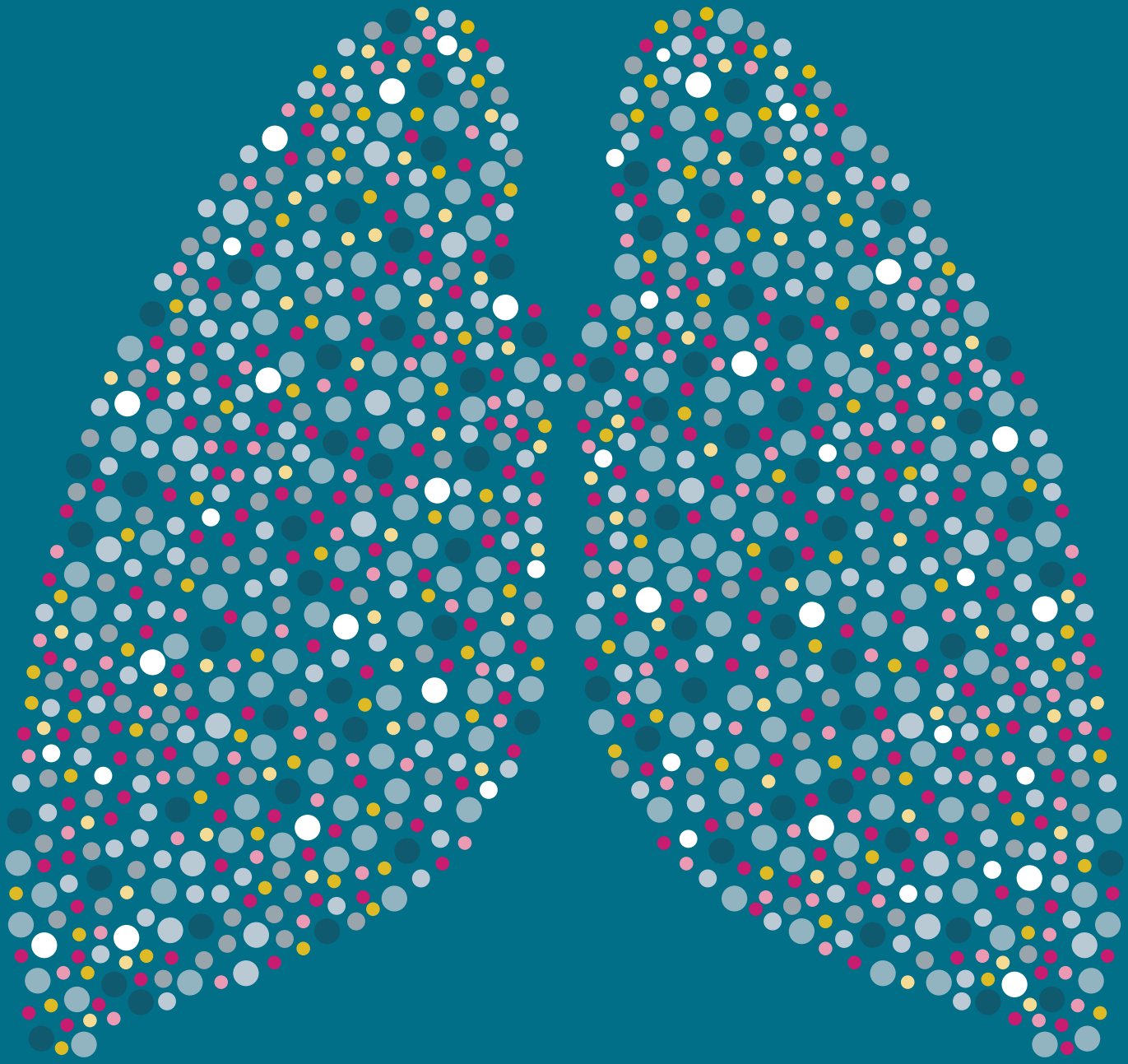

CLINICAL POLICIES & PROGRAM MANUAL

New York City Department of Health and Mental Hygiene
Bureau of Tuberculosis Control

"To breathe with mindfulness is a gift and privilege. Growing up, I learned the practice of Anapana (observation of natural respiration). It was when I was diagnosed with pulmonary tuberculosis—requiring a lung lobectomy—that I experienced the value of this ancient practice. With each mindful breath, I felt alive and grateful. The many hours spent in meditation reignited my lifelong love for painting. I realized that for me, creating art is also a form of meditation. During my TB treatment journey, I received endless love and care from all the staff at the Department of Health. It only felt befitting to create a painting that depicts the essence and beauty of our lungs as a token of my appreciation. The mindful breath and the brush strokes on paper blended together to create this piece of art titled 'Breathe.'" - Sneha D. Maru, MD

MISSION: The New York City (NYC) Bureau of Tuberculosis Control (BTBC) aims to prevent the spread of tuberculosis (TB) and eliminate it as a public health problem in NYC.

GOALS

1 Identify all individuals with suspected or confirmed TB disease and ensure their appropriate treatment, ideally on directly observed therapy (DOT).

2 Ensure that individuals at high risk for progression from latent TB infection to TB disease complete treatment and do not develop disease.

KEY ACTIVITIES

BTBC focuses on the clinical needs of patients and on protecting the public's health through an integrated, dynamic model of core activities and services, including the following:

- Ensure that providers and laboratories report suspected and confirmed TB cases to the NYC Health Department
- Maintain a surveillance system for all TB cases and their contacts, all people suspected of having TB disease, and children younger than five years of age with latent TB infection
- Conduct intensive case management to ensure that TB patients remain under medical supervision until treatment completion, with DOT as the standard of care
- Conduct contact investigations to identify exposed individuals with TB disease or latent TB infection and ensure appropriate treatment
- Operate state-of-the-art chest clinics for TB screening, diagnosis and treatment at no cost to the patient
- Provide medical consultation
- Ensure that all positive cultures for *Mycobacterium tuberculosis* are sent for drug-susceptibility testing and genotyping analysis
- Detect and respond to outbreaks
- Use data to monitor trends, inform programmatic decision-making, and conduct research and evaluation
- Align funding allocations with program priorities
- Collaborate with community-based organizations and healthcare providers to improve TB prevention, care, and management
- Support advocacy to maintain and improve the TB public health infrastructure
- Ensure patient and data confidentiality

CLINICAL POLICIES & PROGRAM MANUAL

Bureau of Tuberculosis Control
New York City Department of Health and Mental Hygiene

Fifth Edition, February 2022

Joseph Burzynski, MD, MPH
Assistant Commissioner, New York City Bureau of Tuberculosis Control

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February 2022

Dear Colleagues,

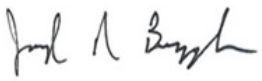
I am excited to share with you the fifth edition of the Bureau of Tuberculosis Control's (BTBC) Clinical Policies and Program Manual, formerly known as the Clinical Policies and Protocols Manual. This new edition presents a broader scope of activities within BTBC, all of which are critical components in the effort to reduce tuberculosis (TB) as a public health threat in New York City (NYC).

With a persistently high global TB burden and increasing TB drug resistance, efforts to identify, treat, and prevent TB remain a critical challenge. TB is spread through the air, the air that we all breathe and share, and our mission is to make sure it is free from the risk of TB. While we have had success over the past 25 years in reducing the incidence of TB in NYC, a large number of people, perhaps as many as one million New Yorkers, have latent TB infection (LTBI) and are at risk of developing TB in the future. To make further progress toward our goal of reduced TB burden and eventual elimination, we will need to make continued progress not only in identifying and treating active forms of TB disease, but also in preventing TB among high-risk individuals.

As we move forward, we will continue to be a leader in the fight against TB. We deliver our services with a focus on patient-centered care and a commitment to the community. We strive to continuously improve through the implementation of new diagnostic tools, treatments, and strategies, and will continue to work with providers and communities across the city to accomplish our collective goals.

As a disease that can impact all aspects of a patient's life, TB often causes tremendous suffering for the individuals and families affected. We must be persistent in our efforts to reduce this burden. I am committed to sustaining our progress and believe that this new edition of the manual will benefit our staff in their day-to-day efforts to care for TB patients in NYC and to protect the public's health. I look forward to the continued support of everyone in BTBC and all of our partners in this effort.

Sincerely,



Joseph N. Burzynski, MD, MPH
Assistant Commissioner, Bureau of Tuberculosis Control

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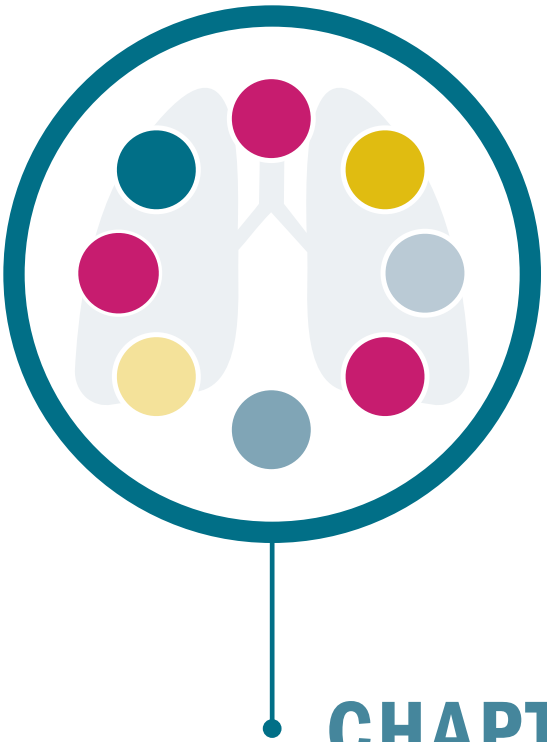


CHAPTER 1: INTRODUCTION

ABOUT THE FIFTH EDITION

This program manual describes activities and policies of the New York City (NYC) Health Department Bureau of TB Control (BTBC) and NYC Health Department TB Clinics related to the prevention, treatment, and control of tuberculosis (TB).

The first version of the manual was published in 1993 and was intended for the medical providers of BTBC as a reference guide for TB diagnosis, treatment, and prevention. With subsequent editions, the manual became more broadly used by other BTBC staff and healthcare providers in the community. Updated editions followed in 1997, 1999, and 2008.

This fifth edition of the manual is intended primarily as a reference document for BTBC staff. As an organization that provides direct clinical and public health services, BTBC has expanded the scope of activities discussed in the manual from previous versions to cover the full breadth of its work.

This manual is not intended to supersede clinical judgment. Instead, its purpose is to outline the functions and practices of NYC's TB Control Program and to provide updated policies, practices, and guidelines regarding TB prevention and care in NYC. Community providers who have questions regarding appropriate TB clinical practice should always contact the **NYC TB HOTLINE** at **(844) 713-0559**.

Guidelines in the manual are based on recommendations from the Centers for Disease Control and Prevention (CDC), the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Infectious Diseases Society of America (IDSA), and the World Health Organization (WHO). Additional references and guidelines include the Curry Center's *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd Edition*, and the American Academy of Pediatrics' *Red Book 2018-2021 Report of the Committee on Infectious Diseases*. Instances where BTBC practice differs from these recommendations have been noted in the text.

The fifth edition of the manual contains numerous tools intended to aid readers as they utilize the manual. These tools include:

1. **Callouts:** In each chapter, there are callouts highlighting resources, guidelines, cross-references, and sources of additional information on a topic.

Forms: Forms available for use by BTBC staff and partners

Clinical guidance: Key clinical recommendations

Laboratory-related information: Laboratory processes, services, and recommendations

Treatment-related information: Recommendations, dosing, side effects, and important drug interactions for TB medications

Links: Links to additional resources and information

Laws governing TB care in NYC: Information about the legal framework guiding TB policy and practice

Information and resources related to HIV: Considerations for TB testing, care, and treatment for persons with HIV infection

Contact BTBC: Guidance about when and how to contact BTBC

2. **Key Sources:** After each chapter, there is a comprehensive list of resources that can be referred to for additional information regarding that topic area.

3. **Appendices:** At the end of the manual, there are additional resources to supplement the information discussed in each chapter. This includes a complete list of BTBC policies, instructions on how to induce sputum, and appropriate dosages for TB medications.

4. **Tuberculosis Classification System:** BTBC uses a modified version of the international system for classifying TB patients. These classifications are based on the pathogenesis of TB and use a rating scale of zero to five. This system is used to ensure consistency in reporting across BTBC's surveillance and electronic medical record (EMR) systems and is referenced throughout the manual. The classification of each patient is informed by laboratory data, clinical judgment, and case management. (See *Appendix A: International Classification of Tuberculosis*.)

ABOUT TUBERCULOSIS

TB is an airborne disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*). TB transmission occurs when a person with active pulmonary or laryngeal TB disease expels droplet nuclei containing tubercle bacilli from their respiratory system into the air by coughing, singing, yelling, or speaking. A susceptible individual may inhale the bacilli and become infected.

TB has two stages: latent TB infection (LTBI) and active disease. An individual is diagnosed with LTBI when they have TB bacteria in their body but their immune system keeps the bacteria from proliferating. These individuals do not feel sick, do not have symptoms consistent with active disease, and cannot transmit TB to others. It is estimated that one-quarter of the world's population has LTBI.

In individuals with active TB disease, *M. tuberculosis* bacteria overcome the body's immune defenses, actively reproduce, and cause illness. These individuals have symptoms and can potentially infect others if their site of disease is respiratory (i.e., pulmonary or laryngeal). Symptoms of respiratory TB include a persistent cough, hemoptysis, chest pain, loss of appetite, weight loss, chills, fever, or night sweats. People can develop TB disease anywhere in their body. However the most common site of disease is the lungs. People infected with TB bacteria have a five to 15% lifetime risk of developing TB disease. Persons with weakened immune systems—such as those with untreated human immunodeficiency virus (HIV) infection or other immunosuppressive conditions—have a much higher risk of becoming ill.

TB is treatable and preventable, but in the absence of effective treatment, TB disease may lead to serious illness and death. Globally, TB is a leading cause of death by an infectious disease, killing more people each year than HIV, malaria, or influenza. The United States (U.S.) is considered a low burden country, with a TB incidence of approximately three cases per 100,000 persons. Within the U.S., however, NYC has a much higher burden of disease—approximately seven cases per 100,000 persons annually.

A detailed description of TB epidemiology, surveillance data, and trends in NYC can be found in the Health Department's **ANNUAL TUBERCULOSIS SUMMARY**, available online at **www.nyc.gov/health**

INNOVATIONS IN TUBERCULOSIS CARE IN THE LAST DECADE

DIAGNOSIS

›› Interferon Gamma Release Assays

When testing for TB infection, there are two categories of tests: interferon gamma release assays (IGRA) and tuberculin skin tests (TST). IGRAs are a newer blood-based test that are more specific for TB infection than the TST. IGRAs are the preferred test for TB infection in NYC Health Department TB clinics and investigations in the community. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection.*)

›› Nucleic Acid Amplification Testing

Nucleic acid amplification (NAA) tests use molecular methods to detect the presence of *M. tuberculosis* complex. The NYC Public Health Laboratory (NYC PHL) and hospital and commercial laboratories use these molecular tests to rapidly confirm the presence of TB, determine if there are genetic mutations that suggest drug resistance, and assist in determining if patients can be released from isolation. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease* and *Chapter 12: Tuberculosis Genotyping and Cluster Investigation.)*

›› Whole Genome Sequencing

Whole genome sequencing (WGS) utilizes genetic information from the entire TB genome and can be used to identify *M. tuberculosis* complex and species within it, detect genetic mutations associated with drug resistance, and identify the presence of single nucleotide polymorphisms (SNP) to characterize and compare TB strains. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease* and *Chapter 12: Tuberculosis Genotyping and Cluster Investigation.*)

›› United States Preventive Services Task Force Grade B Recommendation for LTBI testing

Testing for LTBI among adults at high-risk for TB is now recommended by the new United States Preventive Services Task Force (USPSTF) guidelines at a Grade B level. This means that there is a high certainty of moderate benefit of this service and it should be provided. By identifying persons with TB infection and connecting them to LTBI treatment, future TB cases can be prevented. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection.*)

TREATMENT

›› Update to Clinical Practice Guidelines for Treatment of Drug-Susceptible Tuberculosis

The 2016 ATS/IDSA/CDC treatment guidelines for drug-susceptible TB recommend comprehensive care for all patients with active TB disease, noting that case management, including directly observed therapy (DOT), is essential to ensure effective TB treatment outcomes. These updated guidelines recommend use of daily therapy during the intensive phase and daily or thrice-weekly intermittent therapy during the continuation phase. Biweekly therapy during the continuation phase is no longer recommended. Furthermore, the new guidelines recommend that patients who have TB disease and HIV infection begin

antiretroviral therapy (ART) while being treated for TB, and offer updated recommendations on the timing of initiation of treatment for both diseases. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

Bedaquiline

A new drug, bedaquiline (BDQ), has been approved for use in patients with multidrug-resistant TB (MDR-TB). The addition of a new drug from a novel class of compounds has led to the development of new all-oral regimens for the treatment of MDR-TB, as recommended by the WHO, CDC, ATS, ERS, and IDSA. The use of this new drug is explained in detail in this manual. (See *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults*.)

Treatment for Extensively Drug-Resistant Tuberculosis

The Food and Drug Administration has approved a six-month regimen of BDQ, pretomanid, and linezolid for use in patients with extensively drug-resistant TB (XDR-TB), treatment-intolerant TB, or non-responsive pulmonary TB. (See *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults*.)

Electronic Directly Observed Therapy

Directly observed therapy (DOT) is the standard of care for treating patients with active TB disease in NYC. During DOT, a patient is observed by a trained healthcare worker while ingesting anti-TB medications. BTBC now offers electronic DOT (eDOT) to remotely monitor patients ingesting anti-TB medications in addition to in-person DOT. Live video eDOT (LVDOT) is conducted via video conferencing; with recorded VDOT (RVDOT), the patient submits a recording of themselves taking the medication, which is then reviewed by a DOT worker. eDOT offers increased convenience for both patients and staff. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)

Short Course Regimens for Latent Tuberculosis Infection

Short-course rifamycin-based regimens for LTBI are recommended due to increased safety, tolerability, and treatment completion in comparison to INH. Rifampin for four months and the 12-week regimen 3HP are the preferred regimens in NYC Health Department TB clinics. 3HP consists of a 12-week regimen of once-weekly isoniazid and rifapentine. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.)

Treatment of Tuberculosis and Human Immunodeficiency Virus

Guidelines for the treatment of HIV are rapidly evolving. New recommendations for the treatment of TB patients with HIV infection include the recognition that, for the majority of patients, earlier initiation of HIV treatment decreases mortality. While a complete guide for all possible treatment regimens for patients with HIV infection is beyond the scope of this manual, BTBC provides guidance for treating patients with TB disease who have concomitant HIV infection. Physicians should always coordinate treatment with an HIV provider and refer to the most recent HIV guidelines. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

NEW YORK CITY HEALTH CODE

There have been several changes to the NYC Health Code since the last publication of the manual.

- In 2009, the NYC Health Code was amended to require that healthcare providers submit a discharge plan for all patients with infectious TB disease prior to release from the hospital.
- In 2012, the Health Code requirement to test new entrants to a NYC secondary school was eliminated.
- As of 2017, providers and laboratorians are now required to report any child younger than five years of age with a positive test for TB infection along with the result of their chest radiograph (CXR) and any LTBI treatment regimen initiated. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City.*)
- In 2019, the NYC Health Code was amended to require laboratories to report all results of blood-based tests for TB infection, including negative results.

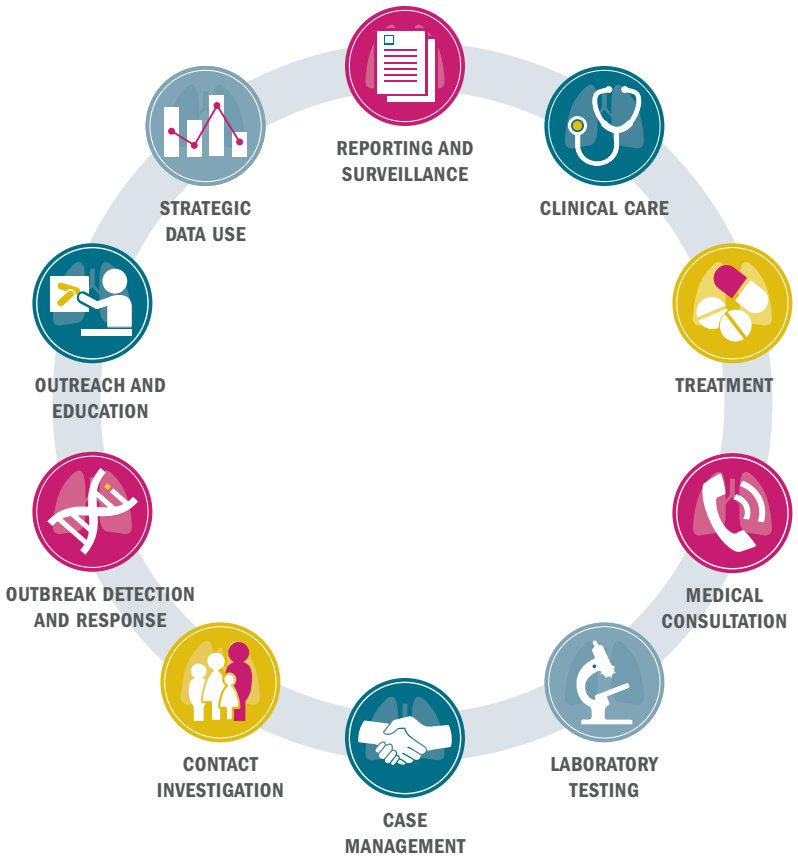
NON-STIGMATIZING LANGUAGE

BTBC is committed to promoting patient-centered, non-stigmatizing language in this manual and beyond. From a patient perspective, common TB-related terminology such as "defaulter," "suspect," or "non-compliant" may be viewed as negative and judgmental, or evoke a sense of blame or shame for the patient with respect to their TB status. In this manual—excluding instances in which references are made to specific local laws and policies—the terms "person lost to follow-up," "person with signs and symptoms consistent with TB disease," and "non-adherent" are used instead. By moving towards patient-centered terminology, BTBC aims to empower patients, recognize their individual personhood, and fight the stigma associated with TB.

THE ROLE OF THE BUREAU OF TUBERCULOSIS CONTROL IN TUBERCULOSIS CARE AND PREVENTION IN NEW YORK CITY

BTBC functions through an integrated and dynamic model of core activities and services. These include surveillance, case management, contact investigation, direct patient care, medical consultation, outbreak detection and response, education, training, outreach, research, and program evaluation. With a focus on the public health and clinical care needs of patients, their families, and NYC communities—and consistent with local, state and national laws, regulations, and mandates—BTBC works to ensure effective TB care, prevention, and control in NYC.

The NYC Health Department operates four TB clinics located in the Bronx, Brooklyn, Manhattan, and Queens. These clinics serve as key TB referral centers for a variety of entities including community healthcare providers, homeless shelters, social service providers, and drug treatment centers. They also evaluate immigrants and refugees who arrive in NYC with a Class B status based on notifications from the CDC Division of Global Migration and Quarantine. Health Department clinics provide comprehensive TB diagnostic and treatment services, including testing and treatment for TB disease and LTBI, sputum



induction, medical evaluation, CXRs, HIV testing, and DOT services. All services and medications at the TB clinics are free of charge to all patients regardless of immigration or insurance status.

TB is a reportable condition in NYC, and staff review all TB reports received by BTBC for timeliness, completeness and accuracy, and to ensure prompt, appropriate, and effective TB diagnosis and treatment for reported individuals. Surveillance for TB disease also enables BTBC to quickly initiate case management and other public health interventions, monitor TB trends, identify and interrupt ongoing TB transmission, and inform programmatic initiatives and policy decisions.

BTBC provides case management services to every patient with TB disease in NYC, persons with clinical suspicion of TB disease, and contacts to infectious TB patients regardless of where they receive clinical care. These services include patient education, patient interviews, medical chart reviews, contact identification, contact evaluation, DOT, and medical consultation. Together, these services ensure that every patient is able to complete TB evaluation and treatment in a timely fashion.

Through community and provider-based outreach efforts, BTBC actively works to detect, treat, and prevent TB in high TB burden populations. Culturally and linguistically appropriate TB educational materials are utilized to raise awareness about TB and engage populations most at risk for developing TB.

Altogether, BTBC weaves clinical and public health practices to provide the best possible TB care to all individuals and communities affected by TB in NYC.

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CHAPTER 2: DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

INTRODUCTION

Evaluation, testing, and treatment for latent tuberculosis (TB) infection (LTBI) among persons at high TB risk are essential components of TB prevention and elimination efforts. Appropriate treatment of persons with LTBI can prevent progression to active TB disease and reduce morbidity and mortality. Although there are several options available for the testing and treatment of LTBI, the Bureau of TB Control (BTBC) prefers the use of blood-based tests and short-course treatment regimens for eligible persons whenever feasible. Routine clinical monitoring and case management can facilitate treatment completion and lead to improved health outcomes.

PRIORITY POPULATIONS FOR TUBERCULOSIS INFECTION SCREENING AND EVALUATION

TB screening refers to the identification of previously unrecognized TB disease or disease precursor in an asymptomatic population by history, examination, tests, or procedures. Prioritization for TB screening is based on research indicating that certain populations are at increased risk for becoming infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) or—if already infected—for progressing to active TB disease. Screening for TB risk among asymptomatic persons should be conducted to identify those for whom a screening test for TB infection is indicated.

Persons at increased risk for TB infection include those with close contact to a person diagnosed with infectious TB disease; those born in or having recently traveled or resided in a country with a high TB incidence (i.e., any country other than the U.S., Canada, Australia, New Zealand, or a country in Western or Northern Europe); and those who live or work in settings where TB exposure may be possible.

Persons at higher risk for progression to active TB disease include, but are not limited to: persons with recent TB infection (within the past two years); immunosuppression (e.g., human immunodeficiency virus [HIV] infection or taking immunosuppressive medications); history of untreated or inadequately treated TB disease; certain medical conditions (e.g., silicosis, end-stage renal disease); and young age (younger than five years of age). *(See Table 2.1: Persons at High Risk for Tuberculosis Infection or Progression to Active Tuberculosis Disease.)*

BTBC has developed a TB RISK ASSESSMENT TOOL to help healthcare providers identify asymptomatic individuals at risk for TB for whom a test for TB infection is indicated. Persons at minimal risk for TB infection are not recommended for testing. (See *Appendix B: Tuberculosis Risk Assessment Tool*.)

TESTS FOR TUBERCULOSIS INFECTION

There is no gold standard test to detect TB infection. Currently available tests for TB infection include interferon-gamma release assays (IGRA) or the tuberculin skin test (TST). Neither IGRAs nor the TST can distinguish between LTBI and active TB. Neither test replaces clinical judgment, as either test may be falsely negative despite the presence of TB infection. The use of both IGRA and TST is not recommended for routine testing. However, it may be helpful in diagnosing TB infection when the first test is negative but clinical suspicion for TB is high or the risk of infection, progression to TB disease, or poor outcome is increased. In these circumstances, a positive result on either test would indicate TB infection.

When testing for TB infection, BTBC prefers an IGRA for persons two years of age and older and uses the TST for children younger than two years of age.

TABLE 2.1: Persons at high risk for tuberculosis infection or progression to active tuberculosis disease

PERSONS AT HIGH RISK FOR TB INFECTION	PERSONS AT HIGH RISK FOR PROGRESSION TO TB DISEASE

• Individuals with close contact to a person diagnosed with infectious TB disease
• Persons born in a country with a high TB incidence*
• Persons who traveled or resided in a high TB incidence area* for one month or more consecutively
• Persons who live or work in settings where TB exposure may be possible:
  • Healthcare facilities§
  • Correctional facilities
  • Homeless shelters
  • Mycobacteriology laboratories
• Infants, children, and adolescents at risk (See *Appendix B: Tuberculosis Risk Assessment Tool*)
	• Close contact to a person diagnosed with infectious TB disease
	• Conversion of test for TB infection¥
	• Persons with immunosuppression, such as:
	  • HIV infection
	  • Immunosuppressive therapy±
	  - Prolonged corticosteroid use (equal to or more than 15 mg/day prednisone for one month or more)
	  - Use of other immunosuppressive medications (e.g., TNF-α inhibitors, JAK inhibitors, IL-1 receptor antagonists, chemotherapy, organ transplant medications)
	  - Some cancers (e.g., leukemias, lymphomas, head, neck, or lung cancers)
	• Persons with previous TB disease
	  • Evidence of old, healed TB lesions on chest radiograph
	  • History of untreated or inadequately treated TB disease
	• Persons with clinical conditions or procedures such as:
	  • Silicosis
	  • Diabetes mellitus
	  • End-stage renal disease
	  • Body weight greater than or equal to 10% below ideal body weight or body mass index less than 18.5 kg/m^2
	  • Organ transplantation
	  • Gastrectomy
	  • Chronic malabsorption syndromes
	  • Jejunoileal bypass
	• Persons who inject illicit drugs or smoke tobacco products
	• Infants and children age younger than 5 years of age with a positive test for TB infection

Source: *Adapted from Centers for Disease Control and Prevention. (2005). Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. Morbidity and Mortality Weekly Report, 54(17), 4-5.*

* Any country other than the United States, Canada, Australia, New Zealand, or outside Western or Northern Europe, is considered a high TB incidence area.

§ Includes hospitals, long-term care facilities, and drug treatment centers

¥ Either by history or evidence of conversion of TB test result (change from negative to positive IGRA result or an increase of 10 mm or more in size of TST reaction) within a 2-year period

± Persons with medical conditions which may require immunosuppressive therapy (e.g., rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriasis) should receive a screening test for TB infection prior to initiation of the immunosuppressant agent(s).

Abbreviations Used: HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; IL-1=interleukin-1; JAK inhibitors=Janus kinase inhibitors; kg= kilograms; m^2=meters^2; mg=milligrams; mm=millimeters; TB=tuberculosis; TST=tuberculin skin test; TNF-α= tumor necrosis factor-alpha

INTERFERON-GAMMA RELEASE ASSAYS

IGRAs are a blood-based in-vitro immunologic assay designed to measure the interferon-γ response of T lymphocytes sensitized to specific *M. tuberculosis* antigens (ESAT-6, CFP-10) that are absent from all bacille Calmette-Guérin (BCG) strains and most nontuberculous mycobacteria (NTM), with the exception of *M. kansasii*, *M. marinum*, and *M. szulgai*. IGRAs have excellent sensitivity (i.e., test is positive when TB infection is present) and, unlike the TST, are unaffected by a person's BCG vaccination status or by their prior sensitization to the majority of NTMs. IGRAs are thus more specific than the TST for *M. tuberculosis* infection (i.e., fewer false-positive results).

IGRAs have been available in the U.S. since 2001; the two IGRAs currently available are the QuantiFERON®-TB Gold Plus (QFT) and T-Spot®.TB (T-Spot). Available IGRAs may change, so current Centers for Disease Control and Prevention (CDC) recommendations should be referenced for the latest guidance. Laboratories report IGRA results according to the reporting algorithms established by the manufacturer. Laboratory results include both qualitative and quantitative data in the provider report.

QFT: QFT results are reported as either "positive," "negative," or "indeterminate." Quantitative data are reported for TB Antigen Tube 1 antigens (TB1; ESAT-6, CFP-10), TB Antigen Tube 2 antigens (TB2; ESAT-6, CFP-10, additional peptides), positive (Mitogen) control, and negative (Nil) control values.

Both TB1 and TB2 antigen tubes contain the *M. tuberculosis* antigens ESAT-6 and CFP-10. The TB1 tube contains peptides from ESAT-6 and CFP-10 that are designed to elicit cell-mediated immune responses from CD4+ T-helper lymphocytes. The TB2 tube contains additional peptides targeted toward cell-mediated immune responses from CD8+ cytotoxic T cells, which have been shown to be more frequently detected in persons with active TB disease versus LTBI and may be associated with recent *M. tuberculosis* exposure.

A QFT result is positive if the Nil value is ≤ 8.0 IU/ml and either TB antigen tube minus Nil is ≥ 0.35 IU/ml and ≥ 25% of the Nil value. A negative QFT result requires both antigen tubes minus Nil to be < 0.35 IU/ml, or ≥ 0.35 and < 25% of Nil value, and the mitogen minus Nil to be ≥ 0.5 IU/ml.

Some QFT results may be indeterminate due to processing errors or the patient's inability to respond to either control. If the results of the QFT are indeterminate, repeat the QFT. If two different QFT specimens yield indeterminate results, clinical judgment is used to determine if the patient has likely TB infection. (See *Table 2.2: Interpretation of QuantiFERON-TB Gold Plus Results*.)

TABLE 2.2: Interpretation of QuantiFERON-TB Gold Plus (QFT) results

<table>
<tr><th>NIL (IU/ml)</th><th>TB1 MINUS NIL (IU/ml)</th><th>TB2 MINUS NIL (IU/ml)</th><th>MITOGEN MINUS NIL (IU/ml)*</th><th>QFT-PLUS RESULT</th><th>REPORT/ INTERPRETATION</th></tr>
<tr><td rowspan="4">≤ 8.0</td><td>≥ 0.35 and ≥ 25% of Nil value</td><td>Any</td><td rowspan="2">Any</td><td rowspan="2">Positive†</td><td rowspan="2">M. tuberculosis infection likely</td></tr>
<tr><td>Any</td><td>≥ 0.35 and ≥ 25% of Nil value</td></tr>
<tr><td>< 0.35 or ≥ 0.35 and < 25% of Nil value</td><td>< 0.35 or ≥ 0.35 and < 25% of Nil value</td><td>≥ 0.5</td><td>Negative</td><td>M. tuberculosis infection NOT likely</td></tr>
<tr><td>< 0.35 or ≥ 0.35 and < 25% of Nil value</td><td>< 0.35 or ≥ 0.35 and < 25% of Nil value</td><td>< 0.5</td><td rowspan="2">Indeterminate‡</td><td rowspan="2">Likelihood of M. tuberculosis infection cannot be determined</td></tr>
<tr><td>> 8.0§</td><td colspan="3">Any</td></tr>
</table>

Source: QuantiFERON-TB Gold Plus (QFT-Plus) Elisa [package insert]. Germantown, MD: Qiagen; 2017.

* Responses to the Mitogen positive control (and occasionally TB Antigens) can be outside the range of the microplate reader. This has no impact on test results. Values > 10 IU/ml are reported by the QFT-Plus software as > 10 IU/ml.

† Where *M. tuberculosis* infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QFT-Plus ELISA. If repeat testing of one or both replicates is positive, the test result is considered positive.

‡ Refer to package insert for possible causes.

§ In clinical studies, less than 0.25% of subjects had interferon gamma levels of > 8.0 IU/ml for the Nil Value.

Abbreviations Used: IU=international units; ml=milliliters; *M. tuberculosis=Mycobacterium tuberculosis*; TB=tuberculosis

T-SPOT: T-Spot results are reported as "positive," "negative," "borderline," or "invalid." Quantitative data are reported for the Panel A (ESAT-6) and Panel B (CFP-10) TB antigens, positive (Mitogen) control, and negative (Nil) control spot counts. Results are interpreted by subtracting the spot count in the Nil control from the spot count in Panel A and Panel B. For a valid test, the Nil control has ≤ 10 spots; if Panel A or B minus Nil has ≤ 4 spots, then the Mitogen must also have ≥ 20 spots for a valid result. T-Spot is the only IGRA test that gives a borderline result.

T-Spot results may be invalid due to inappropriate blood storage conditions, delay in sample transport, patient specific conditions, or laboratory error. In the case of borderline or invalid results, repeat the T-Spot test. If two different T-Spot specimens yield borderline or invalid results, clinical judgment is used to determine if the patient has likely TB infection. (See *Table 2.3: Interpretation of T.Spot.TB Test Results*.)

TABLE 2.3: Interpretation of T-SPOT.*TB* test results

NIL (spots)	PANEL A MINUS NIL (spots)	PANEL B MINUS NIL (spots)	MITOGEN (spots)	T-SPOT.*TB* RESULT	COMMENT
≤ 10	≥ 8	≥ 8	Any	Positive	8 spots or more in either Panel A-Nil or Panel B-Nil (Panel A-Nil **or** Panel B-Nil)
	5, 6, or 7	5, 6, or 7	Any	Borderline*,†	5, 6, or 7 spots (highest of Panel A-Nil **or** Panel B-Nil)
	≤ 4	≤ 4	≥ 20	Negative	Mitogen control has 20 spots or more and **both** Panel A-Nil and Panel B-Nil have 4 spots or fewer
			< 20	Invalid*,‡	Mitogen control has fewer than 20 spots and **both** Panel A-Nil and Panel B-Nil have 4 spots or fewer
> 10	Any	Any	Any	Invalid*,‡	Nil control has more than 10 spots

Source: T-Spot.TB [package insert]. Marlborough, MA: Oxford Immunotec; 2012.

*Refer to package insert for possible causes.

† Results where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5,6, or 7 spots should be considered Borderline (equivocal) and retesting by collecting another patient specimen is recommended.

‡ Invalid results should be reported as "Invalid" and it is recommended to collect another sample and re-test the individual.

TUBERCULIN SKIN TEST

The TST is an in-vivo test that measures cell-mediated immune response to a large number of mycobacterial proteins present in tuberculin (or purified protein derivative [PPD]).

BTBC staff are trained in the placement and reading of a TST in the Mantoux method. (See *Appendix C: Administering the Tuberculin Skin Test*.) In the Mantoux method, a trained healthcare provider injects 0.1 milliliter (ml) of tuberculin intradermally into the volar surface of the person's forearm. The provider instructs the patient to return to the clinic 48 to 72 hours following the injection so that the provider can measure the induration (not erythema) of the skin reaction at the injection site.

BTBC does not accept or recommend self-reading of the TST. The size of the measured induration (a hard, dense, raised formation) and the patient's individual risk factors define the interpretation of the TST. Based on the sensitivity and specificity of the TST and the prevalence of TB in different groups, three cut-points have been recommended for determining a positive tuberculin reaction. (See *Table 2.4: Criteria for Determination of a Positive Tuberculin Skin Test Result*.)

Providers can administer the TST to all persons at risk for TB infection, including pregnant persons and persons with HIV infection. Persons with a documented prior positive TST result (or reliable self-report) do not require repeat testing; additionally, repeat TST testing may cause a prominent local reaction resulting in necrosis of the skin and subcutaneous tissue.

TWO-STEP TUBERCULIN SKIN TESTING: Healthcare workers or others with occupational exposure to TB (e.g., employees or residents of nursing homes and other congregate settings) may be required to have baseline and annual screening for TB. When baseline screening includes the TST, a two-step testing process is performed. If the initial TST is negative, a second TST is administered, typically within one to three weeks after the initial (negative) test. The response to the second TST is recorded as the baseline result.

Some persons with remotely acquired TB infection may have a diminished immune response to the initial test. If a two-step baseline TST is not performed, those testing positive at the next annual testing may be incorrectly identified as being newly infected due to a "boosting" of their immune response by the initial test. Boosting is most common in persons older than 55 years of age and can also occur in BCG-vaccinated persons. Two-step testing is not performed when an IGRA is the initial TB test.

TABLE 2.4: Criteria for determination of a positive tuberculin skin test result

SIZE OF INDURATION	CRITERIA FOR DETERMINATION OF POSITIVE RESULT
≥ 5 mm	Persons who: • have had recent contact to someone with infectious TB disease • have HIV infection or other immunosuppressive conditions • have fibrotic changes on chest radiograph consistent with old TB disease • are currently taking certain medications that can cause immunosuppression, such as: - anti-TNF-α inhibitor treatment (e.g., infliximab, etanercept), JAK inhibitors, Interleukin receptor antagonists - medications after organ transplantation - steroids (equivalent to 15 milligrams of prednisone or more/day for one month or more)
≥ 10 mm	Persons who: • were born in OR traveled/resided ≥ one month consecutively in a country with a high TB incidence rate* • live or work in institutional settings where exposure to TB may be possible± (e.g., healthcare facilities, correctional facilities, homeless shelters, mycobacteriology laboratories) • have medical conditions associated with increased risk of progression to active TB disease, including: - silicosis - diabetes mellitus - end-stage renal disease - gastrectomy - jejunoileal bypass - certain hematologic disorders (e.g., leukemias or lymphomas) - specific malignancies (e.g., carcinoma of the head, neck, or lung) • are younger than 5 years of age • inject illicit drugs
≥ 15 mm	Persons: • at low risk for TB disease • for whom testing is not generally indicated

* Countries with high TB incidence rates include any country other than the United States, Canada, Australia, New Zealand, or a country in Western or Northern Europe.

± As defined by local epidemiological risk and/or regulations. Healthcare facilities includes hospitals, long-term care facilities, and drug treatment centers.

Abbreviations Used: HIV=human immunodeficiency virus; JAK=Janus kinase; mm=millimeters; *M. tuberculosis*=*Mycobacterium tuberculosis*; TB=tuberculosis

COMPARING INTERFERON GAMMA RELEASE ASSAYS AND TUBERCULIN SKIN TESTS

There are advantages and disadvantages associated with each type of test for TB infection. (See *Table 2.5: Comparison of Interferon Gamma Release Assays and Tuberculin Skin Test*.)

TABLE 2.5: Comparison of interferon gamma release assays (IGRA) and tuberculin skin tests (TST)

FEATURE	IGRA	TST
Antigens	• More specific to *M. tuberculosis* complex[a]	• Less specific to *M. tuberculosis* complex
Boosting	• No; two-step testing not needed	• Yes, with serial testing; two-step testing is recommended at baseline in settings that require surveillance testing
False-positives	• Not with BCG, but with a few environmental mycobacteria[b]	• With both BCG and some environmental mycobacteria
Interpretation	• Positive/negative result (may also have indeterminate or borderline results that require retesting) • Minimal inter-reader variability	• Based on size of induration (not erythema) and patient's relative risk for TB exposure or development of disease • Subject to errors during implantation and interpretation
Time frame	• Blood samples must be processed within a manufacturer-determined time frame	• Test must be read between 48 and 72 hours after administration
Minimum number of visits	• One	• Two

a TB antigens ESAT-6 and CFP-10

b False-positive results may occur with *Mycobacterium sulgazi, Mycobacterium kansasii, Mycobacterium marinum*

Abbreviations Used: BCG=bacille Calmette-Guérin vaccine; *M. tuberculosis*= *Mycobacterium tuberculosis*; TB=tuberculosis; TST=Mantoux tuberculin skin test

FALSE-NEGATIVE AND FALSE-POSITIVE RESULTS: Certain medical conditions and other factors may affect the results of IGRAs and TSTs. (See *Table 2.6: Factors associated with false-negative or false-positive results for Interferon Gamma Release Assay and Tuberculin Skin Test*.)

TABLE 2.6: Factors associated with false-negative or false-positive results for interferon-gamma release assays and tuberculin skin tests

CONDITION	FALSE-NEGATIVE*	FALSE-POSITIVE*
Infections	• Viral illnesses (HIV, measles, varicella) • Bacterial illnesses (typhoid fever, pertussis, brucellosis, typhus, leprosy) • Early TB infection (less than 8 weeks) • Severe TB disease (meningitis, disseminated) • Fungal disease	• Exposure to *M. kansasii*, *M. marinum*, and *M. szulgai* (for IGRA) • Exposure to additional NTM (for TST)
Vaccines[1]	• Measles, mumps, rubella • Polio • Varicella • Smallpox	• BCG vaccine (for TST)
Concurrent clinical and/or demographic factors	• Metabolic abnormalities • Chronic renal failure • Primary immunodeficiencies • Malignancies (e.g., lymphomas, leukemia) • Sarcoidosis • Poor nutrition • Very young or elderly age • Protein deficiency	• Transfusion with whole blood from donors with known positive TST
Drugs and technical factors	• Corticosteroids, TNF-α blockers, JAK inhibitors, Interleukin receptor antagonists, or other immunosuppressive medications • Chemotherapy • Material—poor quality, inadequate dose (for TST), improper storage (exposure to heat/light), or expired • Administration—not injected intradermally (for TST) • Reading—inexperienced reader, recording error, read too early/late (TST)	• Reading – inexperienced reader (for TST)
Interpretative	• Misclassification of risk group or erroneous decrease in mm reading of induration (for TST)	• Misclassification of risk or erroneous increase in mm reading of induration (for TST)

Adapted from: Centers for Disease Control and Prevention. (2013). Testing for Tuberculosis Infection and Disease. Core Curriculum on Tuberculosis. What the Clinician Should Know. Atlanta, Georgia.

*Applies to both IGRA and TST except where indicated

[1] The IGRA or TST may be falsely negative if performed after a recently-administered vaccine

Abbreviations Used: BCG=bacille Calmette-Guérin vaccine; HIV=human immunodeficiency virus; IGRA= interferon gamma release assay; JAK inhibitors=Janus kinase inhibitors; mm=millimeters; NTM=nontuberculous mycobacterium; TNF-α=tumor necrosis factor-alpha; TST=tuberculin skin test, TB=tuberculosis

TESTING AMONG PRIORITY POPULATIONS AND SPECIAL CONSIDERATIONS

CONTACTS

Contacts, or persons exposed to an individual with infectious TB disease, represent the group with the highest risk of being infected with TB. Approximately 16% of persons tested through contact investigation in NYC have a positive test result and 1% are diagnosed with active TB disease; thus evaluation of close contacts to persons with active TB disease is conducted as soon as feasible, in consultation with the NYC Health Department. (See *Chapter 11: Contact Investigation*.)

Since it can take up to eight weeks after exposure to *M. tuberculosis* ("window period") for the immune system to mount a response, the initial (baseline) test may be falsely negative if conducted too soon after TB exposure. If the baseline test is negative, and the person has no symptoms or medical risk factors for TB, a repeat test is obtained shortly after the end of the window period, usually eight weeks after the last exposure. Using the same baseline and post-window period test for TB infection is preferred; if not feasible, providers should avoid using a less specific post-window test (i.e., TST) when a more specific baseline test (i.e., IGRA) was used at baseline.

Prompt medical evaluation is conducted for contacts with a positive baseline or post-window period test for TB infection or those with medical risks or symptoms consistent with active TB regardless of the TB infection test result. Contacts younger than five years of age and those who have HIV infection or another immunosuppressive condition are a priority for evaluation since they are at high risk for rapid progression to active TB disease if infected.

PERSONS WHO HAVE HUMAN IMMUNODEFICIENCY VIRUS INFECTION

People living with HIV infection who become infected with TB are at high risk for developing active TB disease. Thus, testing for TB infection occurs as soon as a person is diagnosed with HIV infection, regardless of their epidemiological risk of TB exposure.

Persons with HIV infection who have a positive test for TB infection require additional testing to rule out active TB disease. For those with a negative TB infection test result, clinical judgment is used to determine the need for further evaluation to rule out active TB disease. For those who have advanced HIV infection (CD4 cell count less than 200 cells/cubic millimeter [mm^3]), a negative TB infection test result, and no indications for initiating empiric LTBI treatment, retest for TB infection once anti-retroviral therapy (ART) is started and the CD4 count equals or exceeds 200 cells/mm^3. Annual testing for TB infection is recommended only for patients with HIV infection who are at high risk of repeated or ongoing exposure to persons with active TB disease. For persons living with HIV infection who are contacts to a person with infectious TB, empiric treatment for LTBI is recommended, regardless of CD4 count, previous LTBI treatment, or IGRA/TST result.

PERSONS WITH AN IMMUNOSUPPRESSIVE MEDICAL CONDITION OR TAKING IMMUNOSUPPRESSIVE THERAPY

Persons with an immunosuppressive condition other than HIV infection or who are on immunosuppressive therapy are tested for TB infection with IGRA or TST either 1) at the time of diagnosis of the condition; or 2) before starting immunosuppressive therapy. Persons receiving treatment for various dermatological, rheumatological, and gastrointestinal disorders (e.g., certain forms of arthritis [rheumatoid, juvenile idiopathic, or psoriatic], lupus, inflammatory bowel disease [Crohn's, ulcerative colitis], psoriasis, ankylosing spondylitis, and non-infectious uveitis), certain cancers (e.g., leukemia, lymphoma, head, neck, or lung cancer), or pre- and post-organ transplantation may have impairment of their immune response. A positive IGRA or TST result is indicative of TB infection in all such persons. (See *Table 2.4: Criteria for Determination of a Positive Tuberculin Skin Test Result* for definition of a positive TST result.)

TST or IGRA results in immunosuppressed persons may be falsely negative, either due to the drug therapy or to the underlying medical condition; two-step testing may be indicated if TST is used. The patient is treated for LTBI if any of the tests are positive or if they are a recent contact to a person with infectious TB (once active TB is ruled out). If the IGRA or TST is negative, clinical judgment is used to determine if empiric LTBI treatment is required. Annual testing for TB infection is recommended for persons who are at high risk for repeated or ongoing exposure to persons with active TB disease.

PERSONS WHO LIVE OR WORK IN SETTINGS WHERE TUBERCULOSIS EXPOSURE IS MORE LIKELY

Persons who live or work in settings where TB exposure is more likely may be at risk for TB infection based on local TB epidemiology and risk of transmission. Such settings include healthcare facilities (e.g., hospitals, long-term care facilities, drug treatment centers), correctional facilities, mycobacterial laboratories, and homeless shelters. TB infection testing recommendations or requirements are based on institutional guidelines, as well as state and local laws and regulations. Baseline and annual testing for TB infection is often recommended or required. Updated recommendations from the National TB Controllers Association and CDC for screening and testing healthcare personnel include: individual baseline (preplacement) risk assessment, symptom evaluation and testing of persons without prior TB or latent TB infection (LTBI), no routine serial testing in the absence of exposure or ongoing transmission, treatment for healthcare personnel diagnosed with LTBI, annual symptom screening for persons with untreated LTBI, and annual TB education of all healthcare personnel. Persons undergoing serial testing receive either a two-step TST or a single IGRA as part of their baseline evaluation; the test used for subsequent screening should be the same as the one used at baseline.

The New York State Department of Health (NYSDOH) requires a medical evaluation of all healthcare workers prior to employment in hospitals and diagnostic and treatment centers in New York State, which must include TB screening. Requirements are subject to change. Current guidelines for healthcare facilities and employee TB screening can be found at: www.health.ny.gov

PERSONS WHO WERE BORN, RESIDED, OR TRAVELED IN AREAS WITH HIGH RATES OF TUBERCULOSIS

Regardless of the duration of residence in the U.S., persons who were born or resided/traveled (for one month or longer) in countries with high TB incidence should be screened for TB infection, preferably with an IGRA. Countries with high TB incidence rates include any country other than the U.S., Canada, Australia, New Zealand, or a country in Western or Northern Europe. Some individuals born in high TB incidence countries may have been screened for TB disease with a chest radiograph (CXR) for permanent legal residence in the U.S., but may not have received a test for TB infection. Similarly, persons who resided in or traveled to a country with a high TB incidence for one consecutive month or longer should be screened for TB infection after returning to the U.S.

CHILDREN YOUNGER THAN 18 YEARS OF AGE

Children younger than 18 years of age are tested for TB infection based on individual risk factors following completion of a TB risk assessment. (See *Appendix B: Tuberculosis Risk Assessment Tool*.) Administrative or mandated tests for TB infection for entry to daycare, school, camp, or college are discouraged in the absence of risk factors. The consumption of raw milk or cheese products from outside the U.S. has also been associated with TB infection. Children with known exposure to such products are tested for TB infection and offered treatment if indicated.

PERSONS WHO PREVIOUSLY RECEIVED BACILLE CALMETTE-GUÉRIN VACCINATION

Tests for TB infection can be used among persons who previously received the BCG vaccination. A history of BCG vaccination does not influence the decision to test for TB infection. Since IGRAs do not cross-react with BCG, they are the preferred test for persons with a history of BCG vaccination. Although BCG vaccination can cause a false-positive cross-reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculin is highly variable and decreases over time. The presence or size of a TST reaction does not predict whether BCG vaccination will provide protection against TB disease or whether the reaction is due to BCG vaccination or TB infection. Thus, a positive reaction to the TST in BCG-vaccinated persons is interpreted as indicating TB infection when the person tested is at increased risk of TB infection or progression to active TB disease.

PERSONS RECEIVING LIVE VIRUS VACCINATIONS

Although the TST and IGRAs can be administered in conjunction with all vaccines, the measles, mumps, and rubella (MMR) vaccine and other live attenuated vaccines (e.g., varicella, nasal influenza vaccines) may transiently suppress the immune response to either type of test. When timing TB testing with the administration of the MMR or other live virus vaccines, one of the following three administration sequences may be used:

- The TST or IGRA is performed at the same visit as the MMR/live virus vaccine.
- The TST or IGRA is delayed at least four to six weeks if the MMR/live virus vaccine is given first.

- The TST or IGRA is performed first and results are obtained (e.g., 48-72 hours after TST placement) and then the MMR/live virus vaccine is given.

MEDICAL EVALUATION

Once a person has tested positive for TB infection, the provider must conduct further clinical and radiologic evaluation and rule out active TB disease before an LTBI diagnosis can be established or LTBI treatment can be initiated. All persons who have a current or prior positive test for TB infection are examined by a clinical provider and receive a medical history and physical examination, CXR, and relevant laboratory testing if clinically indicated. In some instances, patients not testing positive should also receive medical evaluation. (See *Table 2.7: Recommended Clinical Evaluation Based on Test for Tuberculosis Infection Results*.)

TABLE 2.7: Recommended clinical evaluation based on test for tuberculosis infection results

RESULT	RECOMMENDED CLINICAL EVALUATION
Negative IGRA or TST	• No further evaluation is needed unless indicated by clinical judgment (e.g., clinical suspicion of active TB, immunosuppression, new TB risk factor, live or work in high-risk setting)
Positive IGRA or TST	• Rule out active TB disease with clinical evaluation, CXR, and other diagnostics as clinically indicated
Indeterminate[a] or invalid[b] IGRA	• Result could be due to error in specimen collection or laboratory processing or to the patient's reduced immune response to the TB antigens (i.e., anergy) • Repeat the IGRA. If 2 separate specimens from a patient yield indeterminate or invalid results, do not repeat IGRA; consider medical evaluation and CXR to rule out active TB
Borderline IGRA[b]	• Indicates an uncertain likelihood of *M. tuberculosis* infection • Repeat IGRA. If 2 separate specimens from a patient yield borderline results, do not repeat IGRA; consider medical evaluation and CXR to rule out active TB

[a] QFT-TB Gold Plus only

[b] T-SPOT.TB only

Abbreviations Used: CXR=chest radiograph; IGRA=interferon gamma release assay; *M. tuberculosis=Mycobacterium tuberculosis*; TB=tuberculosis; TST=tuberculin skin test

CLASSIFICATION OF THE PATIENT AND IMPLICATIONS FOR CLINICAL FOLLOW-UP

After a clinical evaluation, patients are initially classified according to the **INTERNATIONAL CLASSIFICATION OF TUBERCULOSIS**. (See *Appendix A: International Classification of Tuberculosis*.) Further evaluation may require re-classification.

- A patient who has a positive test for TB infection and a normal CXR and no signs or symptoms of TB disease is classified as **CLASS II**. Class II patients are further classified as either **contact**, **medical risk** (e.g., immunosuppression), **population risk** (e.g., from high TB incidence country), or **administrative risk** (e.g., employment or school requirement) and are treated for LTBI as indicated.
- A patient who has a positive test for TB infection and a CXR with calcified granuloma and no signs or symptoms of TB disease can be classified as **CLASS II** and is treated for LTBI. Sputum does not need to be collected to rule out active TB disease.
- A patient who has a positive test for TB infection and an abnormal CXR consistent with active TB disease is classified as **CLASS V** (high or low, based on presence of symptoms or degree of CXR abnormalities), and is evaluated for active TB disease and managed accordingly. (See *Chapter 2: Diagnosis and Treatment of Tuberculosis Disease in Adults*.)
- A patient who has a positive test for TB infection and CXR showing fibrotic lesions suggestive of old, healed TB disease requires a medical evaluation for current symptoms of TB disease and need for treatment. Providers order a complete blood count (CBC), chemistry panel, viral hepatitis screen, and three consecutive sputum samples for smear, nucleic acid amplification (NAA) testing (if sputum is AFB smear-positive), culture, and susceptibility testing. If prior CXRs are not available for comparison, repeat CXR may be obtained after two months to assess stability or changes in radiologic findings.
  - If there are no symptoms of TB disease, providers classify the individual as **CLASS V** (low) and evaluate and treat for active TB disease as indicated.
  - If there are TB disease symptoms, providers classify the individual as **CLASS V** (high) and evaluate and treat for active TB disease as indicated.
- If the patient has a history of treatment for pulmonary TB, patients can be classified based on clinical judgment as:
  - **CLASS V** (high or low, based on symptoms). Providers are recommended to evaluate the patient with sputum testing to rule out active TB disease, decide whether to re-treat, and re-classify based on final evaluation.
  - **CLASS IV** if the patient is asymptomatic and has a detailed history or documentation of treatment. Providers are recommended to evaluate to determine whether to re-treat based on re-exposure and other factors.

MEDICAL HISTORY

A comprehensive medical history is obtained, which includes the following:

- Risk factors for TB infection or, if already infected, progression to TB disease
- Previous testing for TB infection
- Previous treatment for LTBI or TB disease
- Previous or current exposure to a person with infectious TB disease
- Other coexisting medical conditions (e.g., HIV or other immunosuppressive conditions, diabetes)
- Use of prescription and over-the-counter medications, supplements, or herbal products
- Allergic or adverse reactions to medications
- History of liver disease or hepatitis
- Social history including substance use (e.g., drug, alcohol, tobacco) and homelessness
- Test results of prior HIV testing

PHYSICAL EXAMINATION

After obtaining a thorough medical history, providers perform a directed physical examination to assess the possibility of TB disease in specific sites (e.g., cardiac, pulmonary, lymph nodes).

CHEST RADIOGRAPH

All persons with a positive test for TB infection or symptoms consistent with TB disease receive a posterior-anterior CXR to rule out pulmonary TB disease. Children younger than five years of age must have both a posterior-anterior and lateral CXR. In some instances, other views (e.g., apical lordotic) or additional studies (e.g., computed tomography [CT] scans) may be necessary.

If there is documentation of a normal CXR and medical evaluation in the electronic medical record (EMR) within the previous month, a repeat CXR is not necessary unless the patient is currently symptomatic, immunosuppressed, younger than five years of age, or a contact to a person with infectious TB. For all others, clinical judgment is used to determine the need for a repeat CXR.

For persons who are referred or present to a NYC Health Department TB clinic with a report of a positive test for TB infection and a normal CXR, the CXR report is reviewed by a NYC Health Department TB clinic provider who determines whether a repeat CXR is indicated. In general, a repeat CXR is obtained if:

- The patient has symptoms consistent with active TB disease.
- The original CXR was taken more than one month ago in patients with HIV infection, other immunosuppressive conditions, age younger than five years, or those who are contacts to a person with infectious TB disease.
- The language in the CXR report is ambiguous, regardless of the date the CXR was taken.

LABORATORY TESTS FOR PERSONS BEING CONSIDERED FOR LATENT TUBERCULOSIS INFECTION TREATMENT

Routine baseline laboratory studies are indicated for certain persons before initiating LTBI treatment. These studies include: a baseline complete blood count (CBC), a viral hepatitis screen, and a chemistry panel, which consists of serum glucose, creatinine, liver function tests (LFTs), such as aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and total bilirubin. Baseline laboratory studies are obtained for patients with the following conditions or situations:

- HIV infection
- Pre-existing liver disease (e.g., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to three months after delivery) patients
- Taking drugs for other medical conditions that may be hepatotoxic or have drug-to-drug interactions with LTBI treatment (See *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications*.)
- At the provider's discretion

LTBI treatment can be initiated the same day the baseline laboratory tests are drawn to save the patient a visit back to the clinic, as long as the patient can be contacted in the event of an abnormal blood test result that requires follow-up. Abnormal test results are evaluated by a provider as soon as possible or, at the latest, within three business days of starting treatment for LTBI. The provider documents follow-up actions in the EMR. All critical laboratory results are reported to a NYC Health Department on-call physician for timely follow-up.

HUMAN IMMUNODEFICIENCY VIRUS SCREENING

NYC Health Department TB clinics employ opt-out HIV testing for all patients being evaluated for LTBI or active TB disease unless there is a documented prior positive test result or recent negative HIV test result within the past 12 months.

Parental consent for HIV testing of children younger than 18 years of age is not required in New York State. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) Since HIV infection is an important risk factor for progression of LTBI to active TB disease, HIV testing is particularly important for persons meeting the following criteria:

- Previous or current positive test for TB infection
- Previous or current diagnosis of LTBI or TB disease
- Close contact to a person with infectious TB disease
- CXR with abnormalities consistent with old, healed TB disease

In addition, the CDC recommends opt-out HIV screening for the following persons:

- All patients 13 to 64 years of age at least once as part of routine healthcare, regardless of presence or absence of HIV risk factors
- All pregnant persons as part of routine prenatal screening
- Annual HIV screening of asymptomatic persons with risk factors for HIV infection
- More frequent screening (e.g., once every three or six months) as clinically indicated

TREATMENT OF LATENT TUBERCULOSIS INFECTION

Treatment of LTBI in high-risk persons is essential for TB prevention efforts. Completion of an appropriate LTBI treatment regimen can reduce the risk of TB disease by approximately 90%.

All high-risk persons who test positive for TB infection are offered one of the approved treatment regimens for LTBI once active TB disease is ruled out, regardless of age or time since immigration to the U.S. Regimens for contacts initiating LTBI treatment may be modified based on results of drug-susceptibility testing (DST) of the isolate obtained from the source case (index patient); however, LTBI treatment should not be delayed if these results are not known. High-risk contacts (e.g., younger than five years of age or immunosuppressed) are promptly started on LTBI treatment, often during the window period after an initial negative test for TB infection, once active TB is ruled out.

Patients who completed LTBI therapy but are re-exposed to another person with TB disease are evaluated again for the new exposure. For recent contacts to patients with infectious TB, a new CXR is taken and, if normal, a repeat course of LTBI treatment is strongly recommended, especially if:

- The patient has HIV infection or is otherwise immunosuppressed
- The patient has medical risk factors for progression to TB disease
- The patient is younger than 18 years of age
- There is evidence of recent TB transmission around the index patient (e.g., documented IGRA or TST conversions among contacts, additional close contacts with active TB disease)

Likewise, close contacts who have a prior positive test for TB infection but did not receive prior LTBI treatment are advised to receive treatment for the recent exposure.

Clinical providers may have concerns about initiating LTBI treatment, particularly among older persons due to potential side effects of medications; however, advanced age itself is not a contraindication to treatment. As with any treatment, clinical providers weigh the risks and benefits for each individual, based on TB risk factors and results of the clinical evaluation.

TABLE 2.8: Recommended drug regimens for the treatment of latent tuberculosis infection in adults and children

DRUG	INTERVAL AND DURATION	DOSAGE		COMPLETION CRITERIA	COMMENTS
RIF	Daily for 4 months	Adults (max.)	10 mg/kg (600 mg)	120 doses within 6 months	• Recommended for people of all ages • Preferred treatment for people who have been exposed to INH-resistant, RIF-susceptible TB • Use of rifamycins may be limited by potential drug-to-drug interactions† • Some antiretroviral drugs, such as the PIs, NNRTIs, and INSTIs have interactions with rifamycins. Clinicians must consult web-based updates or clinical experts for the latest specific recommendations§ • Children < 2 years require dosing closer to 20mg/kg
		Children (max.)	10–20 mg/kg (600 mg)		
INH and RPT	Once weekly for 12 weeks	Adults and children 2 years of age and older (max.)	INH: Adults and children age 12 years and older: 15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg) Children age 2-11 years: 25mg/kg rounded up to the nearest 50 or 100 mg (900 mg) RPT: 10.0–14.0 kg (300 mg) 14.1–25.0 kg (450 mg) 25.1–32.0 kg (600 mg) 32.1–49.9 kg (750 mg) ≥ 50.0 kg (900 mg max.)	≥ 11 doses within 16 weeks	• Administration by DOT is preferred. • Use of rifamycins may be limited by potential drug-to-drug interactions† • Can be used by person with HIV infection taking antiretroviral medications with acceptable drug-to-drug interactions with RPT (e.g., efavirenz- or raltegravir- containing regimens)§ • Pyridoxine (vitamin B6) supplementation (50 mg once per week) may be recommended*

TABLE 2.8: Recommended drug regimens for the treatment of latent tuberculosis infection in adults and children *(continued)*

DRUG	INTERVAL AND DURATION	DOSAGE		COMPLETION CRITERIA	COMMENTS
INH	Daily for 6 months‡	Adults (max.)	5 mg/kg (300 mg)	182 doses within 9 months	• For patients with HIV infection, INH may be administered concurrently with NRTIs, PIs, NNRTIs, or INSTIs • Pyridoxine (vitamin B6) supplementation (25 mg/day) may be recommended* • Aluminum-containing antacids reduce INH absorption • Acetaminophen, cimetidine, phenytoin, disulfiram, carbamazepine, valproate, clopidogrel, and citalopram levels may be increased with concomitant INH use* • Avoid tyramine-containing foods (e.g., cheese, red wine, certain types of fish)
		Children¶ (max.)	10–20 mg/kg (300 mg)		
	Daily for 9 months‡	Adults (max.)	5 mg/kg (300 mg)	270 doses within 12 months	
		Children¶ (max.)	10–20 mg/kg (300 mg)		
	Twice weekly for 6 months‡	Adults (max.)	15 mg/kg (900 mg)	52 doses in 9 months	• DOT must be used • Pyridoxine (vitamin B6) supplementation (50 mg twice per week) may be recommended*
		Children¶ (max.)	20–40 mg/kg (900 mg)		
	Twice weekly for 9 months‡	Adults (max.)	15 mg/kg (900 mg)	76 doses in 12 months	
		Children¶ (max.)	20–40 mg/kg (900 mg)		

† Use of rifamycins may be limited by potential drug-to-drug interactions (e.g., methadone, certain oral hypoglycemic agents, oral contraceptives)

*Pyridoxine (vitamin B6) supplementation (25 mg/day) may decrease peripheral and central nervous system effects of INH and is used in patients who are using alcohol, pregnant, nursing infants, malnourished or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy.

‡Treatment may be considered as complete at six months for healthy persons older than 18 years of age who have no risk for progression to TB disease and no HIV infection or other immunosuppressive conditions.

¶The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.

§Visit http://aidsinfo.nih.gov for the latest guidelines and complete list of contraindicated medications.

¥For more information, check a drug interaction (https://www.rxlist.com/drug-interaction-checker.htm) website.

Abbreviations Used: DOT=directly observed therapy; HIV=human immunodeficiency virus; INH=isoniazid; INSTIs=integrase strand transfer inhibitor; kg=kilograms; mg=milligrams; NNRTI= non-nucleoside reverse transcriptase inhibitors; NRTI=nucleoside reverse transcriptase; PIs=protease inhibitors; RIF=rifampin; RPT=rifapentine

LATENT TUBERCULOSIS INFECTION TREATMENT REGIMENS

Several LTBI treatment regimens are available in NYC Health Department TB clinics and are listed below. Short-course regimens are preferred for eligible patients as they have been demonstrated to have efficacy, high treatment completion rates, and are generally well-tolerated.

LTBI treatment regimens are generally well-tolerated. However, adverse reactions can occur and close clinical monitoring during treatment is essential in mitigating the risk. Treatment indications, options, duration, methods of administration (i.e., self-administered and directly observed therapy [DOT]), and potential adverse effects are discussed with patients so that an informed decision about the optimal regimen can be made; the discussion and decisions are documented in the EMR. Potential drug-to-drug interactions and individual patient characteristics are considered when selecting a regimen. (See *Appendix J: Recommendations for Patients to Assist with Taking Tuberculosis Medications* and *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications*.)

RIFAMYCINS

Rifamycins are a class of drugs (e.g., rifampin [RIF], rifapentine [RPT], and rifabutin [RBT]) that have been used for many years in the treatment of both LTBI and active TB disease. Rifamycins are generally well-tolerated, and RIF is a commonly used short-course medication for LTBI treatment at NYC Health Department TB clinics. In addition, for contacts of a person with infectious isoniazid- (INH) resistant, RIF-susceptible TB, RIF is the LTBI treatment of choice. RIF is recommended for daily use by self-administration for four months (4R) to treat LTBI in adults and children.

