WG could consider.
- If the WG continues or shifts focus, ACET has to be clear about what they want the WG to do. They can always sunset the WG and bring it back in the future or start a new WG focused on diagnostics.

Vote #1: Drug Shortages
A motion was properly placed on the floor by Dr. Ritger and seconded by Dr. Chen that ACET recommends the 3 Action Steps proposed by the DSWG as stated, with the changes proposed to the second bullet to read, "We strongly encourage exploring a mechanism for accessing the GDF for procurement of TB drugs **and diagnostics** in shortage or otherwise not available in the US. One approach would be to focus on pediatric formulations **as a pilot**." The motion carried unanimously with no abstentions or opposition.

Vote #2: Drug Shortages
A motion was properly placed on the floor by Dr. Loeffler and seconded by Dr. Ritger to sunset the DSWG. The motion carried unanimously with no abstentions or opposition.

Business Item 3: Laboratory Developed Tests

Dr. Glover pointed out that they need to find out what is going to happen in January 2025 with the new Administration in terms of their priorities around the FDA LDT rule. In addition, the FDA guidance on the rule has not yet been released. While it is anticipated to be released by the end of 2024, it is not clear whether this will occur. While there are other issues, those are the 2 looming topics for him. How those shake out will determine whether the ACET LDTWG needs to continue.

ACET Discussion: Laboratory Developed Tests

Ms. Condit indicated that the LDTWG is already approved through June 2025, so a vote is not needed on an action to extend.

Dr. Chen suggested inviting someone to the next meeting to discuss the status and challenges of diagnostics.

Dr. Glover agreed that this could be helpful. In terms of the discussion about the potential for standing up a Diagnostics WG, he pointed out that in order to use some of the diagnostics in the US, they would have to be validated. That falls back into the LDT Rule. If a Diagnostic WG is stood up, they may end up working with the LDTWG or the LTDWG may need to morph into the Diagnostics WG or some of the LTDWG members would need to join the Diagnostics WG. In trying to solidify "the ask," diagnostics are desired that would be submitted for FDA approval in the US and not have the burden on laboratories to bring in diagnostics, validate them, and submit them to FDA for approval. There also needs to be discussion about partnering with US manufacturers about obtaining the approval they need for various populations. Perhaps some manufacturers could be invited to speak to ACET about the issues and challenges.

Dr. DeRoos pointed out that artificial intelligence (AI) is being used for diagnoses in Europe.

Business Item 4: Biennial Letter

Dr. Sosa indicated that the Biennial Letter to HHS is due in 2025. While she recognized that it is her responsibility as the Chair to develop, she would appreciate input on the topics ACET would want to highlight in such a letter. The previous Chair had a WG for the letter and Dr. Sosa would welcome a WG to ensure that she represents the views of ACET accurately.

Vote #1: Biennial Letter
A motion was properly placed on the floor by Dr. Sosa and seconded by Dr. Ritger to create a WG to determine the topics for the Biennial Letter. The motion carried unanimously with no abstentions or opposition.

December 2024 ACET Recommendations	Action
1) <u>Drug Shortages</u>	ACET voted unanimously on the following recommendations pertaining to drug shortages: 1. ACET recommends the addition of the 4 most common oral TB drugs, specifically isoniazid, rifampin, pyrazinamide and ethambutol (including the most frequently used formulations and strengths) to the FDA Essential Medications List. This list was developed to "ensure sufficient and reliable, long-term domestic production of these products, and to minimize potential shortages." Inclusion on the list would prioritize protection of TB medications during shortages and supply chain challenges. 2. ACET recommends that CDC explore a mechanism for accessing the GDF for procurement of TB drugs and diagnostics in shortage or otherwise not available in the US. One approach would be to focus on pediatric formulations as a pilot. 3. ACET recommends that CDC formally invite the HHS Supply Chain and Resilience Coordinator, in whatever form is appropriate, to attend one of ACET's biannual meetings to learn firsthand about the challenges of TB drug shortages and work with ACET to develop solutions.
2) Biennial Letter	ACET voted unanimously to stand up a Biennial Letter WG to determine the topics for the letter due in 2025.

