Supplementary Appendix A

Responsibilities of the Tuberculosis Controller or Tuberculosis Program Manager

Each state or local tuberculosis (TB) control program determines the qualifications and scope of responsibilities for the TB controller and the TB program manager. The roles might be filled by the same person or two different persons.

Key responsibilities include the following:

- Oversight of the TB program, which includes procedures for ensuring standards of care for TB management are met; the TB program is evaluated on the basis of established standards and analyses of program data; and quality-improvement activities are implemented to ensure effectiveness at the system level and to ensure positive outcomes for patients.
- Applying public health laws for TB control, ensuring due process for patients.
- Ensuring that administrative tasks that address funding, budget preparation, and required reporting are completed on the basis of established guidelines.
- Writing funding applications, if applicable, for submission to CDC or the state that are based on funding guidance and consultation with the assigned CDC or state liaison.

For jurisdictions (states, specific large cities, and territories) funded by CDC, substantial reporting responsibilities exist. More detail and assistance is available from the program's CDC program representative.

These jurisdictions should report data for (a) Report of Verified Case of TB (RVCT)(*A1*); (b) Aggregate Reports for TB Program Evaluation (ARPEs) (*A2*); and (c) the Electronic Disease Notification system (EDN) (*A3*). Data should be collected throughout the year regarding cases, contacts, and latent TB infection (LTBI) testing and treatment to complete these reports. National TB Indicators Project (NTIP) data are derived from RVCT and EDN data, and might be used for program evaluation. The annual application for funding should be written in accordance with the guidance provided by CDC. Careful budget calculations in accordance with the guidance, updates on previous years' objectives, new objectives, program evaluation, and human resource development are part of each application. Although TB controllers do not have to do each of these activities themselves, they are responsible for their completion to maintain funding.

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Supplementary Appendix B

Core Public Health Functions and Essential Services

This appendix is adapted from the original report (*B1*) to include examples of how these essential functions and essentials apply to tuberculosis (TB) programs (Boxes B1 and B2).

BOX B1. Core public health functions and essential services

Assessment
Monitor health status to identify and solve community health problems.
Diagnose and investigate health problems.

Policy Development
Inform, educate, and empower people about health concerns.
Mobilize community partnerships and action to identify and solve health problems.
Develop policies and plans that support individual and community health efforts.

Assurance
Enforce laws and regulations that protect health and ensure safety.
Link persons to needed health services and ensure provision of health care when otherwise unavailable.
Ensure public and personal health care when otherwise unavailable.
Evaluate effectiveness, accessibility, and quality of personal and population-based health services.

Research
Research for new insights and innovative solutions to health problems.

BOX B2. Examples of mapping general core functions to specific TB control activities

Core function terminology	**Examples using more common TB control terminology**
Assessment	Examples of assessment of surveillance data • Standard TB case surveillance • Review of statewide hospital discharge summaries • Review of death certificates • Surveillance for newly diagnosed latent TB infection (LTBI) • Review of data (e.g., Report of a Verified Case of Tuberculosis [RVCT]) for cases and latent TB infection registry) from past years to identify important overall as well as population group trends Example of assessment of available TB expertise • State health department • Local health department • University/teaching hospitals • General hospitals • Infection control practitioners • Mycobacteriology laboratories

	Example of assessment regarding training and education • Review match between essential services and available human and financial resources Other
Policy development	Examples of policies regarding case management • Directly observed therapy • Use of incentives and enablers • Recommended interval sputum smears and cultures Examples of policies regarding management of contacts • Timely contact investigation • Clinical and radiologic assessment for TB and LTBI • Appropriate regimens for treatment of LTBI • Indications for directly observed LTBI therapy Examples of policies regarding other screening for LTBI • 2-step testing for new health-care personnel and other employees at risk • Retesting for health-care personnel: annual versus periodic versus as-needed • Testing policies for special populations (e.g., nursing home, correctional institutions, homeless shelters, and foreign-born persons)
Assurance	Examples of assurance: Enforce rules, and regulations, and laws • Use of laws relating to TB (e.g., mandatory case reporting) Examples of assurance: Link to provider care • Making sure that every TB patient receives the recommended clinical management, whether it is provided through a health department clinic, a pulmonary or infectious diseases consultant, or a teaching hospital clinic Examples of assurance: Assuring a competent workforce • Ensuring that key clinical and public health TB personnel receive up-to-date training, whether through in-state programs or through attendance at TB Centers of Excellence (COE) training sites Examples of assurance: Evaluate • Proportion of cases managed with directly observed therapy • Proportion of cases evaluated for co-existing HIV infection • Proportion of cases completing therapy within 6 or 9 months • Annual TB cohort analysis (e.g., [a] completed therapy or cured, [b] not cured, [c] died, [d] transferred to another jurisdiction, or [e] lost-to-follow-up) • Proportion of contact investigations completed • Proportion of persons starting LTBI treatment who complete prescribed course of treatment

These same functions are often also commonly represented in a graph that further illustrates the circular-iterative nature of the process (Figure B1).

FIGURE B1. Core public health functions and essential services

Reference

B1. Institute of Medicine. *The future of public health*. Washington, DC: The National Academies Press; 1988. https://www.nap.edu/catalog/1091/the-future-of-public-health

Supplementary Appendix C
CDC-Funded Resources

CDC provides the following resources for tuberculosis (TB) programs.

TB Centers of Excellence
A primary CDC-funded resource is the TB Centers of Excellence (COEs) for Training, Education, and Medical Consultation (TB COEs) (*C1*), formerly known as the Regional Training and Medical Consultation Centers. The new designation of COEs began in 2018. The COEs are regionally assigned to cover all 50 states and the U.S.-affiliated islands, and provide both in-person and online training courses, educational products, technical assistance for training and education activities, and real-time medical consultation. Services provided by COEs are intended to build expert activities, including hosting TB controllers and other TB program staff to provide customized training in specific aspects of TB control (e.g., mini-fellowships); trainings for members of state and local TB programs regarding how to conduct contact investigations; activities that foster dissemination of new CDC guidance; webinar discussions on treatment of drug-resistant TB or other complicating conditions; and provision of regional diagnosis, treatment, and management of TB patients.

In addition to providing medical advice for managing local TB patients, COEs routinely alert local and state TB controllers about TB patients in their jurisdiction for surveillance and awareness. TB programs and clinical providers are encouraged to use COE services in circumstances in which they do not have a consultant, the consultant is unavailable, or concern or need exists for a second medical opinion. In particular, COE medical consultation services should be sought for cases involving drug-resistance. Additional descriptions of the educational component of the COEs are provided elsewhere in the main text of this report and in Appendix G.

TB Educational Training Network
The TB Education and Training Network (TB ETN) (*C2*) is coordinated by CDC and was formed to bring TB professionals together to share resources and build education and training skills. A full description of TB ETN, its members, and its associated purposes and activities are provided in Appendix G.

TB Program Evaluation Network: State and Large City TB Programs
Program evaluation is an essential part of program management. One forum available to all TB programs is the TB Program Evaluation Network (TB PEN) (*C3*). TB PEN comprises state and local TB program evaluation *focal points* (staff in each jurisdiction directly funded by CDC who are responsible for TB program evaluation activities) and other TB program staff who are working with or interested in program evaluation. TB PEN focal points participate in conference calls bimonthly and a biennial conference in collaboration with TB ETN. A full description is provided in Appendix G.