Side Effects

Possible side effects of rifamycins include the following (see *Table 2.9: Monitoring for Side Effects and Adverse Reactions During Latent Tuberculosis Infection Treatment*):

- Gastrointestinal symptoms such as nausea, vomiting, anorexia, abdominal pain
- Cutaneous reactions such as pruritus (with or without rash)
- Hepatotoxicity, particularly with elevated bilirubin
- Rare hypersensitivity reactions such as fever, headache, dizziness, musculoskeletal pain, and petechiae
- Orange discoloration of body fluids (e.g., tears, saliva, sweat, urine, stool) is expected with use of RIF and is harmless; however, permanent discoloration of contact lenses may occur

Contraindications

Contraindications to the use of RIF include:

- History of severe RIF-induced reaction, including hepatic, skin, and allergic reactions
- Thrombocytopenia

- Severe chronic liver disease
- Current treatment with certain protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase strand transfer inhibitors (INSTI)

Due to drug interactions, RIF must not be used to treat persons living with HIV infection who are taking certain combinations of antiretroviral therapy (ART). In such cases, another rifamycin, such as RBT, can be substituted for RIF. RBT is considered equally effective to RIF in treating LTBI, but has less effect on the metabolism of other drugs given concurrently. RBT may be used with regimens containing NNRTI, PI, and certain INSTI. RBT may also be given to patients on methadone as generally the dose of methadone does not need to be increased. It may also cause less gastrointestinal distress and liver function abnormalities.

Drug-to-Drug Interactions

Use of RIF and other rifamycins can also be limited by the potential for drug-to-drug interactions. RIF increases the metabolism of many medications when given concurrently and can decrease their efficacy (e.g., certain oral hypoglycemic agents, anticoagulants, antidepressants, certain antihypertensives, methadone). In addition, rifamycins decrease the efficacy of hormonal contraceptives and alternative forms of contraception are advised for patients wishing to avoid pregnancy during treatment. (See *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications*.)

ISONIAZID AND RIFAPENTINE

A once-weekly, 12-dose regimen of INH and RPT (3HP) is indicated for use in the treatment of LTBI among the following persons requiring LTBI treatment:

- Patients two years of age and older; data on safety and pharmacokinetics of RPT in children younger than two years of age are not available
- Persons living with HIV infection who are taking ART with acceptable drug-to-drug interactions with RPT (e.g., efavirenz- or raltegravir-containing regimens) (see aidsinfo.nih.gov/guidelines)
- Contacts to a person with infectious TB if isolate is susceptible to both INH and RIF
- Persons who are not currently or planning to be pregnant or breastfeeding

The 3HP regimen can be given by DOT, including electronic DOT (eDOT) using video technology and smart phones. In 2017, a published clinical trial demonstrated that self-administration of 3HP was non-inferior to DOT and could also be used. The decision to use DOT vs. self-administration is based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease. In the absence of additional efficacy data supporting self-administration of 3HP, BTBC policy still recommends the use of DOT, when possible, for patients taking 3HP.

Side Effects

While 3HP is generally well-tolerated, possible side effects include those for INH and RPT, in addition to hypersensitivity syndrome (fever, chills, headache, fatigue, uveitis, urticaria, pruritus, or petechiae). This

syndrome typically presents around the third to fourth week of treatment. (See *Table 2.9: Monitoring for Side Effects and Adverse Reactions During Latent Tuberculosis Infection Treatment*.)

Contraindications

Contraindications to the use of 3HP include:

- Children younger than two years of age
- Persons living with HIV infection who are receiving ART with drug-to-drug interactions with RPT
- Pregnancy (current or planned) or breastfeeding during treatment

ISONIAZID

INH was the standard treatment for LTBI for many years due to its established efficacy in preventing progression to TB disease among those with TB infection. However, with shorter and equally efficacious LTBI regimens now available, such as 4R and 3HP, NYC Health Department TB clinics primarily use INH when the short course regimens cannot be used due to either resistance or intolerance to rifamycins. For contacts, 3HP or INH can be used when the person with infectious TB has INH-susceptible TB.

If INH monotherapy must be used, a 6-month regimen (6H) is recommended, including for children and persons living with HIV; a 9-month regimen (9H) may be used based on clinical judgment. INH is recommended for daily use by self-administration and may be administered concurrently with any ART used to treat HIV infection.

Side Effects

INH is generally well-tolerated. Possible side effects include the following:

- Gastrointestinal symptoms (e.g., nausea, vomiting, anorexia, abdominal pain)
- Jaundice
- Fatigue
- Arthralgias
- Rash
- Elevation of serum liver enzyme concentrations
- Clinical hepatitis
- Peripheral neuropathy

Contraindications

Contraindications to use of INH include:

- History of severe INH-induced reaction, including hepatic, skin, or allergic reactions, or neuropathy
- Severe chronic liver disease

TABLE 2.9: Monitoring for side effects and adverse reactions during latent tuberculosis infection treatment

DRUG	SIDE EFFECTS/ ADVERSE REACTIONS	MONITORING*	COMMENTS*
RIF	• Anorexia • Nausea, vomiting • Icterus • Abdominal pain • Hepatitis • Rash and/or pruritis • Fever or flu-like symptoms • Easy bruising or bleeding • Renal failure • Red discoloration of urine and other secretions	• CBC, LFTs (AST, ALT, and serum bilirubin), and serum creatinine at baseline if clinically indicated • Baseline hepatitis screen for any patient having blood drawn • Repeat monthly labs if baseline results are abnormal, patient has risk factors for toxicity, or patient has symptoms of adverse reactions	• Normal red or orange discoloration of body fluids (e.g., tears, saliva, sweat, urine, stool) • May permanently discolor soft contact lenses or dentures • May develop neutropenia or thrombocytopenia • Hepatitis risk increases with age; underlying liver disease, chronic alcohol ingestion, or intravenous drug use; use of other potentially hepatotoxic drugs; and if pregnant or up to three months postpartum • Many potential drug interactions§ • Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, ketoconazole, coumadin derivatives, hormonal contraceptives, oral hypoglycemic meds (except metformin), digitalis, sulfonylureas, diazepam, ß-blockers; consult with providers prescribing these agents - Methadone dosage may need to be increased; monitor for withdrawal symptoms and consult with methadone maintenance program as needed - May impair glucose control in people with diabetes - Advise patients to use barrier contraception in addition to oral or non-hormonal contraceptives • Contraindicated in patients taking most PIs, NNRTIs, and INSTIs
INH and RPT	• Anorexia • Nausea, vomiting • Flu-like symptoms • Polyarthralgia • Hypersensitivity syndrome including fever, chills, headache. fatigue, uveitis, urticaria, pruritus, or petechiae	• CBC, LFTs (AST, ALT, and serum bilirubin), and serum creatinine if clinically indicated • Baseline hepatitis screen for any patient having blood drawn	• See RIF and INH sections • If present, hypersensitivity syndrome is typically seen around third to fourth weeks of treatment

TABLE 2.9: Monitoring for side effects and adverse reactions during latent tuberculosis infection treatment *(continued)*

DRUG	SIDE EFFECTS/ ADVERSE REACTIONS	MONITORING*	COMMENTS*
INH	• Anorexia • Nausea, vomiting • Abdominal pain • Dark urine • Rash • Hepatitis • Peripheral neuropathy • Jaundice • Persistent fatigue • Weakness • Arthralgia • Mild CNS effects including headache, poor memory or concentration, depression • Acne	• LFTs (AST, ALT, and serum bilirubin) at baseline if clinically indicated • Baseline hepatitis screen for any patient having blood drawn • Repeat monthly LFTs if baseline results are abnormal, patient has risk factors for toxicity, or patient has symptoms of adverse reactions	• Asymptomatic elevation of hepatic enzymes can occur. Mild and transient elevation of serum transaminases occurs in 10-20% of patients taking INH, usually in the first one to three months of treatment but can occur at any time. Most enzyme levels return to normal and generally there is no need to discontinue INH • Hepatitis risk increases with age; underlying liver disease, heavy alcohol ingestion, or intravenous drug use; use of other potentially hepatotoxic drugs; and if pregnant or up to three months postpartum • Pyridoxine (vitamin B6, 25 mg/day) may prevent peripheral neuropathy and should be used in patients who have chronic alcohol use, HIV, cancer, chronic renal or liver disease, malnutrition, diabetes or pre-existing peripheral neuropathy, or are pregnant or breastfeeding infants • Lupus-like syndrome-may consider checking anti--histone antibody • Aluminum-containing antacids reduce INH absorption • Acetaminophen toxicity can occur with concurrent INH use • Cimetidine, theophylline, phenytoin, carbamazepine, valproate, clopidogrel, disulfiram, and citalopram levels may be increased with concurrent INH use. Measure serum concentrations of theophylline, phenytoin, carbamazepine, and valproate in patients receiving INH and adjust dosing if necessary, in consultation with prescribing providers

*Select patients may not need baseline labs done

§For more information, check a drug interaction website (e.g., https://www.rxlist.com/drug-interaction-checker.htm)

Abbreviations Used: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; CNS=central nervous system; HIV=human immunodeficiency virus; INH=isoniazid; LFTs=liver function tests; LTBI=latent tuberculosis infection; mg=milligrams; NNRTI=nonnucleoside reverse transcriptase inhibitors; PI=protease inhibitor; RIF=rifampin; RPT=rifapentine

CLINICAL MONITORING DURING LATENT TUBERCULOSIS INFECTION TREATMENT

While LTBI treatment regimens are generally well-tolerated, side effects and adverse reactions can occur and may negatively impact treatment adherence and completion. Patients on LTBI treatment are educated about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment should such symptoms occur. Educational information and materials are provided in the patient's preferred language and documented in the EMR.

Persons taking LTBI treatment are evaluated by monthly clinical monitoring until treatment completion and are evaluated more frequently if clinically indicated. (See *Chapter 8: Clinical Monitoring and Follow-Up for Tuberculosis Treatment.*)

Persons on monotherapy with RIF or INH who are at low risk for hepatotoxicity or who have started treatment and are tolerating it well may be candidates for monthly nursing follow-up visits, either in clinic or remotely, with referrals to a physician as clinically indicated. Persons on 3HP receive monthly physician evaluations until treatment completion; select patients may have monthly nursing follow-up at the physician's discretion. The monthly monitoring plan is documented in the EMR.

Serum chemistries, CBC, LFTs, or other tests based on specific drugs are performed periodically as needed. Persons taking treatment for LTBI are monitored for signs or symptoms of adverse reactions, including hepatotoxicity, and managed accordingly. (See *Figure 2.1: Latent Tuberculosis Infection (LTBI) Clinical Evaluation and Counseling* and *Figure 2.2: Monitoring for and Management of Hepatotoxicity during Treatment for Latent Tuberculosis Infection*.)

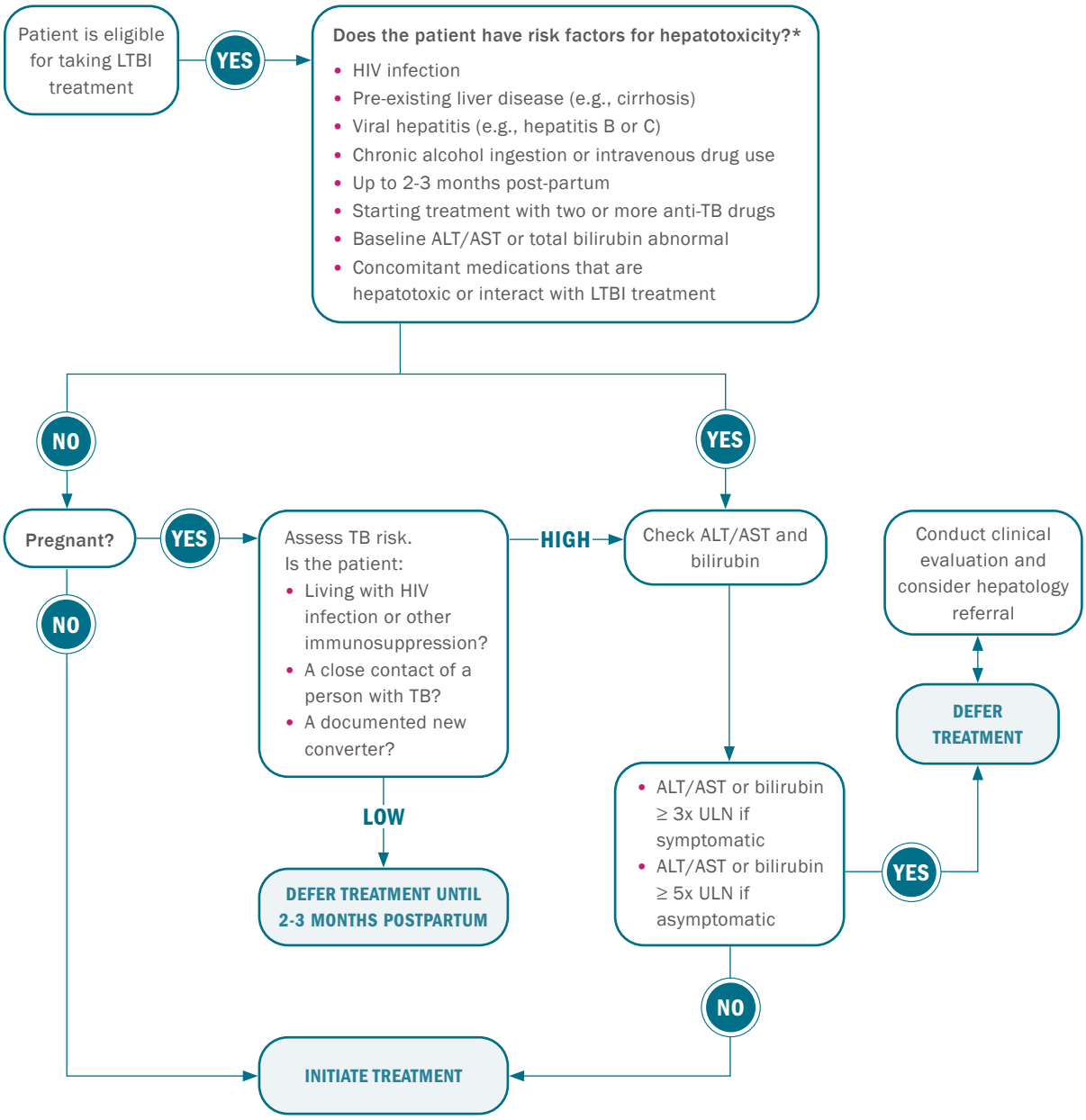
Monthly LFTs are obtained for the patients with the following conditions:

- HIV infection
- Pre-existing liver disease (e.g., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to two to three months after delivery)
- Taking other drugs that may be hepatotoxic or interact with LTBI treatment
- Baseline abnormal LFTs

Mild adverse effects are managed by treating the symptoms without interrupting therapy; whereas, with more severe adverse effects, the offending drug(s) are discontinued and additional clinical and laboratory evaluation are conducted before attempting to restart treatment.

FIGURE 2.1: Latent tuberculosis infection (LTBI) clinical evaluation and counseling

Adapted from: *An official American Thoracic Society Statement: Hepatotoxicity of Antituberculosis Therapy (2006).*

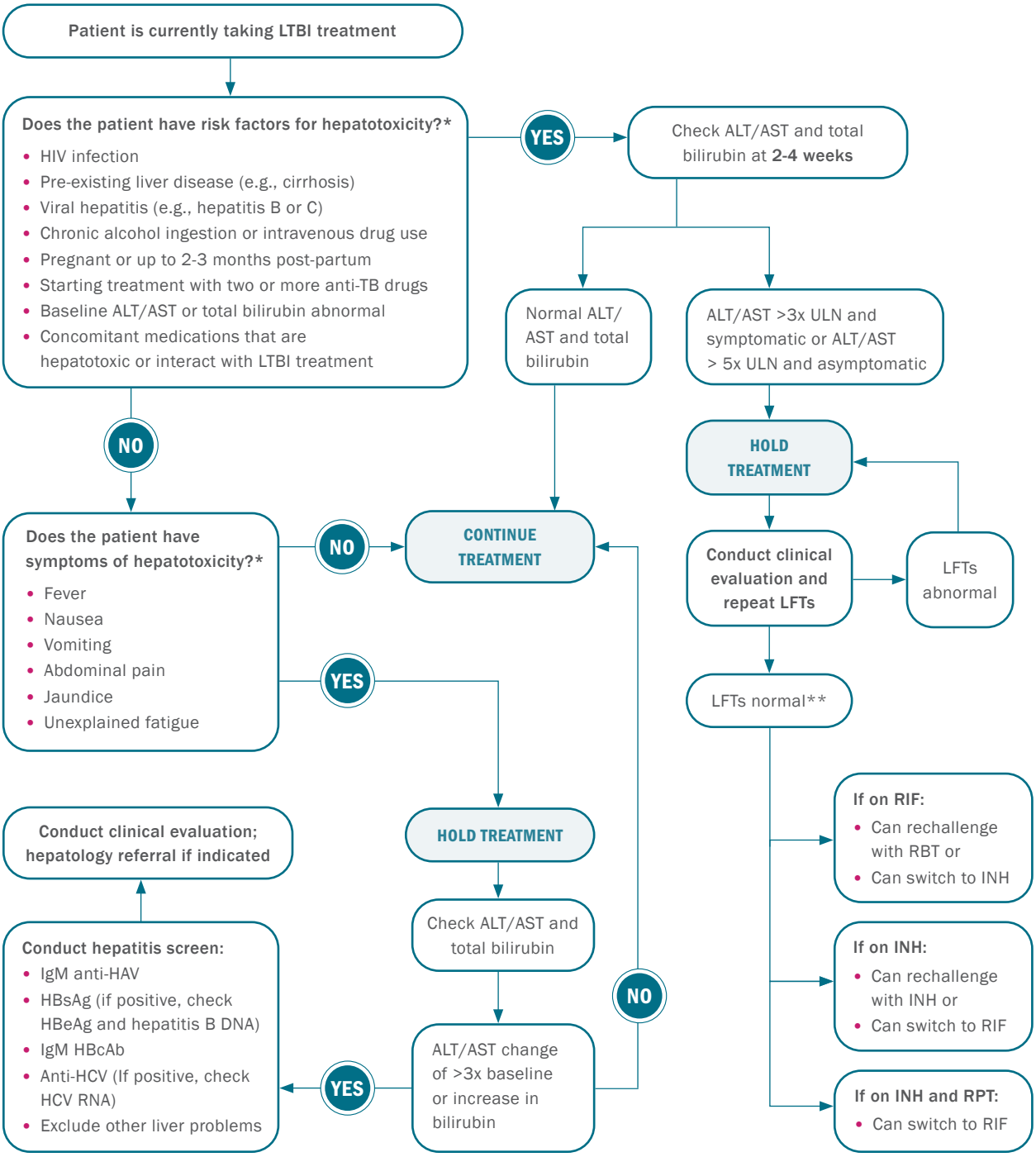


*Age is a risk factor for hepatotoxicity with INH; consider baseline and periodic LFT monitoring monthly, every other month, or at 1, 3, and 6 months as clinically indicated.

Abbreviations Used: ALT=alanine aminotransferase; AST= aspartate aminotransferase; LFT=liver function test; LTBI=latest tuberculosis infection; TB=tuberculosis; ULN=upper limit of normal

FIGURE 2.2: Monitoring for and management of hepatotoxicity during treatment for latent tuberculosis infection (LTBI)

Adapted from: *An official American Thoracic Society Statement: Hepatotoxicity of Antituberculosis Therapy (2006).*



*Age is a risk factor for hepatotoxicity with INH; consider baseline and periodic LFT monitoring monthly, every other month, or at 1, 3, and 6 months as clinically indicated.

**When ALT< 2x ULN or at new baseline

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; HAV=hepatitis A virus; HBcAb=hepatitis B core antibody; HBcAg=hepatitis B core antigen; HBeAg=hepatitis B envelope antigen; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INH=isoniazid; INR=international normalized ratio; LFT=liver function test; LTBI=latent tuberculosis infection; RIF=rifampin; RNA=ribonucleic acid; RPT=rifapentine; TB=tuberculosis; ULN=upper limit of normal

SPECIAL CONSIDERATIONS FOR LATENT TUBERCULOSIS INFECTION DIAGNOSIS AND TREATMENT DURING PREGNANCY

Patients at high risk of TB infection or for progressing to active disease if infected require TB testing during pregnancy. Routine testing for TB infection in all pregnant patients is not necessary, as pregnancy itself does not increase the risk for TB infection; however all pregnant patients should be screened for TB risk and tested accordingly. Either IGRA (preferred) or TST may be used to test patients with TB risk factors, both of which are safe and reliable during pregnancy. A TB risk assessment tool (see *Appendix B: Tuberculosis Risk Assessment Tool*) is used to identify pregnant patients at high risk for TB infection. Pregnant patients are evaluated for TB infection or disease as described below.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

All pregnant patients with a positive test for TB infection are examined by a provider to rule out active TB disease and make recommendations for LTBI treatment. Medical evaluation includes:

- Medical history including TB risk factors, prior TB history and treatment, history of recent exposure to a person with infectious TB disease, and coexisting medical conditions (e.g., HIV or other immunosuppressive conditions, liver disease, hepatitis) and medications
- Social history including substance use (e.g., drug, alcohol, tobacco), risk factors for HIV, homelessness
- Physical examination
- Laboratory tests as indicated
- Test for HIV infection during pregnancy, unless there is prior documentation of a positive HIV test or recent negative test done as part of their obstetrical care

CHEST RADIOGRAPH

A CXR is obtained to assist with ruling out active TB for any pregnant patient with a positive IGRA or TST. The CXR is prioritized for patients with either of the following, even during the first trimester of pregnancy:

- Symptoms suggestive of TB disease (e.g., fever, cough, chills, night sweats, chest pain)
- HIV infection or other immunosuppressive conditions

For pregnant patients with recent close contact to a person with infectious TB, CXR may be obtained in the first trimester based on epidemiologic risk (e.g., evidence of TB transmission among contacts) and clinical judgment. Pregnant patients with HIV infection or other immunosuppressive conditions who are a recent close contact to a person with infectious TB require a CXR in the first trimester even if the IGRA or TST is negative. (See *Figure 2.2: Evaluation of Pregnant Patients at Risk for Tuberculosis*.) For all other pregnant patients with a positive test for TB infection, including a documented IGRA or TST conversion within two years, a CXR can be obtained after the first trimester.

A lead shield must be used to cover the abdomen and pelvis for all pregnant patients receiving a CXR. Pregnant patients may be hesitant to receive a CXR due to concerns about radiation exposure. The amount of radiation exposure from a CXR is very small (0.1 millisievert [mSv], equivalent to 2.4 days of natural background radiation). The risk of untreated active TB disease in a pregnant patient and the possible consequences of congenital TB in the infant far outweigh the theoretical risk from a CXR.

If the CXR is abnormal, prompt evaluation is required to rule out active TB disease, including collecting three sputum samples for acid-fast bacilli (AFB) smear and culture, determining the need for empiric therapy, and reporting the patient to BTBC as potentially having active TB (Class V, high or low). (See *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*.)

If the CXR is normal, LBTI treatment initiation is based on the individual's risk factors as described below.

TREATMENT FOR LATENT TUBERCULOSIS INFECTION

The need to treat active TB disease during pregnancy is well-established. The decision to treat LTBI in pregnant patients must weigh the risk of developing active TB disease against the possible risk of hepatotoxicity from the medications. LTBI therapy is initiated according to the stratification outlined below.

DURING THE FIRST TRIMESTER:

Persons with HIV infection or other immunosuppressive conditions may be considered for treatment during the first trimester. If, at the provider's discretion, treatment is delayed until after the first trimester, close observation for development of symptoms consistent with active TB disease is required.

AFTER THE FIRST TRIMESTER:

Persons with documented IGRA or TST conversion in the past two years may be considered for treatment after the first trimester. Close contacts may also be treated after the first trimester. However, if they are a recent close contact of persons with infectious TB, treatment may be initiated in the first trimester based on epidemiological risk factors (e.g., evidence of transmission to contacts) and clinical judgment.

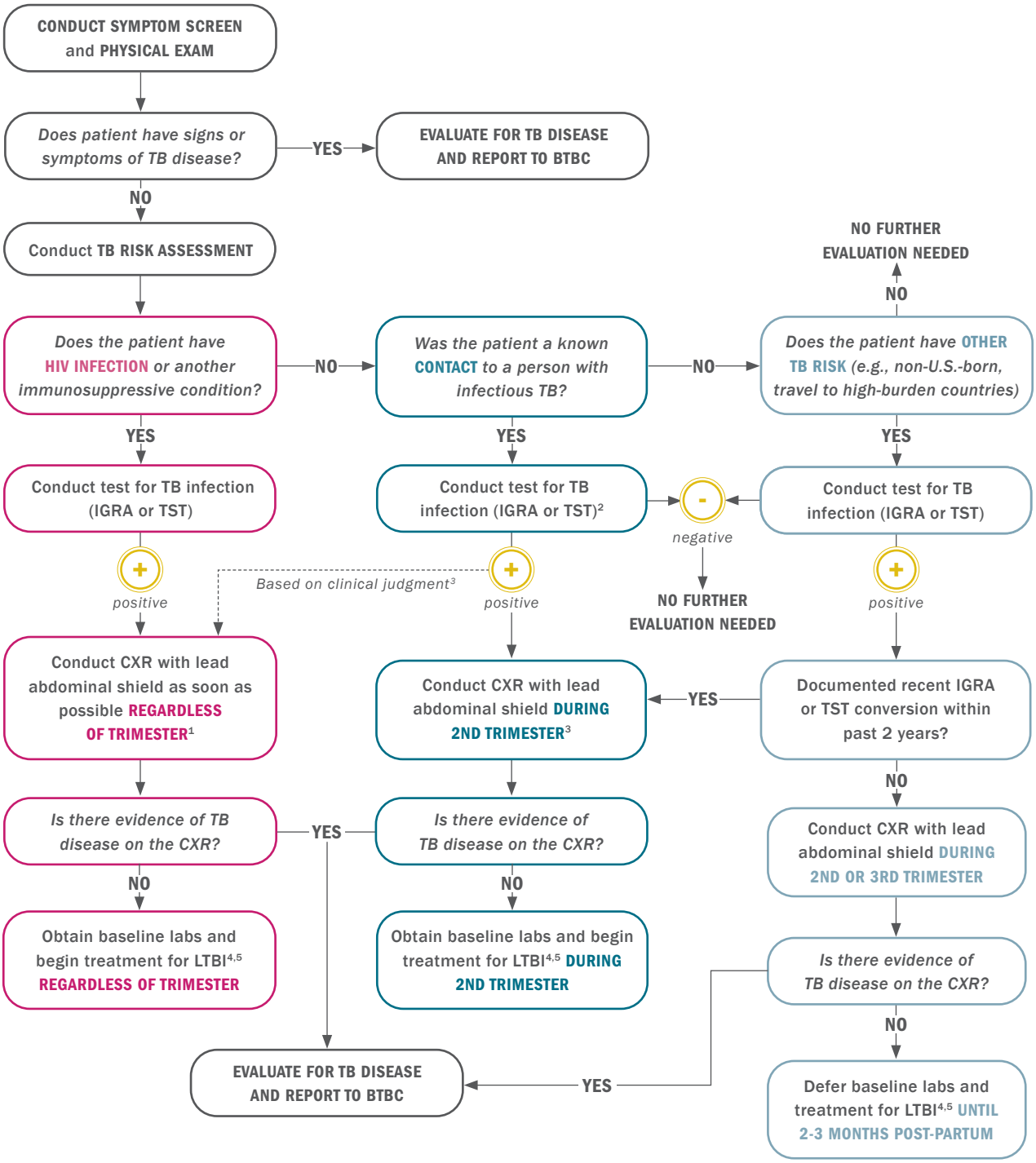
POST-PARTUM:

For all other pregnant patients, LTBI treatment is started two to three months after delivery, including those with population risk or radiographic evidence of old, healed TB disease, once active TB has been ruled out.

REGIMENS FOR PATIENTS WHO BECOME PREGNANT WHILE TAKING TREATMENT FOR LATENT TUBERCULOSIS INFECTION

In general, LTBI treatment is discontinued in patients who become pregnant, unless they have HIV infection or are otherwise immunosuppressed, were a recent converter when LTBI treatment was started, or were a contact to a person with infectious TB disease. If discontinued, to reduce the risk of peripartum hepatitis, LTBI treatment is restarted two to three months after delivery. When treatment is restarted, a full course is given (e.g., previous doses ignored).

FIGURE 2.3: Evaluation of pregnant persons at risk for tuberculosis (TB)



1. A CXR may be obtained in any person with HIV or other immunosuppressive conditions at the discretion of the provider, even if the TB test is negative; 2. Contacts who have a negative test for TB infection require a repeat test after the window period (8 weeks after last exposure ended); 3. Based on epidemiological risk factors and clinical judgment, CXR may be recommended in the 1st trimester for pregnant contacts without HIV infection; 4. Elevated alkaline phosphatase is not an indication to hold LTBI treatment as it may be due to placental origin; 5. Treatment for LTBI includes either RIF or INH. Labs include CBC and LFTs if patient is taking RIF, and only LFTs if giving INH. INH with rifapentine is contraindicated in pregnancy.

Abbreviations Used: CBC=complete blood count; CXR=chest radiograph; HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; INH=isoniazid; LFT=liver function test; LTBI=latent tuberculosis infection; RIF=rifampin; TST=tuberculin skin test

INH has been commonly used for LTBI treatment in pregnant patients. Although INH readily crosses the placental barrier, it is not teratogenic, even when given during the first trimester of pregnancy. Pyridoxine (vitamin B6) is given to pregnant patients taking INH to prevent peripheral neuropathy.

RIF crosses the human placenta and appears in cord blood. Reports of the use of RIF during pregnancy generally involve patients on multiple TB drug therapy, so the sole contribution of RIF to maternal and fetal outcomes is difficult to determine. Though there have not been any controlled data on the use of RIF in pregnancy, extensive use of RIF for the treatment of TB disease in pregnant patients suggests that it is safe to use in most circumstances.

For pregnant persons who were exposed to persons with multidrug-resistant TB (MDR-TB), providers can call the **TB HOTLINE** at 844-713-0559 for consultation. LTBI treatment may be delayed in such cases to avoid possible adverse effects of the medications on the developing fetus. In such cases, pregnant persons receive close clinical follow-up with initial CXR and repeat CXR at regular intervals or if TB symptoms develop (see *Special Considerations for Contacts of Persons with Multidrug-Resistant Tuberculosis*).

BREASTFEEDING

Breastfeeding can be initiated or continued during LTBI treatment of the mother. The drug concentrations in breast milk are typically too low to create toxicity in the infant. However, infants should be monitored for signs of hepatotoxicity or peripheral neuritis. Similarly, the amount of LTBI medication provided by breast milk is inadequate for LTBI treatment (if relevant) of the infant. Infants requiring INH treatment must also receive supplemental vitamin B6.

SPECIAL CONSIDERATIONS FOR DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION IN INFANT AND CHILD CONTACTS

All child contacts to persons with infectious TB require evaluation to determine if they have TB infection or disease. BTBC prioritizes the evaluation of children younger than five years of age, as they are at high risk for TB infection and, if infected, progression to TB disease.

MEDICAL EVALUATION, TESTING FOR TUBERCULOSIS INFECTION, AND CHEST RADIOGRAPH

All child contacts to persons with infectious TB receive an evaluation, including the following:

- Medical history
- Physical examination
- Baseline test for TB infection
  - TST is used for children younger than two years of age
  - IGRA is preferred for children two years of age and older
- CXR

- Children five years of age or older: posteroanterior (PA) view, if test for TB infection is positive; other views (e.g., lateral, lordotic) are obtained as clinically indicated.
- Children younger than five years of age require CXR regardless of test for TB infection result and require both PA and lateral views.

For infants younger than six months of age, providers may use their discretion with respect to performing a TST. A negative TST is not considered reliable until infants are at least six months of age due to their immature immune response. All infant and child contacts with a negative baseline TST receive a repeat test when they are at least six months of age and when at least eight weeks have passed since their last exposure to a person with active TB disease. All other aspects of the evaluation are as noted above.

If children younger than five years of age live in the same household as a person with infectious TB disease, the infectious patient and children are kept separated until one of the following conditions are met:

- The person with infectious TB is taking appropriate treatment and has demonstrated an adequate clinical response to treatment (e.g., AFB-negative smears and improvement in symptoms), or
- The child has started LTBI treatment, including window period prophylaxis.

If the index patient remains infectious despite initiation of therapy (e.g., due to extensive MDR-TB), BCG vaccine can be considered for the child if the test for TB infection is negative (least desirable option). BTBC only uses BCG vaccine for children who are contacts to MDR-TB patients. (See *Appendix D: The Use of Bacille Calmette-Guérin Vaccine*.)

WINDOW PERIOD PROPHYLAXIS OF INFANT AND CHILD CONTACTS

If active TB disease has been ruled out, treatment to prevent TB is initiated during the window period, even if the first IGRA or TST is negative among:

- Contacts younger than five years of age
- Contacts between five to 15 years of age, at the provider's discretion

Window prophylaxis is discontinued if the post-window period IGRA or TST remains negative and the patient:

- Does not have HIV infection or other immunosuppressive conditions
- Is older than six months of age

Some providers may decide to complete a full course of preventive treatment if only a few months are remaining.

A full course of LTBI treatment is completed if the initial CXR is normal and:

- The baseline or post-window period IGRA or TST is positive

- The baseline or post-window period IGRA or TST is negative, but the patient has HIV infection or other immunosuppressive conditions
- There is ongoing exposure to a person with infectious TB or evidence of TB transmission in the household, at the provider's discretion

As with adults, short-course treatment of LTBI is preferred for eligible infants and children whenever feasible. In addition, choice of LTBI treatment depends on DST results of the isolate obtained from the infectious person who is believed to have infected the child.

›› Use RIF for any child, even those younger than two years of age, when the isolate is susceptible to RIF.

›› Use 3HP in children older than two years of age, when the isolate is susceptible to both INH and RIF.

›› Use INH when the isolate is susceptible to INH and other regimens either cannot be tolerated or are contraindicated.

›› If the isolate demonstrates multi-drug resistance, base the regimen on DST results.

Infants are likely to require frequent dose adjustments while on window prophylaxis due to their rapid weight gain. Avoid using sorbitol-containing medications (e.g., INH syrup formulation) since these may cause diarrhea and decrease the parent's motivation to continue the child's prophylaxis. As an alternative to syrup, crush INH tablets and mix with small amounts of soft food (e.g., yogurt, pudding, jam). Based on the dosing, RIF may need to be compounded; for infant and child contacts being seen at NYC Health Department TB clinics, this service is available through the clinic pharmacy by prescription.

SPECIAL CONSIDERATIONS FOR CONTACTS OF PERSONS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

To date, there have not been any published, controlled trials of LTBI treatment after exposure to a person with MDR-TB. Thus treatment protocols for close contacts to persons with MDR-TB are largely based on empirical data and must be individualized based on the drug susceptibility patterns of the index patient's MDR-TB strain. There is well known toxicity with pyrazinamide (PZA)-containing regimens, as well as poor tolerability of most second-line drugs used to treat MDR-TB. The length of treatment may be influenced by age, immune status, and other epidemiological risk factors (e.g., evidence of transmission to other contacts). The decision of whether to provide LTBI treatment for contacts to persons with MDR-TB is therefore complex and must be made in consultation with BTBC experts.

Many experts recommend treatment of such contacts with a fluoroquinolone (FQN) such as levofloxacin (LFX) or moxifloxacin (MFX) if the index patient's MDR-TB strain is sensitive to it. FQNs are recommended even in children since the potential benefit of preventing MDR-TB outweighs the potential risk of toxicity.

Persons receiving two or more anti-TB drugs receive baseline chemistry including glucose and creatinine, LFTs, CBC, and hepatitis profile, as well as HIV testing.

TREATMENT OPTIONS

Current LTBI treatment options for close contacts of persons with MDR-TB include the following:

1. **FQN monotherapy:** It is BTBC policy to use this option if the index patient's TB isolate is susceptible to one or more FQN.
   - Use LFX or MFX in adults.
   - BTBC prefers the use of LFX in children due to a greater body of supporting literature and availability of a liquid formulation of the medication.
2. **Two drugs to which the index patient's TB isolate is susceptible.**
   - A FQN plus a second drug; ethambutol (EMB) is preferred; other options include: ethionamide (ETA), cycloserine (CS), para-aminosalicylic acid (PAS).
     - Use of EMB requires monitoring of vision.
     - Avoid PZA if possible due to potential hepatotoxicity.
   - May use another two-drug regimen for children and adults if there is resistance to FQN, (i.e., pre-extensively drug-resistant TB [pre-XDR-TB]).
3. **No treatment with close monitoring for two years.**
   - Not preferred for patients with a recent documented IGRA or TST conversion or a high risk for progression to active TB disease.
   - Patient requires clinical evaluation and CXR at four, eight, 12, 18, and 24 months.

If the contact is treated, the duration of treatment ranges from six to 12 months. Contacts are treated for nine to 12 months if they either have HIV infection or another immunosuppressive condition or are children younger than five years of age. For patients who are immunosuppressed, consideration may be given to use of a single FQN for a longer duration (nine to 12 months) OR the use of two drugs (for six to 12 months). For all treatment regimens, providers discuss the risks/benefits/potential side effects of the medications with the patient and document in the patient's EMR.

BCG vaccine is rarely used and is only considered for infants (younger than one year of age) exposed to an infectious person with MDR-TB. (See *Special Considerations for Latent Tuberculosis Infection Diagnosis and Treatment of Infant and Child Contacts* and *Appendix D: The Use of Bacille Calmette-Guérin Vaccine*.)

SPECIAL CONSIDERATIONS FOR TREATMENT OPTIONS OF PERSONS WITH RADIOGRAPHIC EVIDENCE OF OLD, HEALED TUBERCULOSIS

For asymptomatic persons with a positive IGRA or TST reaction ≥ 5 mm, along with a CXR that shows fibrotic lesions suggestive of old, healed TB disease, the classification and treatment decision is based on symptoms, clinical exam, and prior LTBI or TB disease treatment. Three sputa are obtained for AFB smear and culture. For patients with an abnormal CXR consistent with TB, a classification of Class V is given if three sputa are collected. If sputa are AFB smear-positive, active TB must be ruled out. (See *Chapter 3:*

Diagnosis of Tuberculosis Disease in Adults.) If sputa are AFB smear-negative and there is no evidence of adequate prior treatment for active TB disease, treatment may be started with INH and RIF, along with PZA and EMB for two months. The patient is classified as Class V (high). Pyridoxine is given to prevent peripheral neuropathy from INH. Monthly clinical follow-up is required. This approach has several advantages: it can be used to treat patients who may have INH-resistant organisms and it allows patients to start treatment at the first medical visit, rather than waiting for the final result of sputum cultures.

RECLASSIFICATION OF THE PATIENT

- If sputum cultures are positive for *M. tuberculosis*, or if sputum cultures are negative for *M. tuberculosis* and if the follow-up CXR at two months shows improvement with empiric treatment, or if the patient responds clinically to medications, providers reclassify the individual as **Class III** and treat for active TB disease.
- If all sputum cultures are negative for *M. tuberculosis* by two months, assess the follow-up CXR:
  - If the CXR shows no change, the lesions are presumed to be inactive. Reclassify the patient as having old TB disease (**Class IV**) and treat as follows:
    - If the patient has no history of TB treatment and does not come from an area with high rates of drug-resistant TB, continue with two additional months of INH and RIF only.
    - If there is a history of TB treatment or the patient comes from an area with high rates of drug-resistant TB, continue all four drugs for an additional two months.
    - Patients with extensive fibrotic disease, HIV infection, or other immunosuppression may be candidates for an additional four months of treatment per provider's discretion.
    - Other diagnoses should also be considered as clinically indicated and the patient may require referral to a pulmonologist.
- If clinical symptoms or CXR show improvement, the lesions presumably were active. Reclassify the patient as having culture-negative active TB disease (**Class III**) and treat as follows:
  - If the patient has no history of TB treatment and does not come from an area of high rates of drug-resistant TB, continue with two additional months of INH and RIF only. Some physicians may continue all four drugs if the patient is tolerating the regimen, due to high rates of INH resistance worldwide.
  - If there is a history of TB treatment, continue all four drugs for an additional two months.

After four months of therapy, an end-of-treatment CXR is obtained, which will serve as a baseline for future reference. Some patients classified as having old TB disease (**Class IV**) or high suspicion of TB (**Class V**) may show improvement on the four-month CXR. These patients are reclassified as having culture-negative active TB disease (**Class III**).

If there is low clinical suspicion of active TB disease (**Class V, low**), and initial AFB smears are negative, an additional option is not to treat until the cultures are finalized. If cultures are negative, there are three

possible regimens for LTBI for persons with evidence of old, healed TB disease and no history of treatment: 4R, 3HP, or 6H.

CASE MANAGEMENT OF PATIENTS WITH LATENT TUBERCULOSIS INFECTION

Patients with LTBI do not feel sick and may face challenges in trying to complete therapy. Monthly clinical monitoring evaluations are scheduled for all patients receiving LTBI treatment. In addition, contacts to persons with infectious TB who are being treated for LTBI at a NYC Health Department TB clinic are assigned a case manager within one month of starting LTBI treatment. Various techniques are utilized to facilitate treatment adherence including: educating patients about the importance of adherence to treatment and about potential side effects, discussing barriers to adherence, and using incentives and enablers when feasible. The patient's preferred language is used for these discussions. Patients are referred for assistance with social services as needed.

To promote treatment adherence and success, DOT is mandatory for persons receiving intermittent LTBI treatment with biweekly INH. DOT is preferred, when possible, for patients receiving 3HP. NYC Health Department TB clinics provide numerous DOT options. In-person DOT is offered to household contacts at the same time the person with infectious TB disease receives DOT. Video DOT has been found to be both cost saving and patient-centered. Video DOT (live [LVDOT] or recorded [RVDOT]) is offered to patients on the 3HP regimen to accommodate their schedules and preferences. Educational materials are provided in the patient's preferred language.

MANAGING INTERRUPTIONS IN TREATMENT AND DETERMINING COMPLETION OF THERAPY

Decisions regarding completion of treatment are based on the total number of medication doses administered, as well as on the duration of therapy. (See *Table 2.8: Recommended Drug Regimens and Dosages for Treatment of Latent Tuberculosis Infection in Adults and Children*.)

- Patients taking RIF must complete 120 doses within six months.
- Patients taking 3HP must complete ≥ 11 weekly doses within 16 weeks.
- If there are interruptions in treatment with INH, patients can be given two to three additional months to complete the regimen.
- If there is a gap greater than three months, the entire course of INH treatment is restarted.
- Children and adults without HIV infection, other immunosuppressive conditions, or other medical risk factors can be considered to have completed treatment after six or more months of INH.

When treatment has been interrupted for more than three months, patients are reevaluated to rule out active TB disease. Patients with lapses in therapy, but who are still able to complete the recommended number of doses in the allotted time frame are encouraged to complete therapy. Patients who do not complete their LTBI treatment within the allotted time frame are evaluated to determine whether or not to restart treatment. If the decision is made to re-treat the patient, the entire LTBI regimen is restarted (e.g., previous

doses are not counted). Specific factors to consider when determining whether to restart treatment include the following:

- Individual's risk for developing active TB disease
- Total number of doses of LTBI treatment administered
- Time elapsed since the last dose of treatment for LTBI
- Patient adherence issues (e.g., previous attempts at completion, willingness to continue)

Patients are encouraged to adhere to the LTBI treatment regimen; however, if a patient has failed three attempts to complete treatment, further attempts may not be indicated. Patients who are at high risk of progression to TB disease (e.g., contacts of persons with infectious TB disease, persons with HIV infection) are advised to return to the clinic if symptomatic to rule out active TB disease.

DISCHARGE OF THE PATIENT FROM CLINIC

Patients receiving LTBI treatment generally may be discharged from NYC Health Department TB clinic care when they return for the final month's supply of medication (e.g., after the third month for patients taking a four-month treatment regimen). The provider performing the monthly evaluation notes in the EMR that the patient:

- Received enough medication for the last month of LTBI treatment; and
- Was discharged from the NYC Health Department TB clinic.

Contacts of persons with MDR-TB who are not treated for LTBI are recommended to have follow-up for two years, including clinical and radiological examinations at four, eight, 12, 18, and 24 months.

Documentation of the test for TB infection results, CXR results, and the LTBI treatment completion is provided to the patient in writing and patients are informed that repeat testing and treatment is generally not indicated except in specific circumstances (e.g., contact to person with infectious TB). The patient is educated to return to the NYC Health Department TB clinic if they develop symptoms consistent with TB.

RE-TREATMENT OF LATENT TUBERCULOSIS INFECTION

Repeat treatment for LTBI in the future should be considered for persons who have subsequently been in close contact with a person with infectious TB disease, including persons who:

- Have HIV infection, are otherwise immunosuppressed, or are at risk for progressing to TB disease
- Are younger than 18 years of age
- Do not have HIV infection, but had close contact to a person with highly infectious TB (e.g., presence of secondary cases or documented conversions of tests for TB infection in other contacts)

When LTBI treatment is repeated, a full course is given based on the assumption that exogenous reinfection may have occurred.

SUMMARY

Diagnosis and treatment of persons with LTBI is essential, particularly among those at highest risk for progression to active TB disease. Among eligible patients, BTBC prefers the use of an IGRA to detect TB infection and short-course regimens to treat LTBI. Routine follow-up and monitoring are used to facilitate treatment adherence and completion and ensure optimal health outcomes. Appropriate LTBI diagnosis and treatment are vital components of BTBC's TB prevention and elimination efforts.

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CHAPTER 3: DIAGNOSIS OF TUBERCULOSIS DISEASE IN ADULTS

INTRODUCTION

Prompt diagnosis and treatment of active tuberculosis (TB) disease improves health outcomes and reduces the spread of TB in the community. Even before the diagnosis is confirmed by laboratory testing, clinicians may initiate TB treatment and recommend that a patient with pulmonary disease restrict social interactions and refrain from work until they are no longer infectious. Recent technological advances enable clinicians to confirm the diagnosis of TB in a more timely and accurate manner, thereby allowing patients to be treated more quickly and minimizing their infectiousness in the community.

DIAGNOSIS OF ACTIVE TUBERCULOSIS DISEASE

Active TB disease can affect nearly any organ of the body. Thus, there are diverse disease presentations that make it difficult to outline a single approach to its diagnosis. The majority of persons diagnosed with active TB disease have pulmonary disease (and are potentially infectious). Nonetheless, a substantial minority of persons have extrapulmonary disease, either with or without pulmonary involvement.

A diagnosis of TB disease is established through a medical history, physical examination, chest radiograph (CXR), and laboratory test results. While a definitive diagnosis of TB disease depends upon a positive culture or nucleic acid amplification (NAA) test result for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex, a high degree of clinical suspicion can be established based on epidemiologic findings, medical history, radiographic findings, and physical examination. Increased clinical suspicion for active TB is warranted for persons with TB risk factors when they fail to improve after initial empiric treatment for conditions such as community acquired pneumonia. Clinicians should consider factors that may affect the typical presentation of TB disease, such as the patient's age and coexisting diseases. TB may present in atypical ways in immunosuppressed patients as well as in young children.

Symptoms of TB disease in extrapulmonary sites may not include cough, but instead reflect the site of disease. For example, individuals with meningeal TB may present with new onset seizures, worsening headache, or meningeal signs.

During an encounter with an individual for whom clinical suspicion for TB disease is high, a complete medical evaluation is performed, including medical history, physical examination, human immunodeficiency virus (HIV) testing, interferon gamma release assay (IGRA) or tuberculin skin test (TST), radiological imaging, and mycobacteriological evaluation (acid-fast bacilli [AFB] smear and culture).

CLINICAL EVALUATION

During the diagnostic process, patients are interviewed to document their medical history. A record of a patient's medical history includes the following:

- **Description and duration of symptoms:** Symptoms of active TB disease are non-specific and may be influenced by the site(s) of disease, but typically include one or more of the following:
  - Cough (including hemoptysis) for several weeks
  - Fever
  - Anorexia
  - Unintended weight loss
  - Night sweats
  - Loss of energy

- **History**
  - Other medical conditions
  - Current or recent medications taken (prescription, over-the-counter, supplements)
  - Other medical care previously obtained for symptoms related to current TB diagnosis
  - TB history, including previous TB treatment, known TB exposure, and/or family history of TB disease
  - If prior treatment for TB disease was obtained in New York City (NYC), the TB electronic surveillance and case management system, Maven, is searched for prior patient records
  - If treatment for TB disease was provided elsewhere in the United States (U.S.) or abroad, efforts are made to obtain relevant information and share with treating providers
  - Social history (e.g., drug and alcohol use, homelessness, incarceration) and occupational history
  - Country of origin and year of entry into the U.S.
- **Physical examination**: A baseline physical exam is conducted for each patient, including a general assessment to detect signs of TB, a directed examination as per symptoms or signs, and an assessment of vital signs (including weight, blood pressure, temperature, and pulse). Although the physical examination cannot be used to confirm or rule out TB disease, it can provide valuable information about the patient's overall condition. Sites of assessment include:
  - Head (including ears, eyes, and throat)
  - Neck
  - Lungs
  - Heart
  - Abdomen
  - Extremities
  - Skin
- **Chest radiograph:** CXRs are obtained for all persons with confirmed TB disease or signs and symptoms consistent with TB disease, including those with only extrapulmonary sites of disease. A baseline posterior-anterior CXR is obtained for all adult patients. Other views (e.g., lateral, lordotic) or additional studies (e.g., computed tomography [CT] scans) are obtained when necessary. A lead shield is used when obtaining a CXR in a pregnant patient or a patient who could be pregnant. Pregnant patients who are being evaluated for TB disease undergo CXR without delay, even during the first trimester.

  Pulmonary TB disease has a myriad of presentations on the CXR that manifest in the parenchyma and pleura, or that can suggest hilar or mediastinal lymphadenopathy. Classic TB disease findings are seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, abnormalities may appear anywhere in the lungs and may differ in size, shape, and density.

Cavitary lesions, when present, are associated with a higher degree of infectiousness and may influence treatment length. Hematogenous spread of TB causes a miliary pattern (one to five millimeter millet seed-like densities) and when seen, prompts the consideration of additional sites of disease. Finally, the CXR may be entirely normal in persons with HIV infection or other immunosuppressive conditions who have culture-positive pulmonary TB disease.

BACTERIOLOGIC EVALUATION

The diagnosis of TB disease is primarily established by obtaining confirmatory mycobacteriology results (positive culture or NAA test results for *M. tuberculosis* complex). Pulmonary TB disease may be diagnosed through collection of sputum (preferably induced), gastric aspirates, or specimens obtained during bronchoscopy, video-assisted thoracic surgery (VATS), or following other thoracic surgery procedures. Specimens for AFB smear and culture are collected whenever there is a clinical suspicion for TB disease. For optimal results, specimens are collected in sterile containers and stored in refrigerated conditions to reduce the growth of microflora and other contaminating organisms present within the specimen.

Many hospitals, certain commercial laboratories, and the New York City Health Department's Public Health Laboratory (PHL) have incorporated the use of NAA testing on certain raw or processed pulmonary specimens. NAA tests can confirm the presence of *M. tuberculosis* complex DNA and detect mutations associated with drug resistance within hours of specimen receipt at the laboratory. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

When requesting NAA tests on extrapulmonary specimens or AFB smear-negative respiratory specimens, approval by the Bureau of TB Control (BTBC) is required if the specimen is being tested at PHL.

- **Sputum:** Sputum induction is the standard procedure for collecting sputum and is performed at all NYC Health Department TB clinics. When inducing sputum, the patient inhales nebulized sterile water, which liquefies airway secretions, promotes coughing, and allows expectoration of respiratory secretions. Sputum is obtained in any individual who is suspected of having pulmonary TB disease.
  - Three sputa specimens are obtained in eight- to 24-hour intervals (over two to three days).
  - At least one sputum specimen is collected in the early morning prior to the patient eating; these specimens have a higher diagnostic yield due to the pooling of respiratory secretions overnight.
  - Sputum induction is especially useful for patients who have trouble producing sputum spontaneously.

  It is important to specify whether the sputum is induced or not, because induced sputum is "more watery" and appears to be just saliva. Some laboratories may throw out induced sputum and report it as an inadequate specimen. (See *Appendix E: Instructions for Performing Sputum Induction*.)

- **Gastric aspirates:** Gastric aspiration can be considered for any individual with signs and symptoms consistent with pulmonary TB disease who either cannot produce sputum spontaneously or with

induction, or when other methods of collecting respiratory specimens are not practical. While gastric aspirates can be collected in adults, it is more commonly done in children. (See *Chapter 7: Diagnosis and Treatment of Pediatric Tuberculosis Disease*.) Gastric aspirates must be neutralized with sodium carbonate within one hour of collection and submitted to the laboratory for mycobacteria culture and smear microscopy. Rapid diagnostic testing for gastric aspirates is limited by poor sensitivity.

›› **Bronchial washings, broncoalveolar lavage, transbronchial biopsy, and lymph node aspiration:** Bronchoalveolar lavage and/or transbronchial biopsy performed with a fiberoptic bronchoscope may be needed to establish a TB diagnosis in some patients. Mediastinal lymph node aspiration may be done by transbronchial needle aspiration, usually performed using endobronchial ultrasound guidance. Specimens should be sent for culture, cytology, and pathology. Bronchoscopy is used in any of the following situations:

- If a patient has a substantial risk of drug-resistant TB (DR-TB) and has initial routine studies that are negative
- If there is suspicion of endobronchial TB
- If additional clinical specimens for the diagnosis of pulmonary TB disease are needed

The following are considerations when performing a bronchoscopy:

- The topical agents used to anesthetize the airways may be lethal to *M. tuberculosis*; these agents are used judiciously.
- The procedure may cause the patient to cough; the post-bronchoscopy specimens, which may have a high diagnostic yield, are collected and sent for AFB smear and culture.

URINE

A first morning, voided-midstream collection is used to ensure a high-quality specimen. Multiple specimens are sometimes necessary to detect mycobacteria. White blood cells (WBC) in urine without any bacteria can indicate TB, as can gross or microscopic hematuria; however, urine smears are usually negative and therefore performing them may not be cost-effective. Collection of urine is avoided if the patient is being treated with broad-spectrum antibiotics at the time of collection; many antibiotics concentrate in the urine and may reach levels that inhibit growth of mycobacteria including the fluoroquinolones (FQN).

BODY FLUIDS

Submission of body fluids (e.g., pleural, cerebrospinal fluid [CSF], blood, pericardial, joint, and peritoneal) for AFB smear and culture is recommended when there is body fluid that is accessible and can be sampled in order to determine site of disease. Whenever possible, submit specimen volumes that are greater than 5 ml to increase the sensitivity of detecting the presence of TB disease.

Certain fluids are submitted for additional tests, such as pH, protein, cell count, glucose, and adenosine deaminase (ADA), as these tests may provide data which help make the diagnosis of active TB when the

smear and/or culture results are negative (which is common). The finding of a high protein, elevated WBC count with lymphocytic predominance, low glucose, and elevated ADA are consistent with TB disease; however, these findings are not pathognomonic. Neutrophilic predominance may be seen when the fluid is examined earlier in the disease process.

TISSUE

In certain cases, referrals to specialists are required for invasive methods to obtain a specimen from the lung, pleura, pericardium, lymph nodes, bones and joints, bowel, peritoneum, kidney, fallopian tubes, epididymis, and from other involved sites when non-invasive techniques are not feasible or other methods are not diagnostic. Many of these sites are suitable for closed techniques such as percutaneous needle biopsy or aspiration.

In patients with disseminated disease, bone marrow biopsy, lung biopsy, or liver biopsy for culture and pathological examination may be considered as part of the diagnostic process.

If specimens are taken for pathological examination, a portion of the tissue is placed in normal saline for mycobacterial culture. If the specimen cannot be shipped promptly to the laboratory, it is refrigerated. Avoid fixing or preserving tissues as these specimens cannot be used for mycobacteria culture.

Percutaneous pleural biopsy demonstrates granulomatous inflammation in approximately 60% of patients with TB, and TB can be cultured in up to 80% of pleural tissue specimens. The combined yield of AFB stains of pleural fluid and biopsy tissue, coupled with mycobacterial culture of pleural fluid and biopsy tissue, can be greater than 90%. VATS has become the procedure of choice in diagnosing pleural disease and further increases the diagnostic yield. Providers obtain sputum specimens for patients suspected of having pleural TB disease in order to rule out simultaneous pulmonary TB.

MICROSCOPIC EXAMINATION (ACID-FAST BACILLI SMEAR)

The AFB smear is often the first diagnostic laboratory test performed on a clinical specimen to detect the presence or absence of mycobacteria. The AFB smear has poor sensitivity for detecting pulmonary TB. In NYC, only about 60% of patients diagnosed with pulmonary TB have a positive AFB smear result from a pulmonary specimen.

The mycobacteriology laboratory reports the AFB smear grade in a semi-quantitative fashion: negative, suspicious (rare), 1+, 2+, 3+, or 4+. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) A positive AFB sputum smear is associated with an increased likelihood of infectiousness.

The genus Mycobacterium consists of more than 200 different species, all of which appear similar by acid-fast staining. Although the detection of AFB in a stained smear provides supportive evidence of a TB diagnosis, an NAA test or culture must be performed to differentiate between members of the *M. tuberculosis* complex and other non-tuberculous mycobacteria (NTM). When AFB are observed and grown in a mycobacterial culture, identification can be performed in several ways.

NUCLEIC ACID AMPLIFICATION TESTS

Rapid deoxyribonucleic acid (DNA)-based NAA tests have become a routine method for detecting the presence of *M. tuberculosis* complex. NAA tests enable more rapid diagnosis and can decrease the time required for detection of drug resistance from weeks to days. This enables faster reporting and earlier initiation of appropriate treatment by providers, both of which may reduce community transmission of TB. Centers for Disease Control and Prevention (CDC)/American Thoracic Society/Infectious Diseases Society of America guidelines recommend that NAA tests should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test results would alter case management or TB control activities. PHL performs NAA testing on AFB smear positive specimens, but does not routinely perform a NAA test on AFB smear-negative specimen unless requested by BTBC. *(See Chapter 4: Laboratory Testing for Tuberculosis Disease.)*

- **NAA tests on acid-fast bacilli smear-positive respiratory specimens:** On AFB smear-positive specimens, NAA tests have excellent sensitivity and specificity. New York State regulations require laboratories to perform rapid diagnostic tests using NAA methods on initial AFB smear-positive sputa or respiratory specimens. If the NAA result is positive, the patient is presumed to have TB disease and begins anti-TB therapy. The positive predictive value of the NAA test is > 95% in AFB smear-positive cases.

  If the NAA result is negative, clinical judgment is used to determine whether to begin anti-TB treatment and whether additional diagnostic tests are needed. The combination of a negative NAA test result and a positive AFB smear may represent infection with a NTM, especially when a second negative NAA result from a second AFB smear-positive specimen is obtained. For patients who have two AFB smear-positive/NAA-negative sputum test results, airborne infection isolation may be discontinued. *(See Chapter 13: Infection Control.)*

- **NAA tests on acid-fast bacilli smear-negative respiratory specimens:** If the NAA result is positive on an AFB smear-negative specimen, the patient is presumed to have TB and anti-TB therapy is started pending culture results. If the NAA result is negative, the diagnosis of TB is not excluded and treatment decisions are based on clinical judgment. Current NAA tests are only 50% to 80% sensitive in detecting culture-positive TB in an AFB smear-negative respiratory specimen in patients suspected to have TB. When the clinical suspicion for TB disease is low, NAA testing is not recommended.

Processes across individual laboratories differ for AFB smear-negative respiratory specimens. In some instances, the provider may need to specifically request that an NAA test be performed if the clinical suspicion for TB is high.

- **NAA tests on extrapulmonary specimens:** For extrapulmonary specimens, NAA testing is only done if the clinical suspicion for TB disease is high. If the NAA test is positive, the diagnosis of TB disease is presumed and is confirmed by culture. If the NAA test is negative, a diagnosis of TB disease is not necessarily excluded.

NAA tests have high sensitivity and specificity on specimens that are AFB smear-positive and are important diagnostic tests, but have some limitations. NAA tests:

- Are not recommended when the clinical suspicion for TB disease is low
- Do not distinguish between live and dead organisms
- Are not recommended after initiation of TB treatment
- Have decreased sensitivity on smear-negative specimens
- Cannot be used to determine biological cure or to monitor response to therapy
- Cannot be used to differentiate between members of the *M. tuberculosis* complex

When a specimen has a positive NAA but no positive TB cultures, the treating provider considers whether the patient has TB disease based on epidemiology and the patient's medical history to determine whether the patient should continue treatment.

NAA tests are interpreted within the context of the patient's signs, symptoms, and risk for TB and are performed in conjunction with AFB smear and culture. Although these direct molecular methods can detect *M. tuberculosis* complex DNA directly from clinical specimens within 24 to 48 hours once received in the lab, mycobacteriology culture remains the gold standard for TB diagnosis.

CULTURE

Public health and commercial laboratories, including PHL, use both liquid (broth) and solid media to culture specimens. When growth is detected in mycobacterial culture, PHL uses various laboratory techniques to aid in the identification of mycobacteria. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Possible mycobacterial culture results include: *M. tuberculosis* complex (only), one or more NTM, or both *M. tuberculosis complex* and NTM.

Once culture growth is identified as *M. tuberculosis* complex, additional laboratory methods are used to characterize the *M. tuberculosis* complex isolates, such as drug susceptibility testing and genotyping. NYS conducts testing for *M. tuberculosis, M. africanum, M. bovis, M. bovis-BCG, M. microti, M. canetti, M. caprae,* and *M. orygis.*

BASELINE LABS

The following laboratory tests should be ordered for all patients as part of the evaluation and diagnosis process:

- Complete blood count (CBC)
- Chemistry panel (blood urea nitrogen, creatinine, uric acid, liver function tests [LFT])
- Viral hepatitis screen
- Other tests as clinically indicated

HUMAN IMMUNODEFICIENCY VIRUS TESTING

Knowing a patient's HIV status is vital to the TB diagnosis process. If the patient is not already known to have HIV infection, an HIV test and counseling is provided to all persons with signs and symptoms consistent with TB disease and those with confirmed TB disease according to the most recent local regulations. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) Effective March 2017 in New York, providers are no longer required to obtain informed consent prior to ordering an HIV-related test. Providers performing an HIV test as part of routine medical care must advise patients that an HIV-related test is being performed prior to ordering the test.

If a patient is known to have HIV infection, a complete history of the patient's HIV treatment is obtained and findings are documented in the patient's clinical record. For patients who test positive for HIV, a referral is made to an HIV specialist for appropriate follow-up and care.

An HIV test should be obtained for all patients suspected or confirmed to have TB disease

PATHOLOGY

Although pathology findings can be suggestive of TB, they are not specific enough to be diagnostic of TB. Prior to the availability of mycobacterial culture, pathology findings were a common method for diagnosing TB disease. Because extrapulmonary TB is commonly culture-negative, pathology results may be the primary laboratory result used to diagnose TB.

Common specimens include:

- Lymph node
- Pleural
- Bone/joint
- Kidney
- Peritoneal
- Pericardial

Whenever TB remains in the differential diagnosis for a patient undergoing an invasive procedure to remove tissue for pathological examination, a non-fixed portion of the tissue sample is reserved to submit for AFB smear and culture. Specimens placed in formalin or fixed for pathology cannot be used for culture.

Patients with the following common pathology results should be reported to BTBC:

- Presence of AFB
- Caseating granuloma
- Tubercles
- Necrotizing granuloma

- Necrotizing inflammation
- Chronic granulomatous lesions/chronic inflammation with granuloma formation

EVALUATION OF EXTRAPULMONARY TUBERCULOSIS DISEASE

Each year in NYC, about 20% of patients have an extrapulmonary site of disease, and an additional 13% have both extrapulmonary and pulmonary sites of disease. Extrapulmonary TB disease is more likely to occur among individuals with HIV infection, patients taking immunosuppressive agents, and young children.

Although culture is the gold standard for confirming the diagnosis of TB, the proportion of patients with a culture-positive isolate is lower among those with extrapulmonary disease than among those with pulmonary disease. When possible, extrapulmonary specimens being sent for pathological analysis should also be sent for culture.

LYMPHATIC TUBERCULOSIS

Lymphatic TB disease most commonly affects cervical or supraclavicular lymph nodes, although any set of lymph nodes can be involved.

- Individuals should be referred for aspiration or biopsy when diagnosing lymphatic TB.
- Aspiration is useful especially if the node(s) demonstrate fluctuance.
- Diagnosis can be established if the culture is positive for *M. tuberculosis* complex.
- Pathology findings of AFB in tissue, caseating granuloma, or caseating necrosis are consistent with, but not diagnostic of, TB disease.
- On CT scan, the presence of enlarged lymph nodes with hypodense centers is suggestive of necrosis, which is common in TB patients with HIV or other immunosuppressive conditions.

PLEURAL TUBERCULOSIS

TB pleural effusion can be due to a rupture of a subpleural caseous focus in the lung into the pleural space. A delayed hypersensitivity inflammatory reaction results in an increase of the permeability of the pleural capillaries to protein. Over time, pleural fluid accumulates and is usually characterized by a lymphocytic-predominant effusion.

The patient may present with a rapid onset of dyspnea, fever, and chest pain with dullness to percussion and decreased breath sounds (unilaterally or bilaterally) on physical examination. When considering a pleural TB diagnosis, a thoracentesis is performed and pleural fluid specimens are sent for:

- AFB smear and culture
- WBC count and differential
- pH, protein, and glucose
- ADA (levels > 40 may be suggestive of pleural TB)

Although neutrophils may predominate early in the disease process, > 50% lymphocytes are typically seen with WBC > 1000/microliter (µl). Pleural/serum protein ratio is typically > 0.5; low pH, low glucose levels, and high ADA levels are also consistent with pleural TB. Positive AFB stains are infrequently seen, with positive AFB culture found in approximately 25% to 75% of specimens.

Pleural biopsy for AFB smear and culture, and pathological examination are likely to increase diagnostic yield and are currently obtained most frequently by open methods via VATS, which is nearly always diagnostic of pleural TB. Three sputa for AFB smear and culture are obtained on all patients with pleural TB. Although a CXR may show no visible parenchymal lesions, cultures of sputum or gastric fluid are positive in 25% to 33% of patients.

TABLE 3.1: Evaluation of extrapulmonary tuberculosis

SUSPECTED SITE/TYPE	APPROACH TO DIAGNOSIS[1]
Disseminated	CXR, lumbar puncture[2,3] (to test for meningitis), biopsy[2] of affected sites if possible, blood[1]
Lymph nodes (especially cervical)	Fine needle aspiration, lymph node biopsy[2]
Meningeal	CT, MRI, lumbar puncture[2,3]
Miliary pattern on CXR	Induced sputum,[2] bronchoscopy with bronchial washing and transbronchial biopsy,[2] and gastric aspirates[2] if needed
Pericardial	Echocardiogram, pericardiocentesis,[2,3,4] pericardial biopsy[2]
Peritoneal	Abdominal ultrasound or CT, paracentesis,[2,3] peritoneal biopsy[2]
Pleural	CXR, thoracentesis,[2,3,4] pleural biopsy,[2] VATS[2]
Skeletal (bone and joint)	CT, MRI, arthrocentesis,[2,3] synovial or bone biopsy[2]

1. Conduct tests as clinically indicated; 2. AFB smear and culture; 3. Body fluids are sent for WBC count with differential, protein, glucose, and ADA; 4. Pericardial and pleural fluid should be sent for pH

Abbreviations Used: ADA=adenosine deaminase; AFB=acid-fast bacilli; CT=Computed tomography scan; CXR=chest radiograph; MRI=magnetic resonance imagery; VATS=video-assisted thoracoscopic surgery; WBC=white blood cells

PERICARDIAL TUBERCULOSIS

The onset of pericardial TB may be subtle, characterized by cardiovascular consequences of constrictive effusion, or abrupt, characterized by fever and precordial pain.