Business Item 5: Future Agenda Items

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

- Give further consideration to the possibility of standing up a Diagnostics WG.
- Consider inviting manufacturers to speak to ACET about the issues and challenges of obtaining the approval they need for diagnostics for various populations.
- Drug shortages will continue to be a topic, so there needs to be a discussion about the letter that needs to be finalized and submitted, the recommendations for that, and ideas for who should be invited to a future ACET meeting to talk about drug shortages.
- Further discuss LDT implementation guidance.
- Potentially continue work on congregate settings (nursing homes, shelters, corrections).
- Discuss the isolation experience, especially by TB patients and the impacts on mental health and potentially trying to collect personal stories or comments about how isolation or delays in diagnosis affected individual patients.
- Consider inviting the American College of Physicians (ACP) to discuss administrative testing for TB and LTBI.
- Discuss pregnancy in terms of severe disease and female genital urinary TB.
- The public health infrastructure was discussed previously and during this meeting in terms of what will be happening with the new TB cooperative agreement and trying to collect some information and touching on the laboratory.
- It would be beneficial to hear about post-TB sequelae in terms of how that is a burden and impacts healthcare in the US.

- The next meeting might be a good time to hear back from research focus groups from TBTC and/or other major funding groups on future directions and research priorities for TB.
- Consider having someone present on repeat testing in low-risk settings.
- It is important to keep a focus on the rising TB rates in the US, the drivers behind those, and whether there are any shifts in resources or approaches to address that.
- An update on the TB workforce would be beneficial.

ACET Discussion: Future Agenda Items

Mr. Watts reported that he followed up on the Congregate Settings WG before they disbanded. There was not enough on which to follow up, so this work would have to start afresh. He was not sure he was ready to recommend that yet before doing more work, especially following up internally at his agency and with CDC on some of the data about people experiencing homelessness and their prevalence and incidence rates.

Dr. Rhodes recalled that during the last Administration, there was a huge push from outside entities and stakeholders to decrease segregate housing with isolation. That also falls into medical isolation. The corrections setting represents a huge captive audience that offers a very good opportunity to treat and stop TB without having to worry about people getting medications. Unfortunately, the recommendations always lag behind. It would be beneficial to keep corrections in the forefront of people's minds.

Dr. Ahmed said that in line with working toward treatment of TBI and considering diagnostic stewardship, she is still puzzled by recommendations from societies for use of TBI screening with low risk, such as colleges requiring it for athletes. She learned recently that the GI societies want repeat testing on patients who go on biologicals. She wondered if perhaps this could be collective addressed or have someone from the American College Association and/or GI. There are likely to be other pockets where this is happening.

Dr. Loeffler said she thought that inviting the most impactful individuals to ACET meetings has the most value.

Ms. O'Brien indicated that We Are TB members would be happy to provide isolation experiences. There are members who can speak to hospitalization and other "congregate settings."

While post-TB sequelae and pregnancy in terms of severe disease and female genital urinary TB are important, it is not clear how ACET would be impactful. This seems more like an NTCA topic.

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 and informative meeting and emphasized that she was looking forward to the work of the committee over the next few months.

Dr. Winston thanked everyone for their participation, discussion, time and contributions. She reminded everyone that the next ACET meeting will be in June 2025, with planning underway to select the specific date based on polling of members regarding availability and preference for a virtual or in-person meeting. She reminded members who are new or newish to be on the lookout for an invitation to orientation.

With no further discussion or business brought before ACET, Dr. Winston officially adjourned the meeting at 11:15 PM on December 4, 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. Adithya Cattamanchi
Dr. Lisa Chen
Dr. William Glover
Dr. Kelly John Holland
Dr. Ann Loeffler
Dr. Kathleen Ritger
Dr. Jason Stout

ACET Members Absent

N/A

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

Mr. Stephen Martin
National Institute for Occupational Safety and Health

CDR Tara Rhodes
Bureau of Prisons

ACET *Ex-Officio* Members Absent

Dr. Gary Rosselle
Department of Veterans Affairs

Dr. David Weissman (Alternate)
National Institute for Occupational Safety and Health

ACET Liaison Representatives Present

Ms. Valerie Adelson
American Thoracic Society

Mr. Jeffrey Caballero
Association of Asian Pacific Community Health Organizations

Mr. Jason Cummins
National Tuberculosis Coalition of America, INC.