TB Program Data
Extensive data collection by CDC provides both individual and aggregate program data. Surveillance data and program data provided in the Aggregate Reports for Tuberculosis Program Evaluation (ARPE) (*C4*), Electronic Disease Notification (EDN) (*C5*) system, and

TB Genotyping Information Management System (GIMS) (*C6*) are of optimal value when the data supplied to those systems by TB programs are checked regularly for accuracy.

Reports from CDC are provided to assist programs in improving the quality of their data. The National TB Indicators Project (NTIP) (*C7*) contains a line listing of all patients included in NTIP reports that can enable each program to confirm information submitted to CDC. The National TB Surveillance System (NTSS) contains a series of reports that TB programs should use to improve surveillance data quality. Programs can search the data from the NTSS at the CDC Wonder database (*C8*). TB programs should incorporate into their protocols routine checks of program data for accuracy at least quarterly.

These reports include the following:

TB Case List Report — Includes all RVCT variables collected, except any date variables. This report enables users to examine all the data for an individual case received by CDC.

Content Validation Report — Contains detailed Health Level 7 (HL7) errors received in messages sent from any given state system. HL7 rules are a set of standards for data formats and content that allows different health information systems to communicate easily and effectively with one another. A code for each error received is specified. For example, a case will appear on this report if the date reported are not equal to or before the date counted.

Case Verification Report — Includes verified cases and nonverified records (i.e., suspect and not a verified case) and generates a spreadsheet listing the case verification classification (i.e., positive culture, positive nucleic acid amplification test, positive smear or tissue, clinical case definition, and verified by provider diagnosis).

Inconsistent Data Report — Contains inconsistencies and outlier conditions received in messages sent from any given state system. An item that appears on this report is not necessarily incorrect; however, it is not consistent with normal expected data. The item might warrant a second look to ensure that a data entry error has not occurred.

Missing and Unknown Report — Generates a list of NTSS data with incomplete missing or unknown variable information.

Counted Case Report — Contains a list of all cases counted for a specific year. The summary report will display aggregate cases counted by quarter and total by year.

Non Counted Case Report — Contains a list of all not-counted cases for a specific year. The summary report displays aggregate cases by quarter and total by year.

Surveillance Frequency Report — Generates frequency tables that display both the number of occurrences and percentages for different RVCT data items pertaining to patient demographics, clinical data, and case follow-up information for counted cases.

Missing Date Report — A list of cases that contains missing critical dates (i.e., report date and count date).

Deleted Case Report — A list of cases that have been deleted by a given state. They will not appear on any other reports.

Message Transmission Report — Provides the total number of HL7 messages sent by a state.

Variables Never Sent Report — Contains a list of any variables that have never been sent to CDC.

Aggregate program data are provided on the CDC Internet site (https://www.cdc.gov/tb/statistics/default.htm).

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Supplementary Appendix D
Tests Used for Evaluation and Monitoring of Persons with Tuberculosis Disease
Multiple tests are used in the diagnosis and monitoring of patients undergoing treatment for tuberculosis (TB) disease (Table D1).

TABLE D1. Tests used for evaluation and monitoring of persons with TB disease

Test	Purpose	Interpretation
Acid-fast bacillus (AFB) smear	For rapid identification of mycobacteria; should be performed in a laboratory by an experienced laboratorian and with enough specimens to ensure accuracy (*D1*)	The presence of AFB can indicate the presence of *M. tuberculosis* or any other acid-fast species. The concentration of AFBs in a respiratory specimen is an indicator of infectiousness (more AFBs = more infectious disease) and serves to track progress as the patient is treated. Reduction in the number of AFBs observed after start of treatment (and eventual conversion to negative) is usually an indicator of treatment success.
AFB culture	Culture is the ultimate standard for identifying living organisms; available at public health laboratories and hospital and reference laboratories; culture is necessary, because drug sensitivity and genetic identification require isolates	A positive culture for *M. tuberculosis* indicates TB disease, regardless of the site of the culture. The initial culture can be used for determining drug susceptibilities. Performing subsequent cultures during treatment is vital for documenting conversion from positive to negative culture, a major indicator of treatment success. A negative culture does not rule out TB disease.
Gastric aspirate	Gastric aspirates can be used for infants, children, and adults unable to produce sputum samples (*D2*)	The aspirate is tested with smear and culture, and nucleic acid amplification tests (NAATs), if available.
Biopsy specimens	Bronchoscopy with or without lung biopsy might be necessary to obtain specimens to determine the presence of TB disease; biopsies of extrapulmonary sites (e.g., lymph nodes or other	Biopsy specimens are treated as any other specimens for smear and culture. Specimens obtained through bronchoscopy can indicate infectiousness and the need for a contact investigation.

	tissue) might be necessary for identifying TB disease	No Food and Drug Administration–approved NAATs are available for extrapulmonary specimens, but certain laboratories have developed tests or validated commercial tests that can be used.
NAATs (e.g., polymerase chain reaction or GeneXpert®)	NAATs should be performed on at least one respiratory specimen from patients with clinical indications of active TB disease, especially when the test result can alter case management or TB control interventions (e.g., contact investigations); new diagnostic modalities using genetic molecular analysis can rapidly, within hours, identify *Mycobacterium tuberculosis* complex (MTBC) and test for genetic mutations associated with rifampin or isoniazid resistance, depending on the instrument; this allows rapid institution of recommended therapy, identification of drug resistance, and decreased transmission of TB	NAATs identify MTBC DNA or RNA, but do not differentiate between live and dead bacteria. Thus, they are useful in identifying MTBC in a person with suspected TB disease, but cannot be used to monitor treatment progress. The GeneXpert® test also identifies *M. tuberculosis* and genetic changes (e.g., mutations) in the *rpoB* gene that can be associated with rifampin resistance. The GeneXpert can also be used to assist in determining when a person can be removed from airborne isolation in a hospital (*D3*). Other tests for individual drug resistance (i.e., isoniazid) are also performed in some NAAT systems.
Drug-susceptibility testing (DST); includes GeneXpert® and the Molecular Detection of Drug Resistance (MDDR) CDC program, and culture-based drug susceptibility	Determines to which drugs the patient's *M. Tuberculosis* is susceptible; use of drugs to which the patient's isolate is resistant can produce additional resistance and can lead to multidrug-resistant (MDR) TB or extensively drug resistant (XDR) TB • First-line DST is available through state and local public health laboratories, and some reference laboratories	Culture of organisms is necessary for providing phenotypic DST; phenotypic DST is the ultimate standard for DST and is supplemented by genetic testing for resistance, because all mutations and combinations of mutations are not known. Both molecular (genetic) and phenotypic (culture-based) DST are useful for • identifying the best initial therapy, and

	Second- and third-line testing is available through some state public health laboratories, CDC, and reference laboratories (e.g., National Jewish Health)	• follow-up if patient progress is inadequate or if the patient is failing while on therapy. DST also • offers insight to guide treatment choices for contacts of patients with TB disease; • provides susceptibility testing to a panel of drugs and should be used when MDR TB is suspected; and • estimates prevalence of primary and acquired drug resistance in a community.
M. tuberculosis genotyping	The initial positive isolates are submitted to the local or state public health laboratory and sent to a CDC-funded public health laboratory for genotyping	Genetic links between cases often imply a shared source of disease. Some genotypes are common and might not indicate case linkage. Genotype information should be interpreted in conjunction with epidemiologic data (*D4*)
Whole-genome sequencing	Available in some research laboratories; provides more discriminatory genotyping and additional information (e.g., the presence of resistance mutations)	Universally available since 2018 through a CDC-funded public health laboratory *(D5–D7*)
Blood tests		
Liver function tests (LFTs)	The majority of anti-TB drugs are metabolized in the liver; thus, baseline testing is essential before starting treatment for TB disease and should be performed before starting LTBI treatment in any persons with known liver disease or risk factors for liver disease	Elevation of LFTs is expected during TB therapy. Usually, medications are not stopped unless the LFTs are 3 times normal with symptoms, or 5 times normal without symptoms (*D8*). If medications should be stopped, they should be held until LFTs return to normal, and then restarted one at a time over a period of days.
Renal function	Anti-TB drugs, particularly those used against MDR TB, can affect the kidneys	Baseline renal function tests should be performed, and repeated periodically throughout treatment, depending on the patient's response to treatment.