- An echocardiogram is obtained to detect pericardial effusion and assess cardiac dynamics.
- BTBC recommends pericardiocentesis or surgical biopsy to obtain a specimen for AFB smear and culture and ancillary testing unless there is a positive culture from another source.
- Positive smears are uncommon.
- Pericardial fluid is usually a lymphocytic exudate.
- ADA level > 40 units/liter (U/L) in pericardial fluid may be helpful in making a diagnosis of TB.
- Cultures are positive in only 25% to 50% of cases.
- Primary surgical intervention with a pericardial "window" may be indicated.

CENTRAL NERVOUS SYSTEM TUBERCULOSIS

MENINGEAL TUBERCULOSIS: Meningeal TB often has an insidious and variable presentation. Initial signs of personality changes, irritability, and anorexia may be followed by headache, neck stiffness, drowsiness, and cranial nerve palsies with eventual progression to coma. It is important to maintain a high suspicion for TB in patients with meningismus since there is nothing pathognomonic about the presentation of TB meningitis. TB meningitis is classified into stages upon presentation; a higher stage correlates with a poorer outcome:

Stage 1: Isolated meningeal disease without focal neurologic abnormalities

Stage 2: Isolated parenchymal disease and neurologic abnormalities without altered consciousness

Stage 3: Parenchymal and meningeal disease with obtundation or stupor

Prompt identification of TB meningitis is crucial, as the clinical outcome is influenced strongly by the stage at initiation of treatment. The key diagnostic procedure is the examination and culture of the CSF. Characteristic CSF findings are:

- Elevated WBC count (mean of 200 with range of 6-500/µl)
- Lymphocytic predominance
- Low glucose (less than 50% of serum)
- High protein

These findings are consistent with, but not diagnostic of, TB meningitis. The diagnosis may be supported by a positive AFB smear, or confirmed by a positive NAA test; however, negative AFB smears or negative NAA and culture tests do not rule out the diagnosis if clinical criteria are highly suggestive. Performing more than one lumbar puncture or submitting more than five milliliters (ml) of CSF increases

the likelihood of obtaining a positive CSF culture. AFB-positive cultures may be observed in 45% to 70% of patients with meningeal disease.

TUBERCULOMA: Patients with intracranial tuberculoma(s) may present with cranial nerve deficits, altered mental status, hemiparesis, seizures, or headache. Concomitant meningitis may be present.

Diagnosis depends on CT or magnetic resonance imaging (MRI) findings and biopsy of the lesion. On imaging studies, tuberculomas usually appear as ring-enhancing lesions.

Patients who are taking appropriate therapy for meningeal, pulmonary, or disseminated TB disease may paradoxically develop intracranial tuberculomas or worsening of symptoms either as a result of immune reconstitution inflammatory syndrome (IRIS), or to tapering of steroids.

DISSEMINATED AND MILIARY TUBERCULOSIS: Although the terms "disseminated" and "miliary" are used interchangeably by some, BTBC considers them to be distinct. BTBC considers TB disease to be disseminated when TB occurs in two or more non-contiguous sites such as in an individual with meningeal and pulmonary TB disease. TB may disseminate either through the blood or lymphatic systems. Miliary TB refers to the pattern of TB within an organ, such as the findings on a CXR of millet seed-like (one to five mm) round/ovoid nodular opacities throughout the lung fields, and represents hematogenous spread.

Confirming disseminated TB disease may require invasive procedures, such as transbronchial biopsy, or tissue biopsy of other organs, such as the lymph nodes, liver, or bone marrow. In patients who are severely immunocompromised or have advanced acquired immunodeficiency syndrome (AIDS), urine or blood cultures obtained by appropriate techniques may yield *M. tuberculosis*. These patients are assumed to have disseminated TB disease, even in the absence of radiologically- or pathologically-demonstrated TB lesions in other organs. If disseminated TB is confirmed, the length of treatment may need to be prolonged. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

SKELETAL TUBERCULOSIS

Bone or joint TB disease most often occurs in the spine (Pott's disease), followed by TB of the hip and knee. The typical presenting symptoms are pain, and when in a weight-bearing joint, difficulty with locomotion. The diagnosis of skeletal TB disease is prompted by abnormal findings on radiological imaging of the involved joint. The diagnosis is confirmed by collecting and culturing tissue or pus if there is an abscess.

GENITOURINARY TUBERCULOSIS

Untreated genitourinary TB disease can lead to scarring of the ureters and chronic renal failure in some patients. For women, untreated TB disease of the reproductive organs is a leading cause of infertility in some parts of the world. A biopsy and/or culture is performed on the affected sites to collect tissue for testing. Urine is also collected for urinalysis (hematuria or pyuria are frequently observed). Three morning urine specimens are collected for AFB smear and culture. Pathology specimens may be indicated, especially if patient has infertility.

GASTROINTESTINAL TUBERCULOSIS

TB can affect any part of the gastrointestinal (GI) tract, from the tongue or oropharynx to the anus. The cecum is the most common GI site. The most common symptoms are anorexia, early satiety, abdominal pain or symptoms of intestinal obstruction. Evidence of coexistent pulmonary TB disease is present in about 25% to 50% of cases. Many patients with GI TB have a stool culture that is positive for *M. tuberculosis*. It is important to note that a positive stool culture could represent organisms either from a GI source or organisms from a pulmonary source that were swallowed. Endoscopy and/or colonoscopy can be used to examine the lumen and obtain specimens for AFB and other cultures. Pathology specimens may also be suggestive of TB disease.

Common, but non-specific findings from a CT scan of the abdomen and pelvis are lymphadenopathy, especially in the retroperitoneum, and bowel wall thickening with associated lymphadenopathy. The presence of enlarged lymph nodes with a hypodense center is suggestive of necrosis, which is especially common in patients with HIV or other immunosuppressive conditions.

PERITONEAL TUBERCULOSIS

Peritoneal TB disease typically presents with weeks to months of abdominal pain often accompanied by distention. Ascites is a common and predominant finding, though systemic symptoms such as fever, night sweats, fatigue, and weight loss may also occur. A paracentesis is performed, a specimen is collected for AFB smear and culture, and a WBC count is obtained with differential, protein, and glucose to aid in the diagnostic process.

- WBC counts are typically 1000 to 2000/µl with > 80% lymphocytes.
- Protein levels are typically elevated (greater than three g/dl), but are lower when underlying liver disease is present; ADA is elevated, and glucose is typically low.
- Culture is positive in up to 70% of cases, though AFB smear is infrequently positive.
- Laparoscopic findings (gross appearance, pathology, or culture) also aid in diagnosis.

CUTANEOUS TUBERCULOSIS

Cutaneous TB disease is rare and presents with chancres and wart-like lesions. These lesions may be the result of direct inoculation of TB in the skin or from hematogenous or lymphatic spread. Cutaneous lesions may be confused with those seen in systemic diseases such as sarcoidosis. Autoinoculation from underlying infected tissues or secretions can also occur.

Staff who work in mycobacteria labs or who work with autopsy specimens occasionally receive an inoculum of TB, which can lead to a condition called “Prosecutor’s Wart.” The diagnosis can be confirmed by performing a biopsy of the lesion and sending the specimen for AFB smear and culture, and pathologic analysis.

DISEASE DUE TO INTRAVESICAL BACILLE CALMETTE-GUÉRIN FOR BLADDER CANCER

BCG is a live attenuated strain of *M. bovis*, which is used as immunotherapy for superficial transitional cell carcinoma of the bladder. The mechanism of action appears to be modulation of the immune response in the bladder, with localized inflammation induced by BCG leading to destruction of cancer cells. Occasionally, treatment for bladder cancer is complicated by disseminated or localized BCG-related disease. A case of *M. bovis*-BCG is not counted as a case of TB by either BTBC or the CDC.

BCG-related disease may present early (i.e., within 12 weeks of the initiation of intravesical therapy) or late (i.e., more than a year after initiation of intravesical therapy). Early disease may be associated with fever, malaise, chills, sweats, weight loss, shortness of breath, and arthralgia. The clinical picture is often consistent with disseminated disease with pneumonitis and/or hepatitis; however, disease may also be localized. The diagnosis is supported by the finding of granulomas on biopsy of affected organs, and while culture may be positive for *M. bovis*-BCG, a negative culture does not exclude the diagnosis.

Late disease is more likely to present locally in the genitourinary tract without associated generalized symptoms of fever, malaise, and weight loss. It is the result of reactivation following initial immunologic control. Biopsy often yields non-caseating granulomas. Culture may or may not be positive for *M. bovis*-BCG. The individual should be tested for TB infection and sputa obtained for AFB smear and culture, as the patient will have an abnormal CXR. Bronchoscopy with biopsy may be indicated. Molecular techniques distinguish *M. bovis*-BCG from *M. tuberculosis*.

M. bovis strains, including *M. bovis*-BCG, are universally resistant to PZA. Some *M. bovis* strains are also resistant to INH. Therefore, susceptibility results are used to guide treatment. Corticosteroids have been used to treat pneumonitis associated with BCG disease, as it may contribute to rapid resolution of symptoms.

SUMMARY

The prompt and accurate diagnosis of active TB disease is essential to improving patient health outcomes and preventing TB transmission. TB disease may present in atypical ways, particularly among those who are immunosuppressed or have extrapulmonary TB disease. Knowledge of local TB epidemiology and TB risk factors are key to promptly identifying those who may have active TB disease. Obtaining adequate diagnostic samples and initiating presumptive treatment when indicated is imperative.

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CHAPTER 4: LABORATORY TESTING FOR TUBERCULOSIS

INTRODUCTION

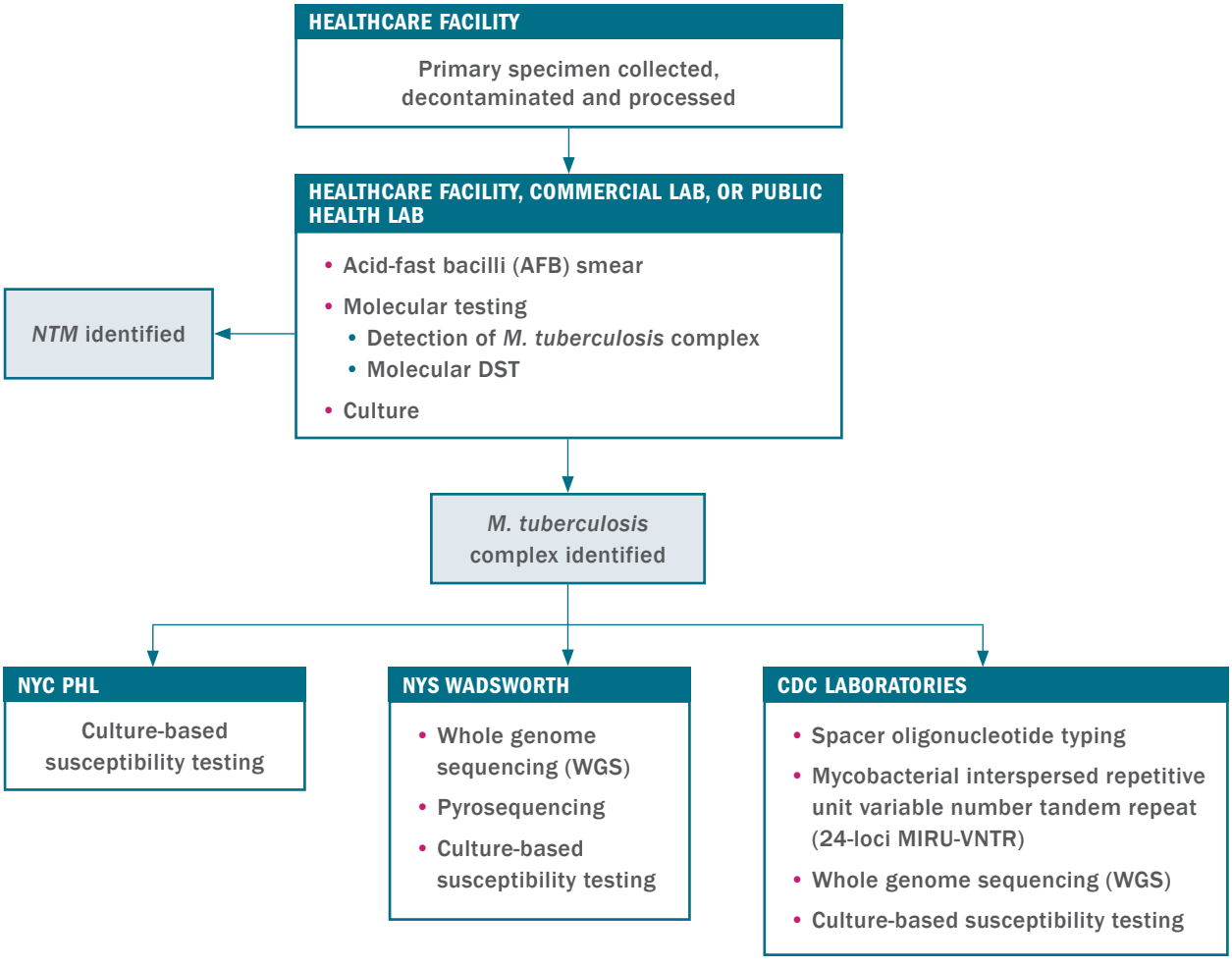
New York City (NYC) specimens undergo multiple types of laboratory testing for tuberculosis (TB). These tests include diagnostic tests for active TB disease, tests for drug susceptibility, tests that predict drug resistance, and genotyping. Prompt and accurate reporting of laboratory results supports appropriate diagnosis, treatment, infection control, surveillance, case management, and other clinical and public health activities.

GENERAL INFORMATION ABOUT LABORATORY TESTS FOR NEW YORK CITY SPECIMENS

Laboratory services and protocols vary depending on laboratory capacity and the facility where a specimen is collected. Specimens often pass through several laboratories in order to complete all required testing. (See *Figure 4.1:*

Mycobacteriology Laboratory Workflow for New York City Specimens.) The NYC Health Department Public Health Laboratory (PHL) performs diagnostic mycobacterial testing for all patients evaluated in a NYC Health Department TB clinic and provides laboratory testing services for NYC healthcare facilities and commercial laboratories. Diagnostic mycobacterial testing is also performed by hospital and commercial laboratories, and additional specialized testing—including susceptibility testing, drug resistance testing, and genotyping—is performed by the New York State (NYS) Department of Health Wadsworth Center (Wadsworth Center) and the Centers for Disease Control and Prevention (CDC). (See *Table 4.1: Laboratory Tests for Tuberculosis Disease Diagnosis, Drug Susceptibility, and Genotyping in New York City*.) The Bureau of TB Control (BTBC) collaborates with clinicians, laboratory partners, and others to facilitate testing and transfer of specimens between local healthcare facilities, commercial laboratories, NYC PHL, NYS Wadsworth, CDC, and contracted CDC laboratories. Specimen collection, handling, and transfer conform to established guidelines and are critical to the prompt and accurate diagnosis and treatment of TB.

FIGURE 4.1: Mycobacteriology laboratory workflow for New York City specimens



Abbreviations Used: CDC=Centers for Disease Control and Prevention; DST=drug-susceptibility test; *M. tuberculosis=mycobacterium tuberculosis*; NTM=nontuberculous mycobacterium; NYC PHL=New York City Department of Health and Mental Hygiene Public Health Laboratory; NYS Wadsworth=New York State Department of Health Wadsworth Center

TABLE 4.1: Laboratory tests for tuberculosis disease diagnosis, drug susceptibility, and genotyping in New York City

TEST TYPE	LABORATORIES	TURNAROUND TIME[1]	NOTES
AFB smear	• NYC PHL • Commercial • Hospital • NYS Wadsworth	Within 30 hours	Specimen types: respiratory, body fluids, tissue Factors influencing sensitivity: • Staining method (fluorochrome technique has a higher sensitivity than carbol fuchsin based techniques) • Experience of the microscopist
NAA tests	• NYC PHL • Commercial • Hospital • NYS Wadsworth	Within 2 to 5 days (some labs do not perform daily)	• Commercial, FDA-approved and non-FDA laboratory-developed tests available • High sensitivity and specificity for testing smear-positive respiratory specimens • Smear-negative respiratory or non-pulmonary specimens can have reduced sensitivity and specificity
Mycobacterial culture	• NYC PHL • Commercial • Hospital • NYS Wadsworth	Mycobacterial growth detection within 1 to 8 weeks Mycobacterial identification by DNA probe within 2 to 3 days of identifying growth	• Many labs finalize cultures at 6 weeks; NYC PHL finalizes cultures after 8 weeks • Reference labs use both liquid and solid culture media • If DNA probe for TB and MAC is negative, specimen might be sent to reference lab for identification
Phenotypic DST	• NYC PHL • Commercial • Hospital • NYS Wadsworth	Reported within 17-30 days from the date of identification of *M. tuberculosis*	• If the isolate has resistance to first-line drugs (except for PZA) by broth-based methods, the isolate is tested by the agar-proportion method for first- and second-line drugs • If susceptibility testing is unsuccessful, mutation analysis can be performed by pyrosequencing or Sanger Sequencing
Molecular DST • GeneXpert MTB/RIF assay • Pyrosequencing • Sanger sequencing • WGS	• NYC PHL • Commercial • Hospital • NYS Wadsworth • CDC	GeneXpert within 24 to 48 hours Pyrosequencing, Sanger sequencing, and WGS within 1 to 2 weeks	• Detection of RIF mutations requires confirmatory testing by sequencing • **GeneXpert:** Highly sensitive for mutations associated with RIF resistance • **Pyrosequencing, Sanger sequencing, and WGS:** Detect mutations associated with resistance to numerous anti-TB drugs
Genotyping • WGS • Spoligotyping • MIRU-VNTR	• NYS Wadsworth • CDC	3 days to 2 weeks	Performed by WGS, spacer oligonucleotide typing (spoligotyping), and mycobacterial interspersed repetitive unit-variable number tandem repeat analysis (MIRU-VNTR) for epidemiologic purposes

1. From time of specimen receipt

Abbreviations Used: AFB=acid-fast bacilli; CDC=Centers for Disease Control and Prevention; DNA=deoxyribonucleic acid; DST=drug-susceptibility test; FDA=Food and Drug Administration; INH=isoniazid; *M. tuberculosis*=*Mycobacterium tuberculosis*; MAC=Mycobacterium avium complex; NAA=nucleic acid amplification; NYC PHL=New York City Public Health Laboratory; NYS=New York State; PZA=pyrazinamide; RIF=rifampin; WGS=whole genome sequencing

Any laboratory conducting mycobacteriology testing for NYS residents must obtain and maintain certification from NYS's Clinical Laboratory Evaluation Program (CLEP).

In addition to diagnostic testing, the NYC Health Code mandates that laboratories either perform drug-susceptibility tests (DSTs) or submit an isolate of the initial culture from any positive *Mycobacterium tuberculosis* (*M. tuberculosis*) specimen to a laboratory that performs DST. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) Laboratories must also submit a portion of isolate to the NYC PHL for genotyping.

TESTS FOR TUBERCULOSIS DISEASE

ACID-FAST BACILLI SMEAR

Specimens collected for mycobacterial testing are typically submitted for both acid-fast bacilli (AFB) smear and culture. Specimen from non-sterile sources (e.g., sputum) require processing by digestion and decontamination of the specimen. The processed specimen is used to prepare a smear that is stained for AFB. AFB smear results are reported within 24-30 hours of specimen receipt.

The smear is important, both clinically and epidemiologically. Typically, AFB smear is the first test result obtained. A positive test result may increase the clinical suspicion of active TB disease. AFB smear prepared from sputum are also used to assess a patient's infectiousness. When positive, the results are reported on a scale which reflects the semi-quantitative estimate of the number of bacilli excreted. (See *Table 4.2: Quantitative Scale for Acid-Fast Bacilli Smears by Stain Used*.)

TABLE 4.2: Quantitative scale for acid-fast bacilli smears by stain used

CARBOLFUCHSIN (X 1,000)	FLUOROCHROME (X 250)	QUANTITY REPORTED
No AFB/300 fields	No AFB/30 fields	*No AFB seen*
1-2 AFB/300 fields	1-2 AFB/30 fields	*Suspicious; recommend resubmission of new specimen*
1-9 AFB/100 fields	1-9 AFB/10 fields	*Rare (1+)*
1-9 AFB/10 fields	1-9 AFB/field	Few (2+)
1-9 AFB/field	10-90 AFB/field	Moderate (3+)
> 9 AFB/field	> 90 AFB/field	Numerous (4+)

Adapted from: American Thoracic Society, Centers for Disease Control and Prevention, & Infectious Diseases Society of America. (2000). Diagnostic standards and classification of tuberculosis in adults and children. American Journal of Respiratory and Critical Care Medicine, 161, 1376-1395

Abbreviations Used: AFB=acid-fast bacilli

Additional diagnostic studies must be performed to confirm a TB diagnosis among patients with a positive AFB smear result since a positive AFB smear does not differentiate between *M. tuberculosis* and nontuberculous mycobacteria (NTM), certain actinomycetes, and other biological species. Sensitivity of a sputum smear is 50 to 80% among patients with pulmonary TB disease. At least 500 to 10,000 bacilli per milliliter (ml) of specimen must be present to detect bacteria on stained smears. In contrast, only 10 to 100 organisms are needed for a positive culture.

NUCLEIC ACID AMPLIFICATION TESTS

Although mycobacterial culture remains the gold standard for the diagnosis of TB disease, culture confirmation of TB may take several weeks or longer from the day of specimen collection. Nucleic amplification assay (NAA) tests identify DNA unique to *M. tuberculosis* complex in raw or processed clinical samples within a few hours. These tests can rapidly detect *M. tuberculosis* DNA with high sensitivity and specificity for respiratory AFB smear-positive specimens, but have lower sensitivity on AFB smear-negative specimens. These tests are not Food and Drug Administration (FDA)-approved for extrapulmonary specimens; however, some laboratories may have validated these tests for extrapulmonary specimens, and they can be used to test patients where there is a high clinical suspicion of TB.

There are various commercial tests currently available for use by hospital, public health, and reference labs.

- **GeneXpert MTB/RIF assay:** Approved by the FDA in August 2013 and used by many hospitals and commercial laboratories, this assay detects DNA of *M. tuberculosis* complex and genetic mutations associated with resistance to rifampin (RIF) in unprocessed sputum and concentrated sputum sediments. The assay is an NAA test using a disposable cartridge in conjunction with the GeneXpert system to extract, amplify, and detect *M. tuberculosis* complex DNA and mutations associated with RIF resistance. As many RIF-resistant isolates are also resistant to isoniazid (INH), RIF resistance can be used as a marker for multidrug-resistant TB (MDR-TB).

AFB SMEAR-POSITIVE RESPIRATORY SPECIMENS: In AFB smear-positive respiratory specimens, the positive predictive value of the NAA test is > 95%. Therefore, if the NAA is positive, presume the patient has TB disease and begin anti-TB therapy, pending culture results. If the NAA is negative, clinical judgment will need to determine whether to begin anti-TB therapy. These patients are likely to have an infection with NTM, especially if a second NAA from an AFB smear-positive specimen also tests negative for TB. For these patients, it may be appropriate to delay anti-TB therapy and contact investigation until culture results are available.

AFB SMEAR-NEGATIVE RESPIRATORY SPECIMENS: In AFB smear-negative respiratory specimens where TB is highly suspected, the diagnosis of TB is not completely excluded by a negative NAA test, as current NAA tests are only 50 to 80% sensitive in detecting TB. A decision about treatment must be based on epidemiological factors, clinical assessment, radiological, and other diagnostic tests while cultures are being finalized. Additional NAA testing may be warranted.

NAA tests can detect nucleic acids from dead as well as live organisms and, therefore, can remain positive for long periods in patients who are taking anti-TB medications or have completed TB treatment. Thus, most NAA tests should be used only for initial diagnosis for patients on TB medication less than one week, and not for follow-up evaluation of patients. The Xpert MTB/RIF should not be performed on specimens from patients where anti-TB medication has been initiated.

For patients with a positive NAA test but negative culture, the treating provider must determine if the patient has TB based on epidemiologic risk factors and/or clinical response to treatment.

NAA tests must be interpreted within the context of a patient's signs and symptoms and should always be performed in conjunction with the AFB smear and culture.

MYCOBACTERIOLOGY CULTURE

Despite advances in molecular detection of *M. tuberculosis* complex, growth of the organism through a culture remains the gold standard for diagnosis. Culture is able to detect as few as 10 bacteria/ml of a specimen, and is necessary for species identification. Pure culture growth of *M. tuberculosis* is necessary to perform phenotypic drug-susceptibility tests (DSTs), whole genome sequencing (WGS), certain molecular DSTs, and genotyping methods.

Specialized culture media are used for mycobacterium. Mycobacteriology laboratories use both liquid media and solid media to culture mycobacteria. Using multiple types of culture media increases diagnostic yield. Liquid media systems allow for rapid growth-detection of mycobacterial within one to three weeks compared with solid media (three to eight weeks' growth). The laboratory will usually issue a negative culture report after six to eight weeks of incubation. NYC PHL incubates cultures for up to eight weeks before reporting them as No Growth or Negative for Mycobacterium species.

When mycobacterial growth is observed in culture, the culture growth may be tested with a DNA probe (e.g., Hologic [formerly Gen Probe] Accuprobe®) to identify *M. tuberculosis* complex or other NTM. Additional testing on solid media may be performed if the DNA probes fail to identify a mycobacterial species. Currently, the NYC PHL primarily uses High Performance Liquid Chromatography (HPLC) by the Mycobacterial Identification (MIDI) system to analyze the mycobacterial culture to identify *M. tuberculosis* complex and many other NTM's. MIDI HPLC is validated for isolates grown on solid medium only. NYS Wadsworth performs multiple laboratory-developed, real-time PCR assays that can identify *M. tuberculosis* complex, species within the *M. tuberculosis* complex, *M. avium* complex, and *M. abscessus* on primary specimens and isolates.

TESTING FOR DRUG SUSCEPTIBILITY AND PREDICTION OF DRUG RESISTANCE

To formulate an effective anti-TB regimen, DST results are needed on initial isolates from all patients. An anti-TB regimen is constructed based on the susceptibility results. Drug susceptibility testing is performed by culture-based (phenotypic) and molecular methods.

CULTURE-BASED SUSCEPTIBILITY TESTING

All initial *M. tuberculosis* complex isolates are tested using culture-based susceptibility. Culture-based susceptibility testing is the gold standard and is performed at PHL regardless of the molecular results. NYS Wadsworth performs WGS only on *M. tuberculosis* isolates, unless WGS predicts resistance. Predicted resistance by WGS is confirmed by culture-based methods at NYS Wadsworth.

DST is routinely performed on the initial positive culture and can be performed in liquid (Mycobacterial Growth Indicator Tube [MGIT] 960; Becton Dickinson) or on solid media (agar proportion method, also known as the conventional method). *M. tuberculosis* complex isolates are routinely tested for susceptibility to first-line drugs: INH, RIF, pyrazinamide (PZA), and ethambutol (EMB). Streptomycin (SM) may also be tested depending on the laboratory. First-line DST results are usually reported within 17-30 days after culture growth has been identified as *M. tuberculosis* complex. Additional testing of first-line and second-line drugs is performed when resistance is observed to any first-line drugs with the exception of PZA (see *Testing of Susceptibility to Pyrazinamide* section). In NYC, when the healthcare facility laboratory cannot perform DSTs, the isolate is sent to a public health laboratory, usually NYC PHL or NYS Wadsworth.

The agar proportion method is performed to confirm resistance on first-line drugs detected in liquid media as well as to look for resistance to second-line drugs. On request, NYS will perform additional liquid-based testing (MGIT) on moxifloxacin (MFX), linezolid (LZD), bedaquiline (BDQ) and clofazimine (CFZ) if first-line resistance is seen on INH and/or RIF. The agar proportion method allows for the calculation of the proportion of organisms that is resistant to a given drug at a specified concentration. This method uses Middlebrook 7H10 agar plates or 7H11 agar plates.

- Countable colonies (50 to 150) are obtained on the drug-free medium.
- The number of colonies observed on the drug-containing medium is then compared with the number on the drug-free medium.
- The proportion of bacilli that is resistant to a given drug is determined and expressed as a percentage of the total population tested. (This proportion has been set at 1%. When 1% or more of the mycobacterial population is resistant to the critical concentration of a drug, that agent is not—or soon will not be—useful for therapy.)

The provider should request that the laboratory perform additional susceptibility testing if the patient continues to either have culture-positive sputum after two to three months of adequate treatment or develops new positive cultures after a period of negative cultures (i.e., patient has culture converted). (See *Table 4.3: Drug Concentrations for Various Methods Used by New York City Reference Laboratories for Mycobacterium Tuberculosis Complex Antimicrobial Susceptibility Testing*.)

TABLE 4.3: Drug concentrations[1] for various methods used by New York City reference laboratories for *Mycobacterium tuberculosis* complex antimicrobial susceptibility testing

	DRUG	BROTH-BASED SYSTEM[2]				SOLID MEDIA AGAR PROPORTION METHODS[2]		
		Bactec MGIT 960				Middlebrook 7H10 Agar		Middlebrook 7H11 Agar
		NYC PHL	NYS	NJH	NJH (Single drug MIC)	NYC PHL	NYS	NJH
FIRST LINE DRUGS	INH	0.1[3]	0.1[3]	0.1[3]	0.025, 0.05, 0.1, 0.2, 0.4, 0.8	0.2	0.2	0.2
	INH (high)	Not Tested	0.4	0.4	N/A	1.0, 5.0	1.0	1.0
	RIF[4]	1.0[3]	1.0[3]	0.5	0.5, 1.0, 2.0	1.0	1.0	1.0
	PZA	100.0	100.0	50, 100, 200, 400	50, 100, 200[3], 400[3]	-	-	-
	EMB	5.0	5.0	5.0	2.5, 5.0, 10.0	5.0	5.0, 10.0	7.5
OTHER DRUGS	AK	-	-	-	1.0, 2.0, 4.0, 8.0	-	1.0, 2.0, 4.0	6.0
	BDQ	-	1.0	-	-	-	-	-
	CM	-	-	-	2.0, 4.0, 8.0	10.0	10.0	10.0
	CPFX[5]	-	-	-	1.0, 2.0, 4.0	2.0	-	-
	CFZ	-	0.5	-	N/A	-	-	0.12, 0.25, 0.5
	CS	-	-	-	N/A	30.0	30.0	60.0
	ETA	-	-	-	1.0, 2.0, 4.0, 8.0	5.0	5.0	10.0
	KM	-	-	-	2.0, 4.0, 8.0	6.0	5.0	6.0
	LFX[5]	-	-	-	0.5, 1.0, 2.0	-	-	-
	LZD	-	1.0	-	0.5, 1.0, 2.0, 4.0, 8.0	-	-	-
	MFX[5]	-	-	-	0.25, 0.5, 1.0, 2.0	-	-	-
	OFX[5]	-	2.0	-	1.0, 2.0, 4.0	-	1.0, 2.0, 4.0	-
	PAS	-	-	-	N/A	2.0, 10.0	10.0	8.0
	RBT	-	-	-	0.12, 0.25, 0.5, 1.0	0.5	0.5, 1.0, 2.0	-
	SM	-	1.0	-	1.0, 2.0, 4.0, 8.0	2.0	2.0	2.0
	SM (high)	4.0	-	-	N/A	10.0	10.0	4.0

1. Concentration in mcg/mL. 2. Phenotypic susceptibility testing: broth-based assay or agar-based assay; any drug resistance found for either method usually means the drug should not be used in the treatment regimen. 3. Critical concentration of the drug in this medium is the MIC that inhibited the growth of all wild strains. The critical concentration to separate a susceptible from a resistant strain is reflected by the highest MIC found for the wild *M. tuberculosis* strain. 4. RIF is the class agent for RPT. Results for RIF reflect RPT susceptibility. 5. FQN testing – each laboratory generally tests 1 member of the class.

Abbreviations Used: AK=amikacin; BDQ=bedaquiline; CFZ=clofazimine; CM=capreomycin; CPFX=ciprofloxacin; CS=cycloserine; EMB=ethambutol; ETA; ethionamide; FQN=fluoroquinolones; INH=isoniazid; KM=kanamycin; LFX=levofloxacin; LZD=linezolid; *M. tuberculosis=Mycobacterium tuberculosis*; mcg/mL=micrograms per milliliter; MFX=moxifloxacin; MGIT=Mycobacterial Growth Indicator Tube; MIC=minimal inhibitory concentration; N/A=Not applicable; NJH=Denver National Jewish Health Advanced Diagnostic Laboratories; NYC PHL=New York City Public Health Laboratory; NYS=New York State; OFX=ofloxacin; PAS=para-aminosalicylic acid; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; SM=streptomycin

Table created in consultation with NJH, NYC PHL, and NYS

On a case-by-case basis, DST may be requested for second-line drugs (e.g., on an isolate without known first-line drug resistance) when a second-line drug (i.e., FQN) is being considered to treat a patient.

For MDR-TB specimens, BTBC selectively requests phenotypic DST for MFX, LZD, CFZ, and BDQ from NYS Wadsworth, and additional drugs for minimum inhibitory concentration DST, from Denver National Jewish Health Advanced Diagnostic Laboratories (NJH).

TESTING OF SUSCEPTIBILITY TO PYRAZINAMIDE

PZA testing is different from that of other first-line drugs, as testing must be measured at a lower pH than the other first-line drugs (pH 6.0 has been chosen for testing PZA in liquid and solid media). Testing for susceptibility to PZA is difficult and results for a single patient may vary between different specimens or results for a single specimen may be discrepant between different laboratories. The specimen can also be tested by molecular methods, such as WGS or Sanger sequencing, which may detect a mutation in the pncA gene that is associated with PZA resistance.

If an isolate shows resistance to PZA, especially if the isolate is resistant to PZA alone, the species of *M. tuberculosis* complex need to be confirmed, because *M. bovis* and *M. bovis*-bacille Calmette-Guérin (BCG) are naturally PZA-resistant, whereas the majority of *M. tuberculosis* isolates are PZA-susceptible. This is especially important if the laboratory identifies isolates only to the level of the *M. tuberculosis* complex.

MOLECULAR METHODS TO DETECT MUTATIONS ASSOCIATED WITH DRUG RESISTANCE

Molecular tests use DNA-based methods to detect *M. tuberculosis* complex and mutations associated with clinical drug resistance. These tests are also referred to as “mutation analysis,” “molecular DST,” or “tests to detect molecular or genetic markers of drug resistance.” They are variations of NAA tests/PCR methods and decrease the time required for identification of *M. tuberculosis* complex and detection of drug-resistance from weeks to days. These tests allow for earlier detection of RIF resistance and initiation of appropriate therapy. This is an area of active investigation and molecular methods are constantly being refined and improved. (See *Table 4.4: Molecular Methods to Detect Drug Resistance by Method* and *Table 4.5: Molecular Methods to Detect Drug Resistance by Drug and Gene Target*.)

GENEXPERT MTB/RIF

GeneXpert MTB/RIF assay: Approved by the FDA in August 2013 for use in hospital, commercial, and public health laboratories, this assay detects DNA of *M. tuberculosis* complex and genetic mutations associated with resistance to RIF in unprocessed sputum and concentrated sputum sediments. The assay is an NAA test using a disposable cartridge in conjunction with the GeneXpert Instrument system. As many RIF-resistant isolates are also resistant to INH, RIF resistance can be used as a marker for MDR-TB.

TABLE 4.4: Molecular methods to detect drug resistance mutations by method

TEST TYPE	DETECTS	SPECIMEN TYPES FOR INTENDED USE
GeneXpert MTB/RIF	*M. tuberculosis* mutations associated with RIF resistance	• AFB smear-positive or smear-negative primary sputum samples or concentrated sediments prepared from induced or expectorated sputa
Pyrosequencing	Mutations associated with resistance to INH, RIF, and FQNs	• Performed on primary specimens and on mixed cultures when other methods are unsuccessful or susceptibility cannot be obtained
Sanger sequencing	Mutations associated with first- and second-line drugs	• Performed on primary specimens and on mixed cultures when other methods are unsuccessful or susceptibility cannot be obtained
WGS	• Speciation of *M. tuberculosis* complex • Mutations associated with first- and second-line drugs	• Requires pure culture growth of *M. tuberculosis*

Abbreviations Used: AFB=acid-fast bacilli; BAL=bronchoalveolar lavages; FQN=fluoroquinolone; INH=isoniazid; *M. tuberculosis*=*Mycobacterium tuberculosis*; RIF= rifampin; WGS=whole genome sequencing

PYROSEQUENCING

Pyrosequencing (PSQ) is a real-time sequencing method that analyzes short reads of DNA in order to detect mutations associated with drug resistance within a specific gene. PSQ is performed to detect mutations associated with resistance to INH, RIF, and FQNs. However, PSQ is not used for detecting pncA gene mutations that may be associated with PZA resistance due to the size of the pncA gene. Therefore, pncA sequencing is primarily determined by Sanger sequencing or whole genome sequencing. Pyrosequencing can be performed on primary specimens and on mixed cultures when phenotypic susceptibility tests are unsuccessful or cannot be obtained.

SANGER SEQUENCING

Sanger sequencing is capable of sequencing long reads of DNA in order to detect mutations associated with first- and second-line drug resistance within a specific gene. However, unlike PSQ, Sanger sequencing is able to detect mutations spread throughout the gene associated with resistance to first- and second-line drugs. Sanger sequencing can be performed on primary specimens and on mixed cultures when phenotypic susceptibility testing is unsuccessful or cannot be obtained.

WHOLE GENOME SEQUENCING

WGS utilizes the TB isolate genome to identify the genus and species, genetic mutations associated with drug resistance, spoligotype results, and single nucleotide polymorphisms (SNP) to characterize and compare TB isolates. WGS requires a pure culture for analysis because many factors interfere with direct-from-specimen analysis.

WGS identifies mutations associated with drug resistance within five to 10 days of specimen receipt at the lab. The interpretation of molecular assays that examine resistance-associated mutations must be done with an understanding of the limitations of the test results. Although the detection of mutations may indicate resistance to a particular drug, the lack of detection of mutations does not confirm drug-susceptibility. These methods do not test for all mutations that may be associated with drug resistance, some of which are known, and others are unknown.

DISCORDANT RESULTS

Discordant results for testing of drug resistance can occur. BTBC communicates with laboratories and the clinician whenever discrepant results are reported. In general, drug resistance found by any method usually means the drug should not be used in the treatment regimen or, if used, cannot be counted upon as an effective agent in the treatment regimen.

Clinicians who have concerns about discrepancies between DST results, molecular mutations, and clinical response should call the TB HOTLINE at 844-713-0559.

TABLE 4.5: Molecular methods to detect drug resistance by drug and gene target*

DRUG	GENE(S)	TEST TYPE				
		Xpert® MTB/RIF	Pyro-sequencing	Sanger sequencing	Whole genome sequencing	Research mutation only[1]
RIF	• rpoB	✔	✔	✔	✔	
INH	• inhA • katG		✔	✔	✔	
	• oxyR-ahpC PR • mabA-inhA PR • mabA				✔	
EMB	• embB			✔	✔	
	• embC-embA PR				✔	
PZA	• pncA				✔	
	• pncA PR			✔	✔	
ETA	• mabA • mabA-inhA PR • ethA				✔	
FQN	• gyrA		✔	✔	✔	
	• gyrB		✔	✔	✔	
SMN	• rrs • rpsL				✔	
KM	• rrs • eis PR			✔	✔	
AK	• rrs			✔	✔	
CM	• rrs			✔		
	• tlyA			✔		
BDQ	• atpe					✔

*There are currently no molecular tests validated for clofazimine or linezolid. This table reflects the mutations that are known at the time of publication.

1. Observed in laboratory-induced resistant strains

Abbreviations Used: AK=amikacin; BDQ=bedaquiline; CM=capreomycin; EMB=ethambutol; ETA=ethionamide; FQN=fluoroquinolone; INH=isoniazid; KM=kanamycin; PZA=pyrazinamide; PR=promoter region; RIF=rifampin; SM=streptomycin

GENOTYPING

Genotyping is a process by which genetic information is used to characterize *M. tuberculosis* strains. NYC conducts universal genotyping on at least one isolate from each culture-positive TB patient using multiple genotyping methods.

Genotyping is a useful tool for distinguishing between relapse and re-infection, supporting and refuting transmission between epidemiologically-linked persons, detecting or confirming outbreaks, investigating and identifying false-positive results (i.e., laboratory cross-contamination), and characterizing TB strains in a population.

Genotyping methods used in NYC include:

- **Whole genome sequencing (WGS):** WGS is currently used to generate spoligotyping results by NYS Wadsworth and CDC, and can provide greater resolution for examining genetic relatedness through analysis of high-quality single nucleotide polymorphisms (SNP), which enables further strain differentiation. The turnaround time for SNP analysis is very quick once WGS sequence data becomes available.
- **Spacer oligonucleotide typing (spoligotyping):** Spoligotyping is a PCR based method with a quick turnaround time. Spoligotyping identifies spacer sequences found in the direct repeat region in the *M. tuberculosis* chromosome. Spoligotyping detects the presence or absence of 43 spacers. The spacing pattern is then translated into a 15-digit octal code that is used to communicate results between laboratories and jurisdictions.
- **Mycobacterial interspersed repetitive unit–variable number tandem repeat (24-loci MIRU-VNTR):** VTNR-MIRU analysis is a PCR based method that determines the number of repeated sequences in 24 defined regions (loci) of the TB chromosome. Similar to spoligotyping, MIRU has a quick turnaround time and uses a standard nomenclature that makes results easy to compare across jurisdictions.
- **IS*6110* restriction fragment length polymorphism (RFLP):** This method measures the number and length of specific DNA fragments in the insertion sequence 6110, a genetic marker unique to members of the *M. tuberculosis* complex. An RFLP result comes in the form of an image with bands that show the pattern and copies of IS*6110*. The images are scanned and analyzed by a computer to compare RFLP results. RFLP is useful as a method for differentiating TB strains when greater than six bands are present. However, RFLP has a slow turnaround time, and results may be difficult to communicate between labs and jurisdictions because different labs do not use the same nomenclature. This method is rarely used in the U.S.

FALSE-POSITIVE INVESTIGATION

A false-positive TB laboratory test result occurs when the reported result has been reported in error, either due to a contamination of a clinical device, a clerical error, or laboratory cross-contamination during specimen processing. A false-positive specimen can lead to the misdiagnosis of TB disease and unnecessary treatment of a patient. It can also lead to unnecessary contact investigations and erroneously counting the patient in the surveillance system. Prompt identification and investigation of specimens suspected to have a false-positive result is important.

BTBC conducts active surveillance for potentially false-positive laboratory results. Patients with a single positive culture from an extrapulmonary specimen are not routinely investigated unless requested. Criteria for initiating a false-positive investigation include:

- Presence of a single *M. tuberculosis* positive respiratory culture in a patient with several culture-negative specimens.
- Clinical signs and symptoms of a patient are not compatible with the TB culture results
- New positive culture in a patient who previously culture converted
- Changes in drug-susceptibility pattern in a patient without suspicion of acquired drug resistance
- Suspected lab cross-contamination
- Matching genotypes among specimens processed together in a laboratory
- Discordant genotypes among culture-positive specimens from the same patient
- Rare strains in multiple patients within a short time period
- Presence of a TB lab strain (H37Rv)

Requests for a false-positive investigation come from BTBC providers and staff, non-BTBC providers, other TB programs, and laboratorians. BTBC works closely with laboratories and providers to investigate all potential false-positive specimens. The false-positive investigation is a stepwise process that requires review of the specimen collection and processing dates, examination of the genotype of specimens and characteristics of the patients involved, and identification of the source of confirmed contamination. When possible, it may be necessary to collect another specimen or test another isolate from the same patient and/or repeat testing of the original sample.

The outcome of a false-positive investigation is determined based on multiple factors. (See *Table 4.6: Outcomes, Definitions, Criteria and Clinical Decisions in False-Positive Investigations*.) It is important to communicate the results back to the treating providers, BTBC staff involved with the case management of the patient, surveillance teams, and the involved laboratories.

TABLE 4.6: Outcomes, definitions, criteria, and clinical decisions in false-positive investigations

OUTCOME	DEFINITION(S)	REASON(S)	CLINICAL DECISION*
Confirmed false-positive	• Specimen is contaminated or • Specimen belongs to another patient	• Cross contamination • Mislabeled specimens • Species misidentified • TB lab strain (H37Rv) identified • Contaminated medical devices	• Patient should usually not be treated for TB
Inconclusive	• Unable to determine if a contamination occurred or source of contamination	• Contamination source could not be identified • Unable to perform further TB testing (i.e., DST or genotype) • Additional specimen is not available	• Decision to treat the patient is made based on clinical factors
Unlikely	• Specimen has a true result or • Specimen is attributed to the correct patient	• Genotypes do not match • Unique genotype identified • Additional specimen confirms previous genotype results	• Patient should be treated for TB • If the physician does not feel TB is the correct diagnosis, must present other clinical data to support decision not to treat the patient

*If the physician suspects TB, the patient should be treated regardless of the false-positive investigation outcome.

Abbreviations Used: DST=drug-susceptibility tests; TB=tuberculosis

OTHER LABORATORY TESTING

Additional diagnostic testing of body fluids such as white blood cell (WBC) count, protein, glucose, and adenosine deaminase (ADA) may be necessary to support the clinical diagnosis of extrapulmonary TB. (See *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*.)

As part of management and clinical monitoring of a patient with TB disease, additional laboratory examinations may be performed including: an HIV test, a complete blood count (CBC), a comprehensive metabolic panel (including assessment of kidney and liver function), thyroid function, and a pregnancy test for persons of childbearing age. Bloodwork results are assessed at the start of treatment and may be used to monitor therapy. (See *Chapter 8: Clinical Monitoring and Follow-Up for Tuberculosis Treatment*.)

SUMMARY

Appropriate and timely collection of specimens for laboratory testing is critical to ensure diagnostic test results are optimized to make clinical decisions. Use of molecular methods to identify TB and determine mutations for drug resistance allows for more timely initiation of appropriate TB treatment and decreased transmission of infectious TB. This is a rapidly changing area with both clinical and epidemiological implications. Continuous communication between laboratories, providers, and BTBC staff is vital to ensure the patient's treatment is based on all available diagnostic information.

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CHAPTER 5: TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS DISEASE IN ADULTS

INTRODUCTION

The overall goals of treatment of active tuberculosis (TB) disease are to cure the patient and to minimize the transmission of *Mycobacterium tuberculosis* (*M. tuberculosis*) to others. The New York City (NYC) Bureau of TB Control (BTBC) follows treatment guidelines as described in the *2016 Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (IDSA)*. Instances where BTBC practice differs from these recommendations have been noted in the text.

The most recent version of the ATS/CDC/IDSA treatment guidelines can be found online at: www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

TREATMENT REGIMENS AND DOSAGES FOR PULMONARY TUBERCULOSIS DISEASE

BTBC recommends that all individuals with signs and symptoms consistent with TB disease or confirmed TB disease receive treatment after specimens have been collected. Treatment is not to be delayed while waiting for confirmation by culture or drug-susceptibility test (DST) results. Before starting therapy, a complete medical evaluation including a history and physical evaluation, baseline complete blood count (CBC), blood chemistries (including assessment of kidney and liver function tests [LFT]), and chest imaging is performed. Viral hepatitis screening may also be performed, and other specimens may be obtained as indicated.

Any treatment regimen for active TB disease relies on the principle of using multiple antibiotics to which the bacterial isolate is either presumed or known to be susceptible. This approach reduces the likelihood of treatment failure and the acquisition of drug resistance. Treatment regimens are divided into an intensive phase and continuation phase. The shorter intensive phase, which usually lasts two months, includes treatment with more drugs than are used during the longer continuation phase, which is typically four to seven months. During each phase, the number of drugs used and/or the frequency of drug administration may vary. Most patients with TB disease are eligible for treatment with a standard six-month regimen.

DIRECTLY OBSERVED THERAPY (DOT) is the standard of care and ensures that patients complete an adequate course of treatment for TB. With DOT, a healthcare worker directly observes every dose of anti-TB medication taken by the patient.

Four options for DOT are offered free of charge by BTBC to any patient receiving care for TB disease in NYC, regardless of the provider caring for the patient:

1. **IN-PERSON CLINIC DOT: patient comes to the clinic for observation**
2. **COMMUNITY DOT: BTBC staff meets the patient in their home or other agreed upon location in the community for observation**
3. **LIVE VIDEO DOT: patient is observed real-time through video conferencing software**
4. **RECORDED VIDEO DOT: patient records themselves ingesting their medication and securely transmits the video for observation**

(See *Chapter 10: Case Management for Patients with Tuberculosis*.)

STANDARD REGIMENS FOR TREATMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS DISEASE

Because DST results for a patient's TB strain are not typically known at the time of treatment initiation, empiric treatment for TB is started with the assumption that a standard regimen will be effective for the majority of patients. If the specimen is smear-positive, nucleic acid amplification- (NAA) positive, and rpoB-negative, it is likely that the patient does not have multidrug-resistant TB (MDR-TB) and that this empiric regimen will be acceptable until further DSTs are known. The standard regimen for treating TB disease consists of a two-month intensive phase of four drugs: isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB), taken daily followed by a four-month continuation phase of INH and RIF taken on

either a daily or intermittent basis. Under certain conditions, the continuation phase may be extended beyond four months (see *Duration of Treatment for Drug-Susceptible Pulmonary Tuberculosis Disease* later in the section).

- Physicians can discontinue EMB before the end of the intensive phase if drug susceptibility testing and/or mutation analysis results show susceptibility to INH and RIF. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)
- Individuals who cannot be evaluated for visual acuity or color vision are not routinely treated with EMB, but the other drugs and dosages in the regimen remain the same.
  - A fluoroquinolone (FQN) may be considered until final susceptibility results are available.
- If clinical response is not adequate after two weeks (i.e., signs and symptoms persist), the addition of drugs to the regimen is considered, as drug resistance may be present. However, other possibilities including poor adherence to TB treatment, poor absorption of TB medication, or extensive disease are considered.
- Pyridoxine (Vitamin B6) is often used in conjunction with INH to prevent side effects in the central and peripheral nervous system. (See *Table 5.3: The Use of Pyridoxine in Tuberculosis Treatment.*)
- At the end of the intensive phase of treatment, EMB is stopped if not previously discontinued and PZA is discontinued unless drug resistance is suspected for the following reasons:
  - Mutation analysis or DST results show resistance to INH or RIF
  - Mutation analysis or DST results are not available and drug resistance is suspected due to a history of TB disease treatment or immigration from an area with high rates of drug resistance
  - If susceptibility results are not received, the lab should be contacted

FOUR-MONTH REGIMEN WITH HIGH-DOSE RIFAPENTINE AND MOXIFLOXICIN: A new four-month regimen is available for the treatment of drug-susceptible pulmonary TB. The regimen consists of a two-month intensive phase of INH, high-dose rifapentine (RPT), PZA, and moxifloxacin (MOX). The two-month continuation phase consists of INH, high-dose RPT, and MOX. (High-dose RPT is 1200 mg/day for a patient who weighs 50 kg or more.) DOT is recommended. Although the pill burden is high, this short regimen may be an advantage for some patients.

The four-month regimen is available to patients age 12 and older. The regimen should not be used during pregnancy or breastfeeding. Patients with human immunodeficiency virus (HIV) infection may use this treatment if receiving an efavirenz-based regimen for HIV.

associated with lower rates of relapse. BTBC does not recommend twice-weekly therapy in the continuation phase; in general, it may be considered for select patients who do not have human immunodeficiency virus (HIV) infection. Patients with HIV infection are treated with daily therapy in both the intensive and continuation phases due to higher rates of relapse and emergence of RIF-resistance.

TABLE 5.1: Drug regimens for pulmonary tuberculosis disease caused by drug-susceptible organisms

INTENSIVE PHASE		CONTINUATION PHASE[1,2,3]		NOTES
Drugs	Interval and Duration	Drugs	Interval and Duration	
INH **RIF** **PZA** **EMB**	7 days/week for 56 doses (8 weeks)	**INH** **RIF**	7 days/week for 126 doses (18 weeks) --- or --- 3 days/week for 54 doses (18 weeks with DOT)[4]	• This is the standard regimen for drug-susceptible TB disease
INH **RIF** **EMB**	7 days/week for 56 doses (8 weeks)	**INH** **RIF**	7 days/week for 217 doses (31 weeks)[3] --- or --- 3 days/week for 93 doses (31 weeks with DOT)[3,4]	• This regimen without PZA is the appropriate regimen for pregnant patients unless MDR-TB is suspected
INH **RPT** **PZA** **MOX**	7 days/week for 56 doses (8 weeks)	**RPT** **MOX** **INH**	7 days/week for 63 doses (9 weeks)	• High-dose RPT: patients who weigh 50 kg or more receive RPT 1200 mg/day

Adapted from: Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195.

1. Biweekly treatment regimens during the continuation phase are not recommended due to high rates of relapse
2. For missed doses, extend treatment to make up the doses
3. Patients with a positive culture at 2 months of treatment should receive a 7-month continuation phase regimen (31 weeks; either 217 doses daily or 93 doses 3 times per week)
4. Not recommended for patients with HIV infection

Abbreviations Used: CXR=chest radiograph; DOT=directly observed therapy; EMB=ethambutol; HIV=human immunodeficiency virus; INH=isoniazid; MDR-TB=multidrug-resistant TB; MOX=moxifloxacin; PZA=pyrazinamide; RIF=rifampin; RPT=rifapentine

INTERMITTENT REGIMENS

Intermittent therapy (i.e., regimens given on a schedule other than daily) is effective for most patients with drug-susceptible TB disease, is offered under DOT, and is only recommended by BTBC in the continuation phase of therapy. Intermittent therapy is easier to administer and may be preferred by patients compared to daily therapy. BTBC does not recommend intermittent therapy during the intensive phase of treatment. Missed doses can lead to treatment failure, relapse, and acquired drug resistance. Patients with treatment adherence less than 80% are placed on daily DOT until it is established that they can be placed on intermittent DOT.

Thrice-weekly intermittent therapy during the continuation phase is preferred to twice-weekly therapy, as it is associated with lower rates of relapse. BTBC does not recommend twice-weekly therapy in the continuation phase; in general, it may be considered for select patients who do not have HIV infection. Patients with HIV infection are treated with daily therapy in both the intensive and continuation phases due to higher rates of relapse and emergence of RIF-resistance.

Once an appropriate regimen has been identified, appropriate dosing is vital to successful treatment outcomes. See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis* for details regarding doses of primary medications used in the treatment of TB disease. Dose will be affected by the frequency of administration: daily or three times per week.

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DURATION OF TREATMENT FOR DRUG-SUSCEPTIBLE PULMONARY TUBERCULOSIS DISEASE

CULTURE-POSITIVE PULMONARY DISEASE: The standard six-month treatment for drug-susceptible TB consists of a two-month intensive phase followed by a four-month continuation phase. Certain patients with culture-positive pulmonary disease have a higher rate of relapse with the standard six-month regimen and benefit from longer treatment. An extended seven-month continuation phase is prescribed for the following:

- Patients who have positive sputum cultures after two months of therapy, regardless of chest radiograph (CXR) results
- Patients whose treatment regimen did not include PZA in the intensive phase or who have PZA-resistant TB
- Patients with extensive disease or a cavitary CXR who have poor response to treatment
- Patients with HIV infection who are not on antiretroviral therapy (ART) during TB treatment

CULTURE-NEGATIVE PULMONARY DISEASE: Clinically-confirmed or culture-negative pulmonary TB disease in patients without HIV infection can be treated successfully in four months, as the initial bacillary load is lower. As a result, for patients whose initial sputum cultures are negative, the intensive phase of treatment is followed by a two-month continuation phase of INH and RIF if drug resistance is not suspected. If the patient has received treatment for TB disease in the past or comes from an area with high rates of drug-resistant TB (DR-TB), INH, RIF, PZA, and EMB are prescribed for the full four months.

TREATMENT OF EXTRAPULMONARY TUBERCULOSIS DISEASE

Although the treatment regimens for extrapulmonary disease are the same as for pulmonary disease, a few extrapulmonary sites of disease are routinely treated for longer periods of time in the continuation phase, regardless of culture results. (See *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease*.) Empiric treatment is more commonly prescribed for extrapulmonary TB disease, as the patient's specimens are more likely to be culture-negative or not sent for culture. The patient's clinical response is considered when determining length of treatment and regimens are individualized accordingly.

SPECIAL CONSIDERATIONS FOR CENTRAL NERVOUS SYSTEM TUBERCULOSIS DISEASE

Central nervous system (CNS) TB can have devastating effects on morbidity and mortality, and as such, empiric treatment is started promptly while awaiting results of AFB smears and cultures. Treatment is identical to the standard intensive phase regimen for pulmonary TB disease. Treatment is similar for adults and children. Some experts recommend higher doses of RIF to penetrate the blood-brain barrier. Ethionamide (ETA) is usually preferred over EMB in children when an oral agent is used, as it is well-tolerated and has increased penetration into the CNS. (See *Chapter 7: Diagnosis and Treatment of Pediatric Tuberculosis Disease*.)

The continuation phase for CNS TB consists of a regimen of INH and RIF for seven to 10 months as long as there is no suspected or confirmed drug resistance. INH, RIF, and PZA penetrate the blood-brain barrier efficiently. EMB and injectable agents penetrate only when the meninges are inflamed. As penetration of some drugs into the cerebrospinal fluid (CSF) is poor, patients will most likely benefit from treatment regimens at the higher end of recommended dose ranges. Some experts advocate the addition of PZA during the continuation phase, as CSF concentrations of RIF are low and PZA readily penetrates the CNS; however, there are no clinical trials to support this approach.

Corticosteroids are routinely recommended when treating any patient with CNS TB, especially when treating a patient with a symptomatic tuberculoma, or any patient with CNS TB disease that has a decreased level of consciousness. Corticosteroids improve survival in individuals with severe disease and may reduce neurologic morbidity as well. If corticosteroids are used in a patient with a tuberculoma, dosages and tapering are similar as those for meningeal TB. Expert consultation with a neurologist is utilized as necessary. Corticosteroids are only given if the patient is on anti-TB therapy. Expert opinion on the optimal dosage for steroids varies; however, BTBC recommends dexamethasone or prednisone be given as follows:

DEXAMETHASONE: In adults, the initial dose is 12 milligrams (mg)/day. The initial dose is given for three weeks and then gradually decreased during the next three to five weeks. Neurologists should be consulted as needed.

PREDNISONE: In adults, corticosteroid dosages that are equivalent to 40 to 60 mg/day of prednisone are recommended with gradual tapering over six to eight weeks.

TABLE 5.2: Treatment of extrapulmonary tuberculosis disease

SITE OF DISEASE	LENGTH OF THERAPY[1]	CONSIDERATIONS
CNS (including Tuberculoma and Meningeal)	9-12 months	If corticosteroids are used, dosages should be tapered (see *Special Considerations for Central Nervous System Tuberculosis Disease*) Intracranial tuberculoma can be treated for a minimum of 9-12 months or longer depending on clinical response. Consultation with a neurologist is recommended.
Cutaneous	6 months	Patients require consultation with a dermatologist
Disseminated	6-9 months	More common in children younger than 5 years of age; at least 9 months of treatment recommended. In adults, 6 months of treatment may be considered, depending on sites and clinical response. Corticosteroids may be useful for treating respiratory failure due to disseminated TB and/or TB meningitis
Genitourinary	6 months	Surgical indications for renal TB include: intractable pain; persistent hematuria; persistent urinary tract infections due to obstruction; or a nonfunctioning or poorly functioning kidney. All patients with renal TB require consultation with an urologist Female genital tract TB may require surgical intervention for residual large tubo-ovarian abscesses. Infertility is a complication of TB disease of the female genital tract and gynecological consultation is routinely pursued
Gastrointestinal	6 months	Patients require consultation with a gastroenterologist or surgeon as appropriate
Lymphatic	6 months	Most commonly affects cervical or supraclavicular lymph nodes, although any lymph node can be involved. Even with lymph node excision, chemotherapy is indicated
Pleural	6 months	The routine use of steroids is not recommended.
Pericardial	6 months	The routine use of corticosteroids is not recommended. Corticosteroids are recommended only in patients at a higher risk of complications (i.e., large pericardial effusions, high levels of inflammatory cells or markers in pericardial fluid, or early signs of constriction). Pericardiectomy or creation of a pericardial window is indicated if there is chronic constriction with adverse hemodynamic consequences (cardiac tamponade)
Peritoneal	6 months	Anyone with confirmed diagnosis of peritoneal TB or signs and symptoms consistent with peritoneal TB is referred to an appropriate GI center or hospital for further evaluation
Skeletal	6-9 months	Joint instability may require surgical intervention prior to the completion of treatment, so most patients with skeletal TB disease require consultation with an orthopedist during TB treatment. For extensive disease, treatment can be extended to 9 months.

Adapted from: Blumberg HM, Burman WJ, Chaisson RE, et al; American Thoracic Society, Centers for Disease Control and Prevention and the Infectious Diseases Society. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003 Feb 15;167(4):603-62.

1. Length of treatment may be extended based on clinical judgment.

Abbreviations Used: BTBC=Bureau of Tuberculosis Control; CNS=central nervous system; GI=gastrointestinal; TB=tuberculosis

USE OF PYRIDOXINE (VITAMIN B6) IN TUBERCULOSIS TREATMENT

Pyridoxine is often used in conjunction with certain anti-TB medications to prevent side effects in the peripheral nervous system. (See *Table 5.3: The Use of Pyridoxine (Vitamin B6) in Tuberculosis Treatment*.)

TABLE 5.3: The use of pyridoxine (Vitamin B6) in tuberculosis treatment

DRUG	B6 DOSE	CONSIDERATIONS
INH	25 mg daily (may be self-administered if patient is on intermittent DOT) --- or --- 50 mg three times per week, if INH given at 900 mg three times per week --- or --- If patient develops peripheral neuropathy, discontinue INH and continue pyridoxine (25 mg daily) until symptoms abate	Indicated for children on meat- and milk-deficient diets and for breast-feeding infants on INH. Also advised for patients with: • HIV infection • Malnourishment (more than 10% below ideal body weight or any wasting disease) • Diabetes • Cancer • Chronic renal disease • Pregnancy • Alcoholism • Pre-existing peripheral neuropathy or taking medications that cause peripheral neuropathy • Chronic liver disease • Other immunosuppressive conditions
CS*	50 mg for each 250 mg of CS to a maximum of 200 mg pyridoxine daily	Required for all patients taking CS

*CS is usually reserved for the treatment of drug-resistant TB.

Abbreviations Used: CS=cycloserine; DOT=directly observed therapy; HIV=human immunodeficiency virus; INH=isoniazid; mg=milligrams

DETERMINATION OF TREATMENT COMPLETION

TB treatment guidelines recommend that treatment is considered complete when 100% of the prescribed doses have been taken. At BTBC, a medical consultant reviews each TB case for treatment completion and, based on clinical judgment, makes a final determination if patients with less than 100% adherence have completed treatment. Clinical judgment is informed by site and extent of disease, radiological findings, sputum culture-positivity at two months of treatment, and drug-susceptibility results. While 100% treatment adherence is always desired, BTBC as a program considers 80% ingested doses of the total prescribed doses to be complete.

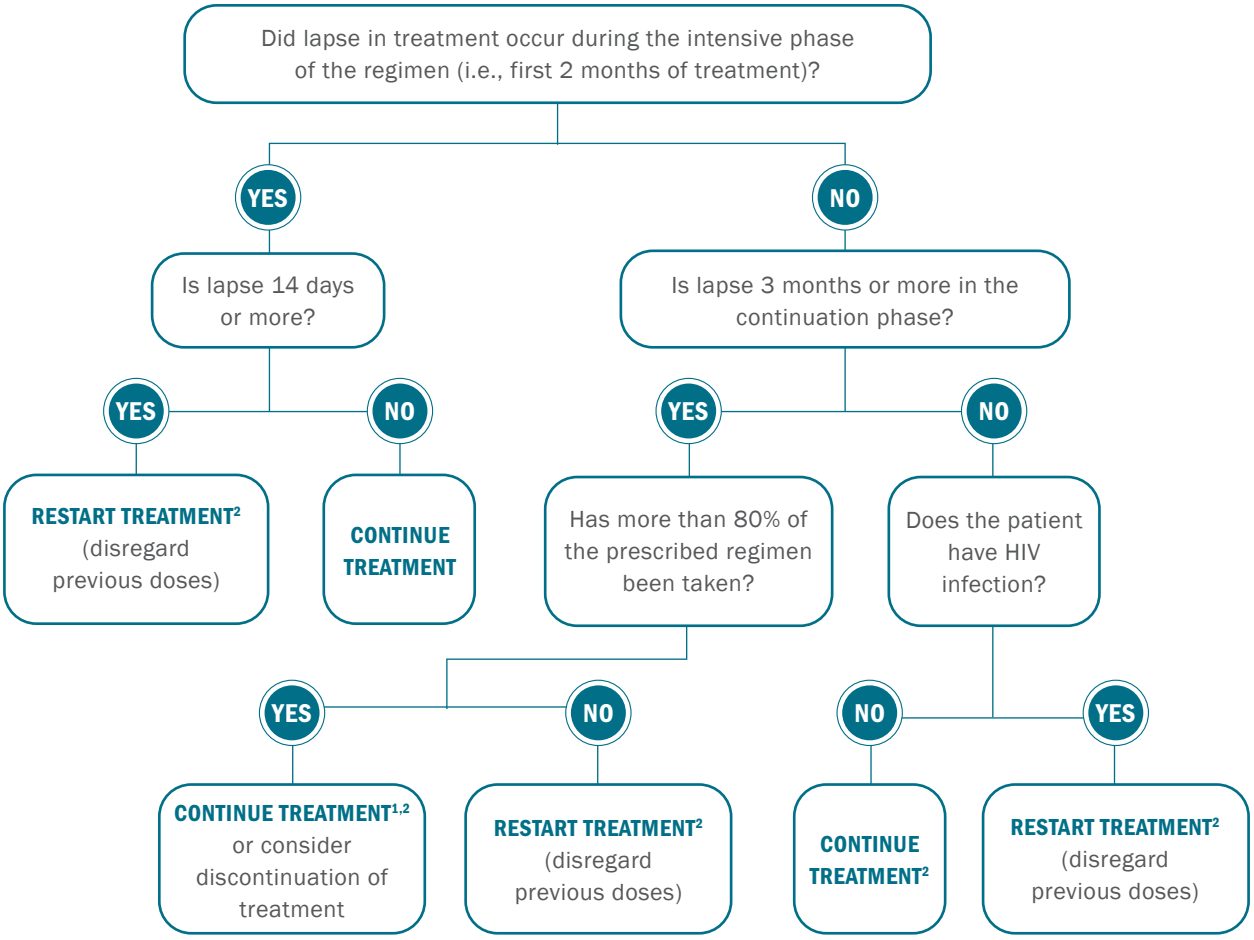
Treatment may be lengthened if all prescribed doses have not been taken within an optimal timeframe. For details regarding the number of doses of medication by regimen and optimal treatment durations, see *Table 5.1: Drug Regimens for Pulmonary Tuberculosis Disease Caused by Drug-Susceptible Organisms* and *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease*.

INTERRUPTED OR INCOMPLETE TREATMENT

If a patient has had interrupted or incomplete treatment, a decision regarding whether to continue the originally prescribed regimen (increasing the duration of treatment to complete the required number of doses) or to completely restart the treatment regimen is made. For managing interruption in treatment, see *Figure 5.1: Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*.

Continuous treatment is more crucial in the intensive phase of treatment because the number of organisms is highest in the beginning of treatment. A short lapse in treatment in the continuation phase would have less of an impact than the same lapse in the intensive phase, as there are fewer persistent organisms to kill. If more than 80% of the prescribed doses were taken before a lapse in treatment, the regimen may not need to be extended or restarted.