ACET Liaison Representatives Present (continued)

Dr. Charles Daley (Alternate)
American Thoracic Society

Dr. Jonathan Golub
International Union Against TB and Lung Disease, North America Region

Tenzin Kunor
RESULTS

Mx. Elizabeth Lovinger
Treatment Action Group

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

Ms. Kate O'Brien
We are TB

Dr. Susan Ray
Infectious Disease Society of America

Dr. Marie-Claire Rowlinson
Association of Public Health Laboratories

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

Dr. Sylvie Stacy
National Commission on Correctional Health

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

Deborah Brown
American Lung Association

Dr. Amee Patrawalla
American College of Chest Physicians

Dr. Robert Benjamin
Stop TB USA

Dr. Mayleen Ekiek
Pacific Island Health Officers Association

Dr. Naveen Patil
Association of State and Territorial Health Officials

Dr. Wendy Thanassi
American College of Occupational and Environmental Medicine

Dr. Lornel Tompkins
National Medical Association

ACET Designated Federal Officer

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

Federal Representatives

Leeanna Allen
Carissa Bisnath
Martha Boisseau
Kevin Borden
Joe Caldwell
Wendy Carr
Terence Chorba
Jeffrey Chrismon
Marah Condit
Tracina Cropper
Tracy Dalton
Nick Deluca
Darian Diepholz
Maria Galvis
Neela Goswami
Elisha Hall

Federal Representatives (continued)

Kathleen DeRoos

Karin Hopkins
Peri Hopkins
Reid Hogan Yarbro
John Jereb
Ronyell Jones
Megan Keaveney
Kathryn Koski
Awal Khan
Chee Lam
Lauren Lambert
Yamileth Lionetti
Philip LoBue
Emily Maass
Suzanne Marks
Susan McClure
Clint McDaniel
Jonathan Mermin
Meredith Moore
Selma Moore
Caroline Morrison
Michele Owen
John Parmer
Shameer Poonja
Drew Posey
Robert Pratt
Sandy Price
Caitlin Reed
Audilis Sanchez
Maria Sessions
Kim Skrobarcek
Kevin Taylor
Kathleen Weitzner
Carla Winston
Sade Wood
Chitvan Yadav
Keming Yuan

Guest Presenters

Elise Caruso, MPH, CHES
CAPT Jessica Clark, MPH, BSN, RN, CCHP
Jamie Posey, PhD
CDR Rebekah Stewart, PhD, MPH, FNP
Jamie Posey, PhD
Kathryn Winglee, PhD
CDR Jonathan Wortham, MD, FAAP

Members of the Public

Mukta Deia
Diane Fortune
Donald Franklin
James Gaensbauer
Daniela Ingram
Leiann Keuth
Amy Painter
Marco Salerno
James Sunstrum
Riana Tadeo
Alexander Tin
Stephanie Wallace
Donna Wegener

Attachment 2: Glossary of Acronyms

Acronym	Definition
ACET	Advisory Council for the Elimination of Tuberculosis
AMD	Advanced Molecular Detection
AMR	Antimicrobial Resistance
AoC	Assurance of Confidentiality
APHL	Association of Public Health Laboratories
AR Lab Network/ ARLN	Antimicrobial Resistance Laboratory Network
ASC	Analytic Steering Committee
ASTHO	Association of State and Territorial Health Officials
ATS	American Thoracic Society
BDQ	Bedaquiline
BOL	Michigan Bureau of Laboratories
BOP	Bureau of Prisons
BPA	Best Practices Advisory
CBO	Community-Based Organization
CBO	Congressional Budget Office
CDC	Centers for Disease Control and Prevention
CDPH	Chicago Department of Public Health
CDPH	California Department of Public Health
CEBSB	Communications, Education, and Behavioral Studies Branch
CLIA	Clinical Laboratory Improvement Amendment
CMS	Centers for Medicare & Medicaid Services
CoAg	Cooperative Agreement
CoE	Center of Excellence
COI	Conflict of Interest
CR	Continuing Resolution
CXR	Chest X-Ray
DC	District of Columbia
DFO	Designated Federal Official
DHHA	Denver Health and Hospital Authority
DHP	Division of HIV Prevention
DHQP	Division of Healthcare Quality Promotion