Hemoglobin A1c (HgbA1c)	Poorly controlled diabetes can make TB disease difficult to cure; baseline and regular monitoring can assess the level of diabetic control	Control of blood sugars can improve and speed TB cure. Regular monitoring, patient education, provision of supplies and insulin, and dietary assistance can all improve diabetic control.
Drug levels — Serum drug level monitoring can be used for patients with the following medical conditions: human immunodeficiency virus infection or acquired immunodeficiency syndrome; diabetes; malabsorption syndromes; renal failure; failure to improve on treatment or TB relapse; and MDR TB	Helpful when a patient is not improving or getting worse, despite a regimen to which the TB is known to be susceptible; Drug-level testing for some drugs might be available through local hospital laboratories; testing for other drugs might only be available at public health laboratories, commercial laboratories, or National Jewish Health	• Drug levels (both peak and trough) provide evidence of malabsorption or hyper-metabolism of drugs. • Used when a patient is not improving or getting worse, despite a regimen to which TB is known to be susceptible. Alternate doses or alternate drugs might be needed, if drug levels identify problems with drug metabolism
Other as needed	Depending on the patient, other tests might be needed	Thorough knowledge of the patient's comorbidities and current medications is necessary for determining ongoing needs during TB treatment
Other tests		
Vision testing	Ethambutol can affect eyesight; baseline and regular retesting for the duration of treatment is necessary for avoiding permanent damage to sight	Both acuity and color vision should be tested before beginning therapy with ethambutol. If treatment is prolonged, or the patient has vision complaints, testing should be repeated and a referral to an ophthalmologist provided.
Hearing testing	Injectable agents (e.g., amikacin, which is used for MDR TB) can permanently damage hearing; baseline testing before beginning treatment and regular monitoring of the patient and retesting as needed can prevent permanent hearing loss	Baseline hearing testing and periodic retesting throughout the term of use can minimize hearing loss resulting from TB treatment.

Imaging		
Chest radiograph (CXR)	A normal posterior-anterior CXR is the standard imaging technique in public health when evaluating a person for TB disease; lateral and decubitus views can be helpful in defining abnormalities observed on posterior-anterior views	Repeat CXRs help to show change (improvement or worsening) or stability over time during treatment. This aids the clinical assessment of the efficacy of treatment.
Chest computed tomography (CT) scan	In many cases, CT can reveal abnormalities that were not apparent or underappreciated in a CXR; CT can therefore help clarify abnormal findings on a CXR	Repeat CTs help to show change (improvement or worsening) or stability over time during treatment. This aids the clinical assessment of the efficacy of treatment.
Other	Magnetic resonance imaging, CT with contrast, and imaging of other body structures might be needed to fully define the extent of TB disease	Sequential imaging might be necessary for assessing treatment effectiveness.

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Supplementary Appendix E

Tests Used for Assessing Latent Tuberculosis Infection

Mantoux Tuberculin Skin Test

The tuberculin skin test (TST) produces a delayed-type hypersensitivity reaction in persons with *Mycobacterium tuberculosis* (TB) infection. TST has been useful for determining how many persons in a group are infected (e.g., as part of a contact investigation) and for screening persons for TB infection; however, practice guidelines (*E1*) recommend performing an interferon-ɣ (IFN-γ) release assay (IGRA) rather than a TST among all persons aged ≥5 years who are likely to be infected with *M. tuberculosis*, who have a low or intermediate risk for disease progression and among whom testing for latent TB infection (LTBI) is warranted. Pediatric guidelines extend IGRA use rather than TST to age ≥2 years (*E2*). A TST is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome. If TSTs are used in any setting, ensure that trained health-care professionals perform, measure, and interpret the TST. Additionally, TST results should be evaluated within the context of each patient's epidemiologic risk factors for infection. For a detailed review of the TST, please see the ATS/IDSA/CDC guidelines (*E1*). Although skin-testing programs should be conducted only among groups at high risk, certain persons might require a TST for employment or school attendance. Diagnosis and treatment of LTBI should always be tied to risk assessment.

Reading the TST

TST induration results should be reported in millimeters, measured across the arm, and with patient risk factors documented for correct interpretation of test results. The TST reaction should be measured from 48 to 72 hours after the TST is administered, measuring induration (not erythema) and test reaction recorded in millimeters, not as negative or positive. Educate the patient and family regarding the importance of a positive TST result. Positive TST reactions can be measured accurately for ≤7 days. Negative reactions can be read accurately for only 72 hours (*E3*).

False-Positive and False-Negative TST Reactions

A small percentage of TST reactions can be caused by errors in administering the test or in reading results. However, false-positive results are more commonly attributable to the cross-reactions caused by the antigens in the tuberculin solution with nontuberculous mycobacteria and vaccination with bacillus Calmette-Guérin (BCG). Clearly distinguishing between reactions caused by infection with *M. tuberculosis* and those caused by other mycobacteria is difficult. However, the larger the induration, the greater the likelihood that the reaction represents *M. tuberculosis* infection.

Similarly, clearly distinguishing between a TST reaction caused by infection with *M. tuberculosis* and a reaction caused by BCG vaccination is difficult. The probability that a TST reaction results from *M. tuberculosis* infection rather than from BCG vaccination increases

- as the size of the reaction increases;
- when the patient is a contact of a person who has TB (especially if that person has infected others);
- when a family history of TB exists or when the patient's country of origin has a high incidence or prevalence of TB; or
- as the interval between vaccination and TST increases (because vaccination-induced

reactivity wanes over time and is unlikely to persist for >10 years) (*E4*).

A history of BCG vaccination is not a contraindication to TST; however, for persons with a history of BCG vaccination, IGRA is the recommended diagnostic test (*E1,E2*).

A false-negative TST will appear as a small or absent induration, when the patient does have LTBI. False-negative TST reactions can be caused by anergy (impaired immunity [e.g., HIV-infected persons]); recent TB infection (defined as <10 weeks after exposure); infants aged ≤6 months; recent application of live virus vaccination (e.g., measles or smallpox); and TST injection too shallow or too deep where the wheal is absent or too small to evaluate. Evaluation of the person's symptoms and risk factors for exposure to TB disease should be part of the LTBI evaluation; the TST should not be the only factor considered in determining whether LTBI exists.