FIGURE 5.1: Reinstitution of interrupted or incomplete anti-tuberculosis treatment



1. Decision to continue treatment is based on clinical factors including length of treatment, length of relapse, AFB smear, CXR results, and other clinical risk factors including immunosuppression
2. Collect specimen and submit for laboratory testing for TB prior to restarting or continuing treatment

Abbreviations Used: AFB=acid-fast bacilli, CXR=chest radiograph; HIV=human immunodeficiency virus; TB=tuberculosis

In patients with HIV infection or other immunosuppressive conditions, the mycobacterial load can rebound rapidly, even with a short lapse in treatment. In such patients, consideration is given to restarting or extending treatment.

Clinical judgment is used to determine if a lapse in treatment is significant and if additional specimens should be collected and sent for repeat testing for TB. If there is a new positive culture, a new DST is obtained in order to inform clinical and public health management.

If there is a lapse in treatment, additional specimens should be collected and sent for repeat testing for TB.

RESTARTING TREATMENT AFTER A SIGNIFICANT LAPSE

If there has been a significant lapse in treatment, a complete clinical evaluation is performed prior to restarting treatment, including a CXR and collection of sputum samples for AFB smear and culture and cultures with molecular and conventional DSTs. For management of treatment lapse, see *Figure 5.1: Reinstitution of Interrupted or Incomplete Anti-Tuberculosis Treatment*.

If the newly collected specimen is culture-positive, treatment is restarted and previous doses are disregarded. Susceptibility testing on culture-positive specimens following a lapse in treatment is requested from the laboratory, even if the previous isolates were drug-susceptible.

DOT is instituted if the patient is not currently receiving DOT. Every attempt is made to ensure that the patient completes a continuous course of TB treatment. If the patient has infectious TB, referral should be made for regulatory evaluation.

TREATMENT FAILURE

Treatment failure is considered in patients with worsening clinical status or CXR due to TB. Treatment failure is defined as a positive TB culture any time after four months of appropriate TB treatment.

As soon as treatment failure is determined, three new consecutive daily sputum samples or other appropriate specimens are sent for smear, culture, and susceptibility testing. Susceptibility testing is requested on the most recent positive TB culture to determine if new drug resistance has developed.

Patients who are clinically stable may be maintained on their current anti-TB regimen ("holding regimen") until DST results are available to guide the choice of medications.

Patients who are clinically deteriorating are given at least two to three new anti-TB medications to which the strain is likely to be susceptible. **A single drug is never added to a failing regimen**, as this can promote further drug resistance. When susceptibility results are available, the regimen is modified accordingly.

DOT is instituted if the patient is not currently receiving it. If treatment adherence is suspected to be an issue, refer for regulatory evaluation (See *Chapter 10: Case Management for Patients with Tuberculosis*).

TREATMENT OF COEXISTING TUBERCULOSIS DISEASE AND HUMAN IMMUNODEFICIENCY VIRUS

Patients who are diagnosed with TB disease and HIV concurrently are started on antiretroviral treatment (ART) early in the TB treatment course. Waiting to initiate ART until after the completion of TB treatment leads to increased all-cause mortality. Patients with severe immunosuppression, especially those with a CD4 count < 50/cubic millimeter (mm^3), should begin ART within two weeks of starting TB therapy. All other TB patients with HIV infection, including patients with CNS TB disease, should start ART within eight to 12 weeks of starting TB treatment.

Although introducing ART early in the TB treatment course leads to a higher rate of immune reconstitution inflammatory syndrome (IRIS), early treatment of HIV offers a clear survival advantage. The only exception to this guidance is for patients with confirmed CNS TB or signs and symptoms consistent with CNS TB. A brisk immune response after starting ART in a patient with CNS TB can result in cerebral edema and a poor outcome. ART may need to be delayed in patients with CNS TB based on clinical judgment. (See section *Immune Reconstitution Inflammatory Syndrome*.)

Given the challenges of managing drug interactions and overlapping toxicities, TB providers carefully coordinate the treatment of patients with TB disease and HIV in consultation with HIV experts. Close attention is paid to the possibility of TB treatment failure, ART treatment failure, IRIS, development of drug resistance, and unique and synergistic overlapping adverse effects for all drugs used. As new ART drugs are developed and more information becomes available, recommendations for the use of these drugs with anti-TB medications will change.

For drug-susceptible TB, a rifamycin-containing anti-TB regimen can be safely administered with most ART. In some situations, rifabutin (RBT) can be substituted for RIF to decrease drug-to-drug interactions and is considered equally as effective as RIF. Daily treatment with DOT during the intensive and continuation phase is recommended. (See *Table 5.4: Treatment Adjustments in TB Patients Receiving a Rifamycin Who are Human Immunodeficiency Virus-Infected and Taking Antiretroviral Agents*.)

If an INH-resistant, RIF-susceptible organism is isolated, it is essential to try to adjust the ART regimen so that a rifamycin can be used. Otherwise the patient will need treatment with a regimen used for MDR-TB.

COMBINATION THERAPY FOR HUMAN IMMUNODEFICIENCY VIRUS

Drug-to-drug interactions between rifamycins and ART regimens containing two protease inhibitors (PI), two non-nucleoside reverse transcriptase inhibitors (NNRTI), or both a PI and an NNRTI have not been well studied. It is not recommended to use ART regimens that contain more than one PI (with the exception of ritonavir-boosted regimens), or a PI and an NNRTI, simultaneously with a rifamycin-containing regimen for the treatment of TB disease.

TABLE 5.4: Treatment adjustments in TB patients receiving a rifamycin who are human immunodeficiency virus-infected and taking antiretroviral agents[1,2]

CLASS OF ANTIRETROVIRAL AGENT	SELECT DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	TREATMENT ADJUSTMENT
Protease Inhibitors (PI)	• Lopinavir/ritonavir (Kaletra®) • Darunavir/ritonavir (Prezista®) • Atazanavir (Ritovaz®) • Atazanavir/ritonavir	• RBT is preferred with PIs • For ritonavir-boosted regimens, RBT is given at 150 mg daily • Double-dose lopinavir/ritonavir can be used with RIF but toxicity is increased • In young children, double-dose lopinavir/ritonavir given with RIF results in inadequate concentrations of the antiretrovirals - Super-boosted lopinavir/ritonavir is advised (if available) by some experts • RIF should not be used with PIs except double-dose lopinavir/ritonavir or super-boosted lopinavir/ritonavir
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)	• Nevirapine (Viramune®) • Efavirenz (Sustiva®) • Rilpivirine (Edurant®) • Emtricitabine, rilpivirine, TDF (Complera®) • Etravirine (Intelence®) • Doravirine (Pifeltro®)	• RIF decreases exposure to all NNRTIs • If nevirapine is used with RIF, lead-in nevirapine dose of 200 mg daily is omitted and 400 mg daily nevirapine dosage is given • With RIF, many experts advise that efavirenz be given at standard dosage of 600 mg daily, although FDA recommends increasing efavirenz to 800 mg daily in persons greater than 60 kg • Rilpivirine cannot be given with RIF or RPT • Etravirine is not given with RIF, but can be used with RBT at usual dosing • Nevirapine can be used with RBT at usual dosing • Efavirenz and RBT use requires dose increase of RBT to 600 mg daily, as such RIF is preferred • Complera® can only be given with RBT; an additional 25 mg tablet of rilpivirine once per day is taken concomitantly with Complera® and with a meal for the duration of the RBT co-administration • Doravirine is contraindicated with RIF • Doravirine can be given with RBT. The dose of Doravirine is increased to 100 mg twice daily with RBT
C-C chemokine receptor type 5 inhibitors (CCR5)	• Maraviroc (Selzentry®)	• Maraviroc cannot be used with RIF; however, RBT can be used

TABLE 5.4: Treatment adjustments in TB patients receiving a rifamycin who are human immunodeficiency virus-infected and taking antiretroviral agents (*continued*)

CLASS OF ANTIRETROVIRAL AGENT	SELECT DRUGS WHOSE CONCENTRATIONS ARE SUBSTANTIALLY DECREASED BY RIFAMYCINS	TREATMENT ADJUSTMENT
Integrase Strand Transfer Inhibitors (INSTI)	• Cabotegravir (Vocabria®) • Raltegravir (Isentress®) • Dolutegravir (Tivicay®) • Dolutegravir coformulated with abacavir and lamivudine (Triumeq®) • Elvitegravir (Viteka®) • Elvitegravir co-formulated with cobicistat, tenofovir and emtricitabine (Stribild®), elvitegravir, cobicistat, emtricitabine, and TAF (Genvoya®) • Bictegravir/emtricitabine/TAF (Biktarvy®)	• Increase dose of raltegravir to 800 mg twice daily with RIF, although clinical trial data show similar efficacy using 400 mg twice daily • Dolutegravir dose is increased to 50 mg every 12 hours with RIF • Do not use RIF with elvitegravir • RBT can be used with all INSTIs except bictegravir/emtricitabine/TAF • Bictegravir/emtricitabine/TAF cannot be used with RIF and should not be used with RBT at this time
Attachment inhibitors	• Fostemsavir (Rukobia®)	• Fostemsavir should not be given with RIF and RPT • Potential weak interaction with RBT-additional action/monitoring or dosage adjustment is unlikely to be required
Combination medicines	• Cabotegravir/rilpivirine (Cabenuva®) • Dolutegravir/lamivudine (Dovato®)[3]	• Cabotegravir/rilpivirine should not be given with RIF, RBT, or RPT • Dolutegravir/lamivudine can be given with RIF or RPT. Because the dose of dolutegravir is too low in Dovato, an additional dolutegravir 50 mg tablet, separated by 12 hours from Dovato, should be taken. This dose adjustment should be maintained for approximately 2 weeks after stopping RIF and RPT as the inducing effect may persist after discontinuation of a strong inducer. • Dolutegravir/lamivudine can be given with RBT

Adapted From: Nahid P, Dorman SE, Alipanah N. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, Clin Inf Dis. 2016; NIH Office of AIDS Research Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV; and University of Liverpool HIV Drug Interaction Checker

1. Knowledge of the contraindications unique to each of the rifamycins is vital when prescribing TB treatment for HIV patients; RIF and RBT cross-react differently and must be used appropriately.
2. The list of antiretroviral medications included in this table is not comprehensive, as medications for the treatment of HIV are continuously changing. See the United States Agency for International Development list of approved antiretrovirals, University of California San Francisco's HIV InSite, and individual drug packaging for more information.
3. Close monitoring of HIV infection is recommended when dolutegravir/lamivudine is used with RIF and RBT.

Abbreviations Used: FDA=Food and Drug Administration; HIV=human immunodeficiency virus; INSTI=Integrase Strand Transfer Inhibitors; kg=kilograms; mg=milligrams; NNRTI=Non-nucleoside Reverse transcriptase inhibitors; PI=protease inhibitor; RBT=rifabutin; RIF=rifampin; RPT=rifapentine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate

SPECIAL DRUG INTERACTIONS WITH RIFAMYCINS

COBICISTAT AND RIFAMYCINS: Cobicistat (Tybost®) is not an ART, but a pharmacokinetic enhancer increasing the amount of other HIV medications in the blood, and is used in combination with other ART in several formulations:

- Darunavir and cobicistat (Prezcobix®)
- Atazanavir and cobicistat (Evotaz®),
- Elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate (TAF) (Genvoya®),
- Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (TDF) (Stribild®)
- Darunavir, cobicistat, emtricitabine + TAF (Symtuza®)

Drug combinations that use cobicistat in combinations with other ART are not used concurrently with RIF. Regimens that contain cobicistat may be used with RBT, but the RBT dose is adjusted to 300 mg every other day or 150 mg per day.

TENOFOVIR ALEFENAMIDE AND RIFAMYCINS: TAF is being used increasingly in fixed-drug combinations in preference to TDF. TAF causes less bone resorption compared to TDF. However, there is a theoretical concern that the rifamycins will cause decreased absorption of TAF. Although there is some clinical evidence that TAF can be used with RIF, at this time, according to the package insert, TAF is contraindicated with rifamycins. There are currently five combination pills with TAF on the market:

- Emtricitabine/TAF/Elvitegravir/Cobicistat (Genvoya®)
- Emtricitabine/TAF (Descovy®)
- Emtricitabine/TAF/Rilpivirine (Odefsey®)
- Bictegravir/emtricitabine/TAF (Biktarvy®)
- Darunavir/cobicistat/emtricitabine/TAF (Symtuza®)

REGIMENS FOR PREGNANT PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Treatment of HIV and active TB disease in pregnant patients is challenging. A basic principle is that patients should receive treatment for both HIV and TB disease during the pregnancy. ART should be initiated as early as possible for treatment of maternal HIV infection and to prevent maternal-child transmission. The care of any patient requiring treatment for both conditions during pregnancy is discussed in consultation with an expert.

LENGTH OF THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS

Recent guidelines suggest that recommended treatment regimens and length of therapy are similar for individuals with HIV infection who are on ART and those who do not have HIV infection. Patients not on

ART should have treatment extended. Short course therapy is possible if a standard rifamycin-containing regimen is used.

In NYC, relapse rates are generally low for patients with HIV and TB. Regardless, if cultures remain positive after two months of rifamycin-based treatment, the therapy is extended to nine months.

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS is an inflammatory response to TB antigens as the body's immune system recovers while on TB and HIV treatment. While IRIS may occur in patients without HIV infection, patients with HIV-associated TB disease who are started on ART regimens seem to be at a particularly increased risk of developing this syndrome.

Onset of IRIS may occur within a few weeks of starting ART, and coincides most closely with viral load decline. If IRIS occurs, the patient appears to clinically worsen, with the development of new manifestations of TB or worsening of existing signs and symptoms of TB. While early initiation of ART is recommended and decreases all cause-mortality, it could lead to an increased risk of IRIS.

The frequency of IRIS is estimated to be approximately 20% among patients with concurrent TB disease and HIV on treatment. IRIS occurs more often in patients with lower CD4 counts, extrapulmonary TB disease, disseminated TB disease, or with a shorter interval between TB treatment and subsequent ART treatment.

IRIS can manifest in a wide variety of sites, including cervical or mediastinal adenopathy, worsening infiltrates on CXR or enlarging CNS lesions. Fever may or may not be present. Patients may experience substantial morbidity due to IRIS even though the prognosis for survival is favorable. The course of IRIS can be brief or prolonged, with multiple recurrences and exacerbations. The diagnosis of IRIS is a diagnosis of exclusion and this relies on: negative culture of clinical samples; decrease in HIV viral load; and lack of other etiologies, such as relapse of TB disease, poor adherence to treatment, adverse effects of drugs, and worsening TB disease due to drug resistance or other infections.

Among patients with CD4 counts less than 100 mm^3, prednisone treatment during the first four weeks after initiation of ART results in a lower incidence of TB-associated IRIS without evidence of an increased risk of severe infections or cancers (40 mg per day for 14 days followed by 20 mg for 14 days).

If IRIS develops, mild and moderate reactions can be managed by reassuring the patients or by prescribing non-steroidal anti-inflammatory agents. While standard treatment for severe IRIS is not well established, some experts advocate the use of corticosteroids, such as when lymphadenopathy may compromise respiration and swallowing, or the development of CNS mass lesions occurs. To treat IRIS, prednisone is prescribed at 50 mg to 80 mg daily for two to four weeks with tapering for six to 12 weeks or longer. In conjunction with the anti-TB regimen, the use of corticosteroids for short periods does not seem to adversely affect the outcome of the TB treatment.

TREATMENT OF COEXISTING TUBERCULOSIS AND NONTUBERCULOUS MYCOBACTERIA

Nontuberculous mycobacteria (NTM) can cause disease in immunocompromised and immunocompetent patients. Severely immunosuppressed individuals, usually with HIV infection, can develop TB disease and disseminated M. avium-intracellulare (MAI) infection concurrently, and must be treated for both conditions. In immunocompetent patients, NTMs may overgrow *M. tuberculosis* in the laboratory. *M. tuberculosis* requires specific laboratory techniques. The decision to treat TB is made on a case-by-case basis. Drugs currently recommended to treat MAI are macrolides (clarithromycin and azithromycin), EMB, and the rifamycins (especially RBT). If RBT cannot be used due to drug interactions, fluoroquinolones (FQN) or parenteral amikacin (AK) have also been used. When treating concomitant MAI and TB disease, RBT is not used at the same time as RIF. If RBT is required for MAI treatment, RIF is replaced by RBT in the anti-TB regimen as well.

In general, patients with coexisting MAI and TB disease can be treated at a NYC Health Department TB clinic for both diseases until TB treatment is completed or TB disease is ruled out. Patients should also be followed up by another expert in the treatment of NTMs to ensure successful treatment outcomes. Following treatment completion for TB, the patient is referred to another provider if continued treatment for the NTM is warranted. BTBC does not treat patients with NTMs alone.

TREATMENT REGIMENS FOR PREGNANT PATIENTS

Treatment for TB disease is initiated for any pregnant patient who has a positive TB culture and for whom there is a high clinical suspicion of TB disease based on symptoms, CXR, and clinical evaluation. For the latter group, treatment may be deferred until the end of the first trimester if the patient is very reluctant to take treatment and the following conditions are met:

- Sputum smears are AFB-negative
- Without HIV infection or other immunocompromising condition
- Without symptoms of TB disease (i.e., cough, fever, night sweats, weight loss)
- Without cavitary lesion on CXR

Treatment regimens for pregnant patients differ from standard treatment regimens in that PZA is avoided as the effect of PZA on the fetus has not been well established; however, PZA is included in the initial treatment regimen for patients with either HIV infection or a probable diagnosis of MDR-TB. Because PZA has been used extensively in pregnant patients internationally without apparent adverse effects, the World Health Organization (WHO) recommends PZA at all stages of pregnancy for all pregnant patients. If the patient has TB that is INH-resistant or intolerant to INH, PZA should be included in the regimen, as the benefit outweighs the risk.

STANDARD REGIMEN FOR PREGNANT PATIENTS

The usual doses of INH, RIF, and EMB are used in the standard regimen unless there are absolute contraindications. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.) If the patient has not been prescribed PZA during the intensive phase, treatment must be extended to nine months. For pregnant patients taking INH, pyridoxine 25 mg/day is given unless the patient is already taking a prenatal vitamin that contains the equivalent amount of pyridoxine.

If pregnancy is discovered while the patient is already on a standard four-drug regimen that includes PZA, and the patient is in the first trimester of pregnancy, the PZA can be stopped. If the first trimester has passed before the pregnancy is discovered, all four drugs are continued (EMB can be dropped if the TB isolate is drug-susceptible), in order to finish a two-month intensive phase of treatment. If the isolate is drug-susceptible and PZA was given during the two-month intensive phase, treatment can be shortened from nine to six months. Otherwise therapy should be continued for nine months.

AFB culture and pathological evaluation of the placenta is requested as part of the diagnosis process. This may help when evaluating the infant for the possibility of congenital TB.

ANTI-TUBERCULOSIS MEDICATIONS IN BREASTFEEDING MOTHERS

The small concentrations of anti-TB drugs in breast milk are not toxic to the nursing newborn. Therefore, breastfeeding is not discouraged for a mother without HIV who is planning to take, or who is taking, INH or other anti-TB medications. Furthermore, the low concentration of anti-TB medications in breast milk is not considered effective treatment for disease or for treatment for latent TB infection (LTBI) in a nursing infant. Mothers with HIV infection should not breastfeed because of the risk of HIV transmission to the infant. (See *Appendix I: The Use of Anti-Tuberculosis Drugs and Pregnancy, Breastfeeding, Tuberculosis Meningitis, and Renal and Hepatic Failure*.)

TREATMENT REGIMENS FOR PATIENTS WITH CHRONIC RENAL FAILURE

In most patients with chronic renal failure, the regimens for TB treatment must be adjusted; the interval between conventional dosages should be lengthened instead of decreasing dosing. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.) No dose adjustment is necessary for: INH, RIF, ETA, and para-aminosalicylic acid (PAS); however, a dose adjustment is required for PZA and EMB. In addition, both PZA and EMB are given after hemodialysis. Three times per week regimens are convenient and should be developed in coordination with the patient's hemodialysis schedule to ensure medications are given after hemodialysis.

There is very little information about how to dose patients who are on peritoneal dialysis. While there is some literature on intraperitoneal administration of anti-TB medications, BTBC recommends patients are dosed per hemodialysis dosing.

The following anti-TB medications are eliminated by the kidney and therefore require a dose adjustment:

- Injectable agents can be used in 15 mg/kg doses, but only two or three times per week. The dose is administered immediately after hemodialysis in patients who are receiving maintenance hemodialysis. Levels of AK, if used, may be helpful in guiding therapy.
- PZA can be used at the usual daily dose in patients with mild to moderate renal insufficiency. In patients with severe renal failure, however, a three times per week dose of 30 mg/kg (range 25 to 35 mg/kg) is recommended. The medication is given immediately after hemodialysis.
- EMB and cycloserine (CS) are excreted primarily by the kidney, and excessive and toxic blood levels can occur in patients with chronic renal insufficiency. Both medications are avoided if possible. When either EMB or CS are used, drug levels should be monitored.
- If EMB is essential to the regimen (e.g., in patients with MDR-TB), 20 to 25 mg/kg doses may be given 3 days per week, but visual acuity and color vision must be monitored closely.
- CS is given immediately after hemodialysis at a dose of 250 mg or 500 mg three times per week.
- FQNs undergo some degree of renal clearance that varies from drug to drug. Levofloxacin (LFX) at 750 to 1000 mg three times per week is adequate for treatment of TB in patients with chronic renal failure. Moxifloxacin (MFX) may be the preferred agent for patients with renal failure, as it is mostly cleared by the liver.

TREATMENT REGIMENS FOR PATIENTS WITH LIVER DISEASE

Many anti-TB drugs are metabolized by the liver. Therefore, patients with underlying liver disease may be more likely to experience liver toxicity from these drugs. In most situations, it is not necessary to reduce the dosages of drugs that are metabolized by the liver (INH, RIF, PZA, and ETA). The administration of RIF with INH can increase the possibility of drug-induced hepatitis during therapy. Close monitoring of patients' liver function and signs and symptoms of toxicity should be more frequent, either biweekly or monthly.

- If it is necessary to exclude one of these agents from the regimen because of elevated LFTs, INH is considered first. If INH is excluded, the patient may be treated with EMB, RIF, and PZA for six to nine months. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis* in *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults*.)
- If RIF is excluded, the duration of treatment will need to be prolonged to 12 to 18 months.
- Depending on the severity of the hepatitis attributed to RIF, a trial of RBT is considered.
- If the TB is drug-susceptible and PZA is the cause of the increased LFTs and excluded from the regimen, INH and the rifamycin are given for at least nine months.
- A FQN can be added if PZA and/or INH is not used in the regimen.

Patients who have viral hepatitis may be difficult to treat because of the underlying hepatic disease and potential drug toxicities. For patients with chronic active hepatitis B, LFTs and hepatitis B deoxyribonucleic acid (DNA) are obtained. If elevated, a gastroenterologist or infectious disease specialist should be consulted regarding further testing and treatment; clinical and LFT monitoring should occur every two to four weeks. For patients with chronic hepatitis C, a hepatitis C viral ribonucleic acid (RNA) load should be obtained. If RNA viral load is elevated, the patient should be referred to a gastroenterologist for evaluation. In these patients, elevated LFTs may be indicative of underlying liver disease and may not be drug induced.

In patients with acute liver failure, a regimen of non-hepatotoxic drugs, also known as a liver sparing regimen —such as an injectable agent, EMB, CS, and a FQN—should be used until the liver function improves. LFX is the preferred FQN to use in patients with hepatic insufficiency. MFX may be used with no change in dosage; however, it should be used with caution, especially in cases of severe hepatic insufficiency. A similar regimen can be used in patients with severe chronic liver disease who cannot tolerate INH or RIF. The duration of therapy depends on whether it is possible eventually to add INH and RIF to the regimen, and on the final regimen that is tolerated.

DRUG INTERACTIONS

Clinically important drug interactions exist between TB medications and other medications, as well as TB medications and certain foods. It is important to be aware of these interactions to ensure quality and safety of care. (See *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications* and *Appendix J: Recommendations for Patients to Assist with Taking Tuberculosis Medications*.) For interactions with specific drugs, providers may use online drug-to-drug interaction trackers, the electronic medical record, or UptoDate.

SUMMARY

All individuals with a confirmed diagnosis of TB disease or signs and symptoms consistent with TB disease begin treatment promptly. Most forms of active TB disease can be treated with the standard six-month regimen. However, treatment regimens are adjusted based on DST results, both molecular and conventional, of a patient's positive culture or due to suspicion of drug resistance. Length of treatment may be adjusted based on site of disease. Completion of treatment is dependent on the number of uninterrupted doses taken in both the intensive and continuation phase. Expert consultation should always be sought for complicated TB treatment issues.

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CHAPTER 6:

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS DISEASE IN ADULTS

INTRODUCTION

Treatment regimens for drug-resistant tuberculosis (DR-TB) are individualized and based on results of susceptibility testing. Guidelines help in establishing an optimal regimen but other factors such as physician and patient preferences, the extent of disease, and procurement of medications are used in choosing the components and length of a therapy. Treatment options with a preference for all-oral regimens are presented in this chapter based on new guidelines. New treatment options offer hope for the possibility of shorter duration therapy for DR-TB.

In addition to standard case management, the New York City (NYC) Bureau of TB Control (BTBC) provides comprehensive clinical oversight to every case of

DR-TB. Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis with resistance to at least isoniazid and rifampin and requires prolonged therapy. Expert medical consultation should be sought for individuals with a confirmed diagnosis of MDR-TB.

PRINCIPLES OF TREATING DRUG-RESISTANT TUBERCULOSIS DISEASE

Drug resistance patterns are categorized based on the drugs to which a TB isolate is resistant, most importantly to isoniazid (INH) or rifampin (RIF) alone or in combination with other medications. MDR-TB refers to a TB isolate resistant to at least INH and RIF. Extensively drug-resistant (XDR-TB) traditionally referred to a TB isolate resistant to INH and RIF, plus a fluoroquinolone (FQN) and at least one of the injectable second-line drugs. This definition was recently revised to include resistance to INH and RIF, resistance to any FQN, and resistance to either bedaquiline (BDQ) or linezolid (LZD), or both. Access to timely drug-susceptibility test (DST) results, both conventional and molecular, is vital to successful treatment outcomes, as these tools aid in the determination and initiation of an effective treatment regimen.

Traditionally, TB medications are categorized based upon their effectiveness and use in a TB regimen and are designated as first-line, second-line, and third-line medications. (See *Table 6.1: Standard United States Classification for Anti-Tuberculosis Medications*.) First-line medications, while most effective in the treatment of TB disease, are the most frequent to be identified as resistant. When possible, any first-line medications found to be susceptible are included in the treatment regimen. Second-line medications are TB drugs used to treat TB disease when first-line medications are no longer available. These are often the medications used in MDR-TB regimens; they are less potent and may have more serious side effects than first-line medications. Finally, third-line medications are used when other TB medications are no longer available. These medications are most commonly used for treatment of XDR-TB, and often have the potential for more adverse reactions. Adverse effects of second- and third-line medications, often serious and intolerable, may preclude the use of these drugs for the full length of therapy. Use of anti-TB medications should not be stopped unless the reaction is severe or cannot be ameliorated by supportive treatment. Recently, additional research and new guidelines have reprioritized the use of these medications in drug-resistant TB as will be discussed later in the chapter. As additional research is published, the classification of these drugs will change and updated accordingly.

Unlike treatment for drug-susceptible TB, there is no “standardized” treatment regimen for DR-TB. Instead, treatment regimens are individualized based upon the patient’s TB isolate DST results as much as is possible. Use of both molecular DST and conventional culture DST are vital to successful patient outcomes and treatment success. The use of molecular methods including whole genome sequencing (WGS) allows for faster susceptibility results and more timely initiation of appropriate therapy. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Any treatment recommendations for DR-TB consider both the DST results of the individual TB isolate as well as the history of any prior TB treatment. If molecular DST results are pending and the patient is clinically stable, a treatment regimen can be delayed until DST results are available. If there is a need to start treatment for the patient, an empiric regimen can be started with at

least three anti-TB medications to which the isolate is likely to be susceptible. Empiric treatment regimens may be determined based on:

- Drug-susceptibilities of close contacts with MDR-TB
- Medications used to treat prior TB disease episodes in the patient
- Epidemiology of drug resistance based on patient's country of birth

Once first- and second-line DST results are known the initial MDR-TB regimen is revised.

In general, the following principles apply to initiation of treatment for MDR-TB:

1. First-line drugs to which the isolate is still susceptible are started or continued
2. A FQN is added (if not already begun) and the organism is susceptible
3. Second-line and third-line drugs are added until there are at least five drugs to which the isolate is susceptible
4. All-oral regimens are preferred
5. Length of treatment is usually at least 15 months (range: 15 to 21 months) after culture conversion. In some instances treatment may be extended due to cavitary disease, delayed culture conversion or if the patient has immunosuppression

In general, any level of resistance to an anti-TB medication indicates that the drug is unlikely to be effective. However, susceptibility testing for pyrazinamide (PZA), ethionamide (ETA), and CM is often inconsistent among laboratories or even within the same laboratory. In the case of partial resistance or inconsistent results, physicians follow the general dictum, "use the medication, but do not depend on it for success."

At times, a patient's regimen may show signs that it is "failing" (e.g., the patient is not clinically improving or cultures are still positive four months after the start of therapy). When this occurs in a patient who has DR-TB, a single new anti-TB medication is never added to the regimen alone; instead, at least two, and preferably three, new anti-TB medications to which the isolate is susceptible are added. Adding multiple new medications to a failing regimen decreases the likelihood that a patient will develop acquired resistance to a single anti-TB medication and improves treatment outcomes overall.

Treatment regimens prescribed for patients with DR-TB are administered by directly observed therapy (DOT), which is the standard of care for treatment of TB disease. (See *Chapter 10: Case Management for Patients with Tuberculosis*.) DOT supports successful treatment outcomes, especially for patients with DR-TB and MDR-TB, as the patient is engaged in a dialogue to foster optimum adherence to reduce the risk of the development of additional drug-resistance or treatment failure. Some patients with DR-TB may require DOT more than once per day depending on the frequency and types of medication; new modalities including video-based DOT are useful for patients requiring observation multiple times a day.

There are no fully intermittent regimens for MDR-TB treatment. Injectable agents, if used, can be given intermittently after the initial phase of treatment. BDQ is given three times per week after the initial two weeks of daily administration. Certain drugs may be given intermittently in patients with chronic renal failure.

Most of the medications used to treat MDR-TB are known to cause fetal abnormalities, or have not been studied adequately regarding their safety in pregnancy. Therefore, persons of childbearing age who have MDR-TB and their partners are strongly encouraged to use birth control if sexually active. Children with MDR-TB are treated with drugs to which their TB, or that of the known source patient, is susceptible. Some FQNs and some third-line medications are not Food and Drug Administration- (FDA) approved in children and must be used after careful consideration of the potential risks and benefits. (See *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

TABLE 6.1: Standard United States classification for anti-tuberculosis medications

FIRST-LINE MEDICATIONS	SECOND-LINE MEDICATIONS		THIRD-LINE MEDICATIONS
Isoniazid	Amikacin	Kanamycin[2]	Bedaquiline
Rifampin	Capreomycin[2]	Streptomycin	Clofazimine
Ethambutol	Moxifloxacin	Levofloxacin	Delamanid[2]
Pyrazinamide	Ethionamide	Linezolid[1]	Imipenem/cilastin[3]
Rifabutin	Cycloserine		Meropenem[3]
Rifapentine	Para-aminosalicylic acid		Amoxicillin/ clavulanate[3]
			High-dose isoniazid[4]
			Pretomanid[5]

Adapted from: Curry International Tuberculosis Center, & California Department of Public Health. (2016). Drug-resistant tuberculosis: a survival guide for clinicians, third edition.

1. Linezolid, while historically considered a third-line drug in the United States, is now more commonly used as a second-line medication.
2. Capreomycin, delamanid, and kanamycin are not currently available in the United States.
3. Amoxicillin/clavulanate is recommended as an adjunctive agent to both imipenem/cilastatin and meropenem; it is not recommended for use alone.
4. NYC BTBC does not use high-dose isoniazid for MDR-TB, unless the patient has W strain. High-dose isoniazid is usually given as 900 mg three times per week.
5. Pretomanid is used as part of a regimen that includes linezolid and bedaquiline.

Abbreviations Used: BTBC=Bureau of Tuberculosis Control; MDR-TB=multidrug-resistant tuberculosis; NYC=New York City

SPECIFIC MEDICATIONS USED TO TREAT DRUG-RESISTANT TUBERCULOSIS

When arranging a regimen for DR-TB disease, medications are chosen based on DST results. Theoretically, any TB medication can be used, unless there is known resistance. Select medications are described in more detail below. For specific medications and dosages for the treatment of DR-TB, see *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.

FIRST-LINE MEDICATIONS

ISONIAZID

In general, once there is known resistance to INH at any tested concentration, use of INH is not recommended in that treatment regimen. The only exception to this rule is when the patient is diagnosed with MDR-TB due to the W strain and W variants. In this instance, high-dose INH can be prescribed. High-dose INH is usually given as 900 mg three times per week. High-dose INH has also been used in nine-month regimens that include injectable agents. (See section *Shorter Regimens Using Injectable Agents*.)

RIFAMYCINS

Most, but not all, TB isolates that are resistant to RIF are also resistant to rifabutin (RBT). Occasionally, a RIF-resistant organism will be reported as sensitive to RBT. This situation is associated with certain genetic mutations. When there is in vitro sensitivity to RBT, it can be added to the regimen along with other oral agents as outlined. However, the effectiveness of RBT in this situation cannot be relied upon. The treatment length is usually 12 to 18 months, depending on the regimen used. With newer drugs such as BDQ and LZD, shorter treatment may be possible. However, data is lacking at this time.

ETHAMBUTOL

If EMB is used in an MDR-TB regimen, the recommended dose is 25 mg/kg/day. A baseline and monthly visual acuity exam and Ishihara's test for color blindness is performed.

PYRAZINAMIDE

If there is mono-resistance to PZA, *M. bovis*, another member of the *M. tuberculosis* complex, is suspected. Repeat testing for PZA resistance may be inconsistent; as such the genetic mutation in the pncA gene may be helpful in determining susceptibility. It is not the practice of the BTBC to use PZA in MDR-TB patients if there is known drug-resistance to PZA.

INJECTABLE AGENTS

Historically, BTBC has used CM as the preferred injectable agent until DST results were known, due to the widespread incidence of W strain and W strain variants seen in NYC in the 1990s that are commonly resistant to streptomycin (SM) and AK/KM. NYC has excellent outcomes using CM. However, recent American Thoracic Society (ATS)/Centers for Disease Control and Prevention (CDC)/European Respiratory

Society (ERS)/Infectious Disease Society of America (IDSA) and World Health Organization (WHO) guidelines for the treatment of MDR-TB recommend against use of CM and instead recommend AK if an injectable agent is used. AK is commonly used for hospitalized patients due to accessibility of the drug, ease of administration intravenously, and the ability to easily monitor drug levels. Administration of intramuscular AK to an outpatient is challenging due to the volume of drug that needs to be administered and level of pain associated with the injection. Laboratories usually test for either AK or KM susceptibility, as there is cross-resistance between these two agents, and resistance to one generally predicts resistance to the other. KM is not available for use in the United States (U.S.).

With the availability of new, safer, and more effective medications, the injectable medications are rarely used today in the outpatient setting. Patients may be started on injectable agents as part of a holding regimen while hospitalized. If an injectable agent is continued, it could be given for six months after culture conversion unless ototoxicity or nephrotoxicity develops. The continuation of the injectable agent for longer than six months after culture conversion is only appropriate if there are no other reasonable treatment options and there is extensive disease, extensive resistance, intolerance to second-line or newer drugs, or when conversion of sputum cultures did not occur within the first two months of treatment.

If an injectable agent is used in a DR-TB regimen, a baseline and monthly audiogram is performed.

FLUOROQUINOLONES

FQNs are the backbone of a successful MDR-TB regimen because they are bactericidal, well-tolerated, and can be given orally. The later generation FQNs, levofloxacin (LFX) and moxifloxacin (MFX), are preferred in the treatment of DR- TB disease. In general, FQNs are not considered for first-line treatment in patients with drug-susceptible organisms unless the patient is intolerant to other first-line drugs. If a FQN is used, molecular and conventional DSTs are requested to confirm isolate sensitivity, as this drug class is typically not included in first-line molecular and conventional DSTs and rates of FQN resistance are increasing. The NYS lab can test for FQN susceptibility using pyrosequencing.

LFX is cleared by the kidney and is the preferred agent for patients with hepatic insufficiency; however, it is used with caution. In patients with renal failure, the interval between doses of LFX is increased. MFX is mostly cleared by the liver and therefore may be the preferred FQN in a patient with renal insufficiency.

- The dose of LFX is 500 to 1000 milligrams (mg) once daily. Doses of 750 or 1000 mg per day are preferable. The higher end of the dose range may be bactericidal. In children older than five years of age, the dose is 8 to 10 mg/kilograms (kg)/day. In children younger than five years of age, the dose is eight to 10 mg/kg/12 hours.
- MFX is usually dosed in adults at 400 mg once per day. Children receive 10 mg/kg/day. Some experts recommend higher doses of MFX in children.
- When used in children, the potential benefit must justify the potential risk. Disclosure of potential risks to the patient is done by the clinician and is documented in the electronic medical record (EMR).

›› LFX and MFX are a category C drug in pregnancy. They are only used if the potential benefit to the mother justifies the potential risk to the fetus. Disclosure of this risk to the patient is done by the clinician and is documented in the EMR.

SIDE EFFECTS:

FQNs are generally considered to be well-tolerated in both adults and children; however, some side effects include:

- Nausea/vomiting/abdominal pain
- Diarrhea (can be due to *C. difficile*, especially MFX)
- Reversible transaminase elevation
- Cholestasis, hepatitis, and hepatic failure (infrequently reported)
- Photosensitivity (except MFX)
- Cardiotoxicity (see *QTc Prolongation*)
  - Prolongation of the QTc interval and possible arrhythmia including Torsade de Pointes
  - Most notably associated with the use of the later generation FQNs (MFX greater than LFX)
  - This side effect is uncommon
    - Baseline and follow-up electrocardiogram (EKG) are not indicated unless otherwise clinically indicated, i.e., if the patient is receiving other QTc prolonging medications
- Central nervous system [CNS] effects
- Peripheral neuropathy
- Worsening muscle weakness in patients with myasthenia gravis
- Tendinopathy/tendinitis (may be more prevalent in the elderly [65 and older], patients on corticosteroids, and patients with organ transplants)
  - May cause tendon rupture
  - Tendinopathy and rupture may be reported even months after drug discontinuation
  - Main site affected is rupture of the Achilles tendon; however, it has also been reported in the shoulder, knee, hand, and plantar aponeuroeses
  - Treatment includes discontinuing the FQN and resting the affected tendon; physical therapy may be needed early in treatment and may be prolonged
- Hypoglycemia and hyperglycemia (All FQNs; may be more prevalent in the elderly or patients with diabetes)
- Hypersensitivity reaction either after a single dose or multiple doses
  - Treatment is discontinued at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity
- Ruptures or tears in the aorta, rarely

In addition, FQNs cause a number of other notable drug interactions:

- Medications with divalent cations, such as aluminum-, magnesium-, or calcium-containing antacids, can decrease the absorption of FQNs
- FQNs can inhibit the metabolism of methylxanthines

LINEZOLID

LZD belongs to the oxazolidinones class of antibiotics and is active against TB, including isolates resistant to many first-line anti-TB drugs. LZD may be used as part of a regimen for treating patients with MDR-TB who have extensive second-line drug resistance or are intolerant to many second-line drugs. LZD is being used more frequently as a second-line drug by BTBC. There is excellent data showing positive outcomes using LZD for patients with pre-XDR-TB and XDR-TB. LZD is usually included as part of the newer all-oral regimens used for MDR-TB.

LZD is available for oral use as well as for intravenous administration and a dose of 600 mg per day is recommended when used for TB. Food may cause delays in LZD absorption, but does not lower peak plasma concentrations. The drug is partly metabolized in the liver and does not affect the cytochrome P450 enzyme system; it is excreted in the urine. The LZD oral suspension contains phenylalanine, and therefore is not given to patients with phenylketonuria. The oral suspension is non-formulary and needs approval by BTBC. LZD can be used in children. Complete blood count (CBC) and SMA-18 profile need to be monitored monthly; if there is evidence of myelosuppression the CBC should be monitored more frequently. Vision is monitored monthly.

LZD is a reversible, non-selective inhibitor of monoamine oxidase and therefore may interact with adrenergic and serotonergic agents. Patients should avoid eating diets high in tyramine (e.g., strong or aged cheese, cured or smoked meats, beers on tap or home-brewed, soy products, and fava or broad beans). Co-administration of drugs containing pseudoephedrine, phenylpropanolamine, selective serotonin reuptake inhibitors, and possibly other antidepressants, is undertaken with caution, as serotonin syndrome may occur. This syndrome manifests as cognitive dysfunction, hyperpyrexia, hyperreflexia, and incoordination, and such patients may need referral to a neurologist or other specialist. The benefit of taking LZD with these drugs must be weighed against these risks.

SIDE EFFECTS:

The following are side effects reported with LZD:

- Optic neuritis (may be reversible)
- Peripheral neuropathy (may be irreversible)
- Myelosuppression including anemia, leukopenia, pancytopenia, and thrombocytopenia (reversible upon discontinuation of the drug)
- Hemolytic anemia
- Diarrhea

- Nausea/vomiting (patients who have recurrent nausea and vomiting, unexplained acidosis, or a low bicarbonate level should receive immediate medical attention to rule out lactic acidosis)
- Liver function test (LFT) elevations
- Tongue discoloration
- Severe hypertension (if taken concomitantly with large amounts of tyramine)

CLOFAZIMINE

CFZ has been used for many years to treat MDR-TB. Since it has in vitro activity against TB, *M. avium-intracellulare* (MAI), and leprosy, this drug has been used in both the treatment of MDR-TB and nontuberculous mycobacteria (NTM). According to the new WHO and ATS/CDC/ERS/IDSA guidelines, CFZ is being recommended in the treatment of MDR-TB and XDR-TB. CFZ is given at a dose of 100 mg per day for most patients.

CFZ for MDR-TB patients is only available from Novartis via an IND application from the FDA. Approval from the institution's IRB and patient consent is required. Contact FDA and Novartis for more information at clofazimine.managedaccess@novartis.com

Obtaining CFZ is a complicated process; the Bureau of TB Control (BTBC) can provide support in obtaining CFZ for MDR-TB patients. As of October 2018, CFZ is only available from the drug supplier Novartis, where a Letter of Agreement needs to be established with the institution. Prior to requesting the drug, a unique patient Investigational New Drug (IND) application approval letter from the FDA must be acquired. This process includes attesting that the institution has an Institutional Review Board (IRB) approval and signed consent from the patient. Once FDA approval is obtained, a unique IND number is assigned to the patient. Novartis requires a copy of the consent form and the IND approval letter from the FDA, as well as a prescription for the drug. A supply of 200 tablets, 50 mg each, of the drug is sent to the institution. The treating physician is responsible for sending annual reports to the FDA, Novartis, and IRB, as well as immediate reporting of adverse events. The patient is monitored monthly, or more frequently if necessary, for continued need for the drug and side effects.

SIDE EFFECTS:

- Pink to brownish-black discoloration of the skin. The degree of discoloration is dose-related and is most pronounced on exposed parts of the body
- Photosensitivity
- Ichthyosis and dry skin; pruritus and non-specific rash
- Reversible, dose-related red-brown discoloration of the conjunctiva, cornea, and lacrimal fluid
- Prolongation of the QTc interval and possible arrhythmia including Torsade de Pointes

- GI side effects such as abdominal and epigastric pain, diarrhea, nausea, vomiting, and GI intolerance
- Central nervous system (CNS) effects (reported in less than 1% of patients) such as dizziness, drowsiness, fatigue, headache, giddiness, neuralgia, and taste disorders
- Rare adverse effects may include splenic infarction, bowel obstruction, stomach or intestinal bleeding

BEDAQUILINE

BDQ is a diarylquinoline, a new chemical class of drugs. In 2012, the FDA gave BDQ fast-track approval for the treatment of MDR-TB, as it demonstrated decreased time to sputum culture conversion. BDQ interferes with the energy metabolism of the cell. It must be used in combination with at least three other drugs to which the patient's TB strain is susceptible, except when used as part of the BPaL regimen. As with any patient treated for MDR-TB, BDQ must be given under DOT. Currently, it is believed there is little resistance to BDQ in the U.S. Previously, BTBC has used BDQ for the treatment of pre-XDR and XDR-TB patients; it is increasingly being used for patients with MDR-TB and mono-RIF resistance. New guidelines place greater emphasis on the use of BDQ as one of the initial agents of an all-oral regimen used to treat MDR-TB.

BDQ is lipophilic and has a long half-life. BDQ should be taken with food. BDQ may prolong the QTc interval and therefore an EKG is obtained before the initiation of therapy and at two, 12, and 24 weeks after the start of therapy. Caution must be used when the patient is taking other medications or has a clinical condition that may prolong the QTc interval. BDQ is metabolized through the cytochrome P450 (CYP) system. Co-administration with rifamycins (e.g., RIF, RPT, and RBT) or other strong CYP3A4 inducers should be avoided. There is limited data on patients with concomitant HIV and MDR-TB.

The recommended dose for an adult being treated for 24 weeks is as follows:

WEEK 1-2: 400 mg (four tablets of 100 mg) given orally, once daily with food

WEEK 3-24: 200 mg (two tablets of 100 mg), given orally three times per week with food, for a total dose of 600 mg per week; the drug can be taken at least 48 hours between doses if a dose is missed

In some cases, patients may receive an additional course of BDQ if necessary to establish a sufficiently potent regimen.

BDQ is generally well-tolerated. The patient should be monitored for symptoms of hepatitis with laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline and monthly or as indicated clinically.

Other frequent adverse events include:

- Nausea
- Arthralgia
- Headache

If the patient is insured, BDQ can usually be obtained through the insurance company. Copayment may be required. Many companies may require prior authorization through the patient's insurance/pharmacy coverage. If the patient is not insured, the Johnson & Johnson Patient Assistance Program should be contacted at 1-800-652-6227 or https://www.jjpaf.org/eligibility/?medication=SIRTURO%C2%AE#step1.

BDQ is supplied by a single distributer. Use of BDQ is coordinated through BTBC's Medical Affairs Office. Call the TB HOTLINE at 844-713-0559 for additional information.

DELAMANID

Delamanid is a nitroimidazole, a class of novel agents used for TB treatment. It has a new mechanism of action, inhibiting the cell wall of TB but the exact mode of action is unknown. It must be given along with a background MDR-TB treatment regimen. It has mild adverse effects, primarily gastrointestinal, and few drug-to-drug interactions; however, it can prolong the QTc interval. In the US, it is available through a compassionate use program.

PRETOMANID

Pretomanid is another nitroimidizole that is used in a regimen, along with BDQ and LZD (BPaL), that has FDA approval for the treatment of pulmonary XDR-, treatment-intolerant, or non-responsive MDR-TB for six to nine months. It is generally well-tolerated, but side effects include peripheral neuropathy, acne, vomiting, headache, low blood sugar, diarrhea, and liver inflammation.

SUGGESTED REGIMENS FOR SPECIFIC DRUG RESISTANCE PATTERNS

Treatment of DR-TB is seldom clear-cut. The use of any medication that was used in a patient who has had prior treatment for DR-TB when DST results are not available should be avoided. Opinions may vary on the best medications to use for an individual patient. Whenever possible, a regimen is crafted based upon available specimen drug-resistance profiles. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis*.)

INH-resistant, RIF-susceptible (INH-R) tuberculosis is one of the most common forms of drug resistance, and is associated with failure, relapse, and acquired RIF resistance if the regimen is not adjusted appropriately.

Mono-RIF resistance is rare and can be associated with cross-resistance to rifabutin (RBT) and rifapentine (RPT). When RIF resistance is present but in vitro susceptibility to RBT is reported, treatment should be the same as in the case of RIF resistance.

The use of laboratory diagnostics is crucial in formulating a successful MDR-TB treatment regimen. Although molecular methods enable the clinician to obtain results more rapidly for certain mutations associated with drug resistance and allow quicker initiation of appropriate therapy, these methods have

different specimen requirements (e.g., Xpert MTB/RIF is performed directly on sputum, WGS is performed on culture). Conventional DST requires a pure culture and laboratories test drugs sequentially. (Standard treatment drugs [i.e., first-line drugs] INH, RIF, PZA, EMB, and SM are tested first, and additional drugs are only tested when resistance has been detected in the standard treatment drugs.) (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

The regimens listed below are suggested recommendations based on specific drug resistance patterns. (See *Table 6.2: Traditional Suggested Regimens for Treatment of Drug-Resistant Tuberculosis*.) For a list of medications for the treatment of MDR-TB and XDR-TB, see *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis* and *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.

ISONIAZID RESISTANCE

Most patients with TB are started on a four-drug regimen consisting of INH, RIF, PZA, and EMB. Once INH resistance is documented, INH is discontinued. High-dose INH is not recommended for patients with INH-resistant TB disease, even when DST indicates that the isolate is susceptible to a high level of INH, but resistant to lower levels of INH.

OPTION A: In 2018, the World Health Organization (WHO) published guidelines for the treatment of INH-resistant TB. The WHO recommended RIF/PZA/EMB/FQN for a total of six months. In 2019, guidelines from ATS/CDC/ERS/IDSA recommended a regimen of RIF/PZA/EMB/FQN for two months followed by RIF/EMB/FQN for four months as the preferred regimen for INH-resistant TB when there is toxicity anticipated or experienced because of PZA or when the patient has noncavitary, lower burden of disease. The BTBC agrees with the recent guidelines that add a FQN to the regimen for treatment of INH-resistant TB.

OPTION B: RIF, PZA, and EMB are used for the duration of treatment. This is the preferred regimen for pregnant patients, as relapse rates are high with RIF and EMB alone. RIF, PZA, and EMB is the only regimen when treating INH-resistant TB that can be given intermittently. If given intermittently, treatment three times per week is preferred. This regimen is given for six to nine months total; the regimen is extended to nine months if the patient is still culture-positive at two months.

After a two-month intensive phase of a RIF, EMB, and PZA regimen, PZA may be discontinued and RIF and EMB are continued for seven more months. The total length of treatment for this regimen is nine months.

OPTION C: If PZA cannot be given during the entire two-month intensive phase (because of drug resistance or intolerance), a regimen of RIF and EMB is used along with a FQN for nine months.

OPTION D: MFX, RIF, PZA, and EMB are used daily for a two-month intensive phase, followed by once weekly MFX and rifapentine (RPT) (1200 mg dose once per week) for four months. This regimen is an acceptable alternative for INH-resistant TB disease if the organism is susceptible to the FQNs. The total length of treatment with this regimen is six months.

TABLE 6.2: Traditional suggested regimens for treatment of drug-resistant tuberculosis

	INITIAL PHASE		CONTINUATION PHASE		TOTAL LENGTH AND NOTES
Resistance Pattern	Drugs	Duration	Drugs	Duration	
INH ± SMN	**OPTION A:** RIF/PZA/EMB/FQN	2 months	RIF/FQN/EMB ± PZA	4 months	• 6 months • Extend to 9 months if still culture-positive at 2 months • PZA may be discontinued for toxicity or noncavitary, lower burden of disease
	OPTION B: RIF/EMB/PZA	2 months	RIF/EMB/PZA RIF/EMB	4-7month 7 months	• 6-9 months • Consider adding a FQN • RIF/PZA/EMB is the preferred regimen in pregnancy
	OPTION C: RIF/EMB/FQN	2 months	RIF/EMB + FQN	7 months	9 months
	OPTION D: MFX/RIF/PZA/EMB	2 months	MFX/RPT[1]	4 months	6 months
INH/PZA ± SMN	RIF/EMB/FQN	2 months	RIF/EMB/FQN	7 months	9 months
RIF	**OPTION A:** INH/PZA/EMB/FQN	2-3 months after culture conversion	INH/PZA/EMB/FQN	10-16 months	• 18 months is the preferred option • 12 months of INH/PZA/EMB/FQN is an alternative option • Consider discontinuation of PZA after 2 months
	OPTION B: *(no SM resistance)* INH/PZA/SM ± EMB				9 months
PZA ± SMN	INH/RIF	2 months	INH/RIF	7 months	9 months
INH/EMB ± SM	RIF/PZA/FQN	2 months	RIF/PZA/FQN	4-7 months	9 months or 6 months after culture conversion, whichever is longer
INH/RIF ± SM	PZA/EMB/FQN/ BDQ/LZD	6 months after culture conversion	PZA/EMB/FQN ± LZD Consider a second course of BDQ	12 months	15-21 months after culture conversion

TABLE 6.2: Traditional suggested regimens for treatment of drug-resistant tuberculosis *(continued)*

	INITIAL PHASE		CONTINUATION PHASE		TOTAL LENGTH AND NOTES
Resistance Pattern	Drugs	Duration	Drugs	Duration	
INH/RIF/ EMB ± SM	PZA/FQN/BDQ/LZD/ CFZ or CS	6 months after culture conversion	PZA/FQN/LZD ± CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ PZA ± SM	EMB/FQN/BDQ/ LZD/CFZ or CS	6 months after culture conversion	EMB/FQN/LZD ± CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ PZA/EMB ± SM	FQN/BDQ/LZD/CFZ/ CS	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion
INH/RIF/ EMB/SM/ KM/ETA/ RBT ± PZA (Pre-XDR-TB)*	FQN/BDQ/LZD/CFZ/ CS Consider BDQ/LZD/ Pretomanid (BPaL) regimen	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	12 months	15-21 months after culture conversion • This resistance pattern is associated with NYC strain W and W variants • Consider BPaL regimen for 6 months
INH/RIF/ EMB/SM/ FQN + second-line reserve injectable agent ± PZA *(XDR-TB)**	FQN/BDQ/LZD/CFZ/ CS Consider BDQ/LZD/ Pretomanid (BPaL) regimen	6 months after culture conversion	FQN/LZD/CFZ or CS Consider a second course of BDQ	Unknown	18-24 months after culture conversion • Consider BPaL regimen for 6 months

1. Jindani A, Harrison TS, Nunn AJ, et al; RIFAQUIN Trial Team. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med*. 2014 Oct 23;371(17):1599-608.

*Based on 2006 WHO definition of XDR-TB

Abbreviations Used: BDQ=bedaquiline; CFZ=clofazimine; CM=capreomycin; CS=cycloserine; EMB=ethambutol; ETA=ethionamide; FQN=fluoroquinolone; INH=isoniazid; KM=kanamycin; LZD=linezolid; MFX=moxifloxacin; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; SM=streptomycin; XDR-TB=extensively drug-resistant tuberculosis

RIFAMPIN RESISTANCE

Isolated rifampin resistance without associated resistance to isoniazid is a rare occurrence. Mono-RIF resistant TB can be treated with INH/EMB/PZA/FQN for a total of 12-18 months. BDQ is increasingly being used in the treatment of rifampin mono-resistant TB and may lead to shorter treatment duration.

A nine-month regimen of INH/PZA/SM ± EMB has proven efficacy but is seldom used due to the difficulties associated with the prolonged use of SM, which must be given for the entire duration of the regimen.

PYRAZINAMIDE RESISTANCE

Isolated pyrazinamide resistance is usually seen in *M. bovis* and requires an extension of therapy. The pyrazinamide is discontinued from the regimen and INH and RIF are used for a total of nine months.

TREATMENT REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS

In December 2018, the WHO released updated guidelines and recommendations with key changes for the treatment of MDR-TB and RIF-resistant TB (RR-TB). The guidelines were developed based on a review of global clinical trials that investigated the effectiveness and safety of various MDR-TB treatment regimens. Major changes in the new WHO guidelines include:

- Recommendation of an all-oral regimen for 18 to 20 months in most patients
- No longer recommending injectable agents KM and CM for use in treatment
- Updated priority ranking of medicines with BDQ, LZD, and CFZ rising in importance in the treatment regimen
    - ETA and the injectable agents AK and SM are becoming less important in the treatment regimen (see *Strategy for Building a Treatment Regimen for MDR-TB*)

CURRENT BTBC PRACTICE

Evolving evidence from innovative research, ongoing clinical trials, and updated guidelines for the treatment of MDR-TB has led to new recommendations for the treatment of MDR-TB. Guidance from the WHO and ATS/CDC/ERS/IDSA based on the information provided by a large individual patient data analysis have led to changes in the recommendations for the treatment of MDR-TB at the BTBC.

Key publications influencing the change in recommendations include the 2018 Lancet article from Ahmad et al. “Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis” and updated WHO guidelines. ATS/CDC/ERS/IDSA have also developed guidelines for the treatment of MDR-TB.

BTBC has had great success in treating patients with MDR-TB and limiting the development of drug resistance, but emerging data and recommendations are helpful in continuing to ensure positive patient outcomes.

Changes in practice at the BTBC include:

- Crafting an all-oral regimen, when possible
- Prioritizing newer drugs that allow shorter treatment duration, such as BDQ, LZD, and CFZ as "first-line" MDR-TB drugs; increasingly, we are transitioning to using the shorter BPaL regimen as first-line treatment for MDR-TB and XDR-TB
- Ensuring susceptibility of medications whenever possible
- Limiting use of injectable agents and prioritizing amikacin or streptomycin if an injectable agent is needed
- Using at least five drugs in the "initiation phase" and at least four in the "continuation phase," except when using the BPaL regimen
- Treating for at least 15 months (range: 15 to 21 months) after culture conversion; XDR or pre-XDR TB may need to be treated up to 24 months after culture conversion

Providers must incorporate updated guidance into clinical practice whenever it is of benefit to patients. BTBC will re-evaluate treatment recommendations as additional information becomes available.

The construction of a regimen to treat MDR-TB integrates all of the information from all types of DST to the extent possible. Currently, molecular testing is not available for all drugs. Cross resistance may develop between some drugs and should be considered when constructing a regimen.

In some instances, it takes time to procure all of the drugs for an all-oral regimen and injectable drugs may need to be used until a regimen with an adequate number of effective drugs can be initiated. This type of regimen is called a bridging regimen.

STRATEGY FOR BUILDING A TREATMENT REGIMEN FOR MDR-TB

The following is adapted from ATS/CDC/ERS/IDSA guidelines; updated guidelines are anticipated in 2022.

OPTION A: ALL-ORAL REGIMEN WITH FIVE EFFECTIVE DRUGS

Step 1: Choose one later-generation fluoroquinolone:

- Levofloxacin
- Moxifloxacin

Step 2: Choose both of these prioritized drugs:

- Bedaquiline
- Linezolid

Step 3: Choose both of these prioritized drugs:

- Clofazimine
- Cycloserine

OPTION B: INJECTABLES

If a regimen cannot be assembled with five effective oral drugs, and the isolate is susceptible, use one of these injectable agents:

- Amikacin
- Streptomycin

Amikacin and streptomycin should be used only when the patient's isolate is susceptible to these drugs. Because of their toxicity, these drugs should be reserved for when more-effective or less-toxic therapies cannot be assembled to achieve a total of five effective drugs.

OPTION C: ALTERNATIVE ALL-ORAL REGIMEN

If needed or if oral agents preferred over injectable agents in Option B, use the following drugs:

- Pyrazinamide
- Ethambutol
- Delamanid

Use pyrazinamide and ethambutol only when the isolate is documented as susceptible. Data on dosing and safety of delamanid are available in children > 3 years of age. Delamanid is only available for compassionate use in the U.S.

Considerations in selecting Option C agents over injectables in order to prescribe an all-oral regimen:

- Patient preferences in terms of the harms and benefits associated with injectables (the use of which is no longer obligatory)
- Capacity to appropriately monitor for significant adverse effects
- Drug-to-drug interactions
- Patient comorbidities

OPTION D: ADDITIONAL DRUGS

If limited options and cannot assemble a regimen of five effective drugs, consider use of the following:

DRUG	CONSIDERATIONS
Ethionamide	Mutations in the inhA region of the Mycobacterium tuberculosis genome can confer resistance to ethionamide as well as to INH. In this situation, ethionamide may not be a good choice unless the isolate is shown to be susceptible with in vitro testing.
Imipenem–cilastatin/ clavulanate or meropenem/clavulanate	Divided daily intravenous dosing limits feasibility. Optimal duration of use not defined. May be used if patient is hospitalized as part of a bridging regimen. Clavulanate is given as amoxicillin/clavulanate.
p-Aminosalicylic acid	Fair/poor tolerability and low performance. Adverse effects reported to be less common in children.
High-dose isoniazid	High-dose isoniazid can be considered despite low-level isoniazid resistance but not with high-level INH resistance.

- Capreomycin and kanamycin
- Amoxicillin/clavulanate (when used without a carbapenem)
- Azithromycin and clarithromycin

PRINCIPLES OF MONITORING DRUG-RESISTANT TUBERCULOSIS DISEASE

›› Sputum AFB smear and cultures (for patients with pulmonary disease) and clinical laboratory tests should be performed monthly for patients with TB isolates resistant to RIF or INH and RIF

›› Monthly clinical laboratory tests are obtained for patients with DR-TB when indicated to monitor for potential drug toxicities

›› Chest radiograph (CXR) is obtained at two months of treatment, periodically when clinically indicated during the continuation phase, and at the end of treatment for patients with DR-TB

›› Other imaging studies are obtained when clinically indicated during treatment

›› If a patient has a positive TB culture after four months of treatment, the most recent positive culture is sent to the clinical laboratory for first- and second-line DST. There are at least two treatment options while the DST results are pending:

1. If the patient is not acutely ill or clinically deteriorating, the current or most recent anti-TB regimen may be continued until the new DST results are available;
2. If the patient is acutely ill or clinically deteriorating, at least two new anti-TB medications are added to the current regimen based on an assessment of the other medications to which the isolate is not known to be resistant. The regimen is revised when the new DST results are available, as indicated

›› If the patient is having an adverse reaction to a specific medication:

1. The medication responsible for the adverse reaction is omitted and the remainder of the anti-TB treatment regimen is continued if enough medications are left in the regimen
2. A previously unused agent is substituted
3. If the adverse reaction cannot be readily identified, all medications are discontinued and restarted one at a time. In some instances of severe toxicity, hospitalization for re-challenge with multiple drugs may be needed
4. If the adverse reaction is mild, the physician may choose to continue treating through the adverse reaction

QTc PROLONGATION

The QT interval is the length of time required for the heart to repolarize following the onset of depolarization. The QT interval is measured from the start of the QRS complex to the end of the T wave on the electrocardiogram (EKG). Rapid heart rate can lead to a shortened QT interval. In order to correct

for this, the QT interval is expressed as the heart rate corrected QT interval (QTc). Prolongation of the QTc interval may predispose the patient to potentially fatal ventricular arrhythmias and sudden death.

Several drugs used in the treatment of TB can cause QTc prolongation. These include the FQNs, CFZ, DLM, BDQ, and pretomanid. LFX is believed to prolong the QTc interval less than MFX. With respect to QTc prolongation, BDQ is the most concerning because of the long half-life of the drug. Patients receiving BDQ should receive an EKG at baseline, and at minimum at two, 12, and 24 weeks of treatment. Patients receiving multiple drugs that can prolong the QTc interval should have monthly EKG monitoring. BDQ is discontinued if the QTc is greater than 500 milliseconds, as the most common ventricular arrhythmias such as torsade de pointes have been associated with this value.

Certain other conditions are associated with prolongation of the QTc interval. These include:

- Bradycardia
- Torsade de pointes
- Hypothyroidism
- Uncompensated heart failure
- Congenital long QT syndrome
- Electrolyte abnormalities: hypomagnesemia, hypokalemia, and hypocalcemia
    - Electrolyte abnormalities may be caused by the injectable agents

It is important to document any medications that the patient is taking. Examples of medication that may prolong the QTc interval include:

- Antiarrhythmic agents: Class IA (quinidine and procainamide) and Class III (amiodarone and sotalol)
- Antimicrobials (FQN, azole antifungals, and macrolides)
- Antidepressants
- Antipsychotics
- Antihistamines
- Antiretroviral agents (specifically protease inhibitors [PI] and efavirenz containing regimens)
- Methadone
- Gastrointestinal (GI) drugs: metoclopromide, cisapride, and ondansetron (Zofran)

SURGERY FOR PULMONARY TUBERCULOSIS DISEASE

In NYC, surgery is usually not recommended as an initial treatment option, because pulmonary TB disease is curable using modern drug regimens in most cases. Surgery remains an option for individuals with MDR-TB or XDR-TB in whom treatment has failed or is not possible because of a lack of sufficient and effective medications. Video-assisted thoracoscopic surgery (VATS) with partial lung resection (lobectomy or wedge resection) has been associated with improved treatment success among patients with MDR-

TB. Although improved outcomes may reflect patient selection and newer surgical techniques, partial lung resection surgery after culture conversion may improve treatment outcomes in patients who receive optimal medical therapy.

In patients with XDR-TB, surgery may be indicated earlier in the course of therapy as drug options are more limited.

INDICATIONS FOR SURGERY

In consultation with medical and surgical experts, surgery is considered when all of the following criteria are met:

- Adequate regimens for MDR-TB have failed to cure or to cause TB cultures to culture convert within four to six months
- The disease is sufficiently localized to allow lobectomy or pneumonectomy
- The remaining lung tissue is relatively free of disease
- The patient is an acceptable surgical risk, with sufficient pulmonary reserve to tolerate the resection
- Sufficient medications are available to treat the patient post-operatively

Even after lung resection, the patient must complete a full course of treatment (15 to 24 months after culture conversion) with medications to which the TB isolate is susceptible. If the patient is culture-negative after surgery, then the date of surgery is considered the culture conversion date.

Some clinical circumstances, such as major bronchial obstruction, severe hemoptysis, or bronchopleural fistula, are additional possible indications for surgery.

SHORTER REGIMENS FOR MULTIDRUG-RESISTANT TUBERCULOSIS

SHORTER REGIMENS USING INJECTABLE AGENTS

Historically, there have been efforts to reduce the treatment duration for MDR-TB using novel combinations of existing drugs. One of the first regimens was the nine-month Bangladesh Regimen, which has been used in some countries with modest success. The intensive phase includes four months of KM, MFX, prothionamide (PTH), CFZ, PZA, high-dose INH, and EMB, followed with five months of MFX, CFZ, PZA, and EMB (KM and PTH are not available in the US). This regimen has been used in countries where full DST is not routinely available.

The STREAM trial also looked at a nine-month regimen of oral drugs plus an injectable agent and high-dose INH along with other oral agents. The Bangladesh regimen, together with the STREAM trial, were important in the development of shorter, all-oral regimens, for the treatment of drug-resistant TB. BTBC does not use this nine-month regimen, as individualized regimens are accessible and preferred. A significant portion of BTBC patients would not be eligible for these regimens.

PRETOMANID AS PART OF THE NIX-TB REGIMEN

Pretomanid is a nitroimidazole approved by the FDA in 2019 for the treatment of XDR-TB. Currently, pretomanid is given in combination with BDQ and LZD. Pretomanid has been developed by the TB Alliance and is distributed by Mylan Pharmaceuticals. NIX-TB is a six-month all-oral three-drug regimen of BDQ, pretomanid, and LZD (BPaL).

- Pretomanid 200 mg orally once per day for 26 weeks
- Bedaquiline 400 mg orally once per day for two weeks and then three times per week for 24 weeks
- Linezolid 1200 mg orally once per day for 26 weeks

Most of the adverse effects of this regimen were due to the toxicities of the individual drugs in the regimen:

- Hepatoxicity
- Myelosuppression
- Peripheral and optic neuropathy (which was the most common)
- QTc prolongation
- Testicular atrophy and infertility
- Lactic acidosis

The regimen is generally well-tolerated. Peripheral neuropathy was a common side effect with dosing of LZD at 1200 mg/day. As a result, LZD is usually given at a dose of 600 mg/day. The recent ZeNix trial showed that LZD could be dosed at 600 mg/day with high cure rates but fewer side effects. It is recommended that drug levels of LZD should be obtained. Levels are drawn as a trough immediately before a dose and then at two hours after the dose. Elevated trough levels (greater than 2 mcg/ml) are associated with peripheral neuropathy. Levels are sent to Denver National Jewish Health Advanced Diagnostic Laboratories and are arranged by the Office of Medical Affairs. Monthly visual monitoring is required. EKG should be monitored monthly due to potential for QTc prolongation.