Acronym	Definition
DMI	Data Modernization Initiative
DNA	Deoxyribonucleic Acid
DoD	Department of Defense
DOJ	Department of Justice
DOT	Directly Observed Therapy
Doxy PEP	Doxycycline Postexposure Prophylaxis
DST	Drug-Susceptibility Testing
DSTDP	Division of STD Prevention
DSWG	Drug Shortages WG
DTBE	Division of Tuberculosis Elimination
DVH	Division of Viral Hepatitis
ED	Emergency Department
EHE	Ending the HIV Epidemic
EHR	Electronic Health Record
EHR	Electronic Health Record
ELC	Epidemiology and Laboratory Capacity
ELR	Electronic Laboratory Reporting
ERS	European Respiratory Society
ET	Eastern Time
FACA	Federal Advisory Committee Act
FDA	(United States) Food and Drug Administration
FRN	Federal Register Notice
GDF	Global Drug Facility
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
HCP	Healthcare Providers/Professionals
HCV	Hepatitis C Virus
Hep	Hepatitis
HHS	(United States) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HUD	(United States Department of) Housing and Urban Development
ICE	(United States) Immigration and Customs Enforcement
ICHS	International Community Health Services
IDSA	Infectious Diseases Society of America
IGRA	Interferon-γ Release Assay
IHSC	Health Service Corps
INH	Isoniazid
IT	Information Technology
ITAP	Independent Test Assessment Program
ITS	Interrupted Time Series
IVDs	In Vitro Diagnostics
KPNC	Kaiser Permanente of Northern California

Acronym	Definition
LDT	Laboratory Developed Test
LDT WG	Laboratory Developed Test Workgroup
LHD	Local Health Department
LTBI	Latent Tuberculosis Infection
MDR-TB	Multidrug-Resistant Tuberculosis
MENA	Middle Eastern or North African
MMG	Message Mapping Guide
MMWR	*Morbidity and Mortality Weekly Report*
MSA	Metropolitan Statistical Area
MSM	Men who have Sex with Men
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
NBS	NEDSS Base System
NCBI	National Center for Biotechnology Information
NCHHSTP, the Center	National Center for HIV, Viral Hepatitis, STD and TB Prevention
NCSD	National Coalition of STD Directors
NEDSS	National Electronic Disease Surveillance System
NEEMA	NCHHSTP Epidemiologic and Economic Modeling Agreement
NEMS	North East Medical Services
NHANES	National Health and Nutrition Examination Survey
NHCHC	National Health Care for the Homeless Council
NIC	National Institute of Corrections
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NNDSS	National Notifiable Diseases Surveillance System
NOFO	Notice of Funding Opportunity
NTCA	National Tuberculosis Coalition of America
NTCA	National Tuberculosis Controllers Association
NTMSC	National Tuberculosis Molecular Surveillance Center
NTSS	National TB Surveillance System
NTSS-CR	National TB Surveillance System Case Report
OGC	Office of General Counsel
OGS	Office of Grants Services
OHE	Office of Health Equity
OMB	Office of Management and Budget
OS	Office of Science
OSQLS	Office of Science Quality and Library Services
OTIS	Online TB Information System
PCP	Primary Care Providers

Acronym	Definition
PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PHIN	Public Health Information Network
PHLs	Public Health Laboratories
PHSKC	Public Health - Seattle & King County
PICO	Population, Intervention, Comparison, Outcomes
POC	Point-of-Care
PRA	Paperwork Reduction Act
PrEP	Pre-Exposure Prophylaxis
PWID	People Who Inject Drugs
PWTB	People With TB
PZA	Pyrazinamide
QA/QC	Quality Assurance/Quality Control
QFT	QuantiFERON
RADx®	Rapid Acceleration of Diagnostics
RCT	Randomized Controlled Trial
RIF	Rifampin
RNA	Ribonucleic Acid
ROI	Return on Investment
RPT	Rifapentine
RVCT	Report of Verified Case of TB
SCDHEC	South Carolina Department of Health and Environmental Control
SHIPS	Scale-up of HIV Prevention Services in Sexual Health Clinics
SME	Subject Matter Expert
SSP	Syringe Services Program
SSuN	STI Surveillance Network
STD	Sexually Transmitted Diseases
STI	Sexually Transmitted Infections
TA	Technical Assistance
TB	Tuberculosis
TB GIMS	Tuberculosis Genotyping Information Management System
TBESC	Tuberculosis Epidemiologic Studies Consortium
TBLISS	TB Latent Infection Surveillance System
TBTC	Tuberculosis Trials Consortium
TEA	Tuberculosis Elimination Alliance
tNGS	Targeted Next Generation Sequencing
UCSF	University of California, San Francisco
US	United States
WG	Working Group
wgMLST	Whole-Genome Multilocus Sequence Typing
WGS	Whole Genome Sequencing