Boosting and Two-Step TST

An initial negative TST in persons who either have never been tested or who have not been tested in years, can be a false-negative. A subsequent test might be positive because of a boosted reaction, but it might be falsely interpreted as a conversion and hence a new infection. A strategy for determining the difference between boosted reactions and reactions caused by recent infection is a two-step TST. The health-care provider should administer a baseline TST. If the reaction is positive, the person probably has LTBI; follow-up for a positive TST and evaluation for LTBI treatment should be administered. If the reaction is negative, the health-care provider should retest 1–3 weeks later. If the reaction to the second test is positive, it is considered a boosted reaction (caused by TB infection that occurred a long time ago).

If the person does have LTBI, a decision should be made regarding treatment. The health-care provider should follow-up for a positive TST and evaluate for LTBI treatment. If the reaction to the second test is negative, the person probably does not have LTBI. The TST should be repeated at regular intervals; a positive reaction might be caused by a recent TB infection. Using the two-step tests for initial baseline skin testing of adults who will be retested periodically is recommended (e.g., for health-care personnel).

IGRAs

For a detailed review of IGRAs, see CDC's updated guidelines for using INF-ɣ release assays to detect *M. tuberculosis* complex (MTBC) infection (*E5*), and the ATS/IDSA/CDC Clinical Practice Guidelines (*E1*). IGRAs are whole-blood tests used to detect MTBC infection. Two U.S. Food and Drug Administration–approved IGRAs are commercially available in the United States: QuantiFERON®-TB Plus and the T.SPOT® TB test (T-Spot) (*E6,E7*). These blood tests measure and compare amounts of IFN-γ released by blood cells in response to antigens. The tests entail mixing fresh whole-blood samples with antigens from MTBC and laboratory controls. Cells that recognize the MTBC antigens release IFN-γ. The amount of interferon released in response to MTBC antigens is compared with the amount released in response to other nonspecific antigens and in the absence of antigens. Both commercially available IGRAs detect T-cell responses.

When administering IGRAs, confirming and arranging for delivery of the blood sample within a specific timeframe is vital for ensuring viability of white blood cells in the blood samples; drawing the blood sample according to the test manufacturer's instructions is also vital as is

scheduling a follow-up appointment with the patient to explain test results and perform a medical evaluation and possible treatment for LTBI, if needed.

Advantages and Disadvantages of IGRAs

IGRAs have multiple advantages. TB-specific antigens are used. A single patient visit is required to conduct the test. The test does not boost responses measured by subsequent tests. Additionally, prior BCG vaccination does not cross-react with IGRA testing. This can be important because the majority of TB cases diagnosed in the United States occur among persons born outside the United States who might have been vaccinated with BCG.

Important disadvantages exist (e.g., errors in collecting and transporting blood or in interpreting assays) that can decrease IGRA accuracy. Also, these tests cannot be used to predict who will progress to TB disease, and they might be more expensive than TSTs. Data are limited regarding use of IGRAs for serial testing among children aged <2 years, among persons recently exposed to *M. tuberculosis*, and persons who are immunocompromised.

IGRA results should be reported in numbers rather than as positive or negative, because cut points for positivity and negativity can vary with the person's risk factors. As with the TST, interpretation of IGRA results and any diagnostic decision should consider the patient's risk factors and other medical history or conditions.

Selecting a Test for Detecting TB Infection

Whereas the most commonly used diagnostic tool for demonstrating prior or current TB infection is the TST, use of IGRAs is becoming more commonplace. The decision to use one test over another is based on each test's advantages and disadvantages, and the specific person or populations being tested (see section on risk assessment for LTBI and Table E1).

TABLE E1. Comparison of interferon-ɣ release assays (IGRA) and tuberculin skin tests (TSTs)

IGRAs	TSTs
In vitro test	In vivo test
Specific antigens	Nonspecific antigens
Requires blood test	No phlebotomy
No boosting	Boosting phenomenon
1 patient visit	2 patient visits
Fixed interpretation criteria	Risk stratified interpretation
Minimal interreader variability	Interreader variability
Variability with serial testing	Low variability with serial testing
Results in minimum of 2 days; depends on whether laboratorians batch samples for testing	Results in 2–3 days
Not affected by bacillus Calmette-Guérin (BCG) vaccination and the majority of nontuberculous mycobacteria	Cross-reacts with BCG and nontuberculous mycobacteria

IGRAs are the preferred method of testing for groups of persons who have poor rates of returning to have their TST read and for persons who have received BCG vaccine (e.g., persons born in countries in Africa, Asia, Latin America, and Eastern Europe).

According to ATS/IDSA/CDC guidelines from 2017, because of the relative sensitivity of the test, TST is the preferred method of testing (over IGRA) for children aged <5 years (*E1,E2*), although IGRA is acceptable (*E4*). Because IGRA has increased specificity for TB infection among children vaccinated with BCG, the American Academy of Pediatrics changed its recommendations in 2018 to a preference for IGRA over TST for children aged ≥2 years (*E2*). For other groups who are tested for LTBI, either TST or IGRA can be used without preference for other groups who are tested for LTBI (e.g., contacts of persons with active TB disease and health-care personnel undergoing routine screening). However, in interpreting a test, particularly in those given BCG, one needs to be cognizant that IGRAs can be more specific than TSTs (*E1*).

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Supplementary Appendix F

Testing for Latent Tuberculosis Infection Among Special Populations and Latent Tuberculosis Infection Treatment Regimens

Testing of Special Populations

Foreign Birth

Persons born in, or former residents of, countries with increased tuberculosis (TB) prevalence have an increased risk for TB exposure and infection (*F1*,*F2*). The majority of persons with active TB disease in the United States were born in other countries. American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and Infectious Diseases Society of American (IDSA) guidelines and the U.S. Preventive Services Task Force (USPSTF) recommend testing all persons who were born in, or resided in, a country with elevated TB prevalence (e.g., countries in Africa, Asia, Latin America, and Eastern Europe).

Persons newly arrived from countries with endemic TB disease are at high risk for latent TB infection (LTBI). Immigrants and refugees are reported to state health departments upon arrival in the United States (*F3*); students and workers do not have any requirements for testing or treatment before arriving in the United States. These persons should be regarded as having had contact with infectious TB disease at some point in their lives, and thus should be screened, tested, and if appropriate, treated for LTBI. Provision of services should never depend on concerns of immigration or residency status.

Contacts of a Person with Infectious TB Disease

Known close contacts of a person with infectious TB disease at any time is a risk factor for LTBI (*F1*). Recent contact (within the previous 2 years) is also a risk factor for progression to active TB disease (*F4*). Persons with recent contact typically undergo evaluation as part of contact investigations conducted by public health departments or infection control practitioners. However, some contacts might not have been identified by those investigations, or the contact might have occurred many years ago when contact investigation was not commonly practiced (e.g., a childhood household member who was sick with or died of TB). If possible, clarify that contact was close to a person with infectious TB disease, not LTBI.

Immunosuppression and Immunomodulation

Even in the absence of a specific known risk factor for exposure to TB, patients should be tested if they are positive for human immunodeficiency virus (HIV), or have current or planned immunomodulation that is likely to substantially elevate the risk for progression from LTBI to TB disease (*F1*). These immunosuppressive conditions typically include

- HIV infection (especially with low $CD4^+$ count or not receiving antiretroviral therapy);
- treatment with a tumor necrosis factor alpha (TNF-α) inhibitor or other bioequivalent agents;
- immunosuppressive cancer chemotherapy or radiation;
- solid organ transplantation;
- chronic, high-dose steroid treatment (typically defined as equivalent of ≥15 mg of prednisone for ≥1 month); and

- immunosuppressive and immunomodulator agents used to treat rheumatologic, dermatologic, gastrointestinal, and other diseases; TB program staff should stay abreast of these agents and new indications for their use.