POST-TREATMENT EVALUATION

Patients with TB resistant to RIF alone or INH and RIF, regardless of the regimen used and the duration of treatment, are at greater risk for post-treatment relapse. The patient is scheduled for surveillance follow-up once completing treatment at four, eight, 12, 18, and 24 months post-treatment. If the patient is treated with a shorter regimen, the patient should have follow-up quarterly during the first year, then twice per year in the second year.

At each visit:

- A medical evaluation is performed to assess for signs and symptoms of active TB
- A CXR is obtained for comparison to the CXR obtained at the end of therapy
- A single sputum specimen is obtained for smear and culture

For patients that remain stable and asymptomatic, no immediate clinical action is taken. For patients seen in a NYC Health Department TB clinic:

- An appointment to review the results of the smear or culture is not routinely needed
- Patients are informed that they will be contacted by telephone if any result is positive
- If the smear is positive for AFB, the patient is recalled for three additional sputa specimens
    - If any specimen is culture-positive for *M. tuberculosis*, the patient is recalled immediately for a complete clinical re-evaluation and the reinstitution of appropriate therapy

SUMMARY

Successful DR-TB treatment outcomes are more likely when effective partnerships are initially established with all members of the treatment team, providers caring for other medical issues, and the patient and family members. BTBC providers craft individualized treatment regimens for DR-TB that are based upon a history of past TB disease treatment or exposure to an infectious person with DR-TB, DST results of the patient's TB isolate, and mutation analysis. Adverse effects of second-line medications are often serious and intolerable; such treatment decisions should be made in consultation with BTBC. BTBC supports ATS/CDC/ERS/IDSA guidelines for the treatment of MDR-TB. Shorter all-oral regimens are increasingly used. This is a rapidly changing field and providers should be kept abreast of new recommendations.

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CHAPTER 7: DIAGNOSIS AND TREATMENT OF PEDIATRIC TUBERCULOSIS DISEASE

INTRODUCTION

Pediatric tuberculosis (TB) differs from TB in adults in clinical presentation, diagnosis, and therapy with attention to drug dosages. Certain pediatric populations are more likely to progress to TB disease once infected; as such prompt diagnosis and treatment is essential for positive outcomes. Pediatric age groups span from infancy to adolescence and each group has distinct characteristics related to their TB diagnosis. In general, children younger than five years of age can present with rapidly disseminated disease, while adolescents (13 to 17 years of age) typically present with “classic” TB disease similar to adults.

CHARACTERISTICS OF PEDIATRIC TUBERCULOSIS DISEASE

The presentation of TB disease in children differs from adults and also varies within pediatric age groups (infants, children, and adolescents), as follows:

- Infants and children younger than five years of age are more likely to develop TB disease once infected than children five to 10 years of age
- Children with TB disease diagnosed as a result of a contact investigation are often asymptomatic
- Wheezing is an occasional manifestation of TB disease in infants due to endobronchial disease or lymph nodes compressing a bronchus

Compared to adults with TB disease:

- Infants and young children are less likely to produce a sputum specimen
- Children are more likely to have culture-negative disease
- Pediatric diagnoses often depend upon clinical and radiological response to anti-TB treatment

MEDICAL EVALUATION

TB evaluation of children differs from adults in several aspects including medical history, chest radiograph (CXR), tests for TB infection, and specimen collection. Children tend to be asymptomatic and/or present with atypical disease, and as such, a high level of suspicion for TB disease is required during the evaluation.

MEDICAL HISTORY

A medical history including a comprehensive review of the child's signs and symptoms as well as the family's prior TB history is obtained.

Signs and symptoms indicating TB disease in pediatric patients commonly include:

- Failure to thrive in infants
- Missed developmental milestones
- Behavioral changes including irritability in infants
- Headaches
- Weight loss and/or lack of weight gain

A complete medical history includes:

- Inquiries about prior TB screening results and treatment of latent TB infection (LTBI) or TB disease for the child
- Prior TB disease among household members of the child, caregivers, and visitors
- Possible TB exposures at congregate settings such as a school or daycare
- Foreign birth/details of any foreign travel

PHYSICAL EXAMINATION

A physical examination is needed for every child undergoing evaluation for TB disease. This includes evaluation of the respiratory system, as well as a directed exam for potential extrapulmonary sites of disease such as peripheral lymph nodes, central nervous system (CNS), bones and joints, liver, and spleen.

TEST FOR TUBERCULOSIS INFECTION

When evaluating a child with signs or symptoms of active TB disease, obtaining a positive test result for TB infection increases the likelihood that the child has TB disease; however, a negative result does not rule out TB disease and further diagnostic evaluation for children at high risk for TB disease is necessary. The New York City (NYC) Bureau of TB Control (BTBC) routinely uses the blood-based interferon gamma release assay (IGRA) test to screen for TB infection in individuals two years of age and older, as few indeterminate results are seen in the NYC Health Department TB clinic population. The tuberculin skin test (TST) is used to screen for TB infection in children younger than two years of age or if a blood sample cannot be obtained.

Children are commonly diagnosed with TB disease as a result of a contact investigation. In this context, and given the low prevalence of TB in NYC, a positive test result for TB infection in children is more likely a sign of recent infection, and can aid in the diagnosis of TB disease. Since it can take up to eight weeks after exposure to *M. tuberculosis* for the immune system to mount a response ("window period"), the initial (baseline) test may be falsely negative if conducted too soon after TB exposure. In general, children who are close contacts to an infectious TB patient and younger than five years of age, or children of any age with immunosuppression and an initial negative test for TB infection, are started on prophylactic treatment (preferably four months rifampin [RIF] [4R]). (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.) The initiation of prophylaxis occurs while awaiting the repeat test for TB infection eight weeks after exposure to an infectious TB patient and active TB disease has been ruled out by CXR and medical evaluation.

By six months of age, children should have developed a strong enough immune response to react to a TST. If an infant is tested with a TST before the age of six months and the result is negative, the test is repeated again at age six months; if positive, the child is re-evaluated for active disease and LTBI treatment is continued for the remaining duration of therapy once TB disease is ruled out. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection* and *Chapter 11: Contact Investigation*.) If the test at six months is negative and the testing is past the window period, then prophylactic therapy can be discontinued.

CHEST RADIOGRAPH

In children younger than five years of age, BTBC recommends a lateral CXR in addition to a posterior-anterior (PA) view to assess for pulmonary TB disease. Children five years of age and older receive a PA CXR only, unless additional views are clinically indicated.

›› When practical, CXR images are interpreted by a radiologist experienced in reading pediatric CXRs.

- CXR abnormalities can be present in children even if they are asymptomatic.
- The most common radiological abnormalities are persistent opacification in the lung in conjunction with enlarged hilar or subcarinal lymph nodes.
- A miliary pattern of opacification is highly suggestive of TB disease.
- Patients with persistent opacification who do not improve after a course of antibiotics should be investigated for TB disease.

SPECIMEN COLLECTION

As part of the diagnostic process for pediatric patients, the most common specimens collected include sputum, gastric aspirates, and cerebral spinal fluid (CSF) via lumbar puncture; other specimens are collected as clinically indicated. Once collected, all specimens are sent for acid-fast bacilli (AFB) smear and mycobacterial culture.

SPUTUM

Sputum induction is a safe and effective method for collecting sputum and performed in children old enough to understand and cooperate with the procedure. Sputum bacterial yields are as good as, or better than, those from gastric aspirates; however, staff training and specialized equipment are required to perform this procedure properly. (See *Appendix E: Instructions for Performing Sputum Induction*.) If possible, sputum is collected for any child with signs and symptoms consistent with TB disease or diagnosed with TB disease. At least three sputa specimens for AFB smear and mycobacterial culture are collected during the diagnostic process.

When TB is highly suspected, nucleic acid amplification (NAA) testing is requested regardless of AFB smear results. A positive NAA test result confirms the presence of TB; however, a negative NAA test result in an AFB smear-negative specimen does not rule out TB disease. (See *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*.)

GASTRIC ASPIRATION

Because young children are often unable to produce sputum **either** spontaneously or with aerosol inhalation, gastric aspirate specimens can be obtained in limited instances when it is especially important for diagnostic or treatment decisions.

- Children should fast for at least four to eight hours before gastric aspiration.
- Children with a low platelet count or bleeding tendency should not undergo gastric aspiration.
- AFB smear and mycobacterial culture are requested for testing.
- NAA testing is recommended if available. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

- The highest bacterial yields from a gastric aspiration are obtained when the patient is hospitalized.
- The specimen is taken as soon as the patient wakes in the morning, while still in bed. The first aspirate of the day will have the highest bacterial yield.
- Approximately 50 milliliters (ml) of gastric contents are aspirated via nasogastric feeding tube during three consecutive mornings.
- Obtaining a gastric aspirate specimen is more important when evaluating a child who has been exposed to an infectious individual with drug-resistant TB (DR-TB).
- Repeat gastric aspirates are not recommended once the child is on appropriate treatment.

LUMBAR PUNCTURE

For additional information on how to collect a gastric aspirate, see *Pediatric TB: A Guide to the Gastric Aspirate Procedure* at: www.currytbcenter.ucsf.edu/products/view/pediatric-tuberculosis-guide-gastric-aspirate-ga-procedure

A lumbar puncture is performed in infants and children with signs and symptoms consistent with congenital TB disease, disseminated TB disease, or TB meningitis. In these instances, the CSF is sent for cell count, protein, and glucose, as well as AFB smear and mycobacterial culture.

VISION SCREENING

Prior to initiating the use of ethambutol (EMB), a standard anti-TB drug, visual acuity and/or color vision are assessed in children old enough to be evaluated. Recent editions of the American Academy of Pediatrics (AAP) Red Book note, however, that the use of EMB in infants and young children whose visual acuity cannot be monitored requires consideration of risks and benefits, but can be used routinely to treat TB disease unless otherwise contraindicated.

- If the child can both identify letters on an eye chart and discriminate colors, this can be used for monitoring potential EMB toxicity.
- If the child can discriminate colors, but cannot identify letters, color vision is used to routinely screen for potential EMB toxicity.
- If the child's vision cannot be evaluated, EMB is only used when the child:
  - Is known or likely to have DR-TB
  - Has HIV infection
  - Is immunosuppressed from another clinical condition

HUMAN IMMUNODEFICIENCY VIRUS TESTING

All patients being evaluated for TB disease, including children, should have a test for HIV. Minors under 13 years of age or persons who are deemed not to have the capacity to consent should be offered HIV testing through a parent or guardian. Children 13 to 18 years of age do not need parental authorization for HIV testing in New York State (NYS). A medical provider ordering the test must conduct an individualized assessment of every older child's or adolescent's ability to understand the nature and consequences of being tested for HIV and to make an informed decision about whether testing should occur. Any patient who tests positive for HIV is referred to an HIV specialist for appropriate follow-up and care. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

CONGENITAL AND NEONATAL TUBERCULOSIS DISEASE

Congenital TB disease is defined as disease acquired by an infant due to exposure to *Mycobacterium tuberculosis* (*M. tuberculosis*) bacilli either in utero or at delivery. Neonatal TB disease is acquired by the baby after birth. The distinction between congenital and neonatal TB is primarily epidemiologic; presentation, management, and prognosis are similar. In pregnant patients with TB disease, regardless of TB treatment status during pregnancy, the placenta should be examined microscopically for granulomas, stained for AFB, and sent for AFB culture.

Congenital/neonatal TB disease can occur in several situations:

1. **TB disease recently diagnosed in a pregnant patient prior to delivery OR TB untreated during pregnancy.** In these instances, the fetus is at risk for congenital TB and prompt evaluation of the neonate and the placenta must be coordinated and planned **prior to delivery** (i.e., submission of the placenta for AFB smear and culture, as well as gross and microscopic pathological examination).
    - When the placenta demonstrates pathological evidence of TB disease, empiric treatment of TB disease in the neonate is necessary.
    - When the placenta does not demonstrate pathological evidence of TB disease and the mother is not infectious, clinical judgment is used to guide the treatment of the neonate.
    - When the placenta does not demonstrate pathological evidence of TB disease, but the mother is infectious, a decision is made to treat the infant for presumptive TB infection. RIF is administered for four months OR until the mother is culture-negative, whichever is longer.
        - Children born to mothers with active untreated disease are more likely to develop TB disease in their first year of life if treatment for LTBI is not given to the neonate.
    - If the pregnant patient is infectious at the time of delivery, plans are made to prevent transmission to the neonate. (See *Chapter 13: Infection Control*.)

2. **The diagnosis of TB in the newborn leads to a retrospective diagnosis in the mother.** As a significant percentage of pregnant patients with pulmonary TB disease are unaware of their diagnosis and/or may be asymptomatic, the diagnosis of TB in the neonate may be the first indication of TB in the mother. These neonates are often born premature, are very ill, and are only diagnosed with TB after unsuccessful treatment for other life-threatening infectious diseases. If the mother is evaluated and found to have a normal CXR, examination for gynecological or other forms of extrapulmonary TB should be performed.

3. **When infectious TB disease is diagnosed in the mother or another individual who has close contact to the infant during the neonatal period, the neonate is at increased risk for transmission of TB after delivery.** If the mother is diagnosed with infectious TB after delivery, the placenta is typically not available for evaluation, making the distinction between congenital and neonatal TB disease in the infant difficult. Regardless of whether the mother or another individual exposed the infant to TB, a full evaluation for TB disease is indicated and clinical judgment is used to determine whether to treat the infant for active disease or presumptive LTBI. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.)

If the mother completed treatment for active TB during pregnancy and there is no evidence of active disease in the mother at the time of birth, there is minimal risk to the infant. The placenta and neonate should still be evaluated; however, there is no need for specific treatment of the neonate once TB disease has been ruled out.

EVALUATING NEONATES FOR TUBERCULOSIS DISEASE

All neonates being evaluated for TB disease have:

- Medical evaluation
- TST (usually negative in newborn infants with congenitally or perinatally-acquired infection)
  - If not performed initially due to presumed lack of immune response, a test for TB infection should be performed at six months of age or older.
- CXR
- Three gastric aspirates on three consecutive days
- Lumbar puncture if there is a high clinical suspicion for active TB disease
- Examination of the placenta if available for pathology and AFB smear and culture

In infants suspected of having congenital TB disease, treatment is started with isoniazid (INH), RIF, pyrazinamide (PZA), and an injectable agent if hospitalized. Amikacin (AK) is recommended, but streptomycin (SM) can be used. Ethionamide (ETA) is considered as an alternative.

- Corticosteroids are added if the neonate has meningitis.

TREATMENT OF PEDIATRIC TUBERCULOSIS DISEASE

The treatment of TB disease in children differs from adults in several aspects. Children younger than five years of age are more likely to be culture-negative and to have been recently exposed to a person with infectious TB disease. In these instances, the drug-susceptibility test (DST) results from the source patient who likely infected the child are used to develop an appropriate treatment regimen. Despite differences in the treatment of TB in adults and children, directly observed therapy (DOT) is the standard of care in pediatric TB as it is in adult TB and is the best way to ensure successful therapy. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)

STANDARD REGIMEN

Children who are treated empirically or who are suspected to have drug-susceptible TB are treated with a four-drug regimen of INH, RIF, PZA, and EMB. Once DST results are available, the regimen is modified accordingly. (See *Table 7.1: Selected Drug Regimens for Pediatric Tuberculosis* and *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.)

Anti-TB medications are administered daily within a specific milligram (mg)/kilogram (kg) dose range. Additionally, children metabolize most drugs more rapidly than adults and therefore may require higher mg/kg dosing. Recent publications recommend daily dosing of RIF at 15 to 20 mg/kg/day. The recommended daily dose of EMB is higher in children than in adults at 20 mg/kg.

Daily dosing of RIF for TB disease is recommended at 15 to 20 mg/kg/day.

EMB may be omitted or discontinued from the regimen if the child:

- Cannot participate in visual acuity/color vision assessments
- Is culture-negative and the isolate of child's source case is drug-susceptible

PZA and EMB are discontinued if:

- The DST of the child's isolate shows sensitivity to INH and RIF.
  - EMB is discontinued once susceptibilities to first-line medications confirm susceptible TB.
  - PZA can be discontinued after the two-month intensive phase.
- The child is culture-negative and the results from the source case show sensitivity to INH and RIF. EMB is discontinued immediately and PZA after completion of the intensive phase.
- The child has no reportable DST results and drug resistance is not suspected. EMB and PZA are discontinued after completion of the intensive phase.

TABLE 7.1: Selected drug regimens for pediatric tuberculosis*

INTENSIVE PHASE		CONTINUATION PHASE[1,2,3]		NOTES
Drugs	Interval and Duration	Drugs	Interval and Duration	
INH **RIF** **PZA** **EMB**[5]	7 days/week for 8 weeks (56 doses)	**INH** **RIF**	**PREFERRED:** 7 days/week for 18 weeks (126 doses) 3 days/week for 18 weeks with DOT[4] (54 doses)	• Drug-susceptible TB disease or TB presumed to be drug-susceptible
INH **RIF** **PZA** **ETA/AK**	7 days/week for 8 weeks (56 doses)	**INH** **RIF**	7 days/week for 28-40 weeks (196-280 doses) --- or --- 3 days/week for 28-40 weeks (84-120 doses)	• TB meningitis when drug resistance is not suspected • Injectable agent commonly added for hospitalized patients is AK • ETA is well-tolerated in children and has increased penetration into the CNS
INH **RIF** **PZA** **EMB**[5]	7 days/week for 8 weeks (56 doses) (PZA and EMB used until susceptibility results available)	**INH** **RIF**	7 days/week for 28 weeks (196 doses) --- or --- 3 days/week for 36 weeks[4] (108 doses)	• *M. bovis*; universally resistant to PZA • When the laboratory identifies *M. bovis*, PZA and EMB are discontinued • The total length of treatment for *M. bovis* is 9 months

Adapted from: Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195.

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*Provided dosages in the table are estimates based on an approximate number of weeks of treatment; actual doses need to be calculated based on patient's actual treatment

1. Biweekly treatment regimens during the continuation phase are not recommended due to high rates of relapse
2. For missed doses, extend treatment to make up the doses, unless there has been prolonged treatment interruption
3. Patients with a positive *M. tuberculosis* culture at 2 months of treatment regardless of CXR, extensive disease, or PZA not given for the 2 month intensive phase should receive a 7-month continuation phase (31 weeks; either 217 doses daily or 93 doses 3 times per week)
4. Not recommended for patients with HIV infection
5. Exclude EMB when the child is not able to participate in monitoring for potential visual toxicities

Abbreviations Used: AK=amikacin; CXR=chest radiograph; DOT=directly observed therapy; EMB=ethambutol; ETA=ethionamide; HIV=human immunodeficiency virus; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; TB=tuberculosis

SPECIAL CONSIDERATIONS FOR DRUG ADMINISTRATION TO YOUNG CHILDREN

- INH or PZA tablets can be divided, crushed, or added to food or liquids such as fruit, juice, pudding, or gelatin.
- RIF may be emptied from the capsule and added to food or liquids just before ingestion.
- Liquid formulations are considered when available; however, sorbitol-free formulations for INH are preferable to reduce the likelihood of gastrointestinal (GI) side effects that may complicate treatment adherence.
- RIF and other first-line agents (except for INH) can be compounded by the BTBC Pharmacy for patients receiving clinical care at a NYC Health Department TB clinic.

LENGTH OF TREATMENT

The six-month treatment duration for culture-positive drug-susceptible TB disease in children is the same as with adults and consists of a two-month intensive phase followed by a four-month continuation phase. In culture-negative pediatric TB, children are treated for six months (instead of the four-month regimen used for adults).

In certain situations, treatment length can be extended based on clinical characteristics and/or site of disease. Treatment length can also be extended based on clinical indication.

In the following situations, treatment is usually given for nine months total; however, it can be extended to 12 months based on clinical judgment:

- Patients who have positive sputum cultures after two months of therapy, regardless of CXR results
- Patients whose treatment regimen did not include PZA in the intensive phase or who are resistant to PZA (i.e., *M. bovis*)
- Patients with extensive disease or who have findings of a cavitary CXR, if poor clinical response to treatment is observed
- Patients with disseminated TB in more than one site of disease
- Patients with HIV infection who are not on antiretroviral therapy (ART) during TB treatment
- Patients who have central nervous system (CNS) TB disease; treatment of CNS TB disease is usually nine to 12 months total

For all other extrapulmonary sites of disease, see *Table 5.2: Treatment of Extrapulmonary Tuberculosis Disease* in *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults.*

For children with hilar adenopathy or extrapulmonary TB disease, treatment should be given for a total of six months with the same regimen as for pulmonary TB.

TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

The treatment of DR-TB in children follows the basic strategy used for adults and is customized according to isolate DST, molecular and conventional. Some experts are now recommending an all-oral regimen in children; however, outcome data is still pending. Expert consultation is necessary to optimize treatment regimens and outcomes. For treatment of DR-TB, see *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults* and *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

SPECIAL CONSIDERATIONS FOR CENTRAL NERVOUS SYSTEM TUBERCULOSIS DISEASE

Children with CNS TB disease can rapidly develop devastating neurological complications and may benefit from hospitalization until their clinical status has stabilized. These patients are at high risk of long-term disability and require specialized care.

Children diagnosed with CNS TB disease have a modified treatment regimen from those with pulmonary TB disease due to poor penetration of most TB medications into the CNS. The AAP recommends starting empiric treatment with either an injectable agent (aminoglycoside or capreomycin [CM]) or ETA as the fourth drug along with INH, RIF, and PZA even before laboratory confirmation of disease, if clinically indicated. INH, RIF, and PZA penetrate the blood-brain barrier efficiently; ETA and the injectable agent penetrate the barrier only when meninges are inflamed. Because the penetration of some drugs is poor (i.e., RIF), treatment regimens for CNS TB and miliary TB will most likely benefit from the higher end of recommended dose ranges. (See *Appendix I: The Use of Anti-Tuberculosis Drugs and Pregnancy, Breastfeeding, Tuberculosis Meningitis, and Renal and Hepatic Failure*.) In NYC, the injectable agent most commonly used while the patient is hospitalized is AK. The AAP recommends ETA as the fourth drug rather than EMB, as it is better tolerated in children and has increased penetration into the CNS. While a daily dose of 15 to 20 mg/kg of RIF is usually recommended, some experts recommend using a dose of 20 to 30 mg/kg/day for infants and toddlers.

Corticosteroids are routinely recommended when treating any patient with CNS TB, especially when treating a patient with a symptomatic tuberculoma, or any patient with CNS TB disease who has a decreased level of consciousness. Corticosteroids improve survival in individuals with severe disease and may reduce neurologic morbidity as well. If corticosteroids are used in a patient with a tuberculoma, dosages and tapering are similar as those for meningeal TB. Expert consolation with a neurologist is obtained as necessary. Corticosteroids are only given if the patient is on appropriate anti-TB therapy. Expert opinion on the optimal dosage for steroids varies; however, most experts recommend two mg/kg per day of prednisone (maximum 60 mg/day) or its equivalent for four to six weeks followed by tapering.

ADVERSE EVENTS IN CHILDREN

Adverse events caused by anti-TB drugs are less common in children than in adults and overall clinical monitoring is similar in adults and pediatric TB patients. The most serious adverse event is the development of hepatotoxicity, which can be caused by most TB medications; however, it is more commonly seen with INH, PZA, and RIF. Serum liver enzyme levels do not need to be monitored routinely unless the child has underlying hepatic disease or symptoms of hepatic disease.

The occurrence of liver tenderness, hepatomegaly, or jaundice results in investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. The patient is evaluated for other causes of hepatitis and anti-TB medications are reintroduced in a step-wise fashion. If continuation of TB treatment is necessary, a liver-sparing regimen can be considered in the interim (i.e., EMB, an injectable agent, and a fluoroquinolone [FQN]). (See *Chapter 8: Clinical Monitoring and Follow-Up for Tuberculosis Treatment*.)

SUMMARY

The diagnosis of TB disease in children requires the provider to have a high index of suspicion, and in young children is in part informed by the diagnosis of infectious TB disease in a family member or caretaker. A TB diagnosis is more likely to be established clinically after empiric treatment has been initiated since children are more likely to have AFB smear- and culture-negative results. Children may need increased mg/kg dosages of some TB medications and tolerate medications better than adults. Outcomes in children are excellent when treatment is initiated promptly.

KEY SOURCES

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CHAPTER 8: CLINICAL MONITORING AND FOLLOW-UP FOR TUBERCULOSIS TREATMENT

INTRODUCTION

All patients receiving treatment for active or suspected tuberculosis (TB) disease on a multidrug regimen are monitored throughout the duration of therapy for response and adherence to treatment, as well as for adverse reactions to their treatment. Comprehensive clinical monitoring and follow-up by a dedicated team of clinical and public health staff supports positive treatment outcomes and ensures adverse reactions are identified and addressed in a timely manner.

MONTHLY CLINICAL MONITORING

As part of the clinical monitoring process, physicians and nurses work collaboratively to evaluate and clinically monitor patients including their response to treatment, development of adverse reactions, and adherence to treatment. In addition, a key component of effective clinical monitoring is use of baseline and follow-up diagnostic tests; these tests are conducted at regular intervals or based on clinical judgment. (See *Figure 8.1: Evaluation and Monitoring Timeline for Tuberculosis Patients with Drug-Susceptible Tuberculosis Disease*.)

PHYSICIAN ASSESSMENT

As part of the monthly clinical evaluation, a medical assessment is conducted and the following items are discussed with the patient. These discussions are conducted in the patient's preferred language and documented in the electronic medical record (EMR):

1. **Signs and symptoms consistent with TB disease and response to treatment:** Patients are evaluated for the presence of signs and symptoms consistent with TB disease during the physical examination. If there is lack of clinical response despite treatment, non-adherence to treatment or drug resistance are considered as potential causes. For patients with a poor response to therapy, sputum specimens are collected for culture and drug-susceptibility tests (DSTs), both molecular and conventional.
2. **Adherence to treatment:** Adherence to treatment regimens, supported by directly observed therapy (DOT), is vital to successful treatment outcomes. While not mandated in New York City (NYC), DOT is strongly recommended and is the standard of care for TB treatment. If patients are not on DOT, they are encouraged to start.
    - For patients on DOT, DOT records are reviewed. When treatment adherence is less than 80%, DOT records are discussed with the patient to identify reasons why and how to improve adherence. If adherence remains low and the patient is infectious, the patient may be referred for regulatory intervention. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)
    - Patients who are prescribed intermittent DOT and who are less than 80% adherent are switched to a daily DOT regimen to ensure treatment success.
    - Patients on self-administered treatment are instructed to bring the last-issued medication bottles to follow-up visits. Pill counts are conducted by the nurse and the information is recorded in the patient's EMR. All patients are asked when and how they take their medications, to describe the appearance of the medications, and the number of pills they take each day.
3. **Medication side effects and adverse reactions:** Anti-TB medications can have varied side effects and adverse reactions ranging from mild to severe. Patients are asked about any side effects or adverse reactions that have occurred during their treatment. (See *Appendix G: Dosages, Adverse Reactions, and Monitoring for First-Line Medications Used to Treat Tuberculosis*.)

4. **Physical examination:** The nature and extent of the physical examination depends on the patient's symptoms, site of disease, and/or medication side effects.
5. **Chest radiograph (CXR) and laboratory tests:** Previous CXR, sputum, and other laboratory test results are reviewed on an ongoing basis. The patient is informed about whether their tests show improvement or deterioration, and the effect on the length of treatment.
6. **Care and treatment plan:** A plan of care is developed for every patient based on evaluation of their current disease status. Because several medical providers may be involved in the care of a patient, it is important to outline a plan of care that details reasons for decisions, names and dosages of medications, and planned length of therapy in order to ensure continuity of care. The plan of care is documented in the EMR and communicated to non-Bureau of TB Control (BTBC) providers when necessary. Changes in treatment plans are communicated to all providers in a timely manner.
7. **Medication orders:** Medication must be ordered through the EMR. Changes in medication orders due to an adverse reaction are noted in the patient's EMR and communicated to other personnel caring for the patient. If medications are stopped for any reason, they are discontinued in the EMR as well.
8. **Review of non-TB medications:** At each monthly follow-up, all current prescribed medications, as well as any vitamins, minerals, and herbal supplements that the patient is taking, are reviewed with the patient and noted in the EMR. If potential drug interactions are identified, a mutually agreed upon plan to resolve them is established and documented.

DIAGNOSTIC ASSESSMENT

CHEST RADIOGRAPH

Repeat CXRs are obtained after two months and at the end of treatment for patients with pulmonary and pleural TB disease to document the radiological response to treatment (see *Reclassification of Patients Being Evaluated for Tuberculosis* later in this section). In patients with culture-negative TB disease, a CXR is obtained at four months if that is the end of treatment. Whenever a patient receives a CXR, the results are reviewed with the patient. Additional CXRs are obtained as clinically indicated.

SPUTUM

Sputum is induced in NYC Health Department TB clinics and sent for acid-fast bacilli (AFB) smear and culture. A positive AFB smear is used as a proxy for infectiousness and is one factor used to determine when airborne infection isolation can be discontinued and/or when patients can be discharged to the community or congregate settings (with some exceptions). **AFB smear conversion is defined as having three consecutive negative AFB sputum smears.** For patients who are initially AFB smear-positive and are being managed as outpatients, specimens are collected every one to two weeks until smears convert to negative. This allows timely decision-making about when patients may be allowed to leave their home, receive visitors, or return to work or school. (See *Chapter 13: Infection Control*.)

Sputum culture conversion within the intensive phase is a strong indicator of successful treatment of pulmonary TB disease. **Culture conversion for drug-susceptible pulmonary TB is defined as documented conversion to a negative culture, without a subsequent positive culture, within 60 days of treatment initiation.** Sputum culture conversion also typically helps identify patients who can complete treatment with six months of therapy.

Sputum should be collected from all patients with pulmonary TB by two months of therapy to document culture conversion. In NYC, sputum should also be collected at the end of treatment to document cure.

- All patients should have a sputum sample taken one to three weeks before the end of the intensive phase if culture conversion has not been documented.
- Sputum is collected from all patients at the end of treatment to document cure. A negative sputum culture at the end of treatment is the only conclusive evidence of cure.
- For patients with isoniazid- (INH) and rifampin- (RIF) susceptible TB disease, it is not necessary to examine sputum monthly once culture conversion is documented for patients with good adherence.
- For patients with RIF-resistant TB disease or INH and RIF-resistant TB, sputum culture results are collected monthly until the end of treatment, and post-treatment evaluations are conducted according to the guidelines under *Post-Treatment Evaluation* in this chapter.
- Sputum specimens are collected more frequently if there has been poor adherence, there are signs of relapse, or the patient is prescribed a regimen that does not include INH and RIF.
- Sputum is collected in NYC Health Department TB clinics via induction. Natural sputum collection for patients obtaining care from the Health Department may be done only in cases where the patient is homebound, has difficulty reaching the NYC Health Department TB clinics, or is unable to produce induced sputum during clinic hours. (See *Appendix E: Instructions for Performing Sputum Induction*.)
- Rarely, a clinically stable patient who is already smear- or culture-negative unexpectedly has a positive AFB smear. If this occurs, two to three specimens are collected within one week (a CXR is obtained if it was not included in the last evaluation), and a new evaluation is conducted. As the patient is already receiving treatment, a nucleic acid amplification (NAA) test is not ordered. Specimens are sent for mycobacterial culture. Patients should be evaluated for relapse or worsening disease and whether additional drugs need to be added to the treatment regimen. The possibility of a nontuberculous mycobacterium or a lab error may be considered while awaiting final culture results.
- If the patient remains culture-positive and/or they fail to improve clinically after four months of adequate treatment, susceptibilities, both conventional and molecular, are requested.

CLINICAL LABS MONITORING

BASELINE BLOOD TESTS

Laboratory tests are obtained for all patients at baseline and appropriate intervals according to the medications used and the presence of side effects. These tests may include:

- Complete blood count (CBC)
- Metabolic chemistry panel (including creatinine and glucose)
- Viral hepatitis screen
- Uric acid values, which are affected by pyrazinamide (PZA) (**NOTE:** An increase in uric acid is not an indication to discontinue PZA, as long as the patient remains asymptomatic)
- Thyroid function tests are performed for patients taking para-aminosalicylic acid (PAS) or ethionamide (ETA) at baseline and periodically
- HIV testing is offered to all patients if their HIV status is unknown or negative

LIVER FUNCTION TESTS

Monthly liver function tests (LFT) are obtained on patients who meet one or more of the following criteria (at the discretion of the treating physician):

- Abnormal baseline LFTs
- HIV infection
- Pre-existing liver disease (i.e., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (i.e., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to two to three months after delivery)
- Taking drugs that may be hepatotoxic or interact with TB treatment

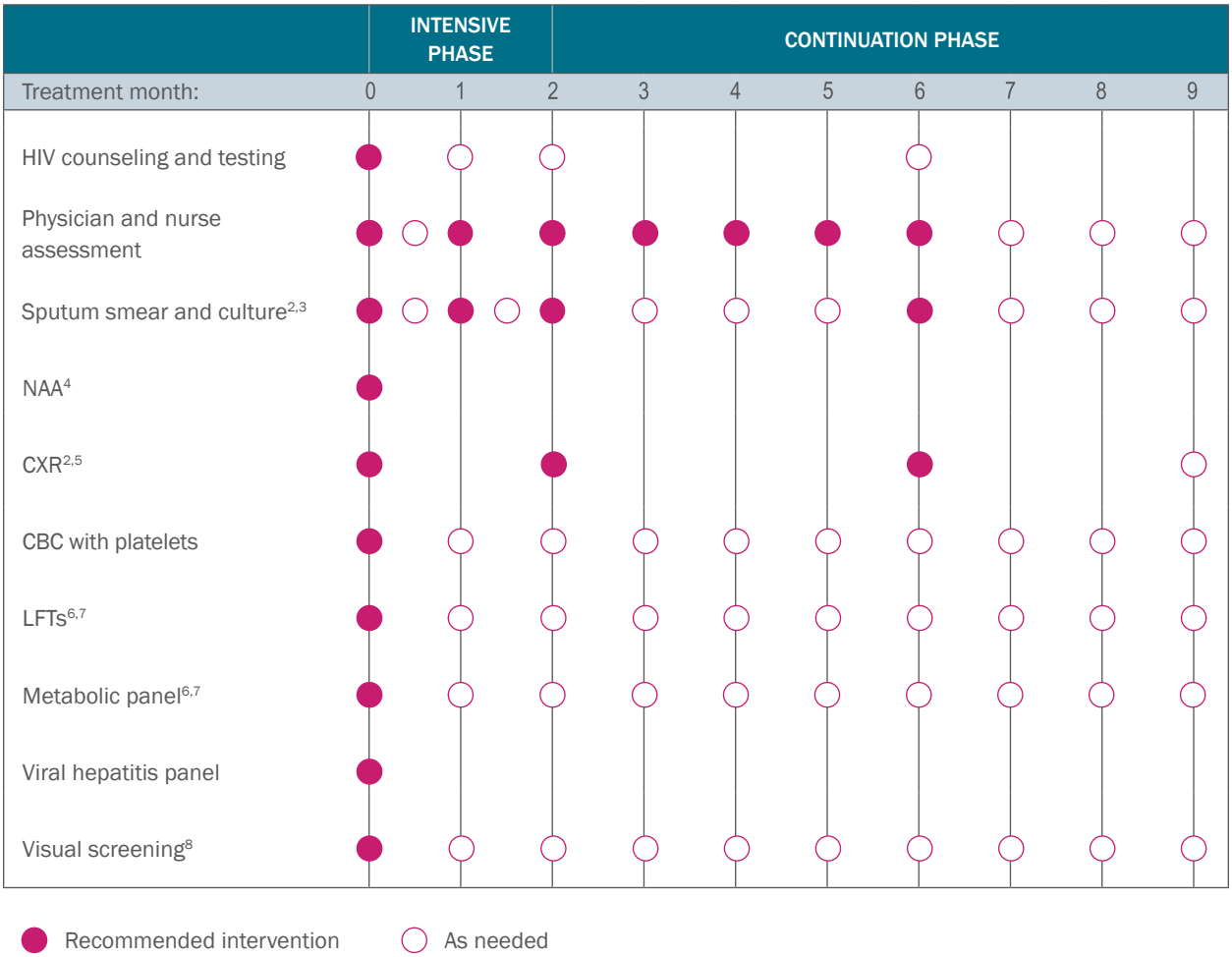
Significantly abnormal laboratory test results must be addressed immediately, independent of the date of the monthly follow-up visit.

NURSE ASSESSMENT

In NYC Health Department TB clinics, the nurse is responsible for performing a monthly assessment of the patient. Nurses document the following information in the EMR:

- Vital signs and patient's weight
- Current signs and symptoms of TB disease and assessment of changes from prior evaluation
- Assessment of treatment adherence

FIGURE 8.1: Evaluation and monitoring timeline for tuberculosis patients with drug-susceptible TB disease[1]



1. This chart applies only to patients whose isolates are found to be drug-susceptible and started on a standard regimen on INH, RIF, PZA, and EMB. If drug resistance is documented, consult an expert in its management. To obtain treatment information and susceptibility results, call the TB HOTLINE at 844-713-0559 during business hours.

2. Sputum smear and culture and CXR apply only to patients with pulmonary TB.

3. Initially at least 3 sputa for AFB smear and culture should be collected in 8 to 24 hour intervals over 48 to 72 hours in order to maximize bacteriologic diagnosis. Most patients (e.g., patients on DOT, patients adherent to the treatment regimen, and patients with INH- and RIF-susceptible TB disease) need monthly sputum tests only until cultures become negative. To document cure, a sputum test should be obtained at the end of treatment. If drug resistance is suspected or documented, expert consultation is sought.

4. NAA testing should be performed on the first AFB-positive smear and on selected smear-negative specimens if the clinical suspicion of TB disease is high.

5. A CXR is obtained for all patients at 2 months. In culture-negative patients, a CXR is obtained at 4 months to document cure. All other patients receive a final CXR at the end of treatment (6 to 9 months) to document cure.

6. Monthly LFTs should be done in patients with the following risk factors: abnormal baseline LFTs; HIV infection; pre-existing liver disease (i.e., alcoholic hepatitis, cirrhosis); viral hepatitis (i.e., hepatitis B or C); history of chronic alcohol ingestion or intravenous drug use; pregnant or postpartum (up to 2 to 3 months after delivery); taking drugs that may be hepatotoxic or interact with TB treatment.

7. Comprehensive basic metabolic panel may include creatinine, LFTs, and uric acid. HgbA1c may be checked in patients who have diabetes.

8. During treatment with EMB and/or LZD, monitor visual acuity and color vision monthly.

Abbreviations Used: AFB=acid-fast bacilli; CBC=complete blood count; CNS=central nervous system; CXR=chest radiograph; DOT=directly observed therapy; DST=drug-susceptibility test; EMB=ethambutol; HIV=human immunodeficiency virus; INH=isoniazid; LFT=liver function test; LZD=linezolid; NAA=nucleic acid amplification; PZA=pyrazinamide; RIF=rifampin; TB=tuberculosis

- Medication side effects and adverse reactions, including:
  - Visual acuity testing and Ishihara's color vision testing for patients taking ethambutol (EMB)/ linezolid (LZD)
  - Hearing tests for patients receiving injectable agents
  - Observation of patient's sclera and nail beds for signs of jaundice

In addition to collecting and documenting the above, nurses engage the patient in a dialogue to ensure the patient has a clear understanding of their medications and next steps in their care. The nurse:

- Reviews patient's knowledge of medication and dosage, potential side effects, and adverse reactions; and instructs the patient about what to report to the physician and nurse
- Reviews the physician's plan of care with the patient
- Reinforces the need for adherence to treatment and follow-up visits
- Reviews any non-TB medications taken by the patient
- Ensures that all physician orders are followed
- Facilitates referrals for follow-up or coordination of care

MANAGEMENT OF ADVERSE REACTIONS

Anti-TB medications can cause a variety of adverse reactions including nausea, vision loss, fatigue, dermatitis, and hepatitis. The development of adverse reactions is influenced by both a specific drug or drug combination and individual patient health factors. In the event that an adverse reaction occurs that cannot be associated with a specific anti-TB medication, all anti-TB medications are discontinued and re-introduced gradually until the cause of the adverse reaction can be identified. If a patient is also taking non-TB medications, close communication with the patient's primary care provider is necessary to coordinate care. Adverse reactions associated with anti-TB medications are summarized in *Table 8.1: Common Adverse Reactions to First- and Second-Line Anti-Tuberculosis Medications*.

DERMATITIS

All first-line anti-TB agents can cause dermatitis (rash); however, the most common cause is PZA, followed by RIF or INH. RIF and the fluoroquinolones (FQNs) can also cause photosensitivity.

HISTORY AND EXAMINATION

When dermatitis occurs, the patient is asked about exposure to other medications or skin preparations, environmental contact, etc., that may be responsible for the reaction. In addition, the patient is examined for evidence of unrelated skin disease (e.g., scabies, contact dermatitis, childhood exanthema, etc.) to ensure they are not the cause.

TABLE 8.1: Common adverse reactions to first- and second-line anti-tuberculosis medications*

REACTION	SYMPTOMS AND SIGNS	USUAL DRUG(S) RESPONSIBLE
Audiovestibular manifestations	Hearing loss, vertigo, new-onset tinnitus	Injectable agents
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	FQNs, PZA, RIF
Dermatitis	Itching, rash, hives, fever, petechial rash	PZA, RIF, RPT, INH; rarely EMB, RBT, or injectable agents
Gastritis	Anorexia, nausea, vomiting, epigastric pain	RIF, RPT, PZA, RBT
Hematologic manifestations	Leucopenia, thrombocytopenia, anemia, eosinophilia	RIF, RBT, RPT, INH, LZD, CM
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	INH, RIF, RPT, PZA, ETA; rarely EMB and RBT
Hypothyroidism	Fatigue, weight gain, sluggish reflexes, depression	PAS, ETA
Joint, muscle, and tendon manifestations	Gout-like manifestations, systemic lupus erythematosus-like manifestations; tendinopathies	PZA, INH, FQNs, RIF
Neurological and psychiatric manifestations	Headaches, depression, agitation, suicidal ideation	INH, FQNs, CS
Peripheral neuropathy	Numbness or paresthesias of feet or hands	INH, LZD, FQNs
Renal manifestations	Hematuria, azotemia	injectable agents, RIF, RPT
Visual manifestations	Vision loss and color blindness, uveitis	EMB, RBT, LZD

*This is not a comprehensive list of adverse reactions. Please consult the drug's package insert, Physicians Desk Reference, or other reference pharmaceutical texts for more information.

Abbreviations Used: CM=capreomycin; CS=cycloserine; EMB=ethambutol; ETA=ethionamide; FQN=fluoroquinolone; LZD=linezolid; PAS=para-aminosalicylic acid; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; RPT=rifapentine

Patients with HIV infection have a variety of dermatologic diseases (which may be either directly or indirectly related to HIV infection or its treatment). Consultation with an appropriate infectious disease service or dermatology clinic may be required.

FOLLOW-UP

If the dermatologic reaction is severe and no other cause is found, anti-TB medications are discontinued promptly and the patient is examined at least weekly until the skin reaction disappears. Patients with a severe dermatologic reaction (e.g., exfoliative dermatitis), or with dermatitis associated with severe

systemic reactions are referred for hospital admission for treatment and the establishment of either a new anti-TB regimen or a re-challenge regimen, under daily surveillance as an inpatient.

If the drug reaction is mild, the patient is initially treated with antihistamines and topical steroids while continuing TB treatment. Clinical discretion is recommended on whether TB medications should be stopped.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

For patients managed at a NYC Health Department TB clinic, re-challenge is appropriate after the skin reaction clears or subsides. It may not be possible to identify the specific causative agent by the characteristics of the skin reaction. Thus, it is appropriate to first restart the two most important medications, RIF or INH, before next trying EMB and then PZA. PZA has been found to be a major cause of skin reactions; most reactions occur within the first four weeks of treatment.

Single daily doses of INH or RIF are given alone for three days with instructions to discontinue promptly if a reaction recurs. The patient is examined in three to four days and:

- If there is no reaction, an alternate drug (RIF or INH) is added with similar instructions. The patient is again reexamined in three to four days.
- If the skin reaction does not recur or if it is not severe, EMB (if this drug was part of the initial regimen) is added. If there is not a reaction to EMB, the regimen of INH, RIF, EMB can be continued and PZA discontinued on the presumption that this caused the skin reaction.

Treatment is continued with the original regimen minus the causative agent; however, the duration of treatment may need to be lengthened. For patients with HIV infection or patients who have extensive pulmonary or disseminated TB disease, a single new drug, such as a FQN, can be added to regimens that lack INH or RIF. FQNs themselves can cause phototoxicity. The new drug is continued for the duration of therapy. In such instances, the addition of a single agent to a successful regimen does not violate the rule of "do not add a single drug to a failing regimen."

The same principles of management apply to patients who experience dermatologic reactions while taking regimens for multidrug-resistant TB (MDR-TB).

HEPATITIS

Hepatotoxicity caused by anti-TB medications varies from asymptomatic increases in LFTs to liver failure. In addition, concurrent use of hepatotoxic non-TB medications or substances (e.g., alcohol) or chronic viral hepatitis increases the risk of developing drug-induced liver damage.

Certain drugs provoke various physiologic adaptive responses in the liver (i.e., INH), which may lead to asymptomatic transient elevations of alanine aminotransferase (ALT) (serum glutamate pyruvate transaminase [SGPT]) or induction of microsomal enzymes; these rarely lead to hepatic damage. However, certain toxins such as alcohol can interfere with the adaptive process and augment liver injury. Concurrent

use of other known hepatotoxic agents is avoided if possible during anti-TB treatment, especially in patients with underlying liver disease.

An increase in serum ALT is more specific for hepatocellular injury than an increase in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]), which can also signal abnormalities in muscle, heart, or kidney. Transaminases tend to be higher in men and in people with greater body mass index. Levels may vary as much as 45% on a single day, with the highest levels occurring in the afternoon. ALT and AST elevation may occur after exercise, hemolysis, or muscle injury.

There are two patterns of LFT abnormalities that may be seen during TB treatment: hepatocellular and cholestatic. A hepatocellular pattern is usually caused by INH or PZA; a cholestatic pattern is caused by RIF. See sections *Hepatocellular Pattern* and *Cholestatic Pattern* for more information. EMB rarely causes hepatitis.

HISTORY AND EXAMINATION

Individuals taking anti-TB medication who develop symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice, etc.) are instructed to discontinue all medications immediately and prompt evaluation by a provider is necessary. When seeing the patient, symptoms are reviewed, a directed examination is performed, and LFTs and a viral hepatitis screen are obtained. In some patients, RIF or PZA may cause gastritis with symptoms similar to those of hepatitis. If there is strong evidence that the symptoms are not related to hepatitis or anti-TB medications and the LFTs remain stable, the entire regimen may be reinstituted promptly, and the individual is followed closely for the recurrence of symptoms. (See *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

FOLLOW-UP

If symptoms disappear promptly and LFTs are normal, drug-induced hepatitis is unlikely. Another cause for symptoms is considered. Depending upon the nature, duration, and severity of symptoms, a decision about further diagnostic study is made.

If the LFTs are abnormal (AST or ALT is three times the upper limit of normal [ULN] with symptoms and five times ULN without symptoms) or if serum bilirubin is elevated, drug-related hepatitis is strongly suspected, and all anti-TB medication(s) are discontinued.

While holding medications, the patient is examined, repeat LFTs are obtained and symptoms are reviewed at least weekly. If symptoms persist for more than two weeks without anti-TB medication(s), or if LFTs continue to worsen, progressive drug-related hepatitis or an unrelated cause of hepatitis may be the cause. Depending upon the severity of the hepatitis, as indicated by clinical findings and LFTs, referral to a gastroenterologist or hospitalization may be necessary.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

The recommendations for restarting anti-TB medications in patients with drug-induced hepatitis are summarized in *Figure 8.2: Restarting Anti-Tuberculosis Medications in Patients with Drug-Induced Hepatitis*. In an outpatient setting, individual reintroduction of medications is no longer preferred, unless otherwise clinically indicated. BTBC providers usually start with two medications depending on presumed toxicity and add drugs sequentially based on clinical response. LFTS are monitored monthly throughout the course of treatment.

Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, RIF is usually implicated if the pattern is cholestatic (bilirubin and alkaline phosphatase [AP] elevated and out of proportion, with little or no changes in ALT/AST). In contrast, INH, RIF, or PZA may be the cause if the pattern is hepatocellular, with enzymes elevated and out of proportion to bilirubin or alkaline phosphatase.

In some cases, in order to avoid discontinuing a rifamycin in the treatment regimen, rifabutin (RBT) re-challenge may be acceptable with close follow-up of patients.

If the patient has extensive pulmonary, meningeal, or disseminated TB disease, has HIV infection, or is critically ill, the institution of a new regimen with a lesser potential for hepatotoxicity (e.g., injectable agent, EMB, FQN), also known as a "liver-sparing regimen," may be indicated even before liver enzymes return to normal.

For all other patients, anti-TB treatment is withheld until symptoms disappear and LFTs are normal, have declined to two times the upper limit of normal, or plateaued. In general, medications are reintroduced at their standard daily dosage. Patients should be examined weekly until LFTs have stabilized.

If hepatitis is caused by any of the drugs in the anti-TB regimen, INH is most likely responsible, followed by PZA, RIF, and EMB (in this order). A longer duration of therapy may be required if the causative agent was INH, RIF, or PZA during the intensive phase of treatment.

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration.

Depending on the drug that is presumed to be the cause of the hepatotoxicity, treatment may need to be extended. Individuals who cannot take INH and RIF are treated for 18 months. Similar principles of management apply to cases of hepatitis induced by "reserve drugs," as drugs are added depending on the isolate's susceptibility (e.g., PAS, ETA, and, rarely, FQNs).

Hepatocellular Pattern

Laboratory tests of patients with hepatocellular patterns are marked by isolated or predominant elevations of serum transaminases, specifically ALT and AST. If the pattern is hepatocellular, it is appropriate to re-challenge first with the agent(s) least likely to have been responsible after LFTs return to normal or decline and plateau. The patient is instructed to stop the medication immediately if symptoms of hepatitis

re-occur. The patient is examined weekly, with LFTs repeated at each visit. (See *Figure 8.2: Restarting Anti-Tuberculosis Medications in Patients with Drug-Induced Hepatitis*.)

There are two ways to re-challenge a patient who has a hepatocellular pattern in LFTs. The preferred way is to restart RIF/EMB for one week and repeat LFTs.

- If PZA is suspected to be the cause of the hepatitis:
  - INH is added for one week and LFTs are repeated
  - If LFTs are stable, patient is treated with INH, RIF, and EMB until susceptibilities are available (assume PZA-induced hepatitis)

Re-challenging with PZA may be hazardous in patients who tolerate the reintroduction of RIF and INH. In this circumstance, PZA may be permanently discontinued, with treatment extended to 9 months. Although PZA can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from PZA re-challenge when the initial hepatitis is moderate to severe.

- If INH is suspected to be the cause of the hepatitis:
  - PZA is added for one week and LFTs are repeated
  - If LFTs are stable, patient is treated with RIF, EMB, and PZA; a FQN may be added (assume INH-induced hepatitis)
- If INH and PZA are felt to be the cause of the hepatitis:
  - RIF, EMB, and a FQN may be given for six to nine months based on clinical judgment (and depending on the length of treatment with PZA)

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration. Whereas the treatment length of an INH, EMB, and PZA (or FQN) regimen is 18 months, successful introduction of RBT (which is less likely than RIF to cause hepatitis) permits treatment completion in six months. If RBT is introduced, LFTs are repeated after one week. If normal, RBT is continued and the patient is monitored weekly for the next several weeks, then monthly until treatment completion.

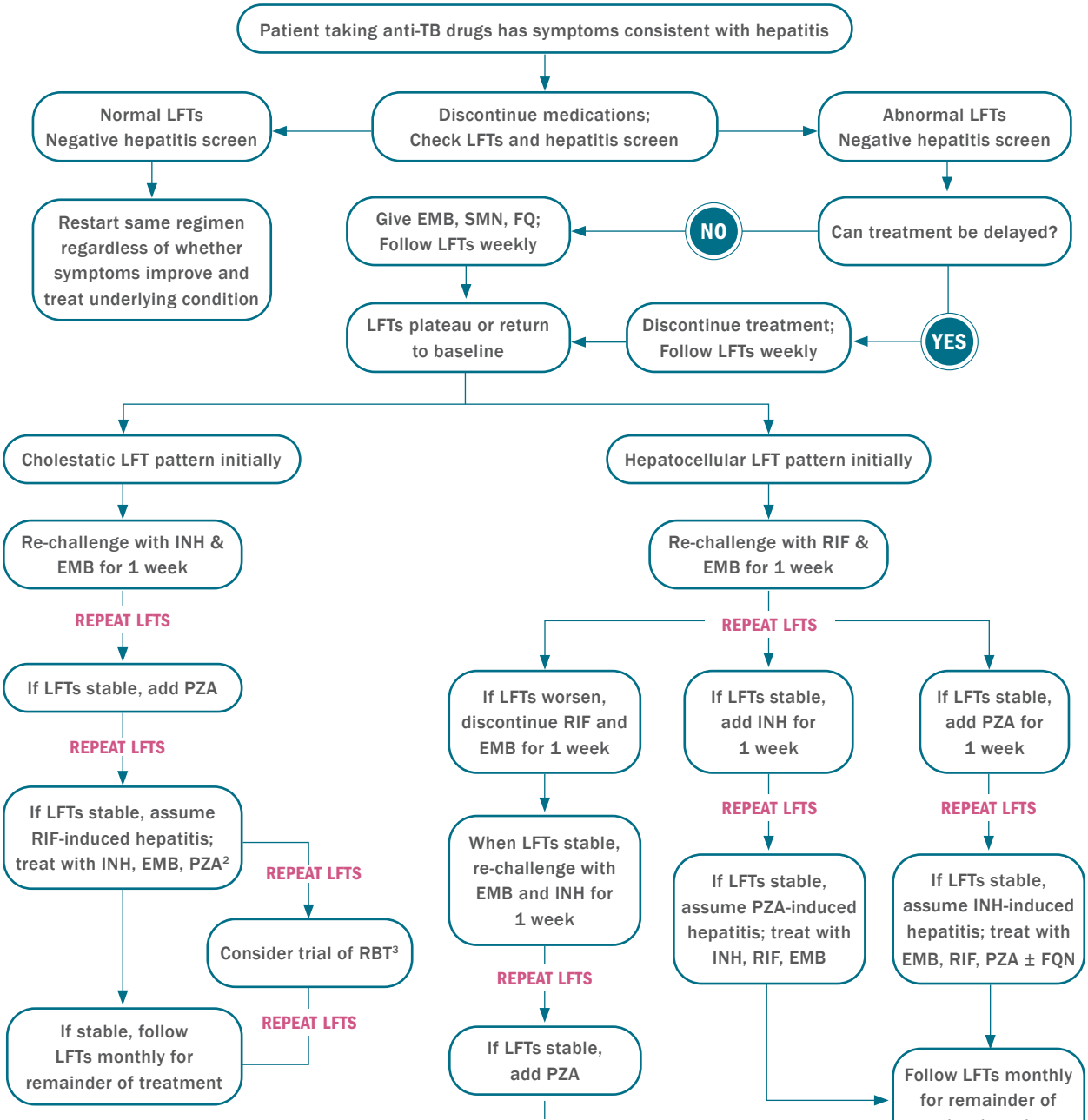
If a rifamycin cannot be used, an additional alternative is adding a FQN to a regimen of INH, EMB, and PZA.

LFTs are monitored monthly for the remainder of therapy.

Cholestatic Pattern

Although the specific cause of hepatitis cannot be identified by the pattern of LFT abnormality, RIF is usually implicated if the pattern is cholestatic (bilirubin and AP elevated and out of proportion, with little or no changes in ALT and AST levels).

FIGURE 8.2: Restarting anti-tuberculosis medications in patients with drug-induced hepatitis



1. Abnormal LFTs are > 3 times the upper limit of normal with symptoms or > 5 times the upper limit of normal without symptoms.
2. A FQN should be considered for the regimen. Treatment needs to last for 18 months unless RBT is added successfully.
3. There may be times when RBT is tried in an attempt to decrease duration of treatment from 18 months to 6-9 months.
4. Some clinicians may prefer to challenge with EMB and RIF sequentially rather than simultaneously.

Abbreviations Used: EMB=ethambutol; FQN=fluoroquinolone; INH=isoniazid; LFTs=liver function tests; PZA=pyrazinamide; RIF=rifampin; RBT=rifabutin; SM=streptomycin

If the initial pattern of hepatitis is cholestatic, the patient is re-challenged with INH and EMB for one week after LFTs return to normal or decline to two times the upper limit or normal, or plateau. LFTs are repeated; if stable and the patient is asymptomatic:

- PZA is added to the regimen for one week. LFTs are repeated.
- If LFTs remain stable, the patient is treated with INH, EMB, PZA (assume RIF-induced hepatitis). A FQN may be added.

The exclusion of a rifamycin mandates extension of treatment length. The substitution of RBT for RIF may be an option when RIF cannot be used in order to avoid an extended treatment duration. Whereas the treatment length of an INH, EMB, and PZA (or FQN) regimen is 18 months, successful introduction of RBT (which is less likely than RIF to cause hepatitis) permits treatment completion in six months. If RBT is introduced, LFTs are repeated after one week. If normal, RBT is continued and the patient is monitored weekly for the next several weeks, then monthly until treatment completion.

If a rifamycin cannot be used, an additional alternative is adding a FQN to a regimen of INH, EMB, and PZA.

LFTs are monitored monthly for the remainder of therapy.

GASTRITIS

Almost any medication can cause gastric irritation in susceptible individuals. Of the first-line anti-TB medications, RIF most often causes gastritis, although PZA is responsible in some instances. Because RIF is the most important member of combined chemotherapy, every effort is made to reintroduce this drug once gastric symptoms resolve. RBT may be substituted for RIF as it causes less gastritis.

HISTORY AND EXAMINATION

Because the symptoms of gastritis (anorexia, nausea, vomiting, and epigastric distress) may be due to drug-related hepatitis, LFTs are obtained for all individuals who present with such symptoms.

FOLLOW-UP

Anti-TB medications are discontinued in symptomatic patients. If LFTs are normal or unchanged from baseline and symptoms persist for four to five days without medication, unrelated gastrointestinal (GI) disease (e.g., peptic ulcer disease, gastritis due to another cause, etc.) is suspected and the patient is referred for appropriate diagnostic study.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

After symptoms subside, medications are reintroduced in a step-wise process. Despite the fact that most gastritis is caused by INH and RIF, they are the two most important medications in an effective TB

treatment regimen. RIF and EMB are restarted for one week. If tolerated, INH is added to the regimen. If INH is well-tolerated, PZA is assumed to be the cause. The treatment duration is extended according to the final regimen successfully reintroduced.

When reintroducing RIF, more success may occur by modifying the pattern of administration. RIF is either administered before bedtime, or the patient is instructed to eat a small meal before taking the medication. If RIF is identified as a cause of gastritis, RBT can be considered as an alternative.

Although antacids may help to alleviate the symptoms of gastritis, they may also interfere with the absorption of INH and FQNs. If used, the patient is instructed to take antacids two hours after taking either INH or a FQN; prolonged use of antacids is avoided. Alternatives to antacids are an H2-blocker or a proton pump inhibitor. However, if these are used and the patient is taking PAS granules, the patient is instructed to take PAS with acidic foods such as yogurt, applesauce, or orange juice, rather than with neutral foods such as milk, because PAS needs to be absorbed in an acidic environment.

If gastritis is caused by PZA, it can be omitted from the regimen with less risk than omitting RIF. If the patient has TB susceptible to INH and RIF, these two medications can be used for a total of nine months.

PERIPHERAL NEUROPATHY

INH may cause peripheral neuropathy, especially in individuals with a predisposing cause, such as alcoholism, diabetes, HIV infection, or malnutrition. Pyridoxine usually, but not invariably, prevents the emergence of INH-induced peripheral neuropathy. Linezolid (LZD) can also cause an irreversible peripheral neuropathy. If symptoms of peripheral neuropathy arise while the patient is taking these drugs, they are discontinued and replaced with an appropriate regimen. Rarely, EMB, and also the FQNs, can be a cause of peripheral neuropathy.

HISTORY AND EXAMINATION

INH is assumed to be the primary cause for paresthesias and numbness of the feet and hands (with or without peripheral motor weakness) in INH-treated patients, even if other predisposing causes are present.

FOLLOW-UP

INH is discontinued in patients with peripheral neuropathy and pyridoxine (25 mg per day) is given (or continued) until symptoms abate. The neuropathy usually subsides over weeks to months, when it is diagnosed early and INH is promptly discontinued. However, neurologic injury may be irreversible if diagnosis is delayed and manifestations become severe; neurologic consultation is obtained if the diagnosis is not clear. In patients with LZD-induced peripheral neuropathy, LZD is discontinued. LZD is reintroduced into the regimen only if symptoms of peripheral neuropathy have resolved and no other reasonable alternatives for the regimen are available.

JOINT MANIFESTATIONS

INH (and rarely, RIF) can induce active systemic lupus erythematosus (SLE), especially in patients with sub-clinical disease. The patient may have only arthralgias or alopecia, or may present with a full-blown pattern of SLE, with arthritis and other systemic manifestations. If INH-induced SLE is suspected, INH is discontinued, and these patients are referred to an appropriate provider. Blood tests should be sent for antinuclear antibodies, anti-double stranded DNA antibody, and anti-histone antibody. Anti-histone antibody, which is usually found in drug-induced lupus, can also be found in SLE; however, it is not specific enough to SLE to make the diagnosis.

PZA invariably causes an asymptomatic increase of serum uric acid because it impairs renal excretion of uric acid; this finding can be used as a measure of PZA adherence. Patients with asymptomatic elevations of uric acid are not treated; however, patients with a history of gout are at increased risk for PZA-related gout attacks. PZA is discontinued in patients with a gouty attack. Allopurinol can lower the baseline serum uric acid level, but not elevations due to PZA.

Hyperuricemia without symptoms of gout is not a reason for discontinuing PZA.

RENAL MANIFESTATIONS

With first line drugs, acute kidney injury (AKI) is a rare and severe complication that can interrupt treatment and cause permanent kidney damage. Although INH and EMB have rarely been associated with AKI, RIF is the most common first-line drug responsible for AKI. RIF can cause acute or chronic nephritis (with or without symptoms), evidenced by proteinuria, hematuria, and sterile pyuria. Renal injury in patients treated for TB disease can also occur due to injectable agents. Acute or chronic renal failure can also occur. The blood levels of EMB, cycloserine (CS), and injectable agents may become markedly elevated in patients with renal function impairment. PZA is metabolized by the liver, but its metabolites may accumulate in patients with renal insufficiency. Potassium and magnesium losing nephropathy is common with the injectable agents, particularly capreomycin (CM), and can usually be managed with oral supplements.

HISTORY AND EXAMINATION

Blood urea nitrogen, serum creatinine, and electrolytes, including magnesium, are monitored serially in patients with underlying renal disease who are receiving EMB, CS, or injectable agents. Urinalysis can be obtained when clinically indicated. Similar studies are done promptly in any patient who has symptoms consistent with acute or chronic nephritis.

FOLLOW-UP

For information on treatment and follow-up in patients with chronic renal failure, see *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.

HEMATOLOGIC MANIFESTATIONS

All first-line anti-TB agents can, in rare cases, lead to hematologic abnormalities. Leukopenia can be caused by RIF (most commonly), INH, PZA, and, rarely, EMB. RIF is the most common cause of thrombocytopenia, although the other first-line drugs may depress platelets as well. A "flu-like syndrome" has been reported with all rifamycins, especially when used intermittently; it consists of an acute episode with fever, chills, and muscle pain that may be associated with severe anemia, thrombocytopenia, and leukopenia. Hemolytic syndromes and other types of anemia rarely occur. Eosinophilia can be seen with CM. LZD can cause pancytopenia and a hemolytic anemia. (See *Figure 8.1: Evaluation and Monitoring Timeline for Tuberculosis Patients with Drug-Susceptible TB Disease* and *Appendix H: Dosages, Adverse Reactions, and Monitoring for Additional Medications Used to Treat Tuberculosis*.)

EXAMINATION AND FOLLOW-UP

If a patient taking anti-TB drugs develops symptoms, signs, or laboratory evidence of significant anemia, leukopenia, or thrombocytopenia that cannot otherwise be explained, all anti-TB drugs are discontinued. The patient is promptly referred to a hematologist for consultation. Blood counts are allowed to recover with sequential reinstitution of the TB medications least likely to have caused the hematologic abnormality.

Each medication is reintroduced gradually (within three to four days) based on clinical judgment, with close follow-up of the CBC and differential. If the medication is absolutely necessary for the patient's regimen and the patient does not have evidence of hemolysis, growth factors to increase blood counts, if available, may be used in consultation with a hematologist. In the case of RIF-induced thrombocytopenia and leukopenia, RBT may be tried while following CBC every one to two weeks.

VISUAL MANIFESTATIONS

Visual adverse effects are a concern with EMB, RBT, and LZD. Both EMB and LZD can cause optic neuritis. Routine vision screenings (visual acuity and color vision) are recommended when patients are on regimens containing either EMB or LZD. Toxic levels of RBT are associated with an increased risk of uveitis that is manifested by visual disturbances.

Elevated serum levels of EMB are associated with the risk of optic neuritis; however, this condition usually resolves completely when EMB is discontinued. When diagnosed late, optic neuritis may progress to severe visual loss. As EMB is cleared largely by renal excretion, individuals with impaired renal function, especially the elderly, are most susceptible, as are adult patients who receive doses of EMB greater than 15 mg/kilogram (kg) body weight per day.

HISTORY AND EXAMINATION

The usual symptoms of optic neuritis are loss of visual acuity for small objects (newsprint, sewing, etc.) and/or impairment of red-green color discrimination.

All patients started on EMB and LZD have baseline visual acuity and red-green color discrimination established at the initiation of therapy.

All patients at risk for renal disease have serum blood urea nitrogen and creatinine tested before treatment with EMB. EMB is used with caution and frequent monitoring of vision and renal function in patients with:

- Renal function abnormalities
- Risk for renal function abnormalities (e.g., elderly patients and patients with diabetes or hypertension)
- Patients with pre-existing, non-correctable loss of vision

Patients are asked about visual changes, and serial tests of visual acuity and color vision are performed to detect early signs of optic neuritis at each follow-up visit.

If the patient already has red-green colorblindness at baseline and the use of EMB is necessary, the patient is referred for specialized ophthalmologic evaluation to assess the degree of colorblindness; treatment decisions are made in conjunction with the ophthalmologist.

FOLLOW-UP

EMB is discontinued immediately if optic neuritis is suspected; the patient is referred for ophthalmology consultation if the visual impairment does not reverse promptly. In some patients, visual impairment due to EMB may take months to resolve.

Patients on LZD also receive monthly vision testing. LZD is discontinued immediately if optic neuritis is suspected; the patient is referred to a specialist if the optic neuritis does not reverse promptly.

AUDIOVESTIBULAR MANIFESTATIONS

HISTORY AND EXAMINATION

Patients receiving an injectable agent have a baseline audiogram and a follow-up audiogram every month. An audiogram is repeated promptly if hearing loss is suspected.

At each monthly examination, patients receiving an injectable agent are asked about changes in hearing, tinnitus, or dizziness.

FOLLOW-UP

The injectable agent is discontinued if hearing loss, vertigo, or new-onset tinnitus occurs. An ear examination is conducted to exclude other sources of these symptoms, such as cerumen or otitis media. An audiogram is performed, and the results are compared with the baseline in order to detect hearing loss. If symptoms or any other evidence of hearing loss is suspected to be unrelated to the injectable agent, the patient is referred to an appropriate provider for consultation.

RESTARTING ANTI-TUBERCULOSIS MEDICATIONS

If significant hearing loss, new-onset tinnitus, or vertigo is demonstrated and any of these reactions cannot be explained otherwise, the injectable agent is eliminated from the regimen.