Acronym	Definition
WHO	World Health Organization
XDR-TB	Extensively Drug-Resistant TB

Attachment 3: ACET Biennial Letter

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

Robert Belknap, MD
Chair
Advisory Council for the Elimination of Tuberculosis
1600 Clifton Road
Atlanta, GA 30329

Dear Dr. Belknap:

Thank you for the Centers for Disease Control and Prevention (CDC) Advisory Council for the Elimination of Tuberculosis (ACET) recommendations to the Department of Health and Human Services (HHS) regarding the U.S. government's response to drug shortages.

HHS is committed to working with the CDC and other HHS operating divisions to continue progress toward Tuberculosis (TB) elimination. In particular, we understand the importance of equitable access to TB evaluation, diagnostic testing, and treatment for all people.

HHS appreciates the ongoing work of ACET to inform and guide the federal government towards this common goal and welcomes any additional comments or suggestions that ACET may have.

Thank you for your interest in this important public health matter.

Sincerely,

Xavier Becerra

Cc:
Dr. Jonathan Mermin, Director, National Center for HIV,
Viral Hepatitis, STD, and TB Prevention, CDC
Carla Winston, ACET Designated Federal Officer
ACET Members

Attachment 4: ACET Drug Shortage Resolution Response

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

Robert Belknap, MD
Chair, Advisory Council for the Elimination of
Tuberculosis
1600 Clifton Road
Atlanta, Georgia 30329

Dear Dr. Belknap:

Thank you for the Centers for Disease Control and Prevention (CDC) Advisory Council for the Elimination of Tuberculosis (ACET) recommendations to the Department of Health and Human Services (HHS) regarding the U.S. government response to drug shortages.

HHS recognizes the impact of drug shortages on infectious diseases of public health importance, including tuberculosis (TB), and is committed to addressing shortages affecting TB treatment. I appreciate the critical role that ACET plays in keeping us informed of potential issues that affect or could affect TB prevention and treatment.

Thank you for your interest in this important public health matter.

Sincerely,

Xavier Becerra

Cc:
Dr. Jonathan Mermin, Director, National Center for HIV,
Viral Hepatitis, STD, and TB Prevention, CDC
Carla Winston, ACET Designated Federal Officer
ACET Members

Attachment 5: ACET CMS NCD for LTBI Letter, Page 1

ACET

Advisory Council for the Elimination of Tuberculosis

October 4, 2024

The Honorable Xavier Becerra
Secretary
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Mister Secretary:

The Advisory Council for the Elimination of Tuberculosis (ACET) provides advice and recommendations regarding the elimination of tuberculosis (TB) in the United States to the Secretary of HHS, the Assistant Secretary of HHS, and the director of CDC. The members of ACET are writing to you to request that the Centers for Medicare and Medicaid Services (CMS) make a National Coverage Determination (NCD) in favor of latent TB infection (LTBI) screening using interferon gamma release assays (IGRAs) for Medicare and Medicaid recipients.

The screening of high-risk individuals for LTBI has been recommended by the United States Preventive Services Task Force (USPSTF) since 1996[1] and was updated in 2023.[2] 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 LTBI screening for those at increased risk.[3] 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.[4] However, CMS does not yet have an NCD for LTBI screening.

TB prevention through the testing and treatment of the estimated more than 1 million Americans on Medicare with LTBI could save millions of dollars over time and prevent untold suffering.[5,6,7] A CMS NCD would facilitate improved reimbursement, a major impediment to providers and clinics to implement LTBI screening, testing, and treatment as recommended by all national guidelines. It would also reduce patient cost-sharing and streamline billing for risk-based LTBI screening. Reimbursement for these services through Medicare would also enable better monitoring, accountability, and quality standards for TB care services.

An NCD for LTBI screening would benefit many people with multiple risk factors as well as poor TB outcomes. Upwards of 15% of Medicare recipients are born outside of

Attachment 5: ACET CMS NCD for LTBI Letter, Page 2

the US, the most important risk factor for TB disease.[8] Furthermore, over 25% of TB disease cases and over 50% of deaths occurs among persons over the age of 65 years.[9,10] These statistics are grim for a preventable and curable disease.