Children

As with adults, health-care providers should assess all children aged <18 years for TB risk factors. Children aged <5 years are especially vulnerable to rapid progression to TB disease if infected. In addition, children have more years of expected life during which progression from latent infection to active TB disease can occur. Among TB risk factors, pediatric guidelines indicate that having a parent born in a country that has an elevated TB rate is an indication that testing is needed (*F2*). This recommendation might indicate testing large numbers of children; therefore, additional prioritization might be required in certain settings. The American Academy of Pediatrics has created four validated risk assessment questions for use among children (*F5*).

Previous Tuberculosis

Persons with radiographic evidence of previous TB that has not been treated have an increased risk for progression to active TB disease. Chest radiograph findings consistent with previous TB include fibrosis or noncalcified nodules, but do not include a solitary calcified nodule or isolated pleural thickening. Health-care providers should test for TB when a person has a previous chest radiograph with findings consistent with previous TB. If the TB test is positive, they evaluate the person for active TB disease, including acid-fast bacilli sputum smear microscopy, culture, and nucleic acid amplification testing.

Other Risks for Progression to Active TB Disease

Persons with certain medical conditions have an increased risk for progression from LTBI to active TB disease. Health-care providers should test for LTBI when a person has a risk for TB exposure and one or more of the following conditions (*F6*):

- end-stage renal disease,
- leukemia or lymphoma,
- silicosis,
- cancer of head or neck,
- intestinal bypass or gastrectomy,
- chronic malabsorption,
- A body mass index of ≤20,
- diabetes mellitus,
- history of or current smoking, or
- injection drug use.

Health-Care Personnel

Mycobacterium tuberculosis transmission is a recognized risk in health-care facilities (*F7*). Transmission is most likely to occur from patients who have unrecognized pulmonary or laryngeal TB, who are not on effective anti-TB therapy, or who have not been placed in airborne infection isolation. Health-care personnel who are infected but never treated for LTBI can also

experience TB disease and infect other staff or patients.

Implementing an effective TB control program in a facility requires risk assessment; early identification, isolation, and complete treatment of infectious TB patients; effective engineering controls (e.g., negative air pressure rooms); a respiratory protection program; and education, counseling, and screening, testing, and treatment for health-care personnel. For further information regarding testing of health-care personnel, refer to current CDC recommendations for testing for LTBI on initial employment and annually, depending on the workers' risk for exposure to TB disease (*F7*). Local and state mandates regarding testing of health-care personnel should be followed, because they incorporate local TB epidemiology.

Other Risks for Exposure to TB Disease

Persons who have a history of being homeless or incarcerated or have been employed in a facility where homeless or incarcerated persons reside can have an increased risk for exposure to infectious TB (*F4*). Risk for exposure varies by specific facility and setting. Local health departments can provide further confirmation that populations in congregate settings require testing.

Screening and testing programs in specific facilities and settings might exist (e.g., screening in certain homeless shelters or correctional facilities). Additionally, legal or regulatory requirements might mandate screening or testing among employees of these facilities or health-care personnel.

Because persons who use alcohol and other noninjecting drugs might be at risk for repeated exposure to others who have TB, a risk assessment and, if necessary, testing for LTBI should be administered on admission to a substance use or alcohol treatment program and on an annual basis, unless these persons are known to be tuberculin-positive. Testing is not recommended for persons who are not members of groups at high risk because this diverts resources from higher priority activities.

LTBI Treatment Regimens

The 9-month regimen of isoniazid (INH) (9H) historically has been one of the preferred regimens (Table F1). However, completion of treatment of LTBI with daily INH is limited by its long duration and its risk for hepatotoxicity. A 6-month regimen of isoniazid (6H) can be used but is less effective than 9H; the NTCA/CDC guidelines include a stronger recommendation for 6H relative to 9H because 9H increases the risk for hepatotoxicity without a clearly demonstrated increase in effectiveness (*F8*). However, short-course rifamycin-based regimens are now preferred over longer-course (6–9-month) INH monotherapy for LTBI treatment (*F8*).

Shorter Treatment Regimens for LTBI

Three months of INH and rifapentine (RPT), also known as the 3HP regimen, demonstrated equal, if not better, efficacy, higher completion rates, and lower hepatotoxicity than 9H among adults (*F9*) and children aged ≥2 years (*F10*). Studies have now demonstrated that 3HP can be a more cost-effective alternative to 9H (*F11,F12*), and 3HP has higher completion rates than 9H (*F9*). A CDC-sponsored study that assessed the adherence to the 3HP regimen with self-administered therapy (SAT) reported that the completion rate with SAT was not inferior to that with directly observed therapy (DOT) (*F12*). Thus, CDC has recommended that 3HP can be administered to adults by using either SAT or DOT, depending on area protocols and patient characteristics (*F13*). This regimen can be administered to all patients aged ≥2 years (*F4*). 3HP

can be administered to persons with HIV infection who are taking antiretroviral medications with acceptable drug–drug interactions with rifapentine (*F13*). 3HP is not indicated for pregnant women or women expecting to be pregnant within the 12-week regimen and among persons exposed to organisms resistant to INH or rifampin. 3HP might be administered by DOT or SAT once a week for 12 weeks, or 11 or 12 doses can be completed within 16 weeks (*F13*).

Rifampin (RIF) administered daily for 4 months (4R) is an alternative to INH, with better completion rates and less hepatotoxicity than with using 9H for adults (*F14–F16*). Reasonable evidence exists for using 4R among children, because observational studies among children support adult randomized clinical trials demonstrating efficacy and hepatotoxicity rates similar to 9 months of INH and lower discontinuation rates (*F17*). In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin can be substituted.

In addition to 3HP and 4R, a third preferred short-course regimen of 3 months of daily INH plus RIF (3HR) has been conditionally recommended for adults and children of all ages and for HIV-positive persons as drug interactions allow (*F8*). However, based on several studies, HIV-negative adults and children with a positive TST who receive 3HR appear to have a similar risk for TB disease, hepatotoxicity, and adverse effects requiring treatment discontinuation as have those who receive 6H or 9H (*F8*).

TABLE F1. LTBE treatment regimens

Drug	Duration* (mos.)	Interval	Minimum doses
Isoniazid (INH) and Rifapentine (3HP)†	3	Once weekly§	12
Rifampin (RIF)§	4	Daily	120
INH and RIF**	3	Daily	90
INH¶	9	Daily**	270
		Twice weekly**	76
	6	Daily	180
		Twice weekly**	52

Source: CDC. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recommend Rep 2020;69(No. RR-1);1–11.

* Completion of therapy is based on the total number of doses administered, not on duration of therapy alone.

† 3HP treatment is regarded as complete with 11 or 12 doses taken within 16 weeks. If treatment is interrupted, doses can be caught up by administering them no more frequently than every 72 hours.

§ Rifampin treatment can be regarded as complete if taken within 6 months.

¶ INH regimens can be administered daily or intermittently (twice weekly). DOT is required for intermittent therapy (*F1*). Completion of therapy for the 9-month regimen of INH is 270 doses in 9–12 months. If interruptions occur in treatment with isoniazid, patients can be administered therapy for 2–3 additional months to complete the regimen. If a gap of >3 months occurs, restarting treatment might be necessary. However, adults with ≥6 months of treatment can be considered as having completed treatment.