QTc PROLONGATION

Several drugs used in the treatment of TB can cause QTc prolongation. These include FQNs, clofazimine (CFZ), delamanid (DLM), and bedaquiline (BDQ). Levofloxacin (LFX) prolongs the QTc interval less than moxifloxacin (MFX). With respect to QTc prolongation, BDQ is the most concerning. Patients receiving BDQ should receive an electrocardiogram (EKG) at baseline, and at minimum at two, 12, and 24 weeks of treatment. BDQ is discontinued if the QTc is greater than 500 milliseconds, as the most common ventricular arrhythmias such as torsade de pointes have been associated with this value. (See *Chapter 6: Treatment of Drug-Resistant Tuberculosis in Adults*.)

DRUG DESENSITIZATION

Drug desensitization following a severe adverse reaction has been tried with most of the first-line agents with varying degrees of success. RIF has been the drug most commonly tried. Desensitization is done in a manner similar to penicillin desensitization, with incrementally increasing amounts of RIF given to the patient until a full dose is tolerated. This is only done in a highly monitored setting, such as the intensive care unit.

PARADOXICAL REACTIONS/IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Paradoxical response, commonly known as immune reconstitution inflammatory syndrome (IRIS), is defined as the clinical or radiological worsening of pre-existing TB lesions or the development of new lesions after initial clinical improvement on effective anti-TB therapy.

Although IRIS may occur at any time during treatment, it usually occurs within weeks of beginning treatment (especially after initiation of antiretroviral therapy [ART]). Although IRIS occurs more commonly in patients with concomitant HIV, IRIS can also occur in patients without HIV.

ETIOLOGY

The etiology of IRIS may be related to reversal of the immunosuppression caused by TB disease once anti-TB therapy has been initiated. The rapid killing of bacilli may cause increased cytokine release, which subsequently causes a severe inflammatory response.

DIAGNOSIS

The paradoxical response occurs most commonly at the initial site of disease. When the paradoxical response occurs in another anatomical site, it frequently involves the central nervous system (CNS). Other

sites of disease include pulmonary, pleural, lymph node, abdominal, and osteoarticular. The diagnosis may only be made after secondary infection, non-adherence with therapy, drug resistance, and adverse effects to medication have been excluded.

TREATMENT

The use of corticosteroids may be considered in the case of prolonged or severe paradoxical reactions. There is not a consensus on the preferred dosage of steroids; however, many experts recommend prednisone (or a prednisone equivalent) be prescribed at 1 mg/kilogram (kg) per day, usually up to 60 mg/day, gradually tapered over several weeks. Some experts prescribe up to 80 mg/kg/day based on clinical judgment. Recurrence with tapering is not common.

- Surgical drainage is considered in the case of tense, painful lymphadenopathy with impending sinus tract formation. Any drainage is sent for AFB smear and culture
- The anti-TB regimen rarely needs to be changed once the diagnosis of paradoxical reaction has been established

REPORTING ADVERSE EVENTS

All severe or life-threatening adverse reactions to medications in patients followed in an NYC Health Department TB clinic must be reported on the Health Department Reportable Occurrences Form. A severe or life-threatening adverse reaction is any Grade 3 or 4 adverse event that leads to temporary or permanent discontinuation of a drug. Below are general definitions of grades of toxicity.

The reportable occurrence form is completed and the patient is followed until the adverse reaction is resolved or until transfer to another medical provider or facility has been confirmed.

TABLE 8.2: Grades of toxicity

GRADE	DESCRIPTION
GRADE 1 (Mild)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required
GRADE 2 (Moderate)	Mild to moderate limitation in activity — some assistance may be needed; no or minimal medical intervention or therapy required
GRADE 3 (Severe)	Marked limitation in activity, some assistance usually required; medical intervention or therapy required, hospitalization possible
GRADE 4 (Life-threatening)	Extreme limitation in activity, significant assistance required; significant medical intervention or therapy required, hospitalization or hospice care probable

BTBC providers must complete a New York City Health Department REPORTABLE OCCURRENCES FORM online for any severe or life-threatening adverse events (e.g., liver injury, anaphylaxis, seizure, or severe dermatitis) leading to hospitalization or death of a patient receiving TB treatment. Forms can be found at https://airs.health.dohmh.nycnet/IntelexLogin/Intelex.

RE-CLASSIFICATION OF PATIENTS BEING EVALUATED FOR TUBERCULOSIS DISEASE

For programmatic purposes, all patients are assigned a TB classification based on the International Classification of TB. (See *Appendix B: Tuberculosis Risk Assessment Tool*.) All patients initially classified as TB Class V, currently being evaluated for active TB disease, are reclassified to the appropriate TB class within four months of the initiation of evaluation.

For example:

- Patients initially classified as TB Class V are reclassified as TB Class III if they have a positive *M. tuberculosis* culture.
- Patients initially classified as TB Class V who do not produce a positive culture for *M. tuberculosis* are re-classified as TB Class III if they are on treatment and improve in a time-course consistent with TB:
  - Resolution of TB symptoms on TB treatment (e.g., cough, fever, sweats, weight loss, chest pains)
  - Improvement of CXR (e.g., improvement or resolution of infiltrates, cavities, and effusions) or in findings of extrapulmonary sites of disease when extrapulmonary TB is present
- Patients initially classified as TB Class V (high or low) who are found to have a negative culture for *M. tuberculosis* are reclassified as TB Class IV if their CXR is stable after two and four months of treatment, and is consistent with "old TB disease." A positive test for TB strengthens this diagnosis. A non-TB diagnosis is also considered.

CASE-CLOSING AND END-OF-TREATMENT EVALUATION

›› At the end of treatment for pulmonary TB disease, a sputum culture and a CXR is obtained.

›› A notation is made in the EMR that the patient has completed treatment and this disposition is also entered into Maven.

›› All patients who complete treatment, except those requiring post-treatment evaluation (see below), are discharged from the clinic.

›› Each patient is given a document stating that they have completed a course of treatment for TB disease.

POST-TREATMENT EVALUATION

The risk of relapse is low in patients with TB susceptible to INH, RIF, and PZA who complete an optimal treatment regimen. Post-treatment evaluation of these patients is rarely productive and is not cost-effective. These patients are advised to return to the NYC Health Department TB clinic for re-evaluation if, in the future, they develop symptoms suggestive of active pulmonary TB disease (e.g., fever, night sweats, weight loss, malaise, or prolonged cough greater than two weeks with or without sputum).

Post-treatment evaluation is also not required for most patients who:

- Have *M. tuberculosis* isolates resistant or intolerant to INH only but susceptible to RIF, PZA, and EMB
- Have completed six months of treatment with all three medications, with or without a FQN

Patients with TB resistant to INH and RIF and patients not treated with a rifamycin-containing regimen because of adverse reaction are at greater risk for post-treatment relapse. Patients are scheduled for surveillance follow-up after completing treatment. The post-treatment follow-up schedule is: four, eight, 12, 18, and 24 months. At each visit:

- A medical history review is conducted to assess symptoms of active TB
- A CXR is obtained for comparison to the CXR obtained at the end of therapy
- A single sputum specimen is obtained for smear and culture

Patients with any positive result for TB are contacted for additional follow-up. If the smear is positive for AFB, three additional sputa specimens are collected.

›› If any specimen is culture-positive for *M. tuberculosis*, the patient is contacted immediately for a complete clinical re-evaluation and the reinstitution of appropriate therapy.

Additional follow-up evaluation is also based on clinical judgment.

MONITORING SERUM DRUG LEVELS

Therapeutic drug monitoring should be done when there is a clear indication for it. New York State (NYS) Clinical Laboratory Evaluation Program approval must be obtained. Routine monitoring of anti-TB drug levels is not recommended in clinical practice. The significance of low serum levels of anti-TB drugs in relation to clinical response has not been demonstrated. Studies have shown that as many as 60% of TB patients had low serum levels of INH or RIF. However, the clinical response to TB therapy did not differ in those with low drug levels when compared to those with normal levels. (See *Appendix K: Procedures for Therapeutic Drug Monitoring*.)

Monitoring serum drug levels can be used in patients with the following medical conditions:

- HIV infection
- Diabetes

- Malabsorption syndromes
- Renal failure
- Failure to improve on treatment/relapse
- MDR-TB
- Suspected non-adherence

LATE COMPLICATIONS OF TREATED PULMONARY TUBERCULOSIS DISEASE

Some patients who have been successfully treated for pulmonary TB disease in the past develop symptoms or have abnormalities on a CXR that raise the possibility of a recurrence of active TB disease. However, other late complications are considered in the differential diagnosis for such patients.

BRONCHIECTASIS AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Bronchiectasis is a well-recognized sequela of pulmonary tuberculosis. Globally, TB is one of the leading causes of bronchiectasis. Bronchiectasis is characterized by irreversible dilatation of bronchi with destruction of elastic and muscular elements of bronchial walls. These changes can lead to recurrent infections and shortness of breath.

Pulmonary TB is also recognized as a cause of chronic airway obstruction. Parenchymal lung destruction can affect pulmonary compliance, resulting in peripheral airway collapse and air trapping. Patients develop cough, wheezing, and breathlessness. Obstructive lung disease can develop during therapy or even after successful therapy.

HEMOPTYSIS

Bleeding from ruptured bronchial veins. Some individuals with fibrotic residuals of pulmonary TB, such as contracted lobes or segments, residual "open healed" cavities, or localized fibrosis, develop hemoptysis due to bleeding from the old, inactive post-tuberculous lesion. In most cases, the origin of the blood is a ruptured bronchial vein that occurs in rich plexuses in the endobronchial mucosa in such lesions. Hemoptysis often begins during an acute viral respiratory infection. It is usually self-limited, but may be so severe as to require emergency surgical resection.

This cause of hemoptysis can be diagnosed only by ruling out the other causes outlined here, as well as active TB (by obtaining multiple sputum cultures). If sputum cultures are negative, and no other criteria prove active TB, patients with hemoptysis should not be re-treated for active TB.

Mycetoma. Healed TB cavities can be colonized by fungi, usually *Aspergillis* species, and evolve into a mass of matted mycelia — a movable, intracavitary "fungus ball." This process is accompanied by the development of vascular granulation tissue in the internal wall of the cavity, which appears on serial

CXRs as a progressive thickening of the cavity wall. In some cases, this thickening is evident even before a mycetoma can be visualized. The granulation tissue is the site of bleeding in some individuals with *Aspergillis*-colonized cavities, usually with mycetoma. Some patients experience massive hemoptysis and require an emergency surgical resection of involved tissue or radiological intervention. Others experience chronic or recurrent hemoptysis of lesser amounts.

The diagnosis can be suspected on the basis of characteristic radiological signs, cultural isolation of *Aspergillis* from sputum, and the presence of serum antibodies, usually against *Aspergillis fumigatus*.

Other causes of hemoptysis. Many conditions unrelated to TB may lead to hemoptysis in patients who were treated for TB in the past. Among these are pneumonia, pulmonary emboli, bronchiectasis, lung abscess, and tumors.

Patients with hemoptysis may need further evaluation such as computed tomography (CT) scan of the chest, and pulmonary/surgical consultation.

CHEST PAIN

Some patients with successfully treated tuberculous pleural effusions experience chest pain over a period of months or years. Some describe pleuritic pain; others, chronic aching or a burning sensation. Often the cause is not clear. Unless there is a demonstrable recurrence of a pleural effusion on the CXR, treatment for active TB is not indicated. Infrequently, chest pain may be due to a spontaneous pneumothorax caused by the rupture of a bleb, which can evolve in an area of pulmonary scarring related to TB.

DYSPNEA

Patients with extensive pulmonary or pleural fibrosis due to healed TB may experience exertional dyspnea. Pulmonary function tests demonstrate a restrictive defect. Except for this cause, the development of dyspnea after successful therapy for TB usually reflects the presence of another, unrelated cause (e.g., chronic obstructive pulmonary disease, asthma, heart disease, and anemia).

RECURRENCE OF COUGH, SPUTUM, FEVER OR WEIGHT LOSS

Such symptoms are nonspecific and may occur from a wide variety of respiratory diseases other than TB. Among these are viral, mycoplasmal, bacterial, fungal, and other respiratory infections; exacerbations of bronchiectasis or chronic bronchitis; and tumors. In such cases, the reinstitution of anti-TB treatment is not indicated unless cultures are positive for *Mycobacterium tuberculosis* or the CXR suggests recurrent TB.

CLUBBED FINGERS

Clubbed fingers may be found in individuals with very advanced pulmonary TB and chronic respiratory insufficiency. However, if a patient who has been previously treated for pulmonary TB subsequently

develops clubbed fingers, another cause—especially a tumor—should be strongly suspected, even if the CXR has not changed.

CHANGES IN THE APPEARANCE OF THE CHEST RADIOGRAPH

In an individual who has been treated for TB, these changes may reflect a recurrence of active TB, even in the absence of symptoms. However, they could be due to completely different causes, including the following:

- **Mycetoma.** A mycetoma is usually characterized by a thickening of the cavity wall or the presence of an intracavitary mass, often manifesting a "crescent" sign.
- **Endobronchial lesions.** Endobronchial lesions that obstruct lobar or segmental bronchi usually lead to an airless, "collapsed" lobe or segment or to chronic organizing pneumonia in the parenchyma distal to the obstruction. Such lobar or segmental lesions should be suspected to be due to a tumor, malignant or benign, or to a foreign body. Appropriate diagnostic investigation should be undertaken.
- **Fluid level in an emphysematous bleb.** Although "open healed" TB cavities are rarely secondarily infected or the site of fluid levels, emphysematous bullae in the area of healed TB may develop fluid levels, especially after lower respiratory infections. These rarely represent reactivated TB.
- **Pleural effusion.** Recurrent TB infection may present as a pleural effusion in a previously treated patient, but many nontuberculous causes must be considered as well. Among these are pneumonia, pulmonary emboli, trauma, tumor, pleurodynia, connective tissue disease, and others.

SUMMARY

Monthly evaluation with periodic ancillary testing as indicated ensures the treatment team promptly detects potential relapse, clinically worsening disease, adherence problems, and medication-related adverse reactions. Together, this coordinated approach to clinical monitoring during TB treatment increases the likelihood of optimal patient outcomes.

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CHAPTER 9: TUBERCULOSIS REPORTING AND SURVEILLANCE

INTRODUCTION

Tuberculosis (TB) has been a reportable condition in New York City (NYC) since 1897; reporting requirements are based on mandates defined by the NYC Health Department. (See *Chapter 17: Laws Governing Tuberculosis in New York City*.) Healthcare providers and laboratories are required to report individuals with confirmed TB disease, those with signs and symptoms consistent with TB, and children younger than five with latent TB infection (LTBI) to the NYC Health Department. Reporting of individuals from multiple sources increases the likelihood that TB cases will be reported in a timely manner. Additionally, universal TB reporting facilitates rapid case identification and case management activities and enables the Bureau of TB Control (BTBC) to: ensure prompt initiation and completion of TB treatment, monitor epidemiologic trends, detect and respond to TB outbreaks, identify high-risk groups, and identify data quality and reporting issues.

TUBERCULOSIS REPORTING

The following sections summarize programmatic implications of the NYC Health Code related to surveillance and case management. See Chapter 17 for a more detailed description of the Health Code.

The NYC Health Code mandates that persons with any of the following criteria or laboratory reports indicating the following are reported to BTBC by healthcare providers and/or laboratories:

- Positive acid-fast bacilli (AFB) smear from any anatomic site
- Positive nucleic acid amplification (NAA) test result for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex
- Positive culture for *M. tuberculosis* complex
- Biopsy, pathology, or autopsy findings consistent with active TB disease
- Clinical suspicion of pulmonary or extrapulmonary TB disease such that the physician or other healthcare provider has initiated or intends to initiate:
  - Airborne infection isolation
  - Treatment for TB disease with two or more anti-TB medications
- Children younger than five with a positive test for TB infection

PROVIDER REPORTING REQUIREMENTS

Healthcare providers, infection control practitioners, and/or administrators of hospitals or other institutions providing care and treatment to patients are required to report all individuals with confirmed TB disease or signs and symptoms consistent with TB disease within 24 hours of diagnosis or clinical suspicion. Individuals should be reported whenever TB is a potential diagnosis, even if bacteriologic evidence of disease is lacking or treatment has not been initiated.

When an individual has an AFB-positive smear or has started treatment for TB disease, reporting should occur immediately. Medical providers must report individuals even though laboratories are also required to report findings consistent with active TB disease. All submitted reports must be timely, accurate, and detailed to ensure that BTBC can appropriately follow up with patients. When requested, providers must also report results for TB infection tests (tuberculin skin test [TST] and interferon gamma release assay [IGRA]), chest radiographs (CXR), other imaging findings, evaluation results, and treatment outcomes of individuals who have been identified as a contact to an infectious TB patient.

In addition to reporting individuals with suspected or confirmed TB disease, the NYC Health Code requires providers to report any child younger than five years of age (up to the day of their fifth birthday) with a positive TB infection test result. For such children, providers must also report qualitative and quantitative TB infection test results (including induration [in millimeters (mm)] for TST), radiography results (CXR, computed tomography [CT], and magnetic resonance imaging [MRI]), as well as any LTBI treatment initiated for these children.

The following essential information must be included when a report is submitted:

- Information needed to identify and locate the individual (e.g., name, date of birth, address, telephone, email address)
- Provider information (e.g., physician's name, reporting facility/practice's address, telephone number, fax number, email address)
- Microbiology and/or pathology test results related to the TB diagnosis (including date specimen obtained, specimen source, and accession number)
- Results of CXRs and other imaging studies obtained to evaluate any TB site of disease including date performed
- Results of tests for TB infection (e.g., IGRA or TST) including date performed
- TB treatment information including date initiated, medications, and dosages
- Airborne infection isolation status

Healthcare providers should report individuals electronically using the electronic UNIVERSAL REPORTING FORM (URF), which is available through Disease Reporting Central at: https://a816-healthpsi.nyc.gov/NYCMED/Account/Login. Information reported on the URF should be as complete as possible. If providers are unable to report electronically, paper reports can be faxed to (844) 713-0557. (See ***Appendix Q: New York City Health Department Universal Reporting Form***.)

MICROBIOLOGY AND PATHOLOGY LABORATORY REPORTING REQUIREMENTS

Microbiology and pathology laboratories are required to report all confirmed TB cases and all laboratory results consistent with TB disease. Microbiology laboratories are required to report via the New York State (NYS) Electronic Clinical Laboratory Reporting System (ECLRS). The following test results must be reported to BTBC within 24 hours of the observed result:

- AFB-positive smears (regardless of anatomic site)
- Cultures positive for *M. tuberculosis* complex
- NAA test results that identify *M. tuberculosis* complex including: *M. tuberculosis*, *M. africanum*, *M. bovis*-bacille Calmette-Guérin (BCG), *M. caprae*, *M. canettii*, *M. microti*, *M. pinnipedii*, *M. bovis*, *M. dassie*, *M. mungi*, and *M. orygis*
- Results of drug-susceptibility tests (DSTs) performed on *M. tuberculosis* complex cultures
- Biopsy, pathology, or autopsy findings consistent with active TB disease, such as: caseating necrosis or caseating granulomas, or presence of AFB in biopsy of lung, lymph nodes, or other specimens
- Any culture or NAA result associated with an AFB-positive smear (even if negative for *M. tuberculosis* complex)

- Any AFB smear, NAA, or culture result obtained on a specimen collected within 12 months of the date a specimen was collected that had an NAA or culture result that was positive for *M. tuberculosis* complex

INTERJURISDICTIONAL NOTIFICATION

Interjurisdictional notification is a process used when TB patients are reported to a jurisdiction where they do not reside. BTBC coordinates with health departments in other jurisdictions to ensure continuity of care for TB patients working or living outside of NYC. When a non-NYC resident is identified as a TB patient and is reported to BTBC, their reporting data is sent to the public health officials of that jurisdiction. For individuals residing in other parts of the United States (U.S.), data are sent to state public health departments. Residents of other countries are typically reported to the national ministry of health. NYC residents initially reported to other local U.S. jurisdictions are in turn reported to BTBC. This bi-directional flow of data ensures that the local health departments are fully informed about the TB status and treatment of their residents and have enough data to initiate case management, contact investigation, and other applicable follow-up in their jurisdiction when warranted.

BTBC uses the INTERJURISDICTIONAL TUBERCULOSIS NOTIFICATION FORM to share and receive information about patients moving out of or into NYC from another jurisdiction. The form can be found at: http://www.tbcontrollers.org/resources/interjurisdictional-transfers/

CureTB is a referral program focused on preventing TB among persons who travel internationally. It links people to TB care by collaborating with ministries or other health authorities in the United States and countries of destination. This is a collaboration between the CDC's Division of Global Migration and Quarantine (DGMQ) and the County of San Diego's TB Control Program. Information on CureTB can be found at: www.cdc.gov/usmexicohealth/curetb.html

DISCHARGE PLANNING AND CASE MANAGEMENT FOLLOW-UP

DISCHARGE PLANNING

Hospitals in NYC are required to confer with BTBC prior to discharging an infectious TB patient from inpatient care. The NYC Health Code mandates that healthcare providers submit discharge plans for approval 72 hours prior to discharging any sputum or respiratory AFB smear-positive patients. Patients with AFB-positive smears for sputum or respiratory specimens (including those who are asymptomatic) who are not suspected of having multidrug-resistant TB (MDR-TB) and who are well enough to be discharged from the hospital may be discharged if they meet select criteria. (See *Chapter 13: Infection Control*.) This requirement helps ensure that patients are eligible for discharge, and that BTBC staff have adequate time to follow up with patients, initiate specific home isolation services, and schedule follow-up clinic appointments as needed.

TREATMENT PLAN

When a patient elects to receive TB care from a community provider instead of at a NYC Health Department TB clinic, the treating physician is required to report the patient's initial and monthly treatment plans to BTBC. Submission of an initial treatment plan allows BTBC the opportunity to offer guidance on the most appropriate treatment regimen for a patient, while the submission of subsequent monthly plans helps ensure that the patient is being seen regularly by a provider and enables BTBC staff to follow up on any potential changes to the treatment regimen. Monthly updates are submitted via the Report of Patient Services (RPS) form, which treating providers fill out and return to NYC Health Department staff. Providers also notify the NYC Health Department whenever treatment is discontinued (e.g., when the provider determines that the patient does not have TB, when treatment was completed, or for any other reason). (See *Chapter 10: Case Management for Patients with Tuberculosis*.)

SURVEILLANCE

All submitted reports are reviewed for completeness, timeliness, and accuracy to determine whether patients are eligible for case management. Mandatory reporting ensures that cases of TB disease are not missed in the community, and that individuals with suspected and confirmed TB receive appropriate diagnosis, treatment, and care.

BTBC staff collect, document, and analyze patient information systematically, and use this data to inform case management activities, ensure TB treatment completion, monitor epidemiologic trends, prepare surveillance reports, submit line-level data to the NYS Department of Health (NYS DOH) and Centers for Disease Control and Prevention (CDC), and identify data quality and reporting issues.

ELECTRONIC TUBERCULOSIS REGISTRY AND CASE MANAGEMENT SYSTEM

BTBC utilizes and maintains Maven (Conduent Inc., Florham Park, NJ), an electronic registry and case management system that serves as the central data repository for all public health activities conducted by the Bureau. This system houses demographic, clinical, and risk factor data, as well as information collected as part of case management activities for all individuals reportable to BTBC. Custom built tools within Maven, such as reports, workflows, and forms, are tailored to the specific needs of the Bureau and assist with all levels of programmatic activities. Data extracted from Maven are used to monitor epidemiologic trends, detect and respond to TB outbreaks, prepare surveillance reports, report aggregated data to the NYS DOH and the CDC, and identify data quality and reporting issues.

CASE ASSIGNMENT

Patients are assigned automatically by the electronic registry and case management system (Maven) based on current criteria from electronic and paper reports. The following priority levels indicate the timeline to initiate case management, with priority level 1 being the most urgent for action (within one business day):

PRIORITY LEVEL 1

- Smear-positive, culture-positive, or NAA-positive
- Left hospital against medical advice or eloped with no specimen collected or with unknown AFB smear results
- Contacts reported with signs and symptoms consistent with TB disease
- Other cases as requested by the Program Director

PRIORITY LEVEL 2

- Cavitary CXR or computed tomography (CT) scan
- Patients younger than 18 years of age
- Patients with HIV infection and one of the following:
  - homeless at the time of report,
  - have a history of prior TB,
  - have a positive test for TB infection result,
  - have ever been in a correctional facility,
  - have pathology findings consistent with TB
- Smear-negative or culture-negative patients confirmed with TB
- Smear-positive pathology results

PRIORITY LEVEL 3

- Patient on 2 or more anti-TB medications (currently or recently) but does not meet criteria for priority levels 1 and 2
- Case previously closed, which did not meet priority levels 1 and 2
- Smear-positive and NAA-negative
- Pathology finding of caseating granulomas, or caseating necrosis from any site

DATA DISSEMINATION

BTBC has a long history of disseminating TB surveillance data to healthcare providers, health agencies, and the public through the production of a surveillance summary that has been published annually since 1900. This report is shared both in hard copy and electronically and contains a comprehensive summary of BTBC activities, summary statistics and trends in the number of cases, and initiatives performed by BTBC in the previous year.

BTBC's ANNUAL TUBERCULOSIS SUMMARY provides robust surveillance data, summaries of core program activities and annual highlights. The report is available online at www.nyc.gov/health, search "TB Report"

Periodically, data may also be disseminated through presentations (e.g., Citywide TB Rounds, Grand Rounds, and other medical talks), BTBC publications (e.g., epi data briefs), publications in the scientific literature, at BTBC's annual World TB Day Conference, and through public use data projects such as Epi Query and NYC Health Atlas.

QUALITY ASSURANCE AND EVALUATION OF DATA

Surveillance data are used to conduct various quality assurance (QA) activities to maintain data accuracy and identify programmatic areas for potential improvement. The TB surveillance and case management system data are routinely evaluated to ensure efficiency of data collection and improve data accuracy and utility. Data are reviewed and analyzed for many reasons, including routine data analyses, reporting, program evaluation, and research. (See *Chapter 16: Program Evaluation and Research*.)

REPORTING TO THE CENTERS FOR DISEASE CONTROL AND PREVENTION AND THE NEW YORK STATE DEPARTMENT OF HEALTH

The Report of Verified Cases of Tuberculosis (RVCT) is the national TB surveillance data reporting form. The RVCT is used by the CDC to collect demographic, clinical, social, and laboratory data for confirmed cases of TB in the U.S. RVCT data are submitted electronically to the National TB Surveillance System (NTSS) on a daily basis. Data are also sent to the CDC's National TB Indicators Project (NTIP) to help monitor progress towards national TB control objectives. In addition to daily reporting of data to the CDC, data are also sent to the NYS DOH TB Control Program quarterly.

SUMMARY

Surveillance is a core TB control activity in NYC. BTBC's surveillance activities help ensure that all patients with TB are identified and treated appropriately and that public health response is timely and effective.

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New York City Health Code can be found at nyc.gov/health; search for "NYC Health Code"

Tuberculosis Annual Reports. nyc.gov. https://www1.nyc.gov/site/doh/health/health-topics/tuberculosis-historical-reports.page.

CHAPTER 10: CASE MANAGEMENT FOR PATIENTS WITH TUBERCULOSIS

INTRODUCTION

Case management is the process by which public health staff monitor and support the care and treatment of patients with tuberculosis (TB). The overall goal of case management aligns with the goals of the Bureau; that all individuals with suspected or confirmed tuberculosis receive an appropriate evaluation and course of therapy when indicated and that all persons at high risk of developing tuberculosis also receive evaluation and therapy if needed. In New York City (NYC), case management consists of a series of coordinated activities across a multi-disciplinary team of NYC Health Department Bureau of TB Control (BTBC) personnel to optimize patient care and treatment outcomes.

CASE MANAGEMENT ACTIVITIES

Case management begins as soon as the patient is reported to BTBC and continues until the patient completes treatment or is no longer receiving care for TB. BTBC staff conduct regular reviews of patient progress, address barriers to treatment adherence, and make follow-up appointments or referrals.

The case management team includes: BTBC physicians and nurses involved in the direct care of the patient, case managers, supervisors and regional managers, directly observed therapy (DOT) observers, epidemiologists, medical consultants (for patients obtaining clinical TB care from a community provider), and other staff (e.g., social workers) as necessary.

Patients are assigned a case management team based on the facility or borough where they are receiving care. Case management is provided to all patients diagnosed with TB in NYC regardless of whether they receive clinical services at a NYC Health Department TB clinic. Because the diagnostic process to confirm TB can be lengthy, case management is also initiated for individuals reported to BTBC with a high clinical suspicion of TB disease.

The activities of case management include:

1. Educating patients about TB
2. Conducting initial interviews and re-interviews
3. Determining the need for a contact investigation, identifying and testing contacts
4. Conducting chart reviews
5. Communicating with patients' healthcare provider(s)
6. Conducting home visits
7. Monitoring TB care
8. Identifying barriers to treatment adherence
9. Ensuring continuity of care
10. Documenting patient information and case management activities in the electronic surveillance and case management system

EDUCATING PATIENTS ABOUT TUBERCULOSIS

Education about TB and TB services is provided to all patients with confirmed TB disease and those with signs and symptoms consistent with TB disease who are assigned for case management. Patients are assigned for case management if they are reported because of a specimen with an AFB positive smear or culture, or are started on two or more drugs for tuberculosis. Initial education of the patient includes information on TB transmission, pathogenesis, symptoms, and treatment. Education is provided in the patient's primary language in a culturally appropriate manner. The patient is provided with opportunities to ask questions and the case manager ensures that the patient feels knowledgeable about their illness and how TB may be spread. Patient education is an ongoing process that occurs throughout case management, and the level and type of information that the patient needs may change over time.

CONDUCTING INITIAL PATIENT INTERVIEWS

Generally, the initial interview is conducted at the first interaction with the patient. The initial interview involves verifying and collecting as much information as possible about the patient, including information that can help identify potential barriers to TB care and treatment that may need to be addressed.

To ensure timeliness of contact investigations for potentially infectious patients, interviews are prioritized for patients with a positive result for acid-fast bacilli (AFB) on a specimen from a respiratory source (e.g., sputum, bronchial fluid, or lung), a positive test for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex (e.g., culture or nucleic acid amplification [NAA] test), or the presence of a cavity on a chest radiograph (CXR). These interviews are conducted within three business days. All other cases are interviewed within five days.

During the initial interview:

- Patients are informed that the Bureau's role is to make sure that the patient receives the best care until the end of their treatment
- Patients are informed that subsequent appointments should be kept, and that they will be informed of any changes in schedule or appointment time
- The patient interview takes place under conditions that are private and the patient is assured that any information provided will be kept confidential, to the extent possible
- Patients are informed about the nature of the questions that they'll be asked, how the information collected will be used, and under what conditions that information might be shared in the context of legal public health activities
- If staff must wear a respirator during the interview, the rationale for doing so is explained to the patient

Ideally, patient interviews are conducted in person. However, there are circumstances in which phone interviews may be the only option (e.g., patient no longer lives in NYC). If the patient is too young to be interviewed or is not able to be interviewed (e.g., the patient has died), a parent, guardian, or next of kin is interviewed. Non-Health Department medical databases and other sources may be searched for applicable information that can inform the initial interview. A chart review is conducted in person at the facility where the patient is receiving care; external health databases may also be used as a supplement to chart reviews. (See *Appendix L: Initial Patient Interview Topics*.)

DETERMINING THE NEED FOR A CONTACT INVESTIGATION, IDENTIFYING AND TESTING CONTACTS

Contact elicitation and subsequent investigations are required for patients diagnosed with signs and symptoms consistent with TB disease from a respiratory site (i.e., pulmonary, upper airways, or laryngeal) whose organism is smear-positive for AFB, NAA, and/or culture-positive for *M. tuberculosis*. During the initial interview with the patient, household contacts and potential sites of exposure (e.g., work or school) are elicited, as well as information regarding extent of exposure, number of contacts, and the environment.

The information from patient interviews, chart reviews, and home assessments is used to clarify the need for and scope of a contact investigation. This includes ascertaining the duration and frequency of symptoms (especially cough), eliciting the names of individuals with whom the patient had contact, and congregate site(s) where the patient spent time during the infectious period (i.e., work, school, house of worship, shelter, etc.).

Contact investigation is an ongoing process that continues throughout the patient's care. (See *Chapter 11: Contact Investigation*.)

CONDUCTING CHART REVIEWS

Chart reviews are conducted to supplement and verify information obtained during the interview. Chart reviews can provide information pertaining to the patient's name, address, telephone number(s), birth date, and health insurance, as well as the healthcare provider's name, address, and identifying information. Chart reviews often provide information that can be of importance when eliciting contacts. Ideally, the chart review should be conducted before the interview as it can help identify areas of concern.

A chart review includes:

- Obtaining information relevant to the treatment or evaluation of the patient's TB condition and other conditions that could impact TB treatment (e.g., human immunodeficiency virus [HIV] status, hepatitis) or are associated with risk factors that may have contributed to the development of TB disease (e.g., immunosuppressive medications or conditions)
- Collecting residential address and other locating information
- Collecting demographic information (e.g., country of birth)
- Collecting information on patient's history of treatment for latent TB infection (LTBI) and/or TB disease
- Collecting names, addresses, and telephone numbers of the patient's primary care provider and any specialists involved in their medical care, previous hospitalizations, and current medications
- Obtaining/gathering information on family and household contacts, social history (e.g., work and school history, history of homelessness, incarceration)
- Making copies of bacteriology, CXR, and computed tomography (CT) reports that can be scanned and attached in the TB surveillance and case management system (Maven)
- Documenting information regarding medications prescribed by the treating physician and isolation information, if applicable

Once collected, these data and all case management activities are input into Maven.

As a public health entity, the NYC Health Department is entitled to review patient medical charts without patient authorization. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

COMMUNICATING WITH PATIENTS' HEALTHCARE PROVIDER(S)

Regular communication occurs between BTBC and a patient's healthcare provider(s) throughout the course of a patient's TB diagnosis and treatment. Members of the BTBC case management team communicate with non-BTBC providers to establish discharge plans for hospitalized patients, follow up on treatment plans, ensure that patients are attending all follow-up appointments, request a completed Report of Patient Services (RPS) form monthly, and help identify and address any barriers to care.

It is important for case managers to establish a relationship with community providers, to stress the importance of coordinating patient care, and to ensure providers know about available medical consultation services. Providers are informed about BTBC's case management role and services, including DOT, sputum induction services, drug-susceptibility tests (DSTs), genotyping, and clinical care services in NYC Health Department TB clinics. Providers are informed about local, State, and national guidelines for TB treatment and monitoring, including the need for specimen collection and documentation of sputum culture conversion. Significant treatment concerns are discussed in collaboration with a BTBC medical consultant and the treating provider.

CONDUCTING HOME VISITS

When a patient is hospitalized with infectious TB disease, a home assessment is attempted prior to the patient's discharge from the hospital. The purpose of the home assessment is to evaluate that the patient has a safe and stable home environment and to determine if all household contacts have been identified. TB testing is offered to any contacts present during the home visit, and if this is declined, BTBC staff facilitate TB evaluation at either a NYC Health Department TB clinic or a community provider.

If the patient is still potentially infectious when leaving the hospital, there are special considerations regarding their discharge home. Other individuals living in the home must agree that the infectious patient can return to the home and the patient must have capacity to separate from others in the home. The patient should sign a home isolation agreement and agree to participate in DOT. (See *Chapter 13: Infection Control* and *Appendix M: Directly Observed Therapy Agreement Form*.) Home assessments are also conducted for patients with infectious TB disease diagnosed in outpatient settings. If there are unstable living conditions and the patient cannot be separated from other household members, the patient should be admitted to the hospital for appropriate airborne infection isolation.

During the patient's TB treatment, at least one home visit is required. Home visits are also useful for confirming the patient's address, particularly for patients at high risk for non-adherence to treatment. Information gathered at the patient's home can sometimes lead to the identification of additional contacts and a better understanding of the relevant details of a patient's life that may inform case management or contact investigation (e.g., seeing a child's shoes or toys when a child was not named in the initial

interview). Further home visits can be done as needed.

MONITORING TUBERCULOSIS CARE

Various activities are conducted throughout case management to ensure continuity of care and to foster treatment adherence. These activities include monitoring medication side effects and physical changes in the patient's condition (e.g., weight gain), updating laboratory and bacteriology tests and results, updating the progress of contact investigations, and ensuring referrals for social services. If the patient is not on DOT, pharmacy checks are routinely conducted to ensure the patient is on appropriate medication, has an adequate supply, and is adherent to treatment. BTBC submits a written request to the pharmacy highlighting the requirement to provide the requested information. The patient's medical record is also routinely monitored to ensure that complete and up-to-date laboratory tests, sputum results, and/or medical information are entered into the electronic surveillance and case management system. For patients with pulmonary TB disease, routine sputum collection to monitor culture conversion within 60 days of treatment initiation is also conducted. Patients are also regularly reminded of upcoming scheduled clinic visits.

IDENTIFYING BARRIERS TO TREATMENT ADHERENCE

As there can be many barriers to care that prevent patients from taking their TB medication or keeping their physician and clinic appointments, patient needs and obstacles to care are identified and addressed whenever possible. These can include language needs, availability of transportation, the patient's preference for place and time of DOT, the ability to swallow pills, and medication side effects. It is also important to review psychosocial status to identify unmet social service needs, the use of alcohol and/or illegal drugs, concerns about the stability or safety of residence or the risk of homelessness, unstable employment or lack of time-off to attend medical appointments, financial concerns, or any pre-existing psychiatric diagnoses. When these conditions are identified, patients are referred to a social worker.

Incentives or enablers are offered to enhance adherence to therapy. In NYC Health Department TB clinics, patients are provided with a MetroCard to ensure transportation cost is not an issue for clinic appointments. When necessary, referrals are provided for a range of services, including housing, food stamps, etc.

Information that may indicate a potential for non-adherence is obtained and documented; barriers to care are addressed on an ongoing basis. Early indicators of poor adherence include:

- Marginal or no acceptance of TB diagnosis
- Complaints that TB medications taste bad or make the patient sick
- Failure to attend monthly follow-up appointments
- No verification of pharmacy pick-up
- Substance abuse
- Slow sputum conversion or delayed clinical improvement
- Clinical deterioration while on TB therapy

ENSURING CONTINUITY OF CARE

When a patient's care is transferred from one provider to another, referrals for care are conducted; this includes transfers between NYC Health Department TB clinics. If a patient plans to relocate, new contact information (address, phone, etc.) is obtained and documented immediately. If the patient is moving out of NYC, the case is referred for interjurisdictional or international notification to the patient's new jurisdiction. BTBC staff continue to follow up with care providers in the patient's new jurisdiction to ensure treatment completion. In these instances, the patient is provided with information on how to reach BTBC in case the transfer does not occur or the patient has any questions.

DOCUMENTING PATIENT INFORMATION AND CASE MANAGEMENT ACTIVITIES IN THE ELECTRONIC SURVEILLANCE AND CASE MANAGEMENT SYSTEM

Patient information and case management activities are documented in BTBC's TB surveillance and case management system. Since different staff in BTBC are involved in a patient's care and require the most up-to-date information, information obtained or case management efforts conducted for a patient are regularly updated in the surveillance and case management system. Such information includes demographics, clinical and social information, current and history of diagnostic workup and treatment, persons exposed in the household and congregate settings, and treatment management plan. In addition, patient information may be used to support legal actions towards non-adherent patients, for data reporting and program evaluation, and research purposes.

DIRECTLY OBSERVED THERAPY

DOT is one of the tools used for effective case management. DOT involves a trained staff member observing the ingestion of each dose of anti-TB medication for part or all of a patient's treatment. DOT is the standard of care in TB treatment and is the best way to ensure that patients complete an adequate course of treatment and that adverse medication effects are promptly identified and assessed.

Patients eligible for DOT include those started on treatment for confirmed TB disease or those with signs and symptoms consistent with TB disease who are not hospitalized, incarcerated, or residing in a nursing home or other residential facility. Although most DOT services in NYC are provided by BTBC, several public hospitals administer DOT for patients under their care. On occasion, DOT is provided for contacts who are at high risk.

BTBC offers four DOT options:

1. **In-person clinic DOT:** Patient comes to the clinic for observation
2. **Community DOT:** BTBC staff meets the patient in their home or other agreed upon location in the community for observation
3. **Live video DOT (LVDOT):** Patient is observed real-time through video conferencing software
4. **Recorded video DOT (RVDOT):** Patient records themselves ingesting their medication and securely transmits the video for observation

Patients are placed on the method of DOT that is most convenient for them. The decision for the best DOT option is made between the physician and the patient. DOT is offered to all patients within NYC, regardless of where they obtain TB care.

If DOT is offered by the physician and accepted by the patient, every dose of medication given on a weekday (excluding NYC-approved holidays) is taken under observation. Most patients take medications daily during the first two months of therapy, while some patients will take medications on an intermittent schedule after the first two months of therapy. Intermittent therapy can be administered only if DOT is accepted by the patient. DOT is provided only on non-holiday weekdays so patients on a daily regimen self-administer on holidays and weekends. For patients on intermittent DOT, DOT schedules are adjusted on holidays to ensure medication doses are observed.

If a patient is not on DOT, monthly pharmacy checks with the pharmacy where the patient receives their medication are conducted to ensure the medication is refilled and picked up by the patient as expected.

ADDRESSING NON-ADHERENCE

Despite proper case management efforts and open communication with patients, some patients miss their clinic or DOT appointments and other follow-up visits. In these instances, return to service (RTS) activities are initiated (i.e., phone calls and home visits) to locate and encourage patients to return to care. If the patient continues to miss appointments and/or DOT visits after these interventions, the patient must be referred for legal interventions. As a last resort, non-adherent patients who are deemed to be potentially infectious must be referred for evaluation for legal interventions if all other efforts were unsuccessful.

FOLLOW-UP OF PATIENTS WITH MISSED CLINIC APPOINTMENTS

Patients who miss NYC Health Department TB clinic appointments are initially contacted by telephone within one working day. If they cannot be reached by phone, the patient is referred for a home visit. Patients seen at a TB clinic may also be mailed a letter with a new clinic appointment if the only means of contacting the patient is a mailing address (i.e., post office box) and the patient specifically requests not to be visited at home and has a valid reason for this request (i.e., issues with domestic violence and a visit to the home could put the patient in potential danger).

For patients younger than 18 years of age whose parent or guardian refuses to permit the child's evaluation or treatment, BTBC works with the Administration for Child Services (ACS) to determine further actions; however, this is an option of last resort after all other attempts to get the child evaluated have failed.

FOLLOW-UP OF PATIENTS WITH MISSED DIRECTLY OBSERVED THERAPY VISITS

Patients on DOT are called the same day of a missed appointment. If the phone call is unsuccessful or if the patient has no phone number, a home visit is conducted at different times from the scheduled observation. Daily DOT patients are considered non-adherent after missing two of five scheduled observations per

week. Patients on intermittent DOT (three times per week) are considered non-adherent after one missed dose of medication. All instances of DOT non-adherence and intervention must be documented in the patient's electronic medical record (EMR) and the electronic surveillance and case management system, Maven. Clinic DOT patients who cannot be located must be referred for further RTS follow-up.

RETURN TO SERVICE EFFORTS

Immediate follow-up is essential for patients who are non-adherent. For patients treated at NYC Health Department TB clinics, clinic staff initiate the first RTS action and, if unsuccessful, refer to regional staff for further actions. For non-adherent patients receiving treatment from non-BTBC providers, RTS actions are initiated once community staff learn that the patient is non-adherent. RTS efforts include reviewing case management notes; attempting additional phone calls and community visits to homes or other locations; conducting hospital, shelter, or prison checks as appropriate; and obtaining additional contact information through the use of other agency databases, social media, and other web-based resources.

Several factors must be considered when deciding how to prioritize finding patients lost to follow-up. The first consideration is whether the patient has enough medication. Patients who have sufficient medication and who report by telephone that they are taking the medication are a lower priority than those who have run out of medication.

Otherwise, prioritization of patients for RTS is as follows:

1. Any patient with multidrug-resistant TB (MDR-TB)
2. Newly-diagnosed patients who have had AFB-positive sputum smears
3. Any child younger than 18 years of age
4. Any patient who has HIV infection
5. Individuals with HIV infection who are contacts of MDR-TB patients
6. Patients with other drug-resistant TB (DR-TB) who have not culture converted
7. Patients with drug-susceptible TB disease who have not culture converted
8. Patients with negative cultures who have received less than six months of treatment
9. Patients with extrapulmonary TB disease

REGULATORY INTERVENTION OPTIONS

For patients who have confirmed infectious TB disease, or have signs and symptoms consistent with infectious TB disease and have a demonstrated inability or unwillingness to adhere to TB evaluation and treatment, regulatory interventions may be necessary. Possible regulatory options include outpatient interventions (e.g., mandated DOT) or mandated detention. Referrals are made only after customary interventions fail to result in patient evaluation or adherence to treatment. All efforts and interventions made to facilitate adherence to prescribed TB treatment regimens must be documented in detail in the electronic surveillance and case management system. Efforts to return patients to medical care must

continue until a regulatory decision is made. Legal intervention is considered when all reasonable efforts to assist the patient in completing the entire course of TB treatment regimen have failed.

The purpose of regulatory intervention is to:

- Prevent potential exposure among members of the public to patients with infectious TB disease who have refused to agree to treatment adherence and isolation
- Ensure that patients with TB disease complete an adequate course of TB treatment
- Ensure that patients with signs and symptoms consistent with TB disease undergo appropriate evaluation
- Prevent the development of acquired drug resistance among TB patients who are unwilling or unable to adhere to an uninterrupted course of treatment

Patients who are eligible to be referred for regulatory intervention include:

- Patients who miss clinic appointments for two or more months and have refused DOT
- Patients who are non-adherent to self-administered treatment, and are unwilling or unable to start or continue DOT
- Patients who have not picked up the appropriate medications, as determined by pharmacy checks
- Patients who continue to be non-adherent even when barriers to treatment adherence have been addressed to the extent possible
- Patients who maintain less than 80% adherence to DOT

NOTICE OF OBLIGATION TO ISOLATE

When a provider has grounds to believe that an infectious or potentially infectious patient will attempt to leave the hospital without authorization, the facility contacts BTBC. BTBC prepares and sends a Notice of Obligation to Isolate (NOI) to the facility. For patients who are deemed infectious and do not meet discharge criteria, the facility is obligated to take steps to prevent the patient from leaving, such as by posting a guard if necessary.

Upon receiving the NOI, the hospital must monitor the patient's activity and take all necessary measures to prevent them from leaving the hospital. BTBC will assess the patient's risk to the public health. Based on hospital and other clinical records, the patient's TB treatment-related behaviors will be evaluated. Additionally, documentation pertaining to case management efforts to identify and address barriers to patient adherence are assessed. To facilitate the Commissioner's Order, clear, convincing evidence of non-adherence must be provided. The evidence must sustain the need of a regulatory action for detention of an individual with active TB disease who is unable or unwilling to adhere to treatment.

BTBC assessment determines whether a Commissioner's Order can be issued. If issued, the Commissioner's Order for Detention will be provided to the hospital within three business days of the issuance of a NOI.

The patient who is to be detained is personally served with the Detention Order by BTBC or hospital staff. When the patient is served, they are informed of the legal authority for the order and their rights, which include the right to request release at any time and the right to an attorney. The order includes BTBC and other Health Department telephone numbers that the patient may call to request legal representation and/or release. The City of New York will assign a lawyer to the patient upon the patient's request.

COMMISSIONER'S ORDERS

The NYC Health Code authorizes the Commissioner of Health to exercise a range of compulsory options to control TB (i.e., to issue "any orders they deems necessary to protect the public health" from someone who is a danger to the public health). (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) The Commissioner is empowered to detain patients with TB disease whose presence in the community constitutes a danger to the public health. However, involuntary detention is generally considered a measure of last resort. Considerable due process safeguards mandated by the NYC Health Code assure that the Commissioner's Orders are issued only when less restrictive alternatives have failed or are not feasible.

Less restrictive orders may be requested by providers treating patients for whom adherence to anti-TB medication is an issue. The provider may request, and the Commissioner may order, that a person with TB disease complete an appropriately prescribed course of medication and/or that a patient's ingestion of medication be monitored through DOT.

TYPES OF COMMISSIONER'S ORDERS:

- **D:** Outpatient examination of patient with confirmed TB disease or person with signs and symptoms consistent with TB disease
- **D1:** Detention in a hospital of individuals who have or are suspected of having active TB and who are unable or unwilling to submit to voluntary examination. A D4 or D5 must be issued if circumstances warrant continued detention after examination confirms active TB disease
- **D2:** Require that persons having or suspected of having active TB complete an appropriate prescribed course of medication for TB and infection control precautions
- **D3:** Require that persons with active TB complete an appropriate prescribed course of medication for TB under direct observation by BTBC staff
- **D4:** Removal and/or detention in a hospital or other healthcare facility of persons having or suspected of having active infectious TB who are considered likely to transmit the disease to others because they are unable or unwilling to observe appropriate infection control precautions. The detention order may be lifted if circumstances change, indicating that the patient is either no longer infectious and/or is able or willing to comply with respiratory isolation or other necessary contagion precautions.
- **D5:** Removal and/or detention in a hospital or other healthcare facility of individuals with active TB (infectious or non-infectious) that, based on past or present non-adherent behavior, cannot

be relied upon to complete the appropriate TB treatment regimen and/or to maintain infection control precautions. This order allows long-term detention, until treatment completion, for patients who require it.

Issuing a Commissioner's Order involves a complex process that takes into consideration patient behavior and clinical characteristics. The decision to issue a Commissioner's Order involves multiple levels of review of the patient's medical and TB treatment histories, including:

- Analysis of all relevant BTBC and hospital records to verify past TB-related behavior
- Documentation of providers' efforts to promote adherence to treatment
- Description of the patient's present circumstances

Once a Commissioner's Order has been issued, patients have clear rights afforded to them during the legal process. Patients detained pursuant to Commissioner's Orders may request release at any time after an order is served. They are entitled to representation by a private or city-appointed attorney. When the detainee requests release, the city has three business days to file an application in Supreme Court seeking a court order authorizing continued detention. This is also known as an order to show cause.

The order to show cause requests the court to schedule an expedited hearing at the facility where the patient is being detained. Patients who do not request release may be held for up to 60 days by Commissioner's Order. If longer detention is anticipated, BTBC must apply for a court order authorizing continued detention. All court orders must be reviewed by the court issuing the order every 90 days thereafter.

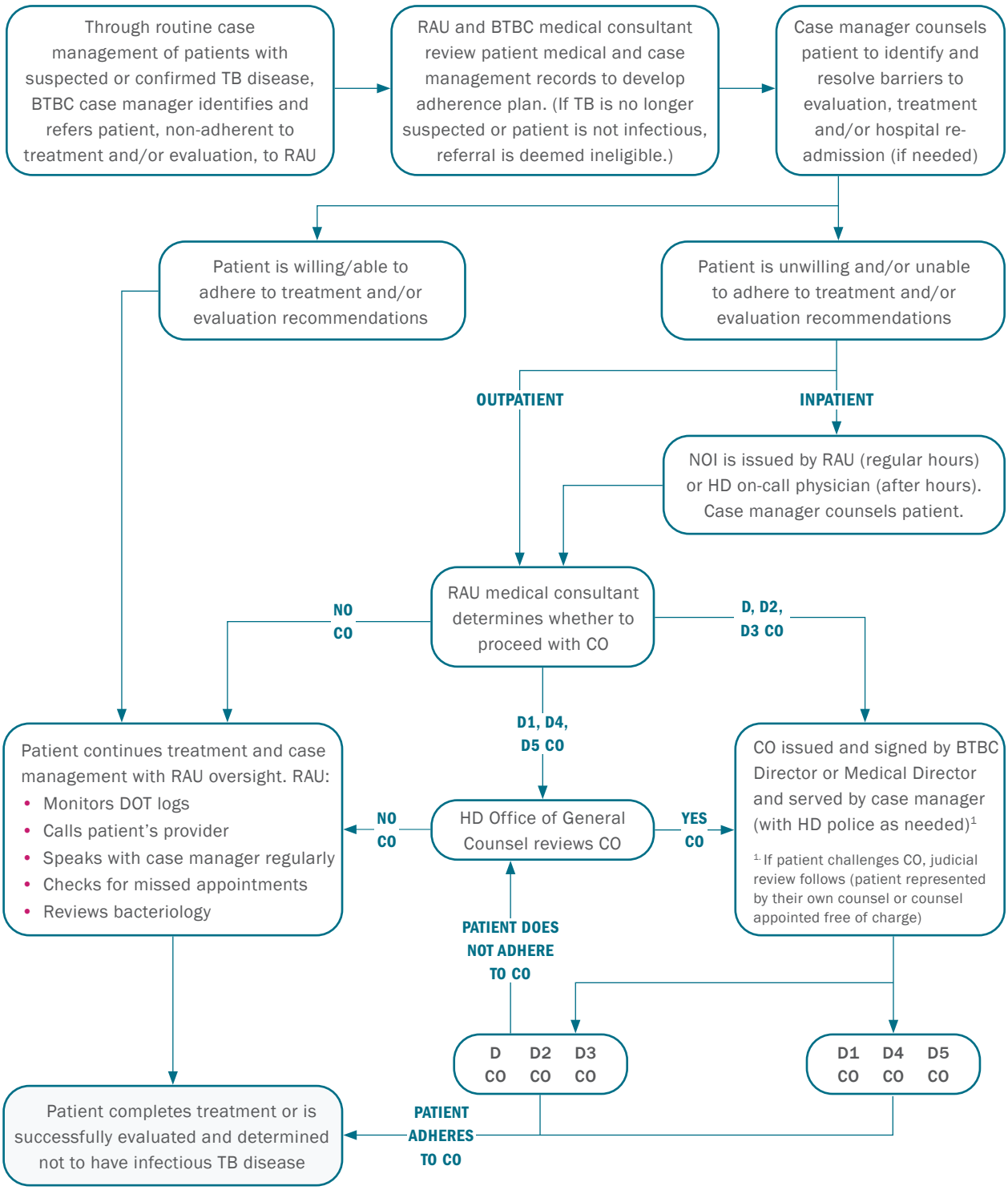
The burden of proof supporting the detention of an individual with TB rests with BTBC, which must provide clear and convincing evidence that the continued presence in the community of the individual with active TB disease presents a danger to public health and that there is no measure short of detention that can be reasonably applied.

Documentation in the form of hospital, clinic, and other medical records constitutes BTBC's evidence that detention is necessary. Certified copies of hospital and other records are required. The records include, but are not limited to:

- All TB-related admissions and clinic visits
- Incident reports for elopement (leaving the hospital without notice)
- Leaving the hospital against medical advice
- Records of visiting nurse and other provider home visits for DOT
- Notes or memoranda from psychiatric, medical, nursing, social worker, or other provider staff

The records require documented observations of a patient's past TB adherence history and other factors that appear to rule out reliance on voluntary completion of prescribed TB therapy. BTBC's access to such records is authorized by applicable City, State, and federal law, and a BTBC representative requests them in writing.

FIGURE 10.1: New York City Bureau of Tuberculosis Control case management and regulatory processes for identifying and addressing non-adherence to TB evaluation and treatment



Abbreviations Used: BTBC=Bureau of Tuberculosis Control; CO=Commissioner's order; DOT=directly observed therapy; HD=Health Department; NOI=notice of obligation to isolate; RAU=regulatory affairs unit; TB=tuberculosis

ENSURING EFFECTIVE CASE MANAGEMENT

Effective supervision of the work of the case management team is essential. Systematic review of these activities are conducted regularly by supervisors. At each review session, any outstanding issues are addressed, including barriers to patient adherence and care, and plans to resolve these issues are developed and implemented.

CASE MANAGEMENT MEETINGS

Case management meetings are held regularly and are attended by the case management team, which includes the medical consultant, physicians and nurses involved in the care of the patient, case managers, case management supervisors, DOT supervisors, epidemiologists, and others as necessary. Matters addressed by the case management team include:

- Treatment regimen and adherence issues: bacteriology results, susceptibility results, timeliness of culture conversion, as appropriate
- Status of contact investigation, with special attention to pediatric contacts, immunocompromised contacts, and contacts to MDR-TB patients
- Completeness of information that has been entered into the TB surveillance and case management system
- Mental, emotional, and cognitive status of the patient and their ability to understand and address their TB diagnosis
- Substance use issues, if relevant to patient care
- Access to transportation for medical appointments
- Usual places of residence, where and how to locate the patient, impending plans to relocate or travel, housing needs, and living situation
- Cultural and religious beliefs that may impact adherence
- Language and literacy barriers
- Work history, school/daycare, and/or any program or congregate setting attendance
- Ability to pay for non-TB-related medical care and need for referral to social services
- Support system such as family, friends, coworkers, religious/spiritual leaders
- Family dynamics that may influence patient care (i.e., parent who does not want children tested for TB infection after an exposure)

MEDICAL CONSULTATION

To ensure that all patients receive the highest quality TB care and achieve treatment success, BTBC offers medical consultation to both BTBC staff and community providers as part of case management activities. BTBC medical consultants are physicians who have years of experience in treating TB disease and LTBI.

This unique BTBC service allows community providers the opportunity to receive expert consultation regarding diagnostic processes, treatment plans, infection control, contact evaluation, treatment of MDR-TB, adverse reactions to medication, and any other TB-related concerns. Recommendations related to TB diagnosis, treatment, and case management are made based on BTBC policies, national guidelines from the Centers for Disease Control and Prevention (CDC)/American Thoracic Society (ATS)/European Respiratory Society (ERS)/Infectious Diseases Society of America (IDSA), and professional experience.

BTBC medical consultation activities include the following:

REVIEW OF CASES: Confirmed TB cases, contacts, and patients being evaluated for TB disease are reviewed on an ongoing basis to ensure that all patients are receiving appropriate treatment and care. Medical consultants provide guidance on TB diagnosis, medical treatment, and case management. Cases are also reviewed for public health considerations including infection control, contact investigation, and the need for regulatory intervention.

DIAGNOSTIC EVALUATION: Diagnosis of TB disease requires a high index of suspicion; use of appropriate diagnostic processes and tests is critical for prompt identification and treatment. Recommendations for diagnostic tests are discussed and the process by which community providers may obtain services available through the NYC Health Department Public Health Laboratories (NYC PHL), the New York State Department of Health Wadsworth Center, CDC, or other laboratories is reviewed.

MULTIDRUG-RESISTANT TUBERCULOSIS CONSULTATION: Treatment for MDR-TB and extensively drug-resistant TB (XDR-TB) patients is complicated, lengthy, and can be difficult to manage. Treatment is individualized for each patient. Recommendations for individualized MDR/XDR-TB treatment are offered, as well as guidance on use of rapid molecular diagnostic tests for clinical decisions, and recommendations for the testing and treatment of individuals exposed to a patient with MDR/XDR-TB. (See *Chapter 6: Treatment of Drug-Resistant Tuberculosis Disease in Adults*.)

HOSPITAL DISCHARGE PLANNING: Hospital discharge plans are reviewed to determine if patients can be safely discharged to an outpatient setting. If the patient remains infectious, guidance to minimize the risk of transmission in the community is also provided. Review steps may include: ensuring that a home assessment has been conducted, assessing the adequacy and tolerance of therapy, ensuring that DOT has been offered, ensuring that appropriate home isolation steps are in place (when relevant), and verifying that an adequate plan for provider follow-up is in place. (See *Chapter 13: Infection Control*.)

TREATMENT RECOMMENDATIONS: BTBC medical consultants provide treatment recommendations for LTBI and active TB disease, including dosing information, optimal medication combinations, and duration of therapy. Special circumstances (e.g., pregnancy, concurrent treatment for renal failure or liver dysfunction) are considered and discussed.

DRUG-TO-DRUG INTERACTIONS: Many patients take medication for other medical conditions that may interact with TB medications. As part of TB disease and LTBI treatment planning, BTBC medical consultants review all medications that patients are currently taking and may recommend adjusting the TB regimen to minimize any drug-to-drug interactions, particularly for patients being simultaneously treated for HIV.

In certain situations, the medical consultant may recommend dose adjustments or drug substitutions of non-TB medications or other interventions.

INFECTION CONTROL: BTBC medical consultants assess infectiousness and determine whether a patient can be released from airborne infection isolation and whether home isolation is needed for patients not hospitalized. Medical consultants can also make recommendations about return to work, school, or other congregate living situations for patients with infectious TB. Recommendations are made based on BTBC's guidelines for infection control practices. (See *Chapter 13: Infection Control*.)

DETERMINE COMPLETION OF TREATMENT: BTBC medical consultants determine when a patient has adequately completed a full course of treatment. This is particularly important for patients who may have had low adherence at any point during their treatment course or were not on DOT.

TRANSMISSION ASSESSMENT AND RELATED RECOMMENDATIONS: BTBC medical consultants review recommendations to initiate and/or complete contact investigations for potentially infectious patients and help staff assess household TB transmission. This process ensures that contact investigations progress appropriately and may entail recommendations for re-interviewing the patient and/or expanding the contact investigation when transmission occurs. (See *Chapter 11: Contact Investigation*.)

FOLLOW UP WITH PROVIDERS: As part of case management reviews, issues may be identified with a patient's care that require the medical consultants to follow up with the patient's community provider. Issues are generally related to potential concerns with treatment, diagnostic testing, adherence, and evaluation, and/or treatment of individuals exposed to a patient with infectious TB disease.

CONDUCT TB ROUNDS AND MEDICAL TALKS: BTBC medical consultants give medical talks and participate in TB Rounds at hospitals throughout NYC. TB Rounds often include a review of a facility's past experience in managing patients with TB, an overview of the epidemiology of TB in NYC, and a review of current recommendations for TB diagnosis and treatment. They may also serve as a forum to review complicated TB cases, explain BTBC's case management process, and inform providers of the latest diagnostic and treatment options. (See *Chapter 14: Outreach and Education*.)

TUBERCULOSIS HOTLINE: The on-call BTBC medical consultant can be reached directly during regular business hours through BTBC's TB Hotline at **844-713-0559**. Through the Hotline, BTBC physicians provide consultation on all aspects of TB diagnosis, treatment, prevention and care, infection control, discharge planning, reporting processes, contact evaluation and treatment, referrals to NYC Health Department TB clinics, and other issues.

POUCH REVIEW

A pouch review is a process by which case management activities are reviewed by case management staff and their supervisors on a regular basis. The objective of the pouch review is to ensure thorough collection of information and accountability in following up on plans and issues to achieve positive patient care outcomes.

COHORT REVIEW

The quarterly cohort review is a tool to improve case management and ensure complete and appropriate treatment and care for tuberculosis patients. During cohort reviews, TB cases are reviewed by the Bureau Director three to six months after assignment to a public health advisor for case management. All aspects of the public health record are reviewed, including medical evaluation and treatment, adherence to therapy, completion of therapy, and contact evaluation if appropriate. (See *Chapter 16: Program Evaluation and Research*.)

SUMMARY

Case management is one of the fundamental TB control activities used to ensure successful treatment outcomes. BTBC provides case management for all patients with confirmed TB disease or signs and symptoms consistent with TB disease, as well as contacts being treated for LTBI. In BTBC, a multidisciplinary case management team is responsible and accountable for coordinating patient care and ensuring completeness of recommended treatment regimens for each patient. Using a patient-centered approach, the case management team works in partnership with patients and their providers to achieve treatment success.

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CHAPTER 11: CONTACT INVESTIGATION

INTRODUCTION

Contact investigation is a key strategy employed by the New York City (NYC) Bureau of Tuberculosis Control (BTBC) to identify individuals recently exposed to patients with infectious tuberculosis (TB) disease (contacts). Contacts are more likely to develop active TB disease than any other risk group. Future cases of TB can be prevented by prompt identification and evaluation of contacts, and by ensuring that those diagnosed with TB or latent TB infection (LTBI) complete treatment.

CONTACT INVESTIGATION ACTIVITIES

A contact investigation begins at the first interview of a patient with infectious TB disease. BTBC staff elicit names and other information for individuals who have spent time (e.g., live or work) with the person while they were infectious. The contact investigation continues until the case management team has made a final status determination for all contacts. BTBC is responsible for identifying, prioritizing, and ensuring evaluation for all contacts.

The activities of contact investigation include:

1. Determining the need for a contact investigation
2. Defining the infectious period
3. Defining the window period
4. Interviewing patients with infectious TB disease and eliciting contacts
5. Conducting a home assessment
6. Prioritizing contacts for evaluation
7. Interviewing and educating contacts
8. Evaluating contacts and determining the need for treatment
9. Screening and testing for human immunodeficiency virus (HIV)
10. Assessing transmission
11. Conducting an expanded contact investigation
12. Conducting case management for contacts being treated for LTBI
13. Supervisory review

DETERMINING THE NEED FOR A CONTACT INVESTIGATION

A contact investigation is performed for all patients with TB disease who are considered to be potentially infectious. Patients are considered potentially infectious based upon a number of clinical factors including site of disease, acid-fast bacilli (AFB) sputum smear and culture status, length of symptoms, and radiographic findings. The likelihood of TB transmission to contacts is influenced by clinical characteristics, the extent and duration of exposure, and environmental factors.

The following factors determine the priority of a contact investigation:

ANATOMICAL SITE OF DISEASE: Patients with pulmonary, laryngeal, or other respiratory sites of disease are potentially infectious as TB is spread through the air. Cough is associated with an increased likelihood of transmission.

RESPIRATORY SPECIMEN TEST RESULTS: A contact investigation is immediately initiated for all patients with a respiratory specimen that is AFB smear-positive and those with a positive nucleic acid amplification (NAA) test or *Mycobacterium tuberculosis* (*M. tuberculosis*) culture. A higher AFB smear grade is associated with increased infectiousness. When NAA test results are negative for TB, but the AFB is smear-positive, the contact investigation may be interrupted if the treating provider does not consider TB as a likely diagnosis and discontinues TB treatment.

RADIOGRAPHIC FINDINGS: Patients with lung cavities observed on their chest radiograph (CXR) and/or computed tomography (CT) scan are more likely to be infectious than patients without cavitation; contact investigations for these patients are prioritized.

SYMPTOMS: A patient's duration and severity of symptoms, such as hemoptysis and productive cough, directly impact likelihood of infectiousness and determine the length of the infectious period.

ENVIRONMENTAL FACTORS: Room size, crowding, ventilation, and degree of air circulation at a site (e.g., home, school, workplace) contribute to the risk of transmission.

AGE: Children have a higher risk of progressing to active TB disease once infected than other age groups. Exposures involving children (e.g., schools, daycares, etc.) are prioritized to identify and treat infected individuals early and prevent progression to TB disease.

MEDICAL RISK FACTORS: Immunocompromised individuals (e.g., people with human immunodeficiency virus [HIV] infection, people on chemotherapy, etc.) are at increased risk of developing TB disease once infected and thus require timely testing, evaluation, and treatment for LTBI.

(See *Table 11.1: Decision to Conduct or Continue Contact Investigation by Bacteriological Status and Clinical Suspicion of Respiratory Tuberculosis*.)

DEFINING THE INFECTIOUS PERIOD

The infectious period is the timeframe during which a patient is most likely to transmit TB to others. Focusing the investigation on the infectious period allows prioritization of contacts who are most at increased risk of infection. The infectious period begins at symptom onset or 12 weeks prior to the start of airborne infection isolation or anti-TB treatment, whichever is earlier. This date may be adjusted based on clinical characteristics and epidemiologic considerations.

The infectious period ends when the patient with active TB disease is isolated, or two weeks after beginning appropriate TB treatment, determined by drug-susceptibility test (DST) results. The infectious period is revised when necessary to account for unusual situations (e.g., when there is a need to change the antibiotic regimen if the isolate is found to be drug-resistant).

DEFINING THE WINDOW PERIOD

Since there can be a delay in obtaining an accurate immune response to *M. tuberculosis* following a TB exposure, BTBC recommends an eight-week window period be established. The window period is therefore defined as the eight-week period after a contact's last exposure to a patient with infectious TB disease.

The window period begins on the day of the contact's last exposure to the infectious patient. For most household contacts, the last day of exposure occurs when the patient is isolated or no longer considered infectious, whereas contacts from a non-household setting (i.e., work or school) may have a different last day of exposure if the infectious patient left these settings before diagnosis.