Resolving these barriers to TB prevention would be an important step forward for health equity and preventing a disease that disproportionately affects groups that have historically experienced greater obstacles to health. The distribution of TB in the US reveals striking disparities; 70% are non-White race, 30% are Hispanic/Latino and 73% are non-US born.[9] Addressing TB 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.[11,12] Because of the intersecting social and structural determinants of health that drive TB disease, these communities often rely on Medicare to facilitate access to basic preventive health services. Many persons in these communities have additional challenges that can increase the risk for TB disease including being on immunomodulating medications, congregate living, unstable housing, and substance use disorder. [13] The lack of a CMS NCD for a disease that affects certain communities disproportionately creates additional barriers to quality preventive care, further perpetuating health inequities.

ACET recommends that the Centers for Medicare and Medicaid Services expedite off the waitlist a review to make a National Coverage Determination (NCD) in favor of LTBI screening using interferon gamma release assays (IGRAs) for Medicare recipients. Such a determination would lift substantial financial and quality of life burdens on individuals, communities, health systems and insurers and protect the health and wellbeing of many persons, especially those in marginalized communities.

Sincerely,

/Lynn Sosa/

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

Cc:
Jonathan H. Mermin, MD, MPH, Director, National Center for HIV, Viral Hepatitis, STD and TB Prevention
Philip LoBue, MD, Division of Tuberculosis Elimination Director, National Center for HIV, Viral Hepatitis, STD and TB Prevention
ACET Members

Attachment 5: ACET CMS NCD for LTBI Letter, References

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[12] US White House. Executive order on further advancing racial equity and support for underserved communities through the federal government – February 16, 2023. https://www.whitehouse.gov/briefing-room/presidential-actions/2023/02/16/executive-order-on-further-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government/

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Attachment 6: Workgroup Slides

Updated LDT WG Charge

LDTWG is being 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 LDTWG is to continue to gather and clarify information regarding the LDT rule and understand outstanding questions once implementation guidance is published.

UPDATE

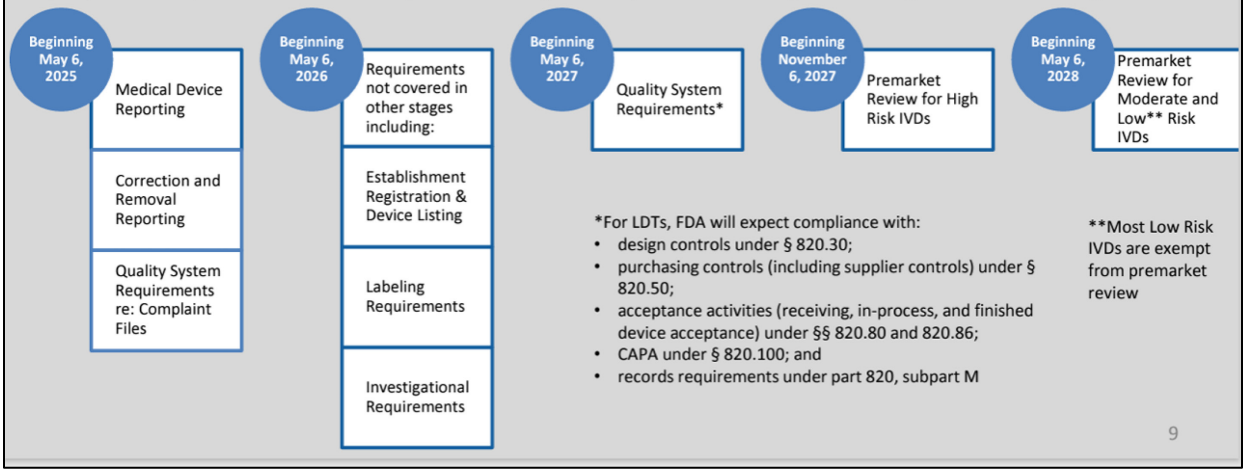
LDT workgroup met on November 22, 2024

Provided an overview of how APHL is working to provide resources to aid Public Health Labs in meeting new requirements

Discussed clinician engagement with the laboratory as it pertains to LDTs

Phaseout Policy

FDA is phasing out its general enforcement discretion approach for LDTs in stages, so that IVDs manufactured by a laboratory will generally fall under the same enforcement approach as other IVDs (i.e., FDA's expectations for compliance will generally be the same), according to the following timeline:



*For LDTs, FDA will expect compliance with:

- design controls under § 820.30;
- purchasing controls (including supplier controls) under § 820.50;
- acceptance activities (receiving, in-process, and finished device acceptance) under §§ 820.80 and 820.86;
- CAPA under § 820.100; and
- records requirements under part 820, subpart M

**Most Low Risk IVDs are exempt from premarket review

9

Previous Webinars

- **May 14, 2024:** Final Rule: Medical Devices; Laboratory Developed Tests
- **June 5, 2024:** Draft Guidances on Enforcement Policy for Certain In Vitro Diagnostic Devices for Immediate Public Health Response in the Absence of a Declaration Under Section 564 (applicable to LDTs) and Consideration of Enforcement Policies for Tests During a Section 564 Declared Emergency (applicable to IVDs)
- **July 16, 2024:** In Vitro Diagnostic Product (IVD): Classification
- **August 22, 2024:** In Vitro Diagnostic Products (IVDs) - MDR Requirements, Correction and Removal Reporting Requirements, and Quality System Complaint Requirements
- **September 24, 2024:** Labeling Requirements for In Vitro Diagnostic Products (IVD), including LDTs, Under 21 CFR 809.10(b)
- **October 24, 2024:** FDA's Total Product Lifecycle Approach to In Vitro Diagnostic Products

December Webinar

Upcoming Webinars

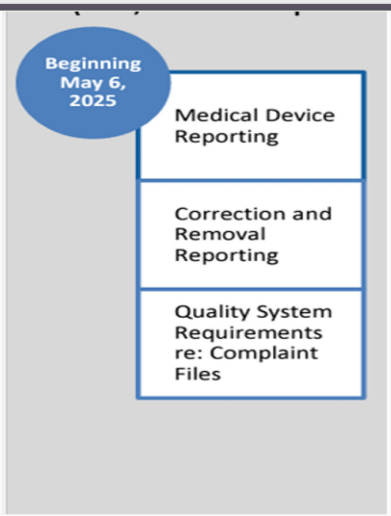
- **December 3, 2024:** Registration & Listing Requirements for In Vitro Diagnostic Products (IVDs), Including Laboratory Developed Tests (LDTs)

- **Presentation, printable slides, and transcript will be available on the FDA webpage after the presentation.**

Association of Public Health Laboratories (APHL) Update

- **LDT Task Force Formation**
- Approved on August 1, 2024
- Composed of quality and subject matter experts to guide APHL staff in developing useful material.
- Workgroups: Infectious Disease (ID), Newborn Screening (NS), Cross-Disciplines (CD) subgroups

Current Focus of Material Development



Considerations

Ongoing legal challenges to the FDA LDT Rule

Priorities of the incoming Administration MAY effect the LDT Rule implementation.

Awaiting implementation guidelines from FDA with specific details that compliment webinars

NEXT STEPS

ACET LDT Workgroup will continue to touch base as we learn more details

Laboratories will continue to work to address the Phase 1 Deadline (May 6, 2025)

Highlight ways in which clinicians can leverage existing avenues to communicate with leadership of laboratories who LDTs they utilize to manage their TB patients and the importance of the testing provided

ACET Drug Shortage Workgroup

December 3, 2024

Ann Loeffler, Chair
Lynn Sosa, SGE
Britt Gayle, HRSA Ex-Officio
Marah Condit, DFO

Workgroup Scope and Meeting Schedule

Scope

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 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

09/16/2024

10/07/2024 – Guest Speaker: Dr. Brenda Waning, Chief, Global Drug Facility, Stop TB Partnership

Proposed ACET Actions

Add oral TB drugs to the list.

We suggest addition of the four most common oral TB drugs, specifically isoniazid, rifampin, pyrazinamide and ethambutol (including the most frequently used formulations and strengths) to the FDA Essential Medications List. This list was developed to "ensure sufficient and reliable, long-term domestic production of these products, and to minimize potential shortages." Inclusion on the list would prioritize protection of TB medications during shortages and supply chain challenges.

Explore a path forward.

We strongly encourage exploring a mechanism for accessing the Global Drug Facility for procurement of TB drugs in shortage or otherwise not available in the US.

One approach would be to focus on pediatric formulations first.

Discuss the issue.

We formally invite the HHS Supply Chain and Resilience Coordinator to attend one of our biannual ACET meetings to learn firsthand about the challenges of TB drug shortages and work with ACET to develop solutions.