** Conditional GRADE recommendation from the National Tuberculosis Controllers Association and CDC; determination of whether consequences outweighed undesirable consequences was uncertain (e.g., with low-quality evidence).

Children

Experts recommend that children aged <2 years might be treated with INH. After attaining age 2 years, children can take 3HP or rifampin regimens (*F5,F18).* All LTBI medications can be crushed and mixed with food for easier administration. INH is commercially available in liquid form; RIF might need to be compounded.

HIV-Infected Persons

For HIV-infected patients with LTBI, 9H is perhaps more effective than 6H, on the basis of long-standing data (*F19–F22*), but no clinical trial data directly compare 9H with placebo, 6H, or 12 months of daily INH (*F8*). RIF is contraindicated for persons taking protease inhibitors, delavirdine, or cobicistat. Rifabutin with dose adjustments can sometimes be substituted for rifampin. The 3HP regimen is not typically recommended for HIV-infected persons unless they are taking antiretroviral medications with acceptable drug–drug interactions with rifapentine (*F14*). Drug–drug interactions between rifamycins and antiretroviral therapy are regularly updated by the U.S. Department of Health and Human Services (https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0). When managing HIV and TB coinfection, consultation with an expert should be obtained.

Persons with Fibrotic Lesions Indicating Previous TB

Persons with fibrotic lesions that are indicative of previous TB should be treated for LTBI if they have a positive TST reaction (at least 5-mm induration) or IGRA test result, no symptoms of TB disease, and negative sputum for acid-fast bacillus (AFB) and cultures.

Persons with fibrotic lesions should be treated only after active TB disease is excluded with sputum collection for AFB and culture. Acceptable regimens include 12 weeks of INH and rifapentine (3HP; 12-dose regimen); 4 months of RIF (with or without INH); 9 months of INH (9H).

Contacts of Persons with Multidrug-Resistant TB

Considering the risk for progressing to multidrug-resistant (MDR) TB disease when prescribing treatment for these persons is crucial; consultation with an MDR TB expert should be obtained.

Pregnancy and Breastfeeding

Women at high risk for progression to TB disease should not delay LTBI treatment while pregnant. Pregnant women can take any of the following regimens for the treatment of LTBI: 4R, 3HR, 9H, or 6H. However, 3HP is not recommended in pregnancy because of limited human data available (*F23,F24*). Breastfeeding is not a contraindication for LTBI treatment. However, patients who are pregnant or breastfeeding should be monitored carefully.

Management of Patients Who Have Missed Doses
When treatment has been interrupted for ≥2 months, the patient should be examined to rule out TB disease. Shorter regimens should be used when possible to increase the chance of treatment completion. DOT should be recommended and arranged, if indicated. Treatment should be extended or restarted if interruptions were frequent or prolonged enough to preclude completion. *Completion of treatment* is based on the total number of doses administered, not on duration alone.

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Supplementary Appendix G
Education and Training Resource List

CDC

Training and Education Products

Many training and education products are available for viewing and downloading on CDC's tuberculosis (TB) Internet site (*G1*). These materials are available in different formats, including fact sheets, brochures, manuals, slide sets, online courses, and videos. Materials are available for both health-care personnel and patients. Print versions of some materials can be ordered online.

- Self-Study Modules on Tuberculosis (*G2*). A series of educational modules designed to provide information about TB in a self-study format for entry-level health-care personnel. The series comprises a total of nine modules that are separated into two courses. The first course, Modules 1–5, provides basic information about TB. The second course, Modules 6–9, provides more specific TB programmatic information. The topics covered by Modules 1–5 include transmission and pathogenesis; epidemiology; targeted testing and diagnosis; treatment; and infection control. Modules 6–9 cover the following topics: managing patients and improving adherence; patient rights and confidentiality; TB contact investigations; and TB outbreak detection and response. All nine modules are commonly used training materials in TB programs across the country. Different forms of continuing education credits are available for each of these modules.
- TB 101 for Health Care Workers Online Course (*G3*). An Internet-based course designed to educate health-care personnel about basic concepts related to TB prevention and control in the United States. The target audience for the course includes newly hired TB program staff and health-care personnel in areas related to TB (e.g., persons who work in correctional facilities or HIV/AIDS clinics).
- Core Curriculum on Tuberculosis: What the Clinician Should Know (*G4*). The Core Curriculum is intended for use as a self-study guide and reference manual for clinicians and other public health professionals caring for persons with or at high risk for TB disease or infection. This curriculum is revised and updated on a regular basis. Continuing education credits are available.
- Understanding the Cohort Review Process (*G5*). The instruction guide describes the cohort review method, how to use it to enhance current TB-related activities, and how to adapt it to your own program area. The 22-minute DVD illustrates the benefits of adopting cohort review and highlights the roles of the cohort review team members.
- CDC Tuberculosis Surveillance Data Training — Report of verified case of tuberculosis (RVCT): Instruction Manual and Participant Manual (*G6*). The instructor manual includes instructions for how to complete each item on the RVCT. It can be used as a reference guide when completing the RVCT. The participant manual is designed to help health-care staff learn how to accurately complete the RVCT. Included are the instructions for how to complete each item on the RVCT and exercises that will help staff apply the instructions to real-life situations.
- TB Contact Investigation Interviewing Skills Course (*G7*). This course is designed as an interactive, skill-building training to improve the abilities of both new and experienced staff who are responsible for conducting TB contact investigation interviews. The course provides an overview of the contact investigation process, basic communication and interviewing skills, and opportunities to apply those skills in role play activities.

TB Centers of Excellence for Training, Education, and Medical Consultation
The TB Centers of Excellence for Training, Education, and Medical Consultation (COEs) (formerly called Model Centers or Regional Training and Medical Consultation Centers [RTMCCs]) (*G8*) are funded by CDC and regionally assigned to cover all 50 states, the U.S. territories, and the U.S.-affiliated Pacific Islands to offer the following activities and resources.

- Training courses that target all public-sector TB providers and staff, including physicians, nurses, case managers, communicable disease investigators, surveillance staff, program managers and supervisors, and outreach staff. For jurisdictions that have dedicated training staff, courses are sometimes developed in a train-the-trainer format in an effort to build the training capacity of state, local, and tribal TB program staff.
- Print materials (e.g., handbooks, manuals, and self-study modules) for health-care providers; TB information cards; posters for physicians on TB treatment regimens; guidelines for implementing DOT and directly observed preventive therapy (DOPT); improving contact investigation performance; diagnosing LTBI; and preventing *M. tuberculosis* transmission in institutional settings; and training materials for numerous target audiences, including school nurses.
- Distance-learning products in different formats (CD-ROM, videos, or Internet-based interactive modules) addressing such topics as TB contact investigation, confidentiality, adherence to treatment, infection control, engineering controls, quality assurance, and clinical concerns.

Find TB Resources Website
CDC maintains an Internet site that is an online searchable database of TB education and training materials and resources available for providers, patients, and the general public (*G9*). Resources are available that apply to particular audiences, including persons who work in the public health field, patients, and targeted groups at high risk (e.g., persons born outside the United States, substance users, homeless persons, persons in correctional facilities, HIV-infected persons, and health-care personnel).