During the window period, a contact's negative test for TB infection is considered preliminary. Steps are taken to ensure all contacts are tested soon after elicitation and then retested once the window period has ended.

TABLE 11.1: Decision to conduct or continue contact investigation by bacteriological status and clinical suspicion of respiratory tuberculosis

RESPIRATORY SMEAR-POSITIVE FOR AFB					
NAA result	Culture result	Clinical suspicion or epidemiologic concern	Contact investigation		
			Start (elicit contacts)	Continue (test high-priority contacts)	Complete
Positive for *M. tuberculosis* OR Not done	Pending		Yes	Yes	Yes, if verified
	Positive		Yes	Yes	Yes
	Negative		Yes	Yes	Yes, if verified
	Not done		Yes	Yes	Yes
Negative for *M. tuberculosis*	Pending		Yes	Delay	Yes, if verified
	Positive		Yes	Yes	Yes
	Negative	High	Yes	Continue	Yes, if verified
		Low	Yes	Delay	No, unless verified
	Not done	High	Yes	Continue	Yes, if verified
		Low	Yes	Delay	No, unless verified
RESPIRATORY SMEAR-NEGATIVE FOR AFB					
NAA result	Culture result	Clinical suspicion	Contact investigation		
			Start (elicit contacts)	Continue (test high-priority contacts)	Complete
Positive for *M. tuberculosis*	Pending	High (cavitary CXR)	Yes	Yes	Yes, if verified
	Positive		Yes, after NAA	Yes	Yes
	Negative	High (cavitary CXR)	Yes, after NAA	Yes (If medical/ epidemiological review determines need)	Yes, if verified
	Not done		Yes, after NAA	Yes	Yes, if verified
Negative for *M. tuberculosis* OR Not done	Pending	High (cavitary CXR)	Yes	Delay	No, unless verified
	Positive		Yes, after culture	Yes	Yes
	Negative	High (cavitary CXR)	Yes	Delay	Yes, if verified
		Low	No	No	No
	Not done	High (cavitary CXR)	Yes	Delay	Yes, if verified
		Low	No	No	No

*When both respiratory smear (positive) and negative NAA are known at time of assignment, and the patient is not being treated for TB, the Network Owning Group will place the case on hold and contacts should not be elicited.

**Provide post-window testing and medical evaluation as appropriate; promptly initiate or continue contact elicitation and testing if previously put on hold or not done, and continue to completion.

Abbreviations Used: AFB=acid-fast bacilli; CXR=chest radiograph; *M. tuberculosis=Mycobacterium tuberculosis*; NAA=nucleic acid amplification; TB=tuberculosis

In certain situations, BTBC physicians may determine the need to extend or create a new window period for contacts who remain in close contact with an infectious patient. This occurs when initial drug therapy is not adequate (e.g., initial treatment with standard TB regimen, but the patient was subsequently found to have drug-resistant TB [DR-TB]), or when the patient with infectious TB becomes newly smear- or culture-positive.

In situations where a second window period needs to be established for contacts (i.e., the first window period has ended but the index patient is still/newly infectious), the following contacts are tested (or re-tested) during the newly established window period and after:

- Contacts who were not initially tested during the first window period
- Contacts who tested negative during the first window period
- Contacts who tested post-window negative

In situations where the first window period is extended, the following contacts are tested (or retested) both during the extended window period and after:

- Contacts who were not initially tested
- Contacts who tested negative during the window period

INTERVIEWING PATIENTS WITH INFECTIOUS TUBERCULOSIS DISEASE AND ELICITING CONTACTS

Once a contact investigation has been deemed necessary, the framework for subsequent patient interviews and the ensuing investigation is determined. All patient interviews are conducted in settings that are private and ensure confidentiality of the patient and any identified contacts.

As part of the initial patient interview, the patient's medical chart is reviewed to obtain information that may assist with either the identification of contacts and exposure sites, or to help establish the infectious period. More specifically, the following information is identified:

- Date of onset of symptoms attributable to TB, which is used to determine the infectious period
- Details of treatment and evaluation (particularly any hospitalizations) during the infectious period
- Next of kin
- Residential address to confirm it matches what is provided upon interview
- Work history
- Other congregate settings where the patient may have spent time during the infectious period

Many patients find it difficult to recall who they have interacted with during their infectious period; to identify all potential contacts and exposure sites, specific prompts and probing questions are used. (See *Chapter 10: Case Management for Patients with Tuberculosis*.) Relevant demographic and contact information for each potential contact identified is elicited. This information allows contacts to be located and evaluated in a timely manner.

CONDUCTING A HOME ASSESSMENT

In the context of a contact investigation, home assessments provide the opportunity to identify individuals not previously mentioned by the patient and environmental conditions that may facilitate TB transmission in the household (i.e., crowding, poor ventilation, etc.). The home assessment is also an opportunity to offer testing to any contacts who may be present at the time of the visit. Trained BTBC staff carry the necessary equipment to test any contacts identified in the home.

PRIORITIZING CONTACTS FOR EVALUATION

Contacts are classified into one of four categories based on the extent of their exposure to a patient with infectious TB disease:

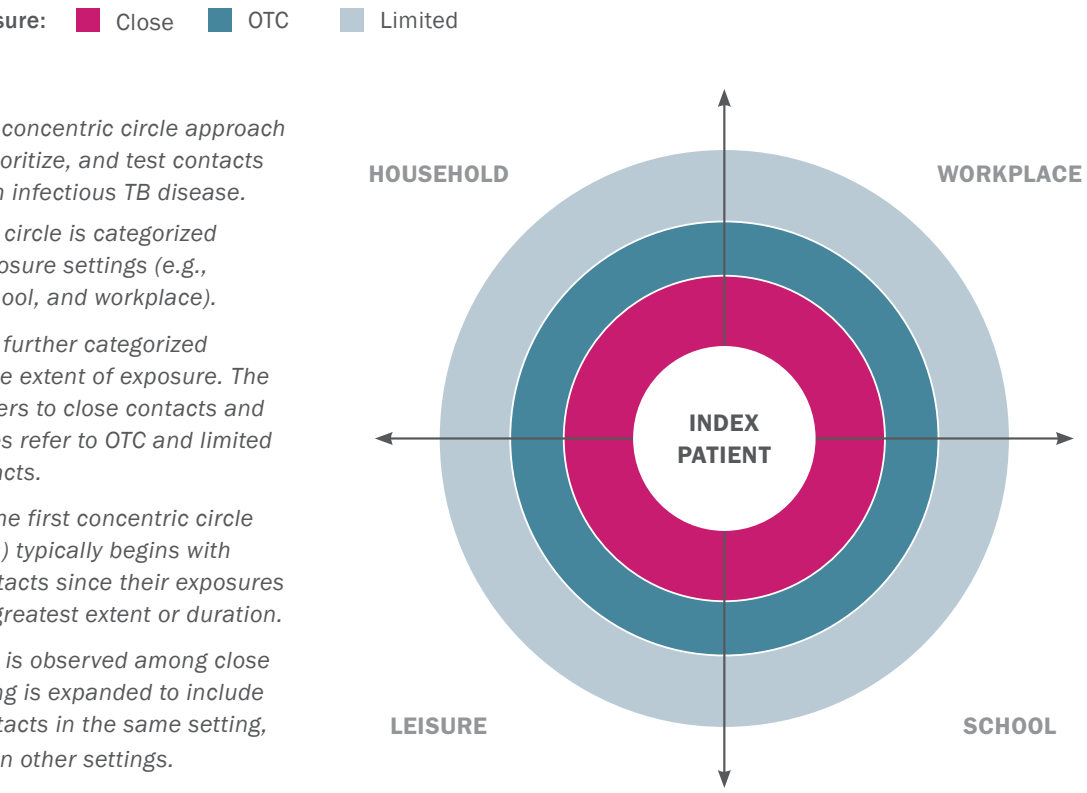
- **Close contact:** Persons who have prolonged, intense, or frequent contact—on average eight hours or more per week of exposure—with a patient with active TB disease during the infectious period.
- **Other-than-close (OTC) contact:** Persons who have less prolonged, intense, or frequent contact with a patient with active TB disease during the infectious period
- **Limited exposure contact:** Persons who have more casual and less extensive exposure than OTC contacts
- **Unknown exposure contact:** Persons who a patient has identified as a contact, but there is insufficient information regarding the extent of interaction and level of exposure

BTBC uses the concentric circle approach to organize, prioritize, and test contacts. The concentric circle is categorized by specific exposure settings (i.e., household, school, workplace, leisure).

Each setting is further categorized according to the extent of exposure. The inner circle refers to close contacts and the outer circle refers to OTC contacts. Evaluation of the first concentric circle (close) typically begins with household contacts since their exposures are usually of greatest extent or duration.

If transmission is observed among close contacts, testing is expanded to include OTC contacts in the same setting, or to contacts in other settings. Sometimes non-household contacts are as close as or closer than household contacts and their testing is not dependent on household results. (See *Figure 11.1: Concentric Circle Approach to Evaluating Contacts and Expanding Tuberculosis Contact Investigations*.)

FIGURE 11.1: Concentric circle approach to evaluating contacts and expanding tuberculosis contact investigations



BTBC uses the concentric circle approach to organize, prioritize, and test contacts to patients with infectious TB disease.

The concentric circle is categorized by specific exposure settings (e.g., household, school, and workplace).

Each setting is further categorized according to the extent of exposure. The inner circle refers to close contacts and the outer circles refer to OTC and limited exposure contacts.

Evaluation of the first concentric circle (close contacts) typically begins with household contacts since their exposures are usually of greatest extent or duration.

If transmission is observed among close contacts, testing is expanded to include either OTC contacts in the same setting, or to contacts in other settings.

Although it is important that all elicited contacts complete evaluation, contacts are prioritized for contact evaluations based upon the following characteristics:

1. Close contacts of patients with clinical characteristics associated with infectiousness:
   - Smear- and culture-positive pulmonary or laryngeal TB disease
   - Cavitary lesions on CXR
2. All contacts (close and OTC) who have one or more of the following factors associated with an increased risk of progressions to active TB disease once infected:
   - HIV infection
   - Other immunosuppressive conditions or taking immunosuppressive medications
   - Low body weight
   - Children younger than five years of age
3. Contacts with symptoms consistent with active TB disease
4. Contacts of an infectious patient with multidrug-resistant TB (MDR-TB)

TABLE 11.2: Criteria for prioritization of contacts and subsequent public health action

CATEGORY	CRITERIA	PRIORITY/ACTIONS
Contacts most likely to be infected	• Close contacts • Contacts exposed to highly infectious patients based on: - AFB sputum smear-positive - Cavitary disease on CXR - Cough • Contacts who were: - Exposed in small, crowded, or poorly ventilated spaces - In close proximity to the patient	• High priority for contact investigation • Initiate contact investigation within 3 working days (phone call and at least 1 home visit)
Contacts at increased risk of developing TB disease once infected	• Children younger than 5 years of age • Contacts with any of these characteristics/conditions: - HIV/AIDS - Other immunosuppressive conditions - Diabetes mellitus - Silicosis - Prolonged corticosteroid therapy (e.g., receiving the equivalent of more than 15 mg of prednisone for longer than 1 month) - Receiving other immunosuppressive agents (e.g., chemotherapy) - Cancers of the head, neck, or lung - Hematologic or reticuloendothelial malignancies (e.g., leukemia, Hodgkin's disease) - Chronic renal failure - Chronic malabsorption syndromes - Intestinal bypass or gastrectomy - Low body weight (10% or more below ideal) - Radiologic evidence of old, healed TB lesions - Various dermatological, rheumatological, or GI disorders (e.g., inflammatory bowel disease, psoriasis, rheumatoid arthritis, chronic hepatitis) who are likely to be placed on medications that may impair their immune systems	• High priority for contact investigation • Initiate contact investigation within 3 working days (phone call and at least 1 home visit)
Contacts to MDR-TB index patients	• Both close and OTC	• Initiate contact investigation within 3 working days (phone call and at least 1 home visit)

Abbreviations Used: AFB=acid-fast bacilli; AIDS=acquired immunodeficiency syndrome; CXR=chest radiograph; GI=gastrointestinal; HIV=human immunodeficiency virus; MDR-TB=multidrug-resistant tuberculosis; mg=milligrams; OTC=other-than-close; TB=tuberculosis

INTERVIEWING CONTACTS

Similar to interviews for patients with active TB disease, all interviews with contacts are conducted under conditions that are private and confidential, whether conducted by phone, in person, or using another method. The identity of the patient with active TB disease is not identified when interviewing contacts (e.g., avoid using gender specific pronouns). The purpose of the interview is to:

- Notify the contact of their exposure to an infectious person with TB disease
- Confirm contact information provided by the index patient including name, phone number, and address
- Ascertain specific medical history information:
  - Are symptoms of active TB disease present?
  - Does the contact have medical risk factors (e.g., immunosuppressive medical conditions)?
  - Any prior history of LTBI or TB disease?
- Educate the contact about TB transmission and the steps and reasons for a contact investigation. This includes:
  - Educating the patient about TB pathogenesis and transmission
  - Explaining why evaluation is recommended for the individual contact
  - Describing the types of tests for TB infection that are available (tuberculin skin test [TST] and interferon gamma release assay [IGRA]), the meaning of results, and the need for a CXR for contacts with a prior history of positive TB test result
  - Explaining the need to perform a test both during the window period and—if the initial test is negative—during the post window period to ensure an accurate result
  - Describing next steps that will occur if the test for TB infection is positive
- Establish a mutually agreed upon plan for evaluation as soon as possible

The details of the interview are documented in the electronic surveillance and case management system. Arrangements are made with the individual to be evaluated at a location mutually agreed upon (e.g., tested in the community by trained BTBC staff, at a NYC Health Department TB clinic, or at a provider chosen by the individual). If the contact chooses to see a community provider, the provider is informed of the contact exposure and window period to ensure that proper evaluation and evaluation results are obtained and entered into the TB case management and surveillance system.

To ensure systematic information is collected on all identified contacts, the TB 77 form is used to collect demographic and clinical risk factors that may influence a contact's risk of progressing to TB disease. The TB 77 can be found on the NYC Health Department intranet at https://nycdohmh.sharepoint.com/sites/dis5/TBadministration/Forms/BTBC%20Forms%20by%20Name/TB%20Testing%20Form%20-%20TB%2077.pdf#search=TB%2077

EVALUATING CONTACTS AND DETERMINING THE NEED FOR TREATMENT

A contact evaluation includes a review of TB symptoms, medical risk factors, and history of TB screening, as well as a test for TB infection (except for individuals with a documented prior positive test result). Although either the TST or a blood-based IGRA can be used to screen a contact for TB infection, BTBC prefers the IGRA for any individual older than two years of age. IGRAs have operational advantages (only one patient visit), as well as greater specificity (decreased false-positive test results due to the bacilli Calmette-Guérin [BCG] vaccination and most other nontuberculous mycobacterium [NTM]).

Any contact with symptoms consistent with active TB disease, who may be immunosuppressed (due to a medical condition or treatment), or who has risk factors for progression to active TB disease once infected (e.g., children younger than five years of age) has a physical examination and a CXR regardless of the initial IGRA or TST test result as soon as possible, and is retested shortly after the window period ends.

Immune-competent contacts or those without medical risk factors who test IGRA or TST negative, but whose last day of exposure is less than eight weeks prior to testing, should be retested shortly after this eight-week (window) period and re-interviewed for TB symptoms.

Contacts who test IGRA- or TST-positive are referred for a CXR and medical evaluation. Close contacts who have tested IGRA- or TST-positive prior to their current exposure are referred for medical evaluation, a CXR, and consideration for treatment (or re-treatment) of LTBI.

Contacts exhibiting signs and symptoms consistent with active TB disease are referred for medical evaluation regardless of their test for TB infection result. (See *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*.)

SPECIAL CONSIDERATIONS FOR EVALUATING CONTACTS

PREGNANT CONTACTS

Individuals who are pregnant and identified as contacts to infectious TB patients undergo evaluation to rule out active TB disease, and if necessary, receive treatment for LTBI. Evaluation includes:

- Medical history (i.e., review of TB symptoms, medical risk factors, and history of TB screening)
- Test for TB infection
- CXR

Pregnant persons with a positive IGRA or TST require a CXR to rule out active pulmonary TB disease. A CXR is immediately obtained for the following persons with any of the following, even during the first trimester of pregnancy:

- Symptoms suggestive of TB disease (e.g., fever, cough, chills, night sweats, chest pain)

- HIV infection or other immunosuppressive conditions
- Recent close contact to a person with infectious TB

If active TB disease is ruled out, treatment for LTBI is based on individual risk factors; however, pregnant patients who have HIV infection and/or are close contacts to infectious TB patients can begin treatment for LTBI during the first trimester of pregnancy. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.)

INFANT AND CHILD CONTACTS

Infants (younger than one year of age) and children younger than five years of age (up to the day of their fifth birthday) who are contacts of persons with infectious TB are at high risk for TB infection and progression to active TB disease and are prioritized for TB screening.

To ensure appropriate evaluation and reduce the risk of progression to active TB disease for infant and child contacts, pediatric evaluations include:

- Medical history
- Physical exam
- Baseline test for TB infection
- CXR (both posterior-anterior and lateral) regardless of the test for TB infection result
- Window prophylaxis treatment until the result from the retest is known

Medical providers may use clinical discretion when performing a test for TB infection on children younger than six months of age, as these tests are not considered reliable until at least six months of age. As a result, some child contacts may have a window period longer than eight weeks if their last day of exposure to an infectious patient was prior to six months of age.

If children younger than five years of age live in the same household as a person with infectious TB disease, the infectious patient is kept out of the home until one of the following conditions is met:

- The person with infectious TB is taking appropriate anti-TB treatment and has demonstrated an adequate clinical response to treatment (i.e., AFB-negative smears and improvement in symptoms).
- The child has started LTBI treatment, including window period prophylaxis.
- If the patient remains infectious due to unresponsive MDR-TB and cannot be separated from the child, BCG vaccine can be considered for the child if the test for TB infection is negative (least desirable option). (See *Appendix D: The Use of Bacille Calmette-Guérin Vaccine*.)

Any infant or child contact with an abnormal CXR consistent with TB requires treatment for active TB disease regardless of the results of baseline or repeat IGRA or TST tests. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection* and *Chapter 7: Diagnosis and Treatment of Pediatric Tuberculosis Disease*.)

CONTACTS TO MULTIDRUG-RESISTANT TUBERCULOSIS

BTBC staff work diligently to ensure that contacts to patients with MDR-TB are evaluated and started on treatment for LTBI when appropriate. Similar to other contacts, evaluations include:

- Medical history
- Physical exam
- Test for TB infection
- CXR, when indicated

Once active disease has been ruled out, a clinical decision of whether to treat for LTBI is made. If treatment is deemed appropriate, the LTBI regimen is based on the index patient's drug-susceptibility results.

If the contact is not treated for LTBI, follow-up evaluations including a physical exam and CXR are conducted at regular intervals (four, eight, 12, 18, and 24 months) to ensure the contact has not developed active TB disease. BTBC staff conduct comprehensive patient education for the contact regarding the symptoms of active TB disease and when to seek clinical care. (See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*.)

ENSURING THE POST-WINDOW EVALUATION OF CONTACTS

If the reaction to the initial (window period) IGRA or TST is negative, contacts are tested again immediately eight weeks after their last date of exposure to the patient with infectious TB disease (i.e., after the window period).

The following individuals are recommended to start window prophylaxis for LTBI, even if the initial test is negative:

- Children younger than five years of age
- Individuals between five and 15 years of age, at the physician's discretion
- Individuals with HIV infection or other immunosuppressive condition

The evaluating provider reviews the window period and ensures that the patient is scheduled for a repeat test for TB infection.

If the reaction to the post-window IGRA or TST is negative and the individual is both asymptomatic and no longer exposed to a patient with infectious TB disease, follow-up is discontinued for immune-competent contacts (including immune-competent children). Window period prophylaxis, if started, can be discontinued. Close contacts have HIV infection or are otherwise immunosuppressed require a full course of LTBI treatment, regardless of age or previous treatment.

If the reaction to the post-window IGRA or TST is positive, the provider completes the evaluation with a CXR and physical examination. Once active TB disease is ruled out, LTBI treatment is initiated.

SCREENING AND TESTING FOR HUMAN IMMUNODEFICIENCY VIRUS

All contacts should be evaluated for HIV infection, as HIV increases the risk of disease progression for persons with LTBI. HIV counseling and testing is offered to all contacts not previously known to have HIV infection. Rapid HIV testing is available at all NYC Health Department TB clinics; all contacts can be referred to a NYC Health Department TB clinic or to their private physician for HIV counseling and testing.

ASSESSING TRANSMISSION IN A CONTACT INVESTIGATION

The results of TB testing and evaluation among contacts are reviewed to assess the likelihood that transmission occurred within an exposure setting. In household contact investigations, BTBC uses the following indicators as criteria to expand the contact investigation using the concentric approach:

- Child born in the United States (U.S.) with no history of travel outside the continental U.S. who tests positive for TB infection or is diagnosed with TB disease
- Contact(s) who are diagnosed with active TB disease (secondary case[s])

Additionally, if 50% or more of the household contacts, regardless of the contacts' country of birth, test positive for TB infection, then the contact investigation will be expanded to include additional contacts.

In household contact investigations, the approach used to determine when expansion of an investigation is necessary is less exact than the analysis used in larger congregate setting exposures.

CONDUCTING AN EXPANDED CONTACT INVESTIGATION

If expansion of a contact investigation is indicated, the next circle of contacts may be in congregate settings such as a workplace, school, correctional facility, hospital/healthcare setting, and shelter or other non-household setting.

A decision to initiate an expanded contact investigation (ECI) in a non-household setting is influenced by multiple factors:

- Identification of transmission among closest contacts (household contacts, family, and friends)
- Presence of medical risks in contacts (e.g., HIV infection, children younger than five years of age)
- Characteristics of the index patient that suggest infectiousness (AFB smear-positive, cavitary CXR, and presence of cough)
- Extent and duration of exposure in the congregate setting

When a decision has been made to initiate an investigation at a congregate setting, a BTBC staff member informs the case management team, coordinates the investigation at the site, and serves as the primary point of contact for the investigation. The infectious patient is informed about the initiation of the ECI, and if relevant, steps are taken to protect the confidentiality of the patient (e.g., the patient may agree to attend the site screening, but is not actually tested).

BTBC works closely with site management by educating them about TB and explaining the need for the investigation. BTBC facilitates testing by explaining how to notify contacts at the site, setting parameters for information exchange, communicating requirements to maintain confidentiality of any patient information site management may be aware of, conducting a walk-through at the site, and establishing the plan for a TB educational session, and notification and testing of contacts. Screening is conducted on site at the convenience of site management. Contacts at the congregate setting who are not evaluated at the site may go to their private provider or may be referred to a NYC Health Department TB clinic or to BTBC staff for follow-up and evaluation. In certain situations, senior level Health Department staff and the Press Office are notified of an ECI initiation, especially for investigations occurring in sensitive exposure settings.

Contact investigation results are reviewed to assess the likelihood that transmission occurred within an exposure setting. (See *Table 11.2: Transmission Assessment Criteria for Contact Investigation in Congregate Settings*.) If there is evidence of transmission at the site, a determination is made about further expansion to other site contacts or possibly other congregate settings identified by the index patient.

Transmission assessments are made by reviewing TB evaluation results using the following definitions:

- **Probable transmission** (prompts expansion of the contact investigation)
  - Contact who has been diagnosed with active TB disease (i.e., secondary case)
  - Contact(s) with a documented test for TB infection conversion from a negative to positive within two years
  - Proportion of positive test results among contacts is higher than expected in a similar non-exposed population and 75% or more of eligible contacts were evaluated
- **Possible** (prompts expansion of the contact investigation)
  - Proportion of positive test results among contacts is higher than expected in a similar non-exposed population and fewer than 75% of eligible contacts were evaluated
- **Unlikely** (contact investigation is not usually expanded)
  - Proportion of positive test results among contacts was less than or equal to expected in a similar non-exposed population and 75% or more of eligible contacts were evaluated
- **Cannot be assessed** (usually need to expand contact investigation)
  - Proportion of positive test results among contacts was less than or equal to expected in a similar non-exposed population and fewer than 75% of eligible contacts were evaluated

On occasion, there may be a need to conduct an environmental assessment at a congregate setting. This typically occurs when there is the possibility that poor ventilation may contribute to a more intense TB exposure. BTBC or other Health Department staff with environmental science expertise are engaged to further investigate an exposure site where findings cannot be readily explained and/or when a secondary case is identified. Environmental assessment findings are shared with site management.

TABLE 11.2: Transmission assessment criteria for contact investigation in congregate settings

ASSESSMENT	CRITERIA
Transmission likely	• Secondary case or • Documented TB test conversion from a negative to positive within two years, or • Proportion of positive test results among contacts is higher than expected in a similar non-exposed population* and 75% or more of eligible contacts were evaluated
Transmission possible	• Proportion of positive test results among contacts is higher than expected in a similar non-exposed population* and fewer than 75% of eligible contacts were evaluated
Transmission unlikely	• Proportion of positive test results among contacts was less than or equal to expected in a similar non-exposed population* and 75% or more of eligible contacts were evaluated
Cannot be assessed	• Proportion of positive test results among contacts was less than or equal to expected in a similar non-exposed population* and fewer than 75% of eligible contacts were evaluated

*Data sources include data from the National Health and Nutrition Examination Survey (NHANES) and Stennis et al. Estimated prevalence of tuberculosis infection among a New York City clinic population using Interferon-gamma release assays. *Open Forum Infec Dis.* 2014 Sept; 1(2)

Abbreviations Used: TB=tuberculosis

SPECIAL CONSIDERATIONS FOR CONTACT INVESTIGATIONS IN HEALTHCARE SETTINGS

Following an exposure in a healthcare setting, BTBC and infection control staff at the facility review the exposure scenario to determine what actions to take. Although facility personnel are responsible for conducting the investigation and New York State (NYS) oversees the investigation, BTBC is available to provide technical assistance and guidance during the investigation, if needed. Typically, the facility's staff contacts are tested by the facility's employee health program, whereas patient contacts (no longer at the facility) may be referred to BTBC for screening and follow-up. Results of contacts who are tested by the facility are shared with BTBC. The final results are reviewed and transmission assessments are made as described above.

CONDUCTING CASE MANAGEMENT FOR CONTACTS BEING TREATED FOR LATENT TUBERCULOSIS INFECTION

Every contact started on treatment or window prophylaxis for LTBI is managed through treatment completion or until the contact is dispositioned. Since case management responsibilities are assigned based upon where the patient obtains care, it is not infrequent that several BTBC staff members are responsible for the follow-up and care of contacts and the infectious patient.

The BTBC staff member managing the contact is responsible for the following:

- Updating the contact's event in the electronic surveillance and case management system
- Reminder phone calls for upcoming medical visits
- Monitoring monthly follow-up medical visits
- Performing "return to service (RTS)" activities
- Collecting/requesting information from the treating provider regarding treatment status and completion for contacts
- Providing treatment and treatment outcome information for all contacts to the BTBC staff managing the patient with infectious TB

The BTBC staff member managing the index patient is responsible for the following:

- Verifying that all contacts are being case managed (done via the electronic surveillance and case management system or discussion with other BTBC staff)
- Knowing the status of all contacts, even if another staff member is managing those individuals
- Reporting the outcome of the contact investigation at the weekly case management meeting where the index patient is being presented

SUPERVISORY REVIEW OF CONTACT INVESTIGATIONS

The status of all contact investigations performed by BTBC are reviewed by supervisory staff on an on-going basis to ensure appropriate care for all patients. The status of contact investigations are also reviewed by the BTBC Director during quarterly cohort reviews for all TB patients. (See *Chapter 16: Program Evaluation and Research*.)

SOURCE CASE INVESTIGATIONS

Source case investigations attempt to identify the unknown person with infectious TB disease who transmitted TB to a child less than five years of age who has been diagnosed with TB disease or who has signs and symptoms consistent with TB disease (i.e., the source who infected the child). Given the low prevalence of TB disease in the NYC population, TB disease in a U.S.-born child who generally stays in the country constitutes evidence of recent transmission. The assumption is that any child with TB disease must have been exposed very recently to someone close to them, and that person may have undiagnosed TB disease. Young children with active TB disease usually do not transmit TB to others, and their contacts are unlikely to be infected.

A source case investigation follows many of the same procedures as a standard contact investigation except that retesting is not required for associates who test negative (unless an index is found; however in those situations a new window period for all contacts around that index patient needs to be set). BTBC staff work closely with parents or guardians to identify anyone "associated" with the child. Parents or guardians

are asked about any child associates who may be symptomatic in order to prioritize evaluation for anyone with symptoms and prevent further exposure to others. Any associate identified is evaluated for symptoms of TB disease, tested for LTBI, and given a CXR and medical evaluation; any associates who have symptoms consistent with TB disease also provide sputum for smear and culture. The source case investigation begins with the closest associates and expands out as needed (i.e., household members, babysitters, day care providers, teachers, etc.).

Regardless of the child's site of disease, a source case investigation is initiated to identify:

- The source case (i.e., the individual with active TB disease who may have infected the child)
- Other secondary TB cases
- Other children and adults who may have been infected in the same setting. These individuals are technically "associates" since children of this age are not routinely considered infectious and thus these individuals are not "contacts."

ADDRESSING NON-ADHERENCE

Adherence to LTBI treatment among contacts is essential to prevent progression to active TB disease. Adherence to the recommended evaluation is essential to ensure that contacts have been fully evaluated for active TB disease and LTBI. Contacts who miss any scheduled appointments by telephone or home visits are followed up with, when necessary. To encourage adherence, phone calls are conducted prior to each appointment. (See *Chapter 10: Case Management for Patients with Tuberculosis* and *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

SUMMARY

Contacts have the greatest risk of developing TB disease compared to other risk groups. As a result, contact investigations are utilized to identify and control TB transmission to prevent future cases of TB disease. To ensure appropriate care and follow-up is provided to all contacts, the case management team works collaboratively, utilizing BTBC staff and resources, as well as external partner cooperation and support.

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CHAPTER 12: TUBERCULOSIS GENOTYPING AND CLUSTER INVESTIGATION

INTRODUCTION

Tuberculosis (TB) is an airborne disease that spreads from person to person. As such, TB transmission is an important driver of TB morbidity. Efforts to identify and interrupt transmission are vital to the New York City (NYC) Bureau of TB Control's (BTBC) TB prevention and care activities.

TUBERCULOSIS GENOTYPING

TB genotyping is a set of laboratory-based techniques used to characterize *Mycobacterium tuberculosis* (*M. tuberculosis*) complex strains based on distinct patterns identified in specific regions of the TB genome. Several TB

genotyping methods are commonly used in the United States (U.S.), including spacer oligonucleotide typing (spoligotyping), variable-number tandem repeat of mycobacterial interspersed repetitive unit analysis (MIRU), IS*6110* restriction fragment length polymorphism analysis (RFLP), and whole genome sequencing (WGS).

TB genotyping results, when combined with epidemiologic data, help to identify TB patients who may be involved in the same chain of recent transmission, or to rule out transmission among patients who are otherwise linked but have nonmatching genotypes. These results can also help distinguish between relapse and re-infection in patients with a prior history of TB disease.

BTBC implemented universal TB genotyping in 2001 using spoligotyping and RFLP analysis, following a NYC Health Code change mandating that at least one *M. tuberculosis* complex isolate from all patients with at least one positive culture for TB be sent for genotype analysis. Nationally, universal genotyping was initiated in 2004 through the National TB Genotyping Service, which conducts spoligotyping and MIRU analysis for all culture-positive patients in the U.S.

Whole genome sequencing (WGS) was made available to TB programs selectively through the Centers for Disease Control and Prevention (CDC) in 2013. In 2018, CDC began sequencing all isolates as part of a planned transition to replace spoligotyping and MIRU with WGS in 2022. NYC began universal WGS in 2016 in partnership with the New York State Department of Health Wadsworth Center. Currently, BTBC uses a combination of genotyping methods to characterize strains, assess transmission, link patients, guide epidemiologic investigation, and detect potential outbreaks.

The NYC Health Code [§ 13.05(a)] mandates that within 24 hours of observing growth of *M. tuberculosis* complex in a culture from any specimen, a portion of the initial culture must be sent for deoxyribonucleic acid (DNA) analysis to the New York City Health Department Public Health Laboratory (NYC PHL). (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

TUBERCULOSIS GENOTYPE REVIEW AND CLUSTER DETECTION

TB genotype results are reviewed by epidemiologists as they are received from labs and are considered alongside patient characteristics and other epidemiologic data. BTBC staff review genotyping results for evidence of potential specimen contamination to quickly identify patients with known outbreak strains, and to support or refute transmission among patients with known epidemiologic links. (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.) Patients whose TB isolates have genotyping results matching at least one other patient with TB disease in NYC are clustered, reviewed, and prioritized for further investigation.

While the genotyping methods used to define clusters have varied over time in NYC, the fundamental components of the cluster detection process and the application of genotyping results to refute/identify potential transmission remain unchanged.

The CDC's National TB Genotyping Service performs universal genotyping for all patients with culture-positive TB in the U.S. using spoligotyping, 24-locus MIRU-VNTR analysis, and whole genome sequencing. The TB GENOTYPING INFORMATION MANAGEMENT SYSTEM (TB GIMS) is a secure web-based system that facilitates the linking of genotyping results with patient data reported to the National Tuberculosis Surveillance System, allowing users to review and analyze data related to TB genotype clusters.

CLUSTER PRIORITIZATION

Patients with TB disease having characteristics suggestive of recent infection and/or with a clustered TB strain suggestive of recent transmission in NYC are reviewed and subsequently prioritized for investigation. Although consensus on an exact definition is not well-defined in the literature, recent transmission generally refers to a transmission event within two years prior to the onset of active TB disease. As such, cases are prioritized for further review using the following considerations:

- Patient characteristics suggestive of recent, local transmission (e.g., young age; human immunodeficiency virus [HIV] infection or other immunosuppression; recent test for TB infection conversion; recent history of healthcare work; homelessness or incarceration)
- Strain characteristics (e.g., strains newly identified in NYC; rapid cluster growth)
- Time component among clustered patients (e.g., diagnosis within 24 months of a previous patient with matching strain and pulmonary TB)
- Infection with a multidrug-resistant (MDR) strain
- Other factors (e.g., date of arrival in NYC among foreign-born patients; similar patient characteristics among clustered patients)

The decision to prioritize a genotype cluster for investigation is multifactorial. The following questions help frame key considerations for prioritizing cluster investigations:

- Are there multiple cases with the same strain identified in the previous 12 months?
- Are recent patients in the cluster sputum smear-positive or do patients have cavitary lesions (i.e., suggestive of infectious TB disease)?
- Did any recent patients have prolonged infectious periods before diagnosis?
- Is a homeless shelter, correctional institution, or other congregate setting involved?
- Do patients have risk factors, such as substance use, that can be associated with difficult or incomplete contact investigations?
- Do patients and their contacts have similar risk factors that suggest an increased risk for disease progression, such as HIV or renal failure?
- Do any patients have drug-resistant TB (DR-TB)?

- Were any cases found among contacts missed by previous contact investigations? Could other contacts have also been missed?
- Were any cases among persons previously identified as contacts but not fully evaluated or treated? Could other contacts be at risk?
- Are epidemiologic links among patients unclear or not identified, or is there reason to suspect that contact investigations have not been adequately thorough?
- Is the cluster comprised of cases with a new genotype in the county or state?
- Is it the same genotype as a known outbreak?
- Has the cluster grown rapidly in the past two to three years?
- Does the cluster include children younger than five years of age?
- Do patients in the cluster have evidence of recent infection (e.g., test for TB infection conversions)?

For additional guidance on TB cluster prioritization, see the CDC document: *Prioritizing Tuberculosis Genotype Clusters for Further Investigation & Public Heath Action* at https://www.cdc.gov/tb/programs/genotyping/Prioritizing_Tuberculosis_Genotype_Clusters_August2017.pdf.

CLUSTER INVESTIGATION

Once reviewed, eligible clusters are assigned to an epidemiologist and investigated systematically to identify links between patients, identify previously unknown exposure sites or contacts, inform transmission hypotheses, and inform potential public health intervention. The extent of investigation varies depending on patient and cluster characteristics and may include the following:

- Review and analysis of patient characteristics (demographic, clinical, social) and other surveillance data
- Medical chart review
- Review of case management, contact investigation, and previous cluster investigation notes
- Consultation with regional and clinic staff
- Patient interview
- Mapping and spatial analysis
- Social network analysis
- External database searches
- Community visits
- Consultation with external stakeholders (e.g., healthcare providers, other city agencies, community organizations)

DATA SOURCES

In addition to review of medical charts, patient characteristics, and other data available in the electronic TB surveillance and case management system, investigators utilize a number of external data sources. These include notes from previous contact and cluster investigations, local social service and medical facilities databases (e.g., shelter history, immunization registry), vital records, social media platforms, and public records databases. Communication with regional and clinic staff are an integral part of cluster investigation and occur throughout the prioritization and investigation process.

PATIENT INTERVIEW

Whenever possible, patients are interviewed in person using a tailored questionnaire. Interviews are semi-structured and open-ended, and consist of questions relating to a patient's current and previous TB history and exposures; current and previous addresses, worksites, and schools; country of birth, travel history and entry into the U.S.; social history; contacts (e.g., family, romantic partners, roommates, friends); leisure sites and activities; history of stay in congregate settings (e.g., shelters, prisons, healthcare facilities); drug and alcohol use; and medical care-seeking history. The time period of focus for cluster investigation is usually longer than for a contact investigation and may include contacts, sites, and activities for the preceding two to five years. Interview guides are adapted to each cluster and are often informed by information gathered through previous patient interviews.

INCLUSION OF NON-GENOTYPED AND OUT-OF-JURISDICTION PATIENTS

The cluster review and investigation process often includes non-genotyped or clinical TB cases and contacts that may be related to the cluster. This includes cases with known epidemiologic links to cluster cases, cases diagnosed in the same time frame and/or within the same geographic area, and/or patients who have similar demographic and clinical characteristics as cases in the cluster of interest. If there is a possibility that related cases have occurred in another jurisdiction, investigators consult the national TB genotyping database and discuss epidemiologic links and possible intervention with local, state, and/or national colleagues.

ASSESSING PATIENT- AND CLUSTER-LEVEL TRANSMISSION

During cluster investigation, transmission assessments are made at both the patient level and the cluster level. (See *Table 12.1: Criteria Used for Patient-Level Tuberculosis Transmission Assessment*.) Patient-level transmission assessment is based on a number of factors, including the following:

- Known TB exposure and/or history of TB disease or test for TB infection results (e.g., prior positive results, test for TB infection conversion)
- Presence and characteristics of epidemiologic links
- Analysis of genotyping results among epidemiologically linked patients
- Presence of a plausible source case in NYC (e.g., a previously diagnosed patient with infectious TB having genotype results that do not refute transmission)

TABLE 12.1: Criteria used for patient-level tuberculosis transmission assessment

ASSESSMENT	CRITERIA

Cases attributable to ***recent*** transmission	• **Definite:** Patients younger than 2 years of age
	• **Likely:**
	  • Known contact to a potentially infectious TB disease patient within 2 years (genotyping does not refute)
	  • Documented test for TB infection conversion within 2 years

Cases attributable to ***local*** transmission	• **Likely:** Known contact to a potentially infectious TB disease patient in NYC (genotyping does not refute)
	• **Unlikely:**
	  • Development of TB disease soon after arrival in the United States
	  • Unique genotype in NYC

Cases attributable to *recent,* ***local*** transmission	• **Likely:** Known contact to an infectious TB patient in NYC within 2 years (genotyping does not refute)
	• **Unlikely:**
	  • Development of TB disease soon after arrival in the United States
	  • Unique genotype in NYC
	• **Possible:**
	  • Patients with culture-negative TB disease or incomplete genotype results (date of entry does not refute)
	  • Patients with exact- or near-match genotype to a potentially infectious TB disease patient within 2 years

Abbreviations Used: NYC=New York City; TB=tuberculosis

Epidemiologic links between patients are assessed and documented according to strength of the link. Patients with a definite epidemiologic link include those who have named each other as contacts, have a contact in common without naming each other as contacts, or have reported history of spending time during a common time period at the same location. Possible links exist among patients who have a similar social network or have spent time in the same area (no specific location), without naming each other as contacts.

At the cluster-level, multiple elements contribute to an assessment of transmission among patients with active TB disease, including patients' clinical, demographic, and social characteristics; geographic distribution of patients; known relationships and exposure sites among patients; underlying population characteristics (e.g., socio-demographic); and strain characteristics and history in NYC. Transmission within a cluster is dynamic across time and space, and assessment changes as new patients are identified.

TUBERCULOSIS OUTBREAKS

A TB outbreak investigation is initiated when there is indication of ongoing recent TB transmission and disease that is higher than expected given the local TB epidemiology, population demographics, and/or prevalence of a given strain in NYC. The goals of an outbreak investigation are similar to the goals of routine TB control and include:

- Quickly identify outbreak-associated patients
- Identify and interrupt transmission
- Ensure prompt TB evaluation and diagnosis
- Ensure treatment completion
- Ensure thorough and complete contact investigations
- Identify mechanisms to prevent future outbreaks

Though the steps in an outbreak investigation are similar to those involved in a cluster investigation, an outbreak investigation often requires greater urgency and resources, may involve multiple stakeholders, and often places greater demands on BTBC. Key components of outbreak response include establishing roles and communication mechanisms; identifying and addressing chain-of-command issues across local, state, national, and other agencies; creating data management systems; ensuring ongoing communication among internal and external partners; reassessing priorities/activities as new information becomes available; assessing available resources/barriers frequently; documenting and assessing response activities (e.g., cost, timelines, impact); and identifying opportunities to prevent future outbreaks.

INITIATING PUBLIC HEALTH ACTION

Cluster and outbreak investigation findings are communicated through multiple mechanisms; public health interventions are developed accordingly. Newly identified contacts or exposure sites and additional information that might inform ongoing case management or clinical care (e.g., patient locating information, past medical history) is communicated to case managers and clinicians immediately, while opportunities to improve routine TB control policies/protocols and community-level interventions may be developed over time in conjunction with multiple stakeholders.

The decision to initiate public health intervention is multifactorial. The following questions help frame key considerations for initiating and guiding public health action in the context of available resources and other factors:

›› Is there reason to suspect false-positive lab results? (See *Chapter 4: Laboratory Testing for Tuberculosis Disease*.)

›› Are there newly-identified contacts or exposure sites? (See *Chapter 11: Contact Investigation*.)

›› Was an opportunity to prevent additional TB cases identified?

›› Was an opportunity to improve routine TB control protocols identified?

›› Is there potential for rapid cluster growth?

- Patient clinical characteristics suggestive of infectiousness
- Patient social characteristics suggestive of high-risk settings/contacts
- Contact characteristics suggestive of high risk for infection or progression
- Barriers to care or delayed diagnoses identified among patients
- Incomplete/difficult contact investigations
- Exposure in congregate setting(s) or healthcare facilities

SUMMARY

Assessment of TB transmission is an integral component of NYC's routine TB care and management activities, and informs public health intervention on multiple levels. Along with epidemiologic data, genotyping is an important tool for understanding local transmission dynamics and informing meaningful public health intervention. TB transmission dynamics are complex and multi-factorial; understanding them often requires extensive knowledge of the patients and communities affected.

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CHAPTER 13: INFECTION CONTROL

INTRODUCTION

Tuberculosis (TB) is an airborne disease that can be transmitted from person to person. Transmission of TB may occur if a person with respiratory TB disease (i.e., TB of the larynx, trachea, bronchi, or lung) coughs, sneezes, or otherwise generates aerosols that contain viable TB in droplet nuclei. If someone nearby inhales the bacteria, they may become infected. It is estimated that approximately 10% of those who are infected will subsequently develop active TB disease. Good infection control practices limit the opportunity for the spread of tuberculosis.

GENERAL PRINCIPLES OF INFECTION CONTROL

Not all patients with TB are infectious; transmission can only occur when infectious aerosols are generated. The following clinical characteristics of a

patient with active respiratory TB disease correlate with an increased risk of infectiousness:

- Presence of cough
- Positive acid-fast bacilli (AFB) sputum smear
- Positive TB sputum culture
- Presence of a cavity on chest radiograph (CXR)

Infection control measures can reduce the risk of transmission of TB. The Bureau of TB Control's (BTBC) infection control policies are consistent with the Centers for Disease Control and Prevention (CDC)'s 2005 guidelines for preventing TB transmission in healthcare settings. The New York State (NYS) Department of Health provides regulatory oversight of infection control measures in healthcare facilities within the state. The New York City (NYC) Health Code provides additional regulatory authority in certain situations, such as oversight of the discharge of a potentially infectious person from a NYC hospital, or detention of a potentially infectious person in a hospital. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.)

HIERARCHY OF INFECTION CONTROL MEASURES

Infection control programs use a hierarchy of measures to reduce the risk of TB transmission. At the highest level, administrative controls reduce risk across an entire clinical setting by decreasing the risk for exposure to persons with active, infectious TB disease. At the next level, environmental controls reduce risk in specific areas by decreasing the concentration of infectious droplet nuclei (aerosols) in an airspace. Finally, personal respiratory protection reduces risk at the individual level by providing additional protection to staff working in high-risk settings.

ADMINISTRATIVE CONTROLS

Administrative controls reduce exposure by enabling prompt identification, isolation, and appropriate treatment of persons with possible infectious TB disease. They include the following activities:

- Assign responsibility to specific person(s) for designing, implementing, evaluating, and maintaining a TB infection control program.
- Conduct a facility risk assessment. Management at the hospital or other healthcare facility review work duties that involve patient care or other interactions that potentially place staff at increased risk for TB transmission. On an annual basis, the experience of the previous year is reviewed to determine if additional transmission scenarios occurred and should be incorporated into an updated risk assessment.
- Develop, implement, and train staff on policies and procedures to ensure early identification, evaluation, and treatment of persons with possible infectious TB.
- Provide prompt triage and management of patients who may have infectious TB in the hospital or other facility.

- Promptly initiate and maintain administrative measures (e.g., placement of patient in isolation waiting room) for persons cared for in outpatient settings who may have infectious TB, and promptly recommend airborne infection isolation (AII) for such patients when they are admitted to an inpatient setting or home isolation when being discharged while infectious.
- Plan effectively for the discharge of the patient by coordinating the discharge with the patient's healthcare provider and promptly performing a home assessment and contact investigation.
- Implement environmental controls. Develop, install, maintain, and evaluate the effectiveness of engineering controls.
- Implement a respiratory protection program. Develop, initiate, install, maintain, and evaluate the effectiveness of the respiratory protection program.
- Implement precautions for cough-inducing procedures. Develop, implement, and enforce policies and procedures to ensure adequate precautions when performing cough-inducing procedures.
- Educate and train staff about infection control-related policies and procedures in place to minimize TB transmission risk.
- Screen healthcare workers for TB infection and disease. Develop and implement an annual TB screening program for staff at risk for TB transmission that also includes details about TB disease and latent TB infection (LTBI).
- 2019 recommendations from the National TB Controllers Association and CDC for screening and testing healthcare personnel include: individual baseline (preplacement) risk assessment, symptom evaluation and testing of persons without prior TB or LTBI, no routine serial testing in absence of exposure or ongoing transmission, treatment for healthcare personnel diagnosed with LTBI, annual symptom screening for persons with untreated LTBI, and annual TB education of all healthcare personnel.
- Promptly evaluate TB exposures or possible episodes of TB transmission. Modify existing procedures or policies when gaps are identified and re-train staff.
- Coordinate activities with NYS or other local health departments when appropriate.

ENVIRONMENTAL CONTROLS

Environmental controls prevent the spread and reduce the concentration of infectious airborne droplet nuclei. Environmental controls in NYC Health Department TB clinic patient care areas include: maintenance of negative pressure relative to the hallways, high-efficiency particulate air (HEPA) filtration, and ultraviolet germicidal irradiation (UVGI).

Airborne infection isolation rooms are the primary environmental control method used in an acute care facility where emergency or inpatient clinical services are provided to persons with possible or confirmed infectious TB. Airborne infection isolation rooms are typically present in inpatient settings, but not in most outpatient or long-term care facilities. In an airborne infection isolation room, the ventilation system

maintains the room at negative pressure relative to adjacent areas. When the door to an airborne infection isolation room is opened, air flows into the room, thus reducing the escape of contaminated air. Additional environmental controls in an airborne infection isolation room may include a HEPA filter and/or UVGI. (See *Table 13.1: Types of Environmental Controls to Prevent the Spread of Tuberculosis*.)

TABLE 13.1: Types of environmental controls to prevent the spread of tuberculosis

Most effective control	**Ventilation** • Controls direction of air flow (usually by negative pressure) to prevent contamination of air in areas surrounding a person with infectious TB disease • Dilutes and removes contaminated air • Exhausts contaminated air to the outside
Supplemental control	**HEPA filtration:** Cleans the air of infectious droplet nuclei **UVGI:** Kills or inactivates TB bacilli in the air

Abbreviations Used: HEPA=high-efficiency particulate air; TB=tuberculosis; UVGI=ultraviolet germicidal irradiation

PERSONAL RESPIRATORY PROTECTION

Administrative controls and environmental controls can substantially reduce TB transmission risk, but not eliminate the risk entirely. To further decrease the risk of TB transmission, a respirator should be worn in the following situations:

- Upon entering an airborne infection isolation room or any other closed air space used for the evaluation of a potentially infectious person who is not wearing a mask
- While performing sputum induction
- When in the home of a potentially infectious person who is not wearing a mask

Only the respirator for which an individual has been fit-tested should be used.

BTBC coordinates and implements the TB Respiratory Protection Program, which is a supplement to the Health Department's Respiratory Protection Program. Although a number of senior management staff are responsible for ensuring compliance with the program, the Respirator Protection Administrator is responsible for implementing the program. Key components of the program include: respirator selection, identification of covered employees, respirator fitting, respirator training, and program evaluation. BTBC staff included in the personal respiratory protection program are required to complete an initial and, thereafter, annual respirator medical clearance, respirator fit testing, and training.

Respirators reduce exposure by filtering out TB bacilli before the person breathes potentially contaminated air. Maintaining optimum fit of the respirator is critical to providing the expected respiratory protection. Facial hair must be minimized because this negatively impacts the respirator fit and results in sub-optimal respiratory protection. Specific respirators (e.g., N95) for TB control (and certain other airborne infectious

diseases) have been approved for such use by the National Institute for Occupational Safety and Health (NIOSH). The "N95" is a government efficiency rating that means that the respirator blocks about 95% of particles that are 0.3 microns in size or larger. Although N95 respirators may resemble surgical masks, they are much more effective at removing TB and other contaminants from inhaled air than are surgical masks. Individuals who cannot achieve an adequate fit with a N95 respirator are fitted and provided with another respirator. During training, respirator users are provided opportunities to handle and wear a respirator until they become proficient. See *Table 13.2: Using Masks and Respirators* to determine when potentially infectious patients use masks and staff use respirators.

TABLE 13.2: Using masks and respirators

SPECIFIC QUESTION	MASK (PATIENT) (A REGULAR "SURGICAL" MASK*)	RESPIRATOR (STAFF) (NIOSH-APPROVED, N95 OR HIGHER*)
Purpose of the ...	Is to reduce transmission from an infectious patient by capturing infectious droplet nuclei before they get into the air	Is to reduce exposure by filtering infectious droplet nuclei out of the air, before wearers breathe the air into their lungs
Who should wear a ...	Persons with potentially infectious TB	Staff who care for or interact with potentially infectious persons
When to wear a ...	**In a hospital setting:** • Patient is suspected of having infectious TB, but not yet placed in airborne infection isolation, and • Whenever patient leaves an airborne infection isolation room for any reason **In an outpatient setting:** • Outside airborne infection isolation room • When obtaining care **At home:** • Spending time with others in a common use area (no need to wear a mask if alone in an unshared room) **In a transportation setting:** • Traveling in bus, or car when accompanied by others	**In a hospital or outpatient setting:** • In an airborne infection isolation room • Performing cough-inducing or aerosol-generating procedures • When administrative or environmental controls are unlikely to be adequately protective **In a patient's home:** • Visiting a patient who is potentially infectious and the patient is not wearing a mask **In a transportation setting:** • Riding in a vehicle with a patient who is potentially infectious and is not wearing a mask

Adapted from: *Centers for Disease Control and Prevention. (2005). Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. Morbidity and Mortality Weekly Report, 54(17), 38-40.*

*Some devices, such as the 3M 1860, are both N95 respirators and surgical masks

Abbreviations Used: NIOSH=National Institute for Occupational Safety and Health; TB=tuberculosis

TUBERCULOSIS INFECTION CONTROL IN HEALTHCARE FACILITIES

Each hospital in NYC has its own detailed infection control plan and protocol for patient isolation. BTBC works directly with healthcare facilities' infection prevention staff or epidemiologists to investigate TB exposures occurring in healthcare settings, and communicates with relevant NYS authorities on a case-by-case basis.

HOSPITAL ADMISSION

Hospitalization is recommended for certain persons who may have active TB disease. These include:

- TB disease in sites with a high likelihood of complications:
  - Central nervous system (CNS)
  - Pericardium
  - Disseminated (more than two sites of disease)
- Presence of:
  - Severe hemoptysis
  - Hemodynamic instability
  - Advanced acquired immunodeficiency syndrome (AIDS)
  - Severe debilitation/inability to care for self
  - Comorbid medical conditions that require treatment in hospital
  - Severe anti-TB drug reactions (e.g., hepatic or dermatologic)
- Persons who reside:
  - In a congregate setting (e.g., long-term care facility, assisted living, or shelter)
  - With immunocompromised individuals
  - In unstable housing

For other patients, even those who may have infectious TB disease, outpatient diagnostic evaluation and treatment initiation is generally preferred.

AIRBORNE INFECTION ISOLATION

When hospitalized, a potentially infectious patient should be placed in an airborne infection isolation room promptly. Isolation is not required for persons with TB that does not involve the respiratory system. Each facility has its own procedures for initiating and discontinuing isolation.

Should an infectious patient require surgery, additional administrative or environmental control measures may be warranted (e.g., scheduling surgery for last case of the day, changing the direction of air flow such that operating room is at negative pressure to surrounding rooms).

USE OF A RESPIRATOR OR MASK

Facilities post notices on the door of the airborne infection isolation room to ensure that all individuals entering the room are aware of the appropriate procedures for entering or leaving the room. These measures require the use of a mask (visitors) or respirators (staff).

RESTRICTION OF ACTIVITIES

While in airborne infection isolation, the patient is restricted to the room unless the patient needs to leave the room for a diagnostic evaluation that cannot be obtained otherwise. In this case, the patient is required to wear a mask.

HOSPITAL DISCHARGE

As mandated by NYC Health Code, providers must submit a discharge plan to BTBC at least 72 hours before the expected hospital discharge of any patient with AFB smear-positive sputum. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City*.) When discharge is anticipated, providers use the necessary forms found at https://www1.nyc.gov/site/doh/providers/health-topics/tuberculosis.page. BTBC responds within 24 business hours of receipt of the discharge plan. Before a hospital discharge is approved by BTBC, a number of factors are considered, including: whether the patient remains infectious, adequacy of the treatment regimen, plan for follow-up with a provider, whether the patient has a verified home address, and whether the home is appropriate for discharge. (See *Figure 13.1: Criteria for Discharging Patients with Tuberculosis from the Hospital*.)

If the patient is considered infectious:

- The patient may not be discharged to a congregate residence or may require home care services
- The patient must agree to home isolation and home directly observed therapy (DOT) (refer to the infection control measures [noted below] for infectious persons discharged on home isolation)
- The treatment regimen must be considered adequate and tolerated (especially in the presence of drug resistance)

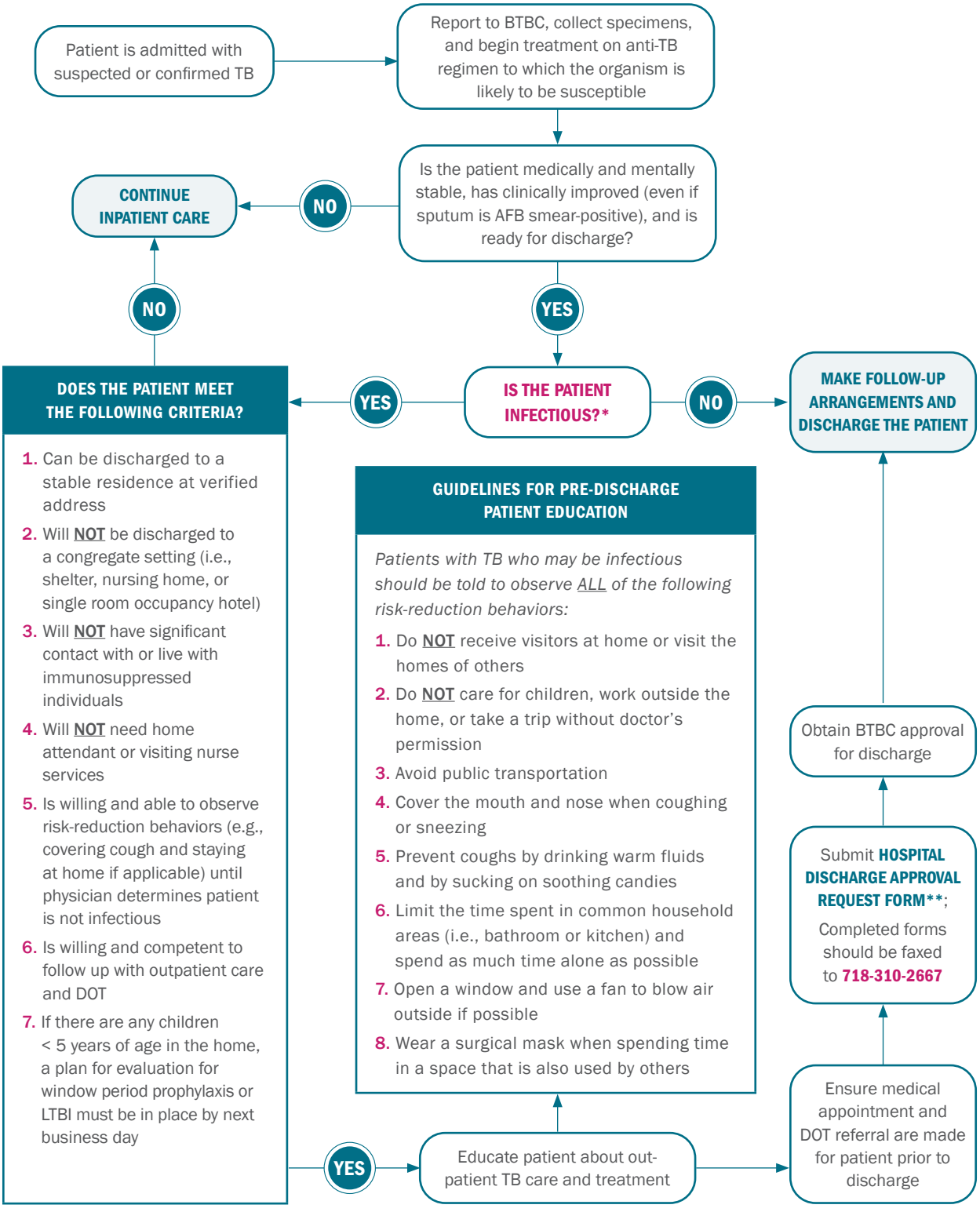
If the patient is considered non-infectious:

- There is no need for home isolation; however, additional considerations may exist before removing restrictions for return to work or school (see sections below)

If a diagnosis other than TB has been established and the patient is not being treated for TB disease, BTBC concurrence is not required before hospital discharge, regardless of AFB sputum smear result.

For patients being discharged to a location outside of NYC, the relevant local public health authorities must agree to the discharge of the patient to their jurisdiction, even if BTBC considers the patient to be non-infectious.

FIGURE 13.1: Criteria for discharging patients with tuberculosis from the hospital



*Determined by the hospital physician in consultation with the BTBC medical consultant based on the entirety of clinical findings.

**Discharge forms can be found at https://www1.nyc.gov/site/doh/providers/health-topics/tuberculosis.page

Abbreviations Used: AFB=acid-fast bacilli; BTBC=Bureau of Tuberculosis Control; DOT=directly observed therapy; LTBI=latent tuberculosis infection; MDR-TB=multidrug-resistant tuberculosis; TB=tuberculosis

INFECTION CONTROL MEASURES IN THE COMMUNITY

Patients diagnosed with infectious TB disease may not require hospitalization for the duration of their infectiousness. In these instances, specific administrative, environmental, and personal protective measures should be employed to protect the health of the patient and the community.

HOME ISOLATION

BTBC encourages and supports home isolation for potentially infectious persons who are medically stable and do not live in congregate settings or have immunocompromised household members. TB patients who are on home isolation and members of their household are required to take measures to prevent the spread of TB in the residence until the patient becomes non-infectious. The patient's permission is requested, but the BTBC has an obligation to reveal the diagnosis and infectiousness to individuals who share the residence, and typically requires household members to assist the patient with activities of daily living so the patient may remain in the living space while infectious. During home isolation, the patient and others residing in the home are not able to receive visitors or have home health services. Home isolation is maintained until the patient is no longer considered infectious. Patients are permitted to spend time in outdoor open air space if safe access is available.

ADMINISTRATIVE CONTROLS IN THE PATIENT'S HOME

Key concepts for administrative control include:

- **Treatment of cases at home is encouraged whenever possible:** Patients are treated at home if their condition does not otherwise require hospitalization.
- **Window period treatment policy:** Exposed household members who are candidates for window period treatment should complete their evaluation and be on medication before the patient is discharged home (or as soon as possible if the patient was not hospitalized).
- **Extension of window period for household contacts:** When there is evidence of non-adherence to therapy in the source patient such that household contacts may have had additional meaningful exposure, the case management team may need to extend the window period of the household contacts.
- **Education:** The infectious patients, family, care providers, and close contacts are educated regarding the purpose of isolation, the patient's responsibility to adhere to the isolation requirements, the activities of daily living support needed, and the potential consequences to the patient of not voluntarily complying with isolation requirements.
- **Home isolation agreements:** The home isolation agreement is made available for review and signature by the patient (prior to discharge). (See *Appendix N: Home Isolation Agreement*.)
- **Directly observed therapy:** Patients on home isolation must accept treatment by DOT.

ENVIRONMENTAL CONTROLS IN THE PATIENT'S HOME OR DURING TRANSPORT

Efforts to increase ventilation and air exchange are generally recommended. In certain situations, such as in a patient with infectious multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB), a HEPA filter may be placed in the person's residence. Patients and their families are advised to do the following:

- When possible, the person with potentially infectious TB disease sleeps alone in a room
- Train the patient in optimal cough etiquette (e.g., cover their mouth and nose when coughing or sneezing)
- Keep windows and doors open (weather permitting) to increase the ventilation and dilution of infectious droplet nuclei in the house
- If a sputum sample needs to be collected at home, instruct the patient to do so in a well-ventilated area away from other residents (e.g., bathroom with an exhaust fan)
- When in a car, open the windows (weather permitting) and turn off recirculating air controls

RESPIRATORY PROTECTION IN THE PATIENT'S HOME OR DURING TRANSPORT

PATIENT: MASK

- The patient does not need to wear mask at home when alone
- The patient wears the mask when attending medical appointments, when using public transportation, or in a car with others

OTHER HOUSEHOLD RESIDENTS: MASK

- The patient is expected to wear a mask when in common spaces of the residence; however, when the patient does not do so, other household residents may wear a mask

HEALTHCARE WORKER: RESPIRATOR

- The respirator to which they have been fit-tested is worn when entering the home or other confined area when interacting with an infectious patient
- A respirator is worn when traveling with the infectious patient in a car

RESTRICTION OF ACTIVITIES

Until a person with potentially infectious TB disease is considered to be non-infectious, they are not permitted to return to work, school, or other congregate settings where the patient could expose individuals to airborne bacteria. While on home isolation, the patient is permitted to leave the home only if there is safe access to outdoor open air space. No visitors are permitted in the home.

DISCONTINUATION OF INFECTION CONTROL MEASURES

PERSONS STARTED ON TUBERCULOSIS TREATMENT AND NO LONGER INFECTIOUS

Several studies published in the last decade have found that once effective TB treatment is initiated, infectiousness decreases much more quickly than previously thought. Meanwhile, laboratory tests can now detect mutations associated with specific drug resistance in respiratory specimens within several days. If these test results confirm both the diagnosis of TB and the lack of mutations associated with drug resistance, physicians can be reasonably certain that the infection is susceptible to the standard TB regimen.

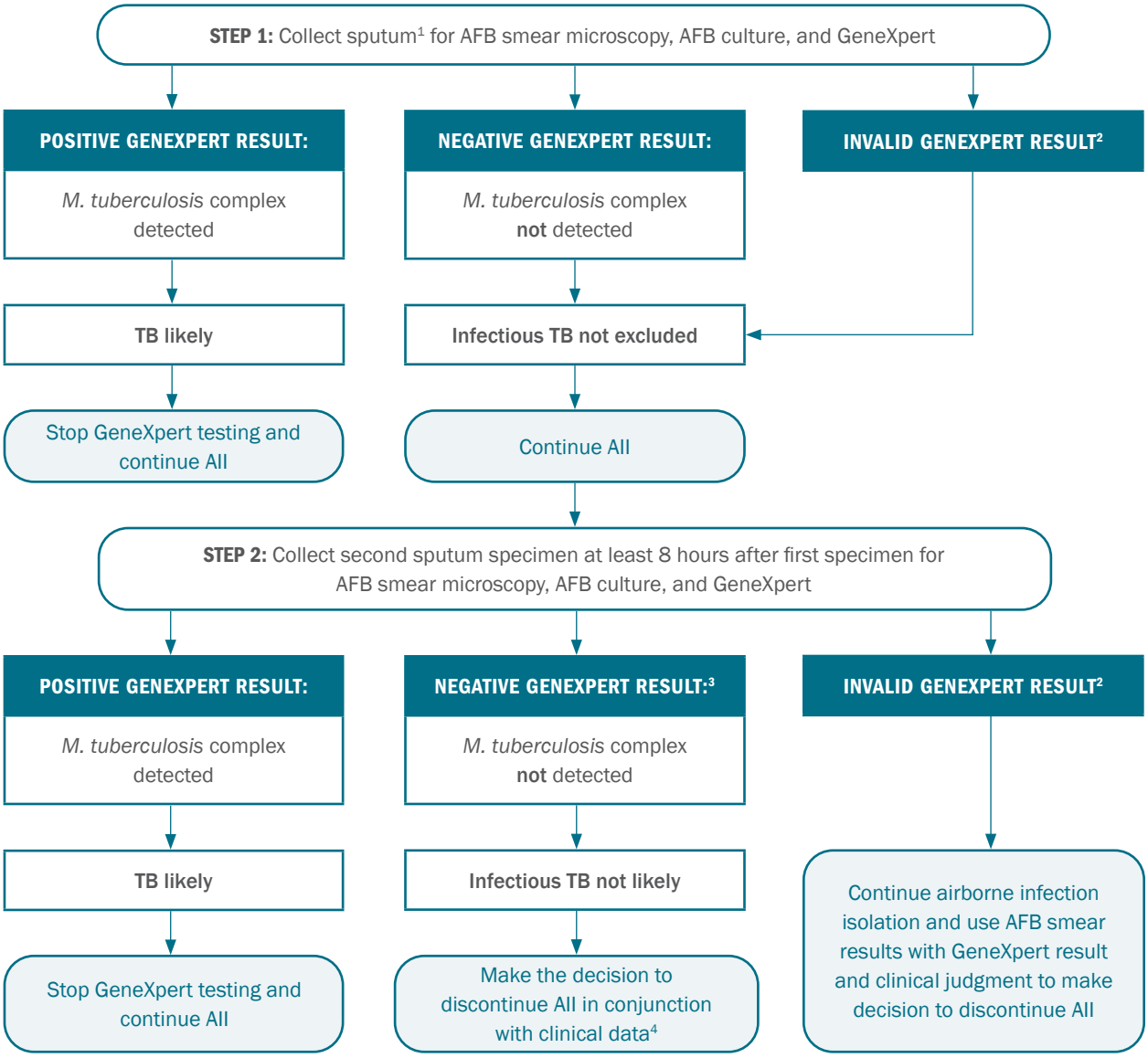
Given this new perspective on infectiousness and the more timely availability of drug susceptibility, it may not be necessary to wait for conversion of an AFB sputum smear from positive to negative before discontinuing airborne infection isolation for a patient with drug-susceptible TB. Although the decision to release a patient from airborne isolation is made by the healthcare facility staff according to facility protocols, BTBC medical consultants are available to assist in determining patient infectiousness.

Infection control measures are continued until an alternative diagnosis is established and any initiated TB treatment has been discontinued. Or alternatively, infection control measures are continued until the patient is taking effective therapy and is no longer infectious.

Once a person is determined to be non-infectious, airborne infection isolation (or home isolation) can be discontinued. The following guidelines may be used to inform whether a person with drug-susceptible TB disease of the lung and airways is determined to be non-infectious; however, a detailed discussion of all available information between an expert clinician and the treating provider is required.

- The patient has drug-susceptible TB (per nucleic acid amplification [NAA] or drug-susceptibility test [DST], conventional and molecular, results)
- The patient is receiving standard multidrug anti-TB therapy and demonstrating acceptable adherence; although the exact length of treatment required to consider the patient non-infectious varies, two weeks is commonly used as a reasonable benchmark
- The patient has a demonstrated clinical response to treatment:
  - Reduction/resolution of cough or fever
  - Reduction in AFB sputum smear grade
- The patient has agreed to continue antituberculosis treatment administered by DOT and to adhere to other treatment recommendations after discharge

FIGURE 13.2: Use of GeneXpert in discontinuing airborne infection isolation for acid-fast bacilli smear-positive patients



Source: National Tuberculosis Controllers Association, Association of Public Health Laboratories. Consensus Statement on the Use of Cepheid Xpert MTB/RIF® Assay in Making Decisions to Discontinue Airborne Infection Isolation in Healthcare Settings. Silver Spring, MD: Association of Public Health Laboratories; 2016. http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf.

1. First morning specimen preferred to maximize diagnostic yield of AFB sputum smear, culture, and GeneXpert.

2. Most laboratories/protocols will automatically retest leftover sample if an initial invalid (failed) result is obtained; in such cases, a reported invalid result reflects repeat testing of a single specimen.

3. If this result is negative following an initial invalid result in Step 1 and infectious TB still is clinically suspected, a repeat test (repeat Step 2) using a new specimen, if available, is recommended in order to improve sensitivity. Alternatively, the clinician may use the single negative GeneXpert result from Step 2 with smear results and clinical information to make the decision to discontinue or maintain airborne infection isolation.

4. Note: This process does not rule out tuberculosis with 100% certainty.

Abbreviations Used: AII=airborne infection isolation; AFB=acid-fast bacilli; *M. tuberculosis=Mycobacterium tuberculosis*; TB=tuberculosis

PERSONS NO LONGER CONSIDERED TO HAVE INFECTIOUS TUBERCULOSIS

Certain patients initially thought to have infectious TB (e.g., those with positive AFB sputum smears) may have an alternative diagnosis established. For example, a patient with AFB smear-positive sputum and a negative TB test (NAA) result (on two specimens) from Cepheid's Xpert® MTB/RIF, combined with other patient data that suggest an alternate diagnosis, may result in the clinician stopping TB treatment (if begun). In this scenario, BTBC endorses the discontinuation of airborne infection isolation. Any restricted activities related to the possible TB diagnosis are suspended. (See Figure 13.2: *Use of GeneXpert in Discontinuing Airborne Infection Isolation for Acid-Fast Bacilli Smear-Positive Patients*.)

DRUG-RESISTANT TUBERCULOSIS

Criteria for considering a patient with certain types of drug-resistant TB (DR-TB) non-infectious are more stringent than those for drug-susceptible TB. Because NAA tests only provide information on a limited number of anti-TB drugs, the final results of DST or other molecular tests are required before the clinician can ensure that the patient with DR-TB is on effective treatment. Considering a patient with MDR-TB or XDR-TB non-infectious is a case-by-case decision that may require smear and/or culture conversion (to negative).

RETURN TO WORK, SCHOOL, OR CONGREGATE RESIDENCE

In most situations, if a person is considered non-infectious, home isolation and other infection control measures can be discontinued. However, providers may reasonably take a conservative approach and include additional requirements, such as culture conversion, in situations including the following:

- The person with TB may interact with immunocompromised individuals or young children
- The TB is MDR or XDR

REGULATORY CONTROLS FOR INFECTIOUS NON-ADHERENT PATIENTS

Through an order issued by the Commissioner of Health, BTBC has the authority to involuntarily isolate and detain an infectious person in a healthcare facility until the person is no longer infectious or until treatment completion. Before such action can be taken, BTBC staff must document that the person has failed to adhere to treatment after being informed about their disease, their infectiousness, and the rationale for treatment. (See *Chapter 17: Laws Governing Tuberculosis Care in New York City* and *Chapter 10: Case Management for Patients with Tuberculosis*.)

SPECIAL CONSIDERATIONS FOR PREGNANCY AND PERIPARTUM INFECTION CONTROL

Separation of a newborn baby from a mother with infectious TB should be avoided whenever possible. The mother should consistently use a mask when with or near the infant. Delivery should be conducted in an airborne infection isolation room. However, in some rare situations, separation of the infant from the mother may be warranted to prevent transmission of TB to the infant. These include:

- Mother refuses to wear the mask consistently around the child
- Mother is highly suspected to have TB disease and has not yet started treatment
- Mother has MDR-TB

In all these instances, BTBC works closely with the mother and treating provider to develop an infection control plan that meets the needs of the patient while also protecting the health of the infant.

If an asymptomatic individual is found to have a positive test for TB infection early in pregnancy as part of a routine evaluation, but refuses a follow-up CXR, providers should encourage a CXR after the second trimester to rule out active TB disease before delivery.

BUREAU OF TUBERCULOSIS CONTROL INFECTION CONTROL PLAN

BTBC's TB infection control plans contain measures for reducing the spread of TB to staff in a specific setting (e.g., NYC Health Department TB clinics, non-clinical setting, and patient residences) and is part of an overall NYC Health Department infection control program that includes blood-borne pathogens and other airborne illnesses. The TB infection control plan details the policies and procedures used to ensure the prompt detection, isolation, and treatment of persons who have suspected or confirmed TB disease. An annual review and modification of the TB infection control plan is performed.

BTBC's infection control program includes the following elements:

1. Assignment of staff responsible for the implementation, coordination, and compliance with the program
2. Risk assessment of work duties and/or work venues where transmission of TB may occur
3. Infection control measures including administrative controls, environmental controls, and personal respiratory protection
4. Identification of work duties that require staff to have baseline and periodic TB screening, testing, medical evaluation, and counseling, as well as work duties that require staff to undergo the medical clearance for and fit testing of respirators, and respirator training
5. Education and training of all BTBC staff
   a. Annual training of staff regarding transmission risks of TB, respirator use, and the measures staff should take to reduce transmission risk in any patient care setting is mandated by BTBC
   b. Whenever possible, this training is conducted in conjunction with other related infectious disease training (e.g., blood-borne pathogen training)

SUMMARY

Infection control practices can effectively reduce the risk of TB transmission. Appropriate treatment of active TB disease rapidly reduces the infectiousness of patients. Coupled with the availability of rapid diagnostic studies to assess drug resistance, an evolved understanding of infectiousness has enabled BTBC to revise infection control guidelines so that most patients with active TB may return to the community more quickly than in the past, without posing a significant risk to the larger community.

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CHAPTER 14: EDUCATION AND OUTREACH

INTRODUCTION

A cornerstone of the New York City (NYC) Bureau of Tuberculosis Control's (BTBC) work is conducting education, training, and outreach activities among diverse stakeholders. These activities ensure that individuals have a clear understanding of the multiple facets of tuberculosis (TB), are familiar with related guidelines and BTBC policies, and know how to access available BTBC resources.

BTBC works to facilitate the detection, treatment, and prevention of TB disease and latent TB infection (LTBI) through collaborative, comprehensive educational and outreach activities.

BUREAU OF TUBERCULOSIS CONTROL STAFF EDUCATION

BTBC staff across job titles and positions function as TB experts in the community, supporting patients through treatment completion, providing guidance to

physicians based on BTBC protocols, and educating the community about TB. To perform this work, staff need appropriate training and education on how to interact with diverse populations and communicate with patients, providers, and the public about TB.

Staff training can be divided into several key categories. These include:

- **CORE TB-RELATED TOPICS:** Core trainings are based on the Centers for Disease Control and Prevention (CDC) Self-Study Modules and are offered to new staff in a classroom (preferred) or virtual setting. Core training covers the medical aspects of TB, such as transmission and treatment, as well as programmatic topics such as surveillance, epidemiology, and case management. Refresher trainings on core topics are integrated into regular trainings and events for all staff.
- **TRAININGS MANDATED BY FEDERAL, STATE, AND LOCAL ENTITIES:** Mandated training requirements vary by Civil Service title and job duties, and include health and safety topics, human resource-related trainings, and topics related to the larger mission and guiding principles of the NYC Health Department (e.g., health equity, language access, and confidentiality).
- **ADMINISTRATIVE:** This includes new or updated programmatic policies, use of the electronic medical record (EMR) system and electronic surveillance and case management system, and human resources-related trainings.
- **PROFESSIONAL DEVELOPMENT:** These opportunities allow BTBC staff to build skills in leadership, management, time management, public speaking, and computer skills.

In addition to the more formal educational opportunities, BTBC also conducts monthly journal club and methods seminars for staff. These events allow BTBC staff to learn about innovations in TB research and practice and stimulate discussions on how to integrate new technologies and practices into daily work. These events also provide an opportunity for staff to engage with and learn about the work being done across the various offices within BTBC.

BTBC posts various policies and resources on an internal web server (intranet) for staff to access and utilize as needed. Training opportunities and other information is shared with staff via regular newsletters. BTBC also conducts monthly update meetings for all staff to learn about policy updates, program changes, and staff-related news.

PATIENT AND COMMUNITY EDUCATION AND OUTREACH

BTBC staff work with patients and communities at increased risk for TB to empower individuals in making informed decisions about their health. The goals of patient and community education and outreach include:

- Increase knowledge and awareness of TB disease, including information about susceptibility, transmission, and treatment
- Assess and influence perceptions, beliefs, and attitudes that may impact care-seeking and treatment initiation

- Refute myths and misconceptions related to TB transmission and treatment
- Demonstrate the benefits of seeking care for symptoms of TB disease
- Increase awareness about LTBI, treatment options (including shorter regimens), healthcare options, and the importance of receiving treatment for LTBI

Community and patient education occurs through a variety of avenues. Patient education occurs throughout the case management and patient care process. (See *Chapter 10: Case Management for Patients with Tuberculosis*.) BTBC also works collaboratively with community partners to develop and distribute linguistically and culturally-tailored TB educational materials; disseminate information through the media; and coordinate community-based, geographically accessible TB testing events in collaboration with local healthcare partners.

Examples of community-based events include TB education workshops, health fairs, the incorporation of TB educational content into English as a Second Language (ESL) classes, and geographically-targeted, community-based TB testing using the Health Department's mobile van. Targeted testing in communities creates more accessible screening opportunities and helps increase the number of individuals who are tested for TB and linked to appropriate care.

BTBC's website also serves as an educational resource for patients and the general community. Pages for the public focus on education about TB risk factors and treatment and how to access services offered by BTBC. BTBC staff also utilize social media to engage the community, posting upcoming events and other information about BTBC resources. The NYC Health Department's official social media feeds occasionally feature TB-related content to promote various events and encourage awareness.

To improve outreach efforts in diverse communities, BTBC staff provide services, education, and outreach in numerous languages; ensure that all materials are easy to read and culturally appropriate; and tailor educational materials and resources to specific audiences.

To accommodate patients' language needs, the Health Department offers interpretation services through Language Line. More information on interpretation and other services for patients with limited English proficiency is available from the Health Department's Language Access Team.

HEALTHCARE PROVIDER EDUCATION AND OUTREACH

Educating and partnering with community providers is a key component of BTBC's work. BTBC staff provide education for healthcare providers across multiple disciplines on guidelines for testing for TB infection, recommended treatment regimens, and BTBC protocols for managing patients. BTBC staff also offer support and guidance on hard-to-manage TB cases. Education, training, and outreach for this group is conducted through a variety of methods: lectures, TB Rounds, "Dear Colleague" letters, a monthly newsletter, online resources, and in-person trainings, meetings and conferences.

Through provider education and outreach, BTBC staff aim to:

- Ensure that providers promptly identify and report individuals with suspected and confirmed TB disease
- Ensure that patients receive appropriate and effective TB evaluation, treatment, and care
- Ensure that individuals who are at high risk for progression from LTBI to active TB disease initiate and complete treatment for LTBI and do not develop disease
- Encourage providers to test for LTBI in individuals who:
  - Are contacts to patients with infectious TB disease
  - Have certain medical risk factors for progression
  - May otherwise be at higher risk for TB

BTBC's TB RISK ASSESSMENT TOOL can be used to identify individuals who should be tested for TB infection. BTBC recommends testing anyone who meet any of these three criteria:

1. **Contacts to infectious TB disease patients**
2. **Patients with immunosuppression**
3. **Persons born in or with prolonged stays in a country with a high TB incidence**

See *Appendix B: Tuberculosis Risk Assessment Tool*.

BTBC coordinates trainings to share best practices in TB management and to foster collaboration with partners within and outside of NYC. BTBC physicians and other staff present TB-related topics at Grand Rounds in hospitals and outpatient facilities, and coordinate TB Rounds with hospitals throughout the city. These medical talks provide an opportunity for BTBC staff to share their expertise with community providers and discuss updates and changes to BTBC protocols. BTBC also co-sponsors an annual conference for World TB Day, giving providers an opportunity to learn about updated TB care guidelines and recommendations and hear from a variety of speakers on TB-related topics.

For more information about upcoming training events for healthcare providers, sign up for the TB ACTION NEWS newsletter by emailing TBOutreach@health.nyc.gov

BTBC has numerous online resources available for providers. BTBC's website serves as an educational resource with information such as technical guidance for reporting requirements, guidelines for testing and treatment, NYC data and epidemiology, and educational materials that providers can share with their patients. BTBC also hosts an online newsletter, **TB ACTION NEWS**, with information about upcoming TB related events, updates to treatment guidelines or relevant policies, and significant TB related topics.

Reporting requirements for providers are available at nyc.gov/health; search for "TB provider resources." Educational materials for patients and additional information on TB diagnosis and treatment are also available on the Health Department website.

EDUCATION AND OUTREACH AMONG COMMUNITY AND POLITICAL LEADERS

BTBC frequently works with elected officials and community leaders to conduct education and outreach activities. BTBC staff disseminate data related to TB in specific communities, participate in local educational and testing events for community members, and provide support for efforts to advocate for and fund TB-related initiatives. Education and outreach activities among community leaders are vital to ensure their support, learn key information about the needs of communities/constituents, and build community trust.

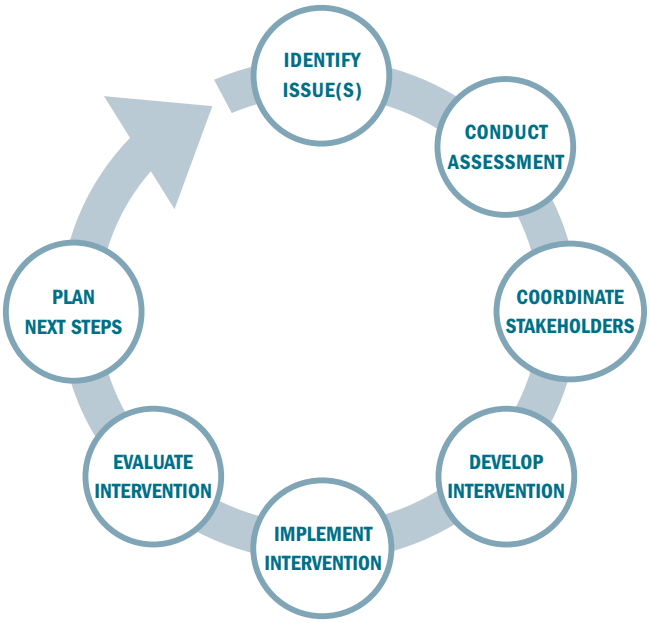
The objectives of community stakeholder education and outreach include:

- Increase awareness of the burden of TB disease within a neighborhood and/or community
- Increase knowledge and awareness of TB
- Increase awareness of Health Department resources related to TB care and management
- Develop partnerships towards developing and implementing targeted outreach efforts

PLANNING FRAMEWORK FOR EDUCATION, TRAINING, AND OUTREACH

BTBC uses a systematic approach to assessing, implementing, and evaluating TB educational, training, and outreach efforts. (See *Figure 14.1: Planning Framework for Education, Training, and Outreach*.)

FIGURE 14.1: Planning framework for education, training and outreach



STEP 1: IDENTIFY ISSUES

Staff use existing NYC Health Department epidemiologic data, census data, and other information to identify populations in NYC at high risk for TB. Examples of factors used to identify populations of concern include:

- Burden of disease
- Presence of traditional TB risk factors (e.g., immunosuppression, non-U.S.-born, contacts)
- Evidence of recent transmission
- High incidence in NYC
- High prevalence of LTBI

This step is also used to identify training needs for staff. Any missed targets or changes in epidemiologic or performance data are analyzed to determine whether staff training might be needed to help address the issue.

STEP 2: CONDUCT ASSESSMENT

Non-mandated training needs for staff are collected through ongoing communication with management and staff surveys. This information is used to develop training objectives that will give staff the skills to better and more efficiently fulfill their job requirements.

For community and provider outreach purposes, data collected through needs assessment enables BTBC to engage stakeholders; better understand healthcare-seeking practices and barriers; explore TB-related knowledge, experiences, and beliefs; identify specific areas of need for each community; and identify existing resources (internal and external) that can be leveraged for intervention development and implementation. This data is gathered through both informal and formal processes. Sources of information include patients, healthcare providers, community stakeholders, and published research.

Examples of assessment strategies include:

- Discuss with infectious disease physicians at Hospital A to determine barriers (lack of knowledge about TB testing and diagnosis) and assets (training opportunities available) to prescribing TB treatment
- Develop a survey and conduct focus groups among NYC Health Department TB clinic patients to assess factors influencing acceptance of shorter treatment regimens (three months of isoniazid [INH] and rifapentine [RPT] [3HP] or four months of rifampin [RIF] [4R])
- Hold a practice session before implementing a new EMR to identify staff training gaps

Next, a qualitative and statistical analysis of needs assessment data is done, and a report is generated that includes recommendations for areas of intervention. Needs assessment methodology, implementation, findings, and recommendations are shared internally and externally in order to verify the accuracy of results, ensure continued stakeholder involvement, and enable other jurisdictions to replicate methods and benefit from findings.

STEP 3: COORDINATE STAKEHOLDERS

For staff training, stakeholders include BTBC staff and external trainers. For community and provider-based outreach, the stakeholders may be broad and diverse. Recognizing that inter-related individual, community, and structural factors influence health beliefs and healthcare-seeking practices, multiple stakeholder groups may be identified depending on BTBC priorities and community-specific characteristics.

STEP 4: DEVELOP INTERVANTIONS

Needs assessment findings and existing BTBC data are used to develop tailored interventions in conjunction with key stakeholders. Interventions reflect BTBC and community priorities, and utilize existing internal and external resources.

1. **Determine goal(s) of intervention** (e.g., train administrative staff to use Excel, increase care seeking behaviors, increase initiation of LTBI treatment)
2. **Define barriers** (e.g., does not know how to use a spreadsheet, does not know symptoms of TB disease, does not know that there is treatment for LTBI)
3. **Determine assets** (e.g., staff have computers, strong community infrastructure, political support)
4. **Determine intervention strategies**
   - Staff training (specific training for BTBC nurses, case managers, or administrative staff)
   - Media campaign (geo-targeted, web-based ads on culturally and linguistically appropriate websites)
   - Community outreach (health fair, mobile van testing in communities where individuals are less likely to seek care)
   - Provider outreach (TB Rounds, World TB Day conference, webinars)
5. **Determine resources required** (e.g., financial, educational materials, staff with particular language skills)
6. **Involve key stakeholders in implementation and division of responsibilities** (e.g., who will conduct training, can community partners distribute flyers, organize press conference, organize community education event, etc.)
7. **Develop appropriate evaluation plan**

STEP 5: IMPLEMENT INTERVENTIONS

For staff trainings, workshops are implemented with support from key staff and external trainers where relevant. For community and provider outreach, BTBC partners with community leaders, healthcare providers, and other entities to operationalize strategies to reduce TB and improve community health.

STEP 6: EVALUATE INTERVENTIONS

BTBC works to develop adaptable and replicable approaches for the development and implementation of tailored, sustainable interventions to improve staff effectiveness, improve healthcare access, and reduce TB in NYC.

HOW IS PROGRESS MEASURED? What tool or device (surveys, tests, and data from other sources) will be used to measure the expected changes? Consider what is needed to ensure the resources/capacity (time, staff, funding, etc.) to perform the measurement.

1. **Process evaluation:** How well is the intervention being implemented (ex. how many posters were distributed, how many people attended event, quality of educational materials, effectiveness of educational presentations/workshops, etc.)?
2. **Impact:** What is the change in knowledge, attitude, and behaviors of the target population (did the participants in the workshop increase their knowledge about TB; was there an increase in intention to get tested/treated) or did a certain recommended policy get implemented?
3. **Outcome:** Did the intervention improve health? (In the long term, have TB rates gone down in the target population? Did individuals who tested positive start and complete treatment?)

STEP 7: PLAN NEXT STEPS

1. Identify lessons learned
2. Share evaluation and results with stakeholders
3. Provide preliminary results to program staff and stakeholders to maintain their interest and help them see value in TB control activities
4. Identify program or evaluation problems that can be addressed immediately
5. Develop plan to communicate findings to stakeholders
6. Determine need for any policy/programmatic changes, leading to Issue Identification

SUMMARY

BTBC's education and outreach activities are integral to maintaining an effective TB program. BTBC staff engage providers, patients, communities, politicians, and other staff members to improve patient care and work towards TB elimination in NYC. Using innovative approaches such as mobile van testing and TB Rounds, BTBC continues to expand the number of New Yorkers educated about TB. In addition, targeted testing allows BTBC to educate and screen the communities at highest risk for TB in NYC.

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CHAPTER 15: TUBERCULOSIS EVALUATION FOR NEW ARRIVALS AND STATUS ADJUSTERS

INTRODUCTION

Each year, millions of individuals apply for permanent United States (U.S.) residency (new arrivals). To reduce the spread of infectious disease in the U.S., applicants are required to undergo an overseas medical examination that includes a screening for tuberculosis (TB). The Bureau of TB Control (BTBC) receives hundreds of notifications annually for individuals who require additional TB follow-up after arrival in the United States. BTBC is federally required to follow up with all new arrivals with an address in New York City (NYC) who have a TB classification.

In addition to new arrivals, hundreds of thousands of individuals apply to change their immigration status (status adjusters) on an annual basis. Status adjusters have their initial medical screening, which includes a screening for TB.

NEW ARRIVAL MEDICAL SCREENING FOR TUBERCULOSIS

The medical screening for TB among persons overseas applying for U.S. immigration status and nonimmigrants who are required to have an overseas medical examination is an essential component of the medical evaluation designed to detect and treat infectious forms of TB among applicants and to reduce the risk of spread of TB after immigration. In an effort to reduce the spread of TB, persons coming to the U.S. as immigrants, refugees, or other legal permanent residents are required to be screened for TB prior to their arrival. Individuals entering the U.S. as non-immigrants, including those on temporary visas, do not require pre-entry medical screenings.

OVERSEAS MEDICAL SCREENING PROCESS

Using the TB Technical Instructions developed by the Centers for Disease Control and Prevention (CDC), specialized overseas physicians, referred to as panel physicians, screen applicants for active TB disease prior to United States immigration. (See *Figure 15.1: Process Overview: Overseas Medical Screening Exam for Tuberculosis*.) A complete medical screening examination for TB disease consists of a medical history, physical examination, interferon gamma release assay (IGRA) when required, chest radiograph (CXR) when required, and sputum smears and culture testing for *Mycobacterium tuberculosis* (*M. tuberculosis*). Requirements vary based on age of applicant and the WHO-estimated TB disease incidence rate in the country where the exam occurs.

For applicants 15 years of age and older, medical screenings consist of a medical history, physical exam, and CXR. If the panel physician determines that any of the following are present, the applicant is required to provide three sputum specimens for acid-fast bacilli (AFB) smear and culture for mycobacteria:

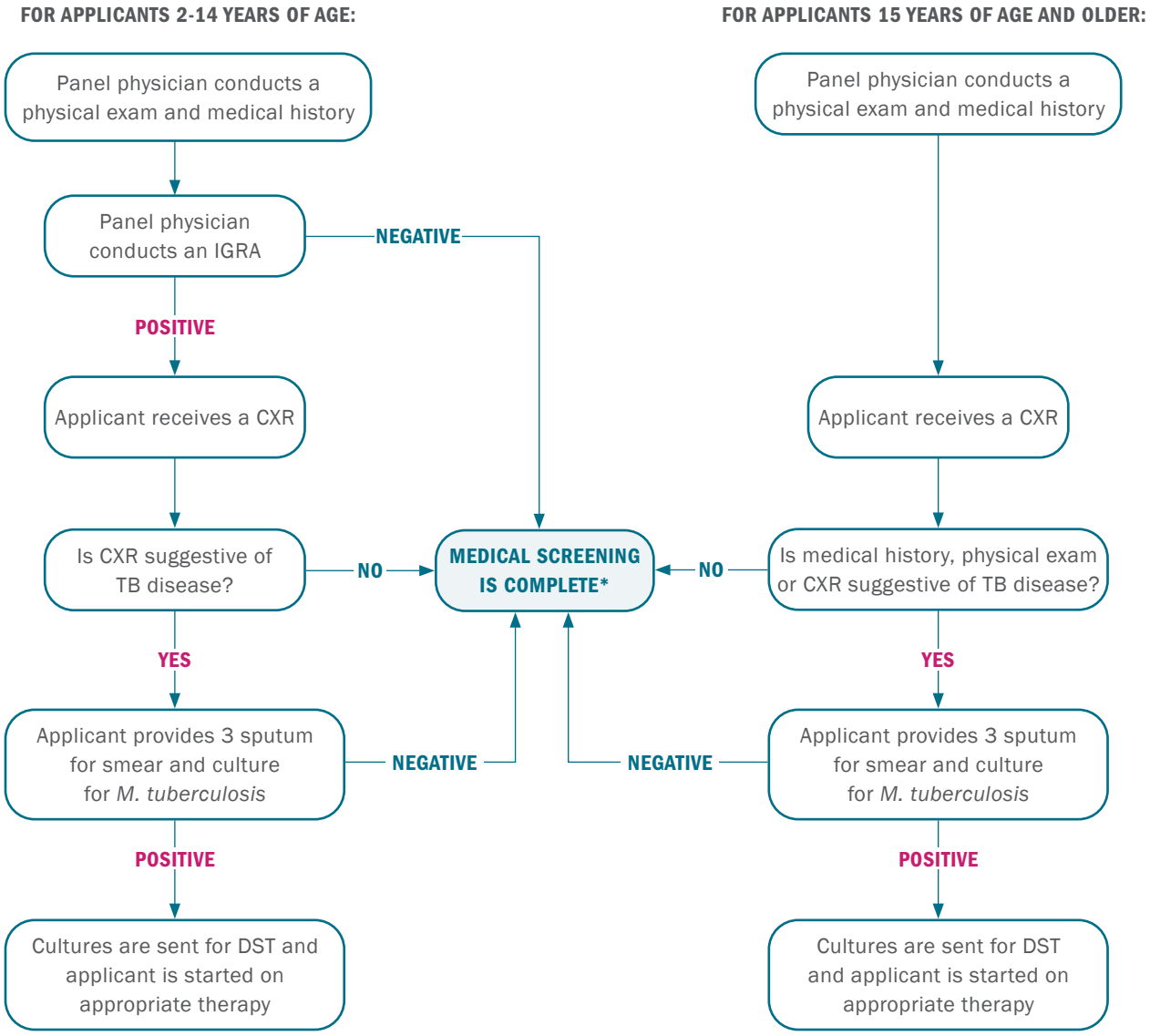
- The CXR is suggestive of TB disease
- The applicant has signs or symptoms consistent with TB disease
- The applicant has human immunodeficiency virus (HIV) infection

If mycobacterial culture growth is observed, the laboratory determines whether *M. tuberculosis* complex and/or a nontuberculous mycobacterium (NTM) is present.

For applicants two to 14 years of age living in countries with a World Health Organization (WHO)-estimated TB incidence rate of 20 cases or more per 100,000 persons, panel physicians will administer an IGRA as part of the medical screening process; in the event that the country of origin does not have an IGRA licensed for use, the tuberculin skin test (TST) can also be used. If the IGRA is interpreted to be positive or the applicant has signs and symptoms consistent with TB disease, the panel physician will perform a CXR. If the CXR is abnormal consistent with TB, child applicants may also be required to provide three sputum specimens for AFB microscopy and culture. If the CXR is normal, child applicants are not required to initiate latent TB infection (LTBI) therapy in their country of origin; they are referred to the health department upon arrival in the U.S. for LTBI treatment.

All applicants younger than two years of age living in countries with a WHO-estimated TB incidence rate of 20 cases or more per 100,000 persons have a physical examination and history provided by a parent or guardian. If the applicant has signs and symptoms consistent with TB disease or HIV infection, the panel physician also administers a test for TB infection (IGRA or TST), a CXR (anteroposterior or posterior-anterior view and a lateral view), and the applicant provides three sputa specimens for AFB microscopy and culture.

FIGURE 15.1: Process overview: Overseas medical screening exam for tuberculosis



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***If patient is diagnosed with latent TB infection, treatment is deferred until the applicant is in the U.S.**

Abbreviations Used: CXR=chest radiograph; DST=drug-susceptibility test; IGRA=interferon gamma release assay; TB=tuberculosis

Applicants for immigration to the U.S. are screened as directed by the CDC's TB Technical Instructions for Panel Physicians. These instructions can be found at: www.cdc.gov/immigrantrefugeehealth/exams/ti/panel/tuberculosis-panel-technical-instructions.html

OVERSEAS TUBERCULOSIS CLASSIFICATIONS

Panel physicians assign each applicant a TB classification based on the results of their TB medical screening:

- **No TB Classification:** Applicants who have no findings suggestive of TB disease or LTBI. Travel clearance is for six months from the time the evaluation is complete.
- **Class A TB Disease:** Applicants with confirmed active TB disease. This also includes applicants with extrapulmonary TB who have a CXR suggestive of pulmonary TB disease, regardless of sputum smear and culture results. These applicants are not cleared for travel until completion of treatment unless a waiver is granted.
- **Class B0 TB, Pulmonary:** Applicants who were diagnosed with active TB disease or presented to the panel physician while on TB treatment and successfully completed treatment with directly observed therapy (DOT) under the supervision of a panel physician prior to immigration. Travel clearance is valid for three months from the date final cultures are reported as negative.
- **Class B1 TB, Pulmonary:** Applicants have signs or symptoms, physical exam, or CXR findings suggestive of TB disease, **OR** have known HIV infection, but have negative AFB sputum smears and cultures and are not diagnosed with TB disease. This classification also includes applicants who were diagnosed with TB disease, refused DOT treatment, and are returning after treatment and completion of one-year wait. If all parts of the examination are complete, travel clearance is valid for three months from the date final cultures are reported as negative.
- **Class B1 TB, Extrapulmonary:** Applicants diagnosed with extrapulmonary TB disease with a normal CXR and negative sputum smears and cultures. Travel clearance is valid for three months from the date final cultures are reported as negative.
- **Class B2 TB, LTBI Evaluation:** Applicants who have a positive test for TB infection, but otherwise have a negative evaluation for TB disease. Contacts with a positive IGRA or TST ≥ 5 mm must receive this classification in addition to a Class B3. Travel clearance is valid for six months from the time the evaluation is complete.
- **Class B3 TB, Contact Evaluation:** Applicants who are a recent contact of a known TB case (have been exposed to an individual with confirmed infectious active TB disease), regardless of IGRA or TST results. If the IGRA or TST is positive and there is no evidence of TB disease, there will be two classifications, B2 and B3; if negative, B3 only. Information about the source case, name, alien number (if applicable), relationship to contact, and drug resistance of TB disease must also be document. Travel clearance is valid for six months from the time the evaluation is complete.

BUREAU OF TUBERCULOSIS CONTROL NEW ARRIVAL ACTIVITIES

COLLECTION AND PROCESSING OF NEW ARRIVAL INFORMATION

BTBC receives a notification for each new arrival who receives any A or B TB classification and has a NYC address listed as their destination. These notifications inform BTBC that an individual has moved into the area and requires prompt follow-up and evaluation. The CDC's Division of Global Migration and Quarantine (DGMQ) manages and processes all overseas medical examination documents and TB classification results. CDC DGMQ transmits Alien Notification Packages via the Electronic Disease Notification (EDN) system and sends email notifications to BTBC regarding all new arrivals to NYC. A designated unit, the BTBC Immigrant and Refugee Unit (IRU) is primarily responsible for responding to notifications, in collaboration with other BTBC staff and community providers. BTBC staff access the EDN system on a daily basis, downloading EDN TB worksheets, overseas medical examination forms, and other documents associated with new arrivals with TB classifications.

CONTACTING NEW ARRIVALS FOR DOMESTIC TUBERCULOSIS EVALUATION

BTBC IRU staff are assigned new arrivals to follow up with based on the individual's listed address in NYC. Staff initiate contact with new arrivals and begin processing the individual for TB evaluation at either a NYC Health Department TB clinic or a non-Health Department provider. New arrivals are contacted in the following order of priority:

1. Children up to 15 years of age in each class
2. TB Class A
3. TB Class B1-untreated
4. TB Class B0-completed treatment
5. TB Class B2 or B3

Staff contact these new arrivals by phone, email, mail, or home visit and refer them to a NYC Health Department TB clinic or a medical provider of their choice for domestic TB evaluation. In some cases, new arrivals will be unreachable or may refuse to be evaluated for TB. When this occurs, all relevant information is documented in the new arrivals' EDN TB Follow-Up Worksheets and BTBC staff follow guidelines provided by CDC DGMQ.

OUTREACH AND PATIENT INTERVIEWS FOR NEW ARRIVALS

When new arrivals present at a NYC Health Department TB clinic for their scheduled initial evaluation, assigned staff meet with and educate them about TB and next steps in their care. BTBC staff discuss the new arrival's current TB status, the TB evaluation process at BTBC, and the importance of keeping all clinic appointments. Additionally, all patient data listed in EDN is confirmed and information is updated as needed. All information discussed with new arrivals is done in a culturally sensitive manner and services and information are provided in their primary language. Interpretation services are available when necessary.

EVALUATION AND FOLLOW-UP OF NEW ARRIVALS BY BUREAU OF TUBERCULOSIS CONTROL AND NON-BUREAU OF TUBERCULOSIS CONTROL PROVIDERS

NYC Health Department TB clinics are the primary location for new arrivals with TB notifications to receive evaluations and follow-up care once in NYC. BTBC physicians examine each new arrival based on BTBC's policies for evaluating patients for TB; examinations include a physical exam, CXR, and sputum specimens for AFB and culture when necessary. BTBC IRU staff are responsible for obtaining outcomes of TB evaluation from the patient's electronic medical record (EMR) and the BTBC electronic surveillance and case management system (Maven), and transferring required data and information into the EDN TB worksheet until a final disposition is recorded in the EMR. BTBC staff submit completed EDN TB worksheets to CDC DGMQ. If a new arrival decides to receive follow-up care at a community provider, a chart review is conducted to obtain all information needed for EDN.

All new arrivals are followed up with until a final treatment determination has been made by the medical provider; while some new arrivals will not require any additional follow-up, others may be diagnosed with LTBI or active TB disease and start treatment. New arrivals requiring additional follow-up or treatment are monitored and EDN is routinely updated as required until the patient completes treatment or is no longer followed up by BTBC.

In addition to EDN, information on new arrivals who are found to have active TB disease or have signs and symptoms consistent with TB disease is entered into Maven.

(See *Chapter 2: Diagnosis and Treatment of Latent Tuberculosis Infection*, *Chapter 3: Diagnosis of Tuberculosis Disease in Adults*, and *Chapter 5: Treatment of Drug-Susceptible Tuberculosis Disease in Adults*.)

NEW ARRIVAL COHORT REVIEWS AND QUALITY ASSURANCE

To ensure the highest quality care for each new arrival receiving evaluation and treatment from BTBC, various quality assurance (QA) mechanisms are employed. Similar to general case management activities, each quarter BTBC conducts a cohort review for new arrivals. During the new arrival cohort review, staff present on the follow-up and outcomes for each of their patients to supervisors, BTBC physicians, and other staff. (See *Chapter 16: Program Evaluation and Research*.)

In addition to cohort reviews, supervisors conduct biweekly reviews of all assigned new arrivals. This process ensures prompt and appropriate tracking, evaluation, referral, and follow-up of data and information.

STATUS ADJUSTER MEDICAL SCREENING FOR TUBERCULOSIS

Status adjusters are individuals applying to change their U.S. visa immigration status. As these individuals are already in the U.S. when applying for this change, their required medical examination is completed by a U.S.-based civil surgeon. Similar to the evaluation of new arrivals, the status adjuster medical screening includes a TB component.

Effective October 2018, CDC DGMQ released updated guidelines for the evaluation of status adjusters, which include:

- Mandated use of IGRA for all applicants two years of age and older
- CXR for applicants with:
  - A positive IGRA result; or
  - Known HIV infection, regardless of IGRA result; or
  - Signs or symptoms of TB disease, regardless of IGRA result; or
  - Extrapulmonary TB, regardless of IGRA result
- Mandated reporting of applicants with LTBI to the local health department

STATUS ADJUSTER TUBERCULOSIS CLASSIFICATION

Civil surgeons assign each applicant a TB classification based on the results of their TB medical screening:

›› **No TB Classification:** Applicants without clinical findings of TB disease, without known HIV infection, and with a negative IGRA. This includes applicants with a remote history of TB disease who have a negative IGRA, no current signs or symptoms of TB disease, and no known HIV infection.

›› **Class A TB:** All applicants with active TB disease. This class includes applicants who are diagnosed with TB disease by the civil surgeon and health department AND applicants who present to the civil surgeon already on TB treatment at the time of their medical exam. This class also includes applicants with extrapulmonary TB who have a CXR suggestive of TB disease, regardless of sputum smear and culture results.

›› **Class B0, Pulmonary TB:** Applicants who were diagnosed with TB by the civil surgeon and health department during the medical examination process and successfully completed treatment on DOT.

›› **Class B1, Pulmonary TB:** Applicants who have signs or symptoms, physical exam, or CXR findings suggestive of TB disease; or have known HIV infection. These applicants are referred to the health department for additional evaluation, but have negative AFB sputum smears and cultures and are not diagnosed with TB disease.

›› **Class B1, Extrapulmonary TB:** Applicants with extrapulmonary TB, a normal CXR, and negative sputum smears and cultures (if required).

›› **Class B2 TB, LTBI:** Applicants who have a positive IGRA, or history of a positive IGRA, and a CXR not suggestive of TB disease. All of these applicants must be reported to the health department of jurisdiction.

›› **Class B1, Other Chest Condition (non-TB):** Applicants with an abnormal CXR suggestive of disease that is not TB and no clinical signs or symptoms suggestive of active TB.

Civil surgeons perform the medical examination for people applying for adjustment of status for U.S. permanent residence according to the procedures prescribed in the CDC's Technical Instructions for Civil Surgeons. These instructions can be found here: https://www.cdc.gov/immigrantrefugeehealth/civil-surgeons/tuberculosis.html

Effective October 2018, all status adjusters with a positive IGRA result must be reported to the local health department. In NYC, reports must include the IGRA test result, CXR result, and patient contact/demographic information. Reports can be submitted electronically at https://a816-healthpsi.nyc.gov/NYCMED/Account/Login.

SUMMARY

Providing appropriate TB evaluation and follow-up to all new arrivals and status adjusters is vital to TB prevention and care efforts. Within BTBC, various staff provide information and care in a culturally appropriate manner, working with new arrivals to ensure understanding and adherence to BTBC processes. BTBC works collaboratively with CDC DGMQ and others to evaluate and treat this high-risk population and reduce the spread of TB in NYC.

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CHAPTER 16: PROGRAM EVALUATION AND RESEARCH

INTRODUCTION

The New York City (NYC) Bureau of TB Control (BTBC) uses data from the tuberculosis (TB) clinics and the TB surveillance registry to develop program indicators, analyze and improve data collection processes, and inform general knowledge regarding the treatment and care of patients with active TB disease and latent TB infection (LTBI). Indicators are evaluated by comparisons with local and national goals.

DATA SOURCES AND ROUTINE ANALYSIS

Through its public health activities, including surveillance, case management, contact investigation, and direct clinical care, BTBC collects data that can then be used for analysis, program evaluation, and research activities. BTBC staff diligently work to collect a vast amount of data on every TB patient diagnosed

in NYC. These data are analyzed strategically to maximize programmatic impact. While there are many potential data sources, the primary mechanisms for managing and accessing these data are BTBC's electronic TB surveillance and case management system and the clinic electronic medical record (EMR). The TB surveillance and case management system contains data relevant to public health activities on all persons reported to BTBC with signs and symptoms consistent with TB disease, confirmed TB cases, and children younger than five years of age who are reported with LTBI. The EMR contains clinical data for any person who accesses BTBC's clinics for medical care.

Routine analysis of surveillance data occurs on an ongoing basis to monitor trends, describe and understand local TB epidemiology, and monitor progress toward TB elimination. Each year, BTBC publishes an annual summary of the surveillance data for the previous year. Routine data analysis also includes monitoring "sentinel populations" to ensure that groups at increased risk for TB are monitored for changes in trend. Ad hoc analyses are also conducted to inform real-time programmatic decision-making.

Data is also used to inform, monitor, and evaluate investigations of TB including contact investigations, expanded contact investigations, cluster investigations, and outbreak investigations.

PROGRAM EVALUATION

BTBC's cross-cutting evaluation initiatives are designed to assess the effectiveness of current practice and new interventions, and to assess program performance against local and national targets. To optimize resource allocation and impact of program activities, interdisciplinary staff across BTBC collaborate to conduct program evaluation and quality assurance (QA).

COHORT REVIEW

The cohort review process consists of quarterly meetings for all staff responsible for patient care and case management. The cohort review is BTBC's most important method of program evaluation; developed by BTBC and implemented in 1993, cohort reviews provide a multi-disciplinary forum to review the management of each patient and ensure accountability at all levels of TB care. They allow clinicians, managers, and other staff to discuss challenging management issues, especially patients who are non-adherent, have drug-resistant TB (DR-TB), have numerous contacts, or require assessment in multiple congregate settings. Cohort reviews allow the Bureau Director to assess the coordination of units across BTBC.

Objectives of the cohort review process are to:

- Ensure the comprehensive case management of all patients with active TB disease
- Promote effective supervision and teamwork
- Uphold the case management team's accountability for TB patients and all persons exposed to infectious TB
- Improve timeliness of appropriate patient management interventions
- Maintain reliability of the TB registry as a surveillance and epidemiology data resource

- Provide outcome analysis, as measured against previous cohorts, other regions, and local and national targets
- Identify, track, and follow up on any patient-specific clinical and case management issues
- Motivate staff by highlighting their accomplishments in managing patients and challenging them to exceed or maintain previous achievements

Cohort reviews take place three to five months after the patient is diagnosed with TB disease, a point in the case management process where most patients will be approaching the completion of therapy and contact evaluations are finalized.

Each cohort review meeting consists of three distinct sections:

1. A review of the epidemiology of NYC with a focus on the region/patients being presented that quarter
2. Individual case presentations
3. A review of the cohort performance indicators

During the epidemiologic overview, an analysis of the patients in the cohort is given for the city as well as the patients in the region being presented. Certain patients are highlighted, such as those with DR-TB or patients under the age of 18. In addition, outcomes of source case investigations, expanded contact investigations, and cluster investigations that involve patients from that quarter are presented.

Following the epidemiologic overview, all patients confirmed to have active TB disease who reside in NYC and were diagnosed within a specific quarter are presented to the Bureau Director in a standardized format. The Bureau Director reviews each patient, verifying details such as the patient's clinical status, appropriateness of the treatment regimen, treatment adherence, treatment completion, and outcome of the contact investigation. Staff familiar with the patient, including physicians, nurses, and Public Health Advisors and supervisors involved in case management efforts, provide additional information as necessary. The Bureau Director identifies potential clinical, case management, and contact investigation issues. As each patient is presented, issues or problems identified during the meeting are documented. After the meeting, individual staff are assigned to follow up on all issues identified.

Following the case presentations, an assigned BTBC staff member presents indicator data for patients discussed at the meeting including preliminary treatment completion, sputum culture conversion, directly observed therapy (DOT) adherence, and timeliness of case management activities. Final results of cohort patients and contacts from the same quarter of the prior year are presented including a review of patients who did not complete treatment and the reasons for non-completion.

The cohort review process is a fundamental program evaluation and QA mechanism designed to ensure all patients diagnosed with TB disease who reside in NYC receive high quality care and treatment. Cohort reviews have been adopted nationally (and internationally) as a necessary program evaluation process and are part of BTBC's Cooperative Agreement with the Centers for Disease Control and Prevention (CDC).

PROGRAMMATIC INDICATORS

BTBC uses national and local indicators to assess program impact and success. To ensure BTBC can appropriately evaluate progress, all indicators utilized are clearly defined, ambitious but feasible to accomplish, and routinely reviewed with leadership and disseminated to staff.

Some of BTBC's key performance indicators include:

- Completion of treatment
- Acid-fast bacilli (AFB) sputum culture conversion within 60 days
- Susceptibility testing for drugs
- Human immunodeficiency virus (HIV) testing
- Submission of isolates for genotyping
- Proportion of infectious cases with contacts identified

While indicators are being calculated and reviewed on an ongoing basis, data is shared on a quarterly basis with BTBC leadership and other stakeholders. Indicator results are compared against previous quarters and years, as well as the national average, to determine where improvements are needed.

NATIONAL INDICATORS

NATIONAL TUBERCULOSIS INDICATORS PROJECT

CDC's National Tuberculosis Indicators Project (NTIP) is a monitoring system for tracking progress toward national objectives by TB control programs. The national targets are updated every five years to ensure that programs continue to improve performance. NTIP uses data it receives from CDC-funded TB programs across the country through various reporting mechanisms including Report of Verified Case of TB (RVCT) forms, Aggregate Reporting for Program Evaluation (ARPE) on contacts and the Electronic Disease Notification (EDN) System.

The NTIP categories by which BTBC and other programs are evaluated include:

- TB case rates
- Treatment and case management of persons with active TB disease
- Contact investigations
- Evaluation of immigrants and refugees (new arrivals)
- Completeness of data reporting to the CDC

NTIP also allows TB programs to monitor the elements informing the CDC's calculation of the funding formula for states, territories, and large cities receiving direct financial assistance through a Cooperative Agreement. The funding formula is a calculation based on the burden of TB and program performance influencing the allocation of federal aid by the CDC. Monitoring these variables also allows BTBC to monitor program performance in comparison to other jurisdictions.

Performance indicators also directly impact funding so completeness and accuracy of data reported to the CDC and other funders is vital. A full list of NTIP indicators can be found at: www.cdc.gov/tb/programs/evaluation/indicators/default.htm.

AGGREGATE REPORTING FOR PROGRAM EVALUATION: While many TB indicators focus on the burden, diagnosis, and treatment of patients with active TB disease, the ARPE reports on the outcomes of contact investigation efforts in aggregate. (See *Chapter 11: Contact Investigation*.) The ARPE report is submitted to the CDC annually.

Indicators reported by the ARPE include:

- Number of cases with contacts identified
- Number of contacts identified
- Number of contacts evaluated
- Number of secondary TB cases identified
- Number of contacts infected with LTBI
- Number of contacts started on treatment for LTBI
- Number of contacts that completed treatment for LTBI
- Reasons treatment not completed

REPORTING TO FUNDING ENTITIES: Reporting of BTBC indicators and activities to stakeholders is a necessary step in program evaluation. Stakeholders include BTBC leadership, NYC Health Department Division of Disease Control, NYC Commissioner of Health, NYC Mayor, New York State Department of Health (NYS DOH), and CDC. The frequency of reporting depends upon the stakeholders and type of report. Key reports include NYC Quality and Performance Review (QPR), NYS report, and CDC Annual Performance Report. Collectively, these reports represent highlights of the extensive amount of work performed by BTBC staff in the treatment, care, and prevention of TB in NYC.

RESEARCH

BTBC staff routinely engage in research to better understand the epidemiology of TB in NYC, to identify populations at increased risk for TB, and to study treatment interventions and patient outcomes.

OBSERVATIONAL STUDIES

BTBC staff are most frequently engaged in descriptive and observational studies using data from the TB registry. These studies tend to focus on surveillance trends, identifying and describing populations at increased risk for TB infection and disease, clinical treatment outcomes, outcomes of contact investigations, and other public health activities. BTBC frequently collaborates with students, fellows, and academic partners on research projects.

CENTERS FOR DISEASE CONTROL AND PREVENTION TUBERCULOSIS TRIALS CONSORTIUM

For the last 20 years, BTBC has participated in the Centers for Disease Control and Prevention (CDC) TB Trials Consortium (TBTC). TBTC is a federally funded research consortium focused on improving TB diagnostics, modalities for treatment, and length of TB treatment for persons with TB infection and disease. The purpose of TBTC is to conduct research that will improve the knowledge surrounding the diagnosis, management, treatment, and care of TB patients. As one of a number of institutions TBTC partners with, NYC Health Deparment TB clinics have worked in close collaboration with Columbia University as a clinical study site for TBTC.

NEW YORK CITY TUBERCULOSIS RESEARCH CONSORTIUM

BTBC actively seeks out partners for research collaboration and, in 2012, founded the NYC TB Research Consortium, which brings together BTBC, academia, laboratories, and other researchers to collaborate on projects focusing on TB in NYC. The group's activities include the following:

- Conducting research projects to inform TB prevention, care, and management policies and practices
- Collaborating on epidemiologic and clinical studies to advance TB research
- Pursuing funding opportunities
- Mentoring new researchers and students to develop research skills for future public health careers

For more information or to join the NYC TB Research Consortium, contact TB-epi@health.nyc.gov.

SUMMARY

Program evaluation and research are fundamental aspects of BTBC's activities and functions. BTBC's various program evaluation mechanisms ensure continuous improvement and accountability with TB prevention and care activities. BTBC's involvement in research, both clinical and programmatic, improves the TB knowledge base and provides evidence for various interventions that can be employed by other TB programs and medical institutions. Together, multi-disciplinary staff, partners, and funders contribute to these activities in order to improve patient outcomes and experience.

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CHAPTER 17: LAWS GOVERNING TUBERCULOSIS IN NEW YORK CITY

INTRODUCTION

This chapter summarizes the laws and regulations applicable to tuberculosis (TB) control in New York City (NYC).

Reporting of TB and several aspects of TB control practices are governed by various New York State (NYS) and NYC laws, namely: the NYS Sanitary Code (contained in Volume 10 of the New York Codes, Rules and Regulations [NYCRR]), the NYS Public Health Law, and the NYC Health Code. Further, pursuant to the NYC Charter, legal mandates are at times issued by way of mayoral Executive Order.

These laws balance individuals' privacy and civil liberty interests with public health concerns directed at controlling the spread of TB.

This section describes laws related to:

1. Confidentiality and disclosure of patient information
2. Reporting requirements
3. Investigation, isolation, exclusion requirements, and enforcement mechanisms for non-adherent patients

CONFIDENTIALITY AND DISCLOSURE OF PATIENT INFORMATION

Protection of patient confidentiality is of utmost importance to public health and patient care. Maintenance of confidentiality promotes cooperation among patients, their families, and their communities with TB testing, treatment, prophylaxis, and contact investigations. The loss of patient confidentiality undermines trust between the Health Department and NYC residents, potentially hindering the ability of the Health Department to protect the public's health.

LAWS GOVERNING THE CONFIDENTIALITY OF PATIENT INFORMATION

The Health Department is legally required to treat all patient information received from patients and healthcare providers with the highest level of confidentiality.

The NYC Health Code requires the Health Department to keep confidential all medical, epidemiologic, and surveillance reports and records that contain individually identifiable patient information reported to or maintained by the Health Department, and limits disclosure of identifiable information to authorized persons to protect the health of an individual or the public [NYC Health Code §§ 3.25(a)(1), 11.11(a)]. NYC law also requires aggregate data to be prepared in a manner that does not reasonably enable patient identification [NYC Health Code § 11.11(a)(2)]. The NYC Health Code allows individuals to consent in writing to the disclosure of their own medical records to themselves, their treating provider, or to a court, provided that information regarding other individuals, including contacts, is excluded from the disclosure [NYC Health Code §§ 3.25(a)(2), 11.11(b)].

NYS Public Health Law § 2221 provides for the confidentiality of patient TB records maintained by physicians, government agencies, and others, allowing them to be shared only with State or local health authorities, such as the Health Department, and requiring such health authorities to maintain confidentiality except where disclosure is authorized by law. Violation of this provision is a misdemeanor offense [NYS Public Health Law § 2230].

The confidentiality of patient information is also extensively regulated by the Federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA established a national legal standard for protecting the privacy of protected health information (PHI) from disclosure by certain entities. HIPAA defines PHI as any health or medical information that can identify or be linked to a specific individual [45 CFR § 160.103]. PHI may be transmitted or maintained in any form or medium (electronically, on

paper, or orally), but excludes certain educational and employment records, and records of a person who has been deceased for more than fifty years [45 CFR § 160.103]. HIPAA gives individuals the right (with a few limited exceptions) to access and obtain a copy of their own PHI, authorize the sharing of their PHI, and request amendments to their medical records [45 CFR §§ 164.508, 164.524, 164.526].

HIPAA's confidentiality mandates are limited to "covered entities," defined as healthcare providers who transmit billing and payment information in electronic form (e.g., most doctors, hospitals, laboratories, and pharmacies), health plans (e.g., Medicare, Medicaid, and private health insurance companies), and healthcare clearinghouses (i.e., entities that perform billing services) [45 CFR § 160.103]. HIPAA delineates very limited circumstances under which covered entities can share PHI without patient consent (e.g., information needed for treatment of the patient or for payment purposes) [45 CFR § 164.506].

The NYC Health Department is a hybrid entity under HIPAA; it operates both as a public health authority and as a provider of healthcare through Health Department clinics, including Bureau of TB Control (BTBC) clinics. Information collected by the Health Department as a public health authority, which is not a "covered entity" under HIPAA, is exempt from HIPAA, but is still governed by State and local confidentiality law. Health Department clinics, as HIPAA "covered entities," must comply with HIPAA's confidentiality and disclosure requirements.

DISCLOSURE OF PATIENT INFORMATION FOR PUBLIC HEALTH REASONS

Public health activities are an exception to the stringent HIPAA, NYS, and NYC confidentiality requirements.

In enacting HIPAA, Congress was very clear that the act not impede public health practices [42 USCA § 1320-d-7(b)]. Under HIPAA, covered entities are permitted to disclose PHI without patient consent, and without giving the patient an opportunity to agree or object to the disclosure, to a public health authority authorized by law to receive such information, such as the Health Department, "for the purpose of preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions" [45 CFR § 164.512(b)(1)(i)]. HIPAA also allows disclosure of PHI by a covered entity to patient contacts or individuals "who may otherwise be at risk of contracting or spreading a disease or condition" if the covered entity or public health authority is authorized by law to do so in the course of a public health intervention or investigation [45 CFR § 164.512(b)(1)(iv)]. Thus, HIPAA permits disclosure of PHI, as necessary, to TB patient contacts.

The NYS Sanitary Code narrowly allows disclosure without patient consent under certain circumstances, including for public health reasons. Specifically, 10 NYCRR §2.17 permits NYS Department of Health and NYC Health Department personnel authorized to receive TB-related medical reports to "disclose information contained in such reports when in his judgment it will serve the best interest of the patient or his family, or contribute to the protection of the public health," including releasing information to entities involved in TB control, such as in connection with contact investigations. NYC Health Code §§ 3.25(b) and 11.11(c) also permit disclosure by authorized Health Department personnel to a treating provider or agency involved

in TB prevention, treatment, or the provision of social services, or "to any person when necessary for the protection of public health."

Disclosure by the Health Department or HIPAA entities of confidential health information/PHI must be limited to the minimum information necessary for the intended purpose [NYC Health Code § 11.11(c); 45 CFR §§ 164.502(b)(1), 164.514(d)(3)(iii)(A)]. To help preserve confidentiality, the receiving individual or entity should be informed of the obligation to maintain confidentiality except if further disclosure is necessary for patient treatment or for the protection of the health of others [NYC Health Code §§ 3.25(b), 11.11(c)].

HIPAA carves out limited exceptions to the "minimum necessary" requirement, including when the PHI is disclosed to treat a patient, when the patient requests the information or authorizes its disclosure, or when the records are required pursuant to certain laws [45 CFR § 164.502(b)(2)]. NYS law allows TB records to be subpoenaed, produced, and placed into evidence if the court deems them relevant in an action for a violation of the NYS Public Health Law, NYC Health Code, or other local TB control law [10 NYCRR § 2.18].

In accordance with confidentiality laws, and consistent with its goal of maintaining public trust and confidence in its processes, the Health Department attaches the highest level of confidentiality to PHI it receives from patients, healthcare providers, and other sources. PHI is only released as necessary for the Health Department to carry out its public health mandate.

SUMMARY OF THE LEGAL FRAMEWORK FOR CONFIDENTIALITY AND DISCLOSURE OF PATIENT INFORMATION:

- **State and local law require the Health Department and all healthcare providers to treat patient information with the highest level of confidentiality.**
- **Healthcare providers (including Health Department clinics), as well as insurance companies and entities that assist in billing, must also abide by HIPAA's confidentiality and disclosure requirements.**
- **All healthcare providers must provide confidential patient information to the Health Department upon request pursuant to NYC and NYS law; HIPAA, State, and local law all have a "public health" exception enabling such disclosure.**

CONFIDENTIALITY AND DISCLOSURE OF IMMIGRATION STATUS

In NYC, TB evaluation and treatment is provided regardless of immigration status; the law strictly limits Health Department employees from asking about or sharing an individual's immigration status.

Pursuant to mayoral Executive Order No. 41, Health Department and other city agency officers and employees cannot inquire into an individual's immigration status in performing TB investigations, providing treatment, or for any other purpose unless:

- Such information is necessary for the determination of a program, service, or benefit eligibility; or
- The officer or employee is required by law to inquire about such person's immigration status.

Further, immigration status is considered confidential information, and can only be disclosed by the Health Department:

- Upon the individual's written consent;
- If required by law;
- To another NYC officer or employee as necessary in carrying out the Health Department's or other NYC agency's mission;
- Where the individual is suspected of illegal activity other than mere status as an undocumented immigrant, or such information is necessary to apprehend another person suspected of illegal activity other than mere status as an undocumented immigrant; or
- Where disclosure is necessary in furtherance of an investigation of potential terrorist activity.

Limiting questions regarding immigration status, maintaining confidentiality when immigration status becomes known, and informing individuals regarding these confidentiality requirements gains patients' trust and increases the likelihood that immigrants will seek evaluation and treatment for TB, respond to Health Department investigations, and accept and abide by treatment protocols.

For specific questions about confidentiality and disclosure of personal health or other information:

- **Health Department personnel should contact their supervisors; supervisors who cannot answer staff questions should contact the Health Department Office of the General Counsel or a Health Department Privacy Officer**
- **Non-Health Department healthcare providers should call 311**

HUMAN IMMUNODEFICIENCY VIRUS TESTING REQUIREMENTS, INFORMED CONSENT, AND CONFIDENTIALITY AND DISCLOSURE OF HUMAN IMMUNODEFICIENCY VIRUS/ACQUIRED IMMUNODEFICIENCY SYNDROME INFORMATION

NYS law exclusively regulates reporting and confidentiality of information related to human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), which are not defined or treated as "communicable diseases" in NYS. There are no applicable NYC Health Code provisions or any other local laws or regulations elsewhere in NYS relating to HIV information.

Providers offer all TB patients and their contacts HIV testing due to the implication for the diagnosis and treatment of TB, as well as the NYS requirement that HIV testing be offered as part of patient care. HIV-related patient information is subject to more stringent confidentiality and disclosure requirements than TB and most other patient information. NYS Public Health Law Article 21 Title 3 and Article 27-F, and 10 NYCRR Part 63, regulate HIV testing, confidentiality, and disclosure. In recent years, NYS HIV law has changed to improve HIV testing uptake and ease the sharing of HIV-related patient information to improve patient outcomes.

Effective March 28, 2017, providers are no longer required to obtain informed consent prior to ordering

an HIV-related test, including elimination of written consent for HIV testing in New York State correctional facilities. However, providers performing an HIV test as part of routine medical care, at a minimum, must advise that an HIV-related test is being performed prior to ordering an HIV-related test [§ 2786 and § 2139].

When a patient is told that an HIV test is being performed, a note must be placed in the patient's record that the patient was so notified [§ 2781(2)]. The provider must tell the patient each time an HIV test is being performed and document it in the patient's record [§ 2781(2)].

There are specific requirements regarding confidentiality and disclosure of HIV-related patient information. All persons who obtain HIV-related patient information in the course of providing healthcare or social services to a patient are required to maintain confidentiality [§ 2782(1)], except that disclosure is permitted to:

- The patient and any person the patient authorizes pursuant to a release of confidential HIV information [§§ 2134, 2782(1)(a)-(b)]
- A healthcare provider or facility in connection with treatment of the patient, the patient's child, or a contact of the patient; and any agent or employee of the provider or facility in connection with treatment or reimbursement [§§ 2782(1)(c)-(d)]
- A patient contact, but without revealing the identity of the protected individual or other contacts [§ 2134]
- A healthcare facility or provider in connection with organ and human body part and matter procurement for transplant, therapy, research, or education [§ 2782(1)(e)]
- A person authorized to make medical decisions for the patient, as necessary for treatment [§ 2782(4)(e)]
- A healthcare facility and authorized staff or government organization in connection with accreditation or oversight [§ 2782(1)(f)]
- A federal, State, or local health officer when disclosure is mandated by law (such as a physician's obligation to disclose an HIV diagnosis to the NYS Commissioner of Health (§ 2130)) [§ 2134, 2782(1)(g)]
- An authorized agency in connection with foster care or adoption of a child [§ 2782(1)(h)]
- Insurance companies and billing entities, with appropriate authorization if necessary [§§ 2782(1)(i)-(j)]
- Any person to whom disclosure is ordered by a court pursuant to NYS Public Health Law § 2785 (provides for court ordered disclosure in limited circumstances including where there is a "clear and imminent danger" to an individual or the public health) [§ 2782(1)(k)]; confidential HIV information cannot be released pursuant to a general subpoena [10 NYCRR § 63.6(k)]
- Authorized corrections agency and facility personnel [§§ 2782(1)(l)-(o)]
- An attorney appointed to represent a minor pursuant to social services law or the family court act [§ 2782(1)(p)]

- An executive or administrator of an estate if necessary to fulfill their obligations [§ 2782(1)(q)]

Documentation of HIV-related information must be made in the patient's medical record so that it is readily accessible for care and treatment [10 NYCRR § 63.7(a)]. In addition, a State or local health officer, such as authorized Health Department personnel, may disclose confidential HIV-related information:

- To the patient and any person the patient authorizes pursuant to a release of confidential HIV information [§§ 2134, 2782(2)(b)]
- To the patient's contact(s) but without revealing the identity of the protected individual or other contacts (the Health Department is required to notify any known contacts of an HIV case if the treating healthcare provider has not done so) [§§ 2133(3), 2134, 2782(2)(c)]
- To any person to whom disclosure is ordered by a court pursuant to NYS Public Health Law § 2785 (provides for court-ordered disclosure in limited circumstances including where there is a "clear and imminent danger" to an individual or the public health) [§ 2782(2)(d)]; confidential HIV information cannot be released pursuant to a general subpoena [10 NYCRR § 63.6(k)]
- When used in the aggregate as part of agency programs to improve HIV quality of care (but without patient-identifying information) [§ 2135]
- When used to assess comorbidity or completeness of reporting and to direct program needs (provided patient-identifying information is not released outside the department) [§ 2135]
- For public health purposes, information may be shared with other health departments or the patient's current treating provider
- As otherwise authorized or required by federal or State law [§§ 2135, 2782(2)(a)]

Persons in receipt of confidential HIV-related information pursuant to the above exceptions are obligated to maintain confidentiality [§2782(3)]. Oral or written disclosure of confidential HIV information must be accompanied by a statement prohibiting re-disclosure except where disclosure is made pursuant to the patient's written consent, for treatment of the patient or the patient's child, or to third-party payers [10 NYCRR §§ 63.5]; under most circumstances, disclosure must be documented in the patient's medical record [10 NYCRR § 63.7(b)].

The law regarding HIV testing, confidentiality, and disclosure is ever-changing; BTBC staff should check with the Office of the General Counsel or a Health Department privacy officer whenever they have an issue related to disclosure. Additional information regarding HIV testing, consent, reporting test results, and other HIV resources are available at https://www1.nyc.gov/site/doh/providers/health-topics/infectious-diseases.page#hiv.

REPORTING REQUIREMENTS

Prompt reporting enables BTBC to evaluate a patient's treatment plan and reinforces to providers the importance of adherence to prescribed treatment. Physicians, laboratories, healthcare facilities, and other providers must report suspected or confirmed cases of active TB disease, for persons alive or deceased, within 24 hours of diagnosis [10 NYCRR §§ 2.10, 2.11; NYC Health Code §§ 11.03(a), 11.03(b)(2), 13.03(a)], and must continue to report on various aspects of patient treatment [NYC Health Code § 11.21(a)]. Animal care providers and facilities are also required to report confirmed cases of TB disease in animals to the Health Department [NYC Health Code §11.25(a)(2)]. Further, if no physician or other clinician is in attendance, heads of private households or of any institution, including child care services, schools, camps, hotels, shelters, or correctional facilities, have a duty to report an individual likely to have active TB disease [10 NYCRR § 2.12; NYC Health Code §§ 11.05(c), 43.19(e), and 47.27(e)].

Healthcare providers must provide access to necessary paper and electronic medical records to authorized Health Department staff as requested [NYC Health Code § 11.03(e)].

REPORTING SUSPECTED OR CONFIRMED CASES OF TUBERCULOSIS DISEASE BY PHYSICIANS AND MEDICAL FACILITIES

Medical providers are required by NYS and NYC law to report all patients, alive or deceased, with suspected or confirmed TB disease to the Health Department within 24 hours [10 NYCRR §§ 2.10, 2.11; NYC Health Code §§ 11.03(a), (b)(2)]. Providers are encouraged to call the Health Department immediately if they have questions about screening, treating, or reporting a suspected or confirmed TB case. (See *Chapter 9: Tuberculosis Reporting and Surveillance*.)

NYC Health Code § 11.03(a) requires providers to report patients who meet at least one of the following criteria:

- Clinical suspicion of pulmonary or extrapulmonary TB such that the physician or other healthcare provider has initiated or intends to initiate isolation or treatment for TB disease
- Acid-fast bacilli (AFB)-positive smears (from any anatomic site)
- Nucleic acid amplification (NAA) test (e.g., Roche's COBRAS®AMPLICOR, the Gen-Probe® Amplified™ Mycobacterium Tuberculosis Direct [MTD] Test) positive for *Mycobacterium tuberculosis* (*M. tuberculosis*) complex (including *M. tuberculosis*, *M. africanum*, *M. bovis*-bacille Calmette-Guérin [BCG], *M. caprae*, *M. canettii*, *M. microti*, *M. pinnipedii*, *M. bovis*)
- Culture-positive for *M. tuberculosis* complex
- Biopsy, pathology, or autopsy findings consistent with active TB disease, including caseating granulomas in