The Tuberculosis Education and Training Network
The TB Education and Training Network (TB ETN) is coordinated by CDC and was formed to bring TB professionals together to network, share resources, and build education and training skills (*G10*). Membership includes representatives from TB programs, correctional facilities, hospitals, nursing homes, federal agencies, universities, the American Lung Association, and other U.S. and international organizations interested in TB education and training. TB ETN is helping to build a cadre of TB educators and trainers with improved skills and abilities, knowledge of available resources, and ability to serve as a resource for high-priority needs (e.g., TB outbreaks and implementation of new guidelines). TB ETN sponsors a biennial conference with presentations and workshops on health education, training, and communication topics.

TB Program Evaluation Network: State and Big City TB Programs
Program staff should widely share lessons learned with other programs and consider publishing results for the larger public health community. One forum available to all TB programs is the TB Program Evaluation Network (TB PEN). TB PEN comprises state and local TB program evaluation *focal points* (staff in each jurisdiction directly funded by CDC who are responsible for TB program evaluation activities) and other TB program staff who are working with or interested in program evaluation. TB PEN focal points participate in conference calls every other month to

share program evaluation successes and challenges to assist one another in improving the quality of their TB program activities. TB PEN collaborates with the TB Evaluation and Training Network (TB ETN) on a biennial conference that enables TB PEN focal points to learn from in-person educational sessions, scientific research lectures, poster presentations, and program evaluation updates at local, state, and federal levels, and from networking with program evaluation colleagues. The TB PEN Steering Committee also maintains an online wiki site that contains program evaluation and quality improvement resources (*G11*).

Other Education and Training Resources

TB infection control products, Mantoux skin testing products, patient education materials, and provision of education and training technical assistance are all available on CDC's Internet site (*G12*). CDC regularly publishes American Thoracic Society (ATS)/CDC and CDC/Advisory Council for the Elimination of Tuberculosis (ACET) statements and guidelines regarding diagnosis, treatment, and control of TB, as well as slide sets and other print materials (e.g., articles from the *Morbidity and Mortality Weekly Report*, other reports, and fact sheets).

TB Program Managers Course

This course is offered periodically by CDC to TB controllers, program managers, public health advisors, and nurse consultants with programmatic responsibilities at the state, city, and regional (within a state) levels. The purpose of the course is to provide participants with the knowledge, skills, and abilities needed to manage a TB prevention and control program, and to assist them in developing a detailed action plan to implement these characteristics at their respective worksites in the form of a planning guide. CDC TB program consultants can provide the details.

Stop TB USA

Stop TB USA provides notification and a summary of education and training updates, current course information, and new educational resources through the biweekly electronic *TB Wire* (*G13*).

National TB Controllers Association

The National TB Controllers Association (NTCA) holds an annual meeting for the national TB control community (*G14*). Widely attended, it offers a principal opportunity for professional development of TB program staff. The National TB Nurse Coalition, the National Society of TB Clinicians, and the Society for Epidemiology in TB Control meet annually during the NTCA meeting. The sections also provide educational opportunities for constituents throughout the year. Some regional TB controller groups offer annual opportunities for their members to participate in training and education activities.

National Jewish Health

National Jewish Health has trained expert TB clinicians for decades and is known worldwide for its TB expertise (*G15*). National Jewish Health provides training for fellows, residents, medical students, and postdoctoral candidates; offers a lecture course on TB on a regular basis; and provides a telephone consultation service on nontuberculous mycobacteria for physicians. It also serves as a training ground, providing extensive opportunities for fellowships for post-degree candidates.

Selected State and Local TB Programs

State and local health departments offer opportunities and resources for TB training and education, including

- annual or other regular TB conferences or symposia,
- contact investigation and interview training,
- technical assistance regarding TB control to all counties,
- training programs for public health staff. and
- TB case conferences and cohort reviews as training mechanisms for clinical, nursing, and outreach staff.

Medical Professional Organizations

Because they are involved with medical practice, research, education, advocacy, and public health, medical professional organizations are principal partners in TB control efforts. Organizations whose memberships include primary care medical practitioners can make substantial contributions to the control, prevention, and elimination of TB by including TB in their training and education agendas. The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) are two of the medical professional organizations that support TB control efforts in the United States. Medical professional organizations can

- provide TB education to their members through meetings, symposia, statements, and Internet sites;
- serve as venues for better communication between the private medical and public health sectors;
- promote the TB research agenda locally and nationally; and
- advocate for resources for strong TB control globally and in the United States.

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Supplementary Appendix H
Research Questions

Despite a sustained decrease in tuberculosis (TB) disease incidence in the United States during the previous 6 decades, with the existing tools, TB will not be eliminated by 2050 (*H1*). Persons born outside the United States now contribute >70% of TB incidence in the United States (*H2*), and without reducing the incidence of TB in countries of origin, TB will not be eliminated in the United States. No silver bullet is on the horizon to combat the disease and make substantial progress in reducing TB incidence worldwide.

Practical innovations for combating the disease are still lacking, and substantial gaps exist in the fundamental understanding of how TB causes disease: Only a rudimentary understanding exists of how the pathogen evades intracellular killing and the immune system. Additionally, no refined understanding exists of the biochemical pathways that characterize the different stages of infection and disease and how to exploit them. Scientific discoveries have the potential to (a) lead to development of effective vaccines and more potent therapeutics that can cure active TB disease within 2 months — or latent TB infection (LTBI) within 1 month; and (b) reveal biomarkers that can identify persons with LTBI who are most at risk for having TB disease or predict relapse after treatment. Redoubling efforts and resources is needed for eliminating TB in the United States and globally. Local, national, and international research is needed to answer some of the following questions and lead to TB elimination worldwide.

Shortening Treatment of Drug-Susceptible and -Resistant TB
The length of and drugs used in treatment of active TB disease have not changed in >40 years. Treatment still requires at least a four-drug regimen with a minimum of 6 months of duration and administration of treatment under directly observed therapy (DOT). This lengthy treatment with DOT requirements increases its cost to TB programs and is a substantial burden to patients, resulting in inadequate adherence and treatment outcomes. Shortening treatment of active TB disease to <6 months remains a crucial research priority for facilitating treatment completion and overall better outcomes.

During the previous 10 years, new and repurposed drugs have progressed into clinical trials, promising an optimal combination of new and existing drugs for a new regimen for drug-susceptible disease. However, these new research efforts have been tempered with the results from multiple Phase 2 and 3 treatment-shortening TB clinical trials with the use of newer fluoroquinolones that have not been effective in lowering the treatment to 4 months (*H3–H5*). From these trials new hypotheses are emerging that point to the importance of limited drug distribution into lesions and organ systems that affect sterilization of populations of tuberculosis bacilli, making shortening of treatment less likely. Notwithstanding those results, other promising ongoing Phase 2 and 3 clinical trials with new (bedaquiline or pretomanid) and repurposed (rifampin, rifapentine, moxifloxacin, linezolid, or clofazamine) drugs that are being used in investigating treatment-shortening regimens for both drug-susceptible and -resistant disease (*H5*,*H6*).

In a study of a randomized dose-ranging trial for pulmonary TB, substituting rifampin for daily rifapentine increased the proportion of participants who became culture-negative for *Mycobacterium tuberculosis* by ≤13%, and the higher exposure of rifapentine was within the

range of potency thought to be needed for shortening treatment to 4 months. After these promising results, in Study 31, a CDC and National Institutes of Health partnership, investigators proposed evaluating the efficacy of a high-dose rifapentine-containing regimen to determine if the single substitution of rifampin for rifapentine makes reducing treatment to 4 months possible (*H7*). A Phase 3 randomized study, RIFASHORT, proposes a trial to assess 1,200-mg and 1,800-mg rifampin-based regimens of 4 months' duration (*H8*). A Phase 3 randomized study, TRUNCATE-TB, from Singapore proposes a trial to assess novel intensive-phase regimens, followed by retreatment regimens for those who relapse. Regardless of these promising new studies, a need exists for randomized controlled clinical trials of even shorter and more effective regimens with newer drugs that get closer to the ultimate goal of a 2-month treatment for TB disease.

Drug-Resistant TB

Treatment regimens for drug-resistant TB use drugs that are less effective, more toxic, and more expensive than those used for drug-susceptible disease. Among patients with multidrug-resistant (MDR) TB disease, ongoing clinical trials of different combinations of second-line drugs and newer drugs are ongoing that attempt to lower the treatment from 18 months to <12 months (*H9*). A standardized treatment regimen based on the Bangladesh MDR TB treatment lasting <12 months has been used in different countries with promising results in shortening treatment. On the basis of the analysis of the metadata from these studies, the World Health Organization (WHO) updated its treatment guidelines for drug-resistant TB in May 2016 and included a recommendation for using a standardized shorter MDR TB regimen of seven second-line drugs with an injectable (*H10*). This new recommendation was expected to be of great benefit to the majority of MDR TB patients worldwide. However, as stated in the updated guidelines, the quality of the evidence supporting these recommendations is low and comes mostly from observational studies with suboptimal follow-up data regarding relapses. In addition, serious reservations exist for potential inappropriate use of this regimen, resulting in worsening resistance (e.g., the emergence of extensively drug-resistant [XDR] TB disease). A need exists for randomized controlled clinical trials that test shorter and more effective regimens based only on oral regimens and fewer and less toxic drugs.

TB Treatments for Special Populations

Studies of TB treatment among pregnant women, breastfeeding women, children, and patients with extrapulmonary disease are lacking. Particular attention should be given to studies of the optimal treatment of children with drug-susceptible and -resistant TB. Additionally, children should be included across all stages of clinical trials to close the gap in the paucity of data. More data are needed regarding length of treatment for all forms of extrapulmonary disease.

Delivery of TB Treatment

The predominant delivery of TB treatment globally is still DOT. However, this one-size-fits-all strategy for treatment delivery has limitations (*H11*). Operational research is greatly needed among different populations and settings that, in addition to treatment outcomes, consider programmatic feasibility, cost-effectiveness, and patient acceptability to optimize strategies of treatment delivery. For example, video DOT has been reported in certain settings to have similar adherence rates as in-person DOT (*H12*).

Treatment of LTBI

An important component of the elimination of TB in the United States remains treatment for persons with LTBI. Until recently, the need to provide a safe and effective short-course LTBI treatment was a major priority for research because the main treatment for LTBI was INH administered for 9 months, which is historically associated with inadequate adherence and treatment completion rates. Since 1995, when the last *Essential Components of a Tuberculosis Prevention and Control Program* was published, several fundamental studies of short LTBI treatment regimens have been completed and that support using shorter regimens.

Studies of short regimens with 3 or 4 months of daily rifampin have demonstrated high quality of evidence with low rates of hepatotoxicity and treatment discontinuation, but these studies were associated with low quality of evidence for efficacy (*H13*). However, in a recent open-label, 9-country trial in which >6,000 patients with LTBI were randomized to receive treatment with a 4-month regimen of daily rifampin (4R) or a 9-month regimen of daily isoniazid (9H), 4R was demonstrated to be not inferior to 9H in preventing active TB, and was associated with higher treatment completion rates and substantially lower rates of hepatotoxicity (*H14*).

Since 2011, a short-course regimen of weekly rifapentine and isoniazid for a total of 12 doses or 3 months (3HP) for treating LTBI has become available with high quality of evidence for efficacy and effectiveness (*H15*). In a landmark study, 3HP administered by DOT compared with INH was associated with statistically significant better treatment completion rates and less hepatotoxicity (*H16*). In a follow-up study among children aged 2–17 years, similar findings were demonstrated (*H17*). Other studies of 3HP have also reported consistently higher completion rates than INH for 9 months (*H18,H19*).

Despite the good results with shorter regimens for LTBI, INH given for 9 months has tended to remain the treatment of choice in the United States among certain providers because of the perceived association of higher cost with 3HP and the initial recommendation that it be administered by DOT. Studies have now demonstrated that 3HP might be a more cost-effective alternative to 9H, particularly if the cost of rifapentine decreases, and if the effectiveness of 3HP can be maintained without DOT (*H20,H21*). A CDC-sponsored study that assessed the adherence to the 3HP regimen taken by self-administered therapy (SAT) reported that the completion rate with self-administration was not inferior to that with DOT (*H22*). Consequently, CDC has now recommended that 3HP can be administered with either SAT or DOT, depending on area protocols and patient characteristics (*H23*).

Additional research priorities for treatment of LTBI include the following:

- Randomized studies among children with the use of rifampin for LTBI treatment, because the majority of the evidence comes from observational studies among adults.
- Studies that assess the feasibility of self-administered therapy with 3HP among different populations in varying settings.
- Studies regarding shorter regimens that account for patients' preferences, comorbidities, and programmatic practices.
- Investigations to define the extent of programmatic monitoring of patients for LTBI treatment, because no randomized trials are available for guiding the frequency of testing or the thresholds for interrupting treatment.
- Treatment regimens for persons likely to be infected with MDR TB strains.

Diagnostic Tools

Molecular Tests

Since the publication of the 1995 *Essential Components of a Tuberculosis Prevention and Control Program*, tests based in molecular technologies have advanced rapidly. GeneXpert MTB/RIF was approved by the Food and Drug Administration and recommended for use globally in 2010 by the World Health Organization (WHO) (*H24*). A newer generation GeneXpert test is expected soon for point-of-care testing both for TB and for rifampin resistance. A next-generation cartridge is also in development and might replace conventional culture as a primary diagnostic tool in certain parts of the world. Operational research is needed to assess the best environments to use these emerging technologies.

Interferon-ɣ Release Assay

Interferon-ɣ release assay (IGRA) testing was introduced in the United States in 2005. The last CDC IGRA guidelines were published in 2010 (*H25*). IGRA tests are now available for use in the majority of public health clinics and by private health-care providers. Although substantial progress has been made in documenting IGRAs' utility, further studies and research are urgently needed to help determine the value and limitations of IGRAs under special conditions and among selected populations. Questions about IGRAs remain.

- Can sensitivity and specificity of IGRAs be improved by testing methods, algorithms, application of different interpretation criteria, or inclusion of additional antigens?
- What is the best approach for determining cut points for IGRA interpretation, including situations where nil values are high or mitogen values are low?
- To what extent does inclusion of a borderline interpretation improve IGRA accuracy?
- What causes variation in IGRA results and to what extent?
- What magnitude of change in interferon-ɣ response indicates new infection?
- After exposure, how long before an IGRA becomes positive?
- What is the clinical significance of IGRA reversion, and how do we limit this phenomenon?

In summary, to eliminate TB, efforts should be redoubled in basic and translational research to develop biomarkers of disease progression, new vaccines, new drug candidates, and new options for shorter regimens. Operational research projects are needed to improve access and delivery of rapid diagnostics and treatment, and to assess quality of treatment.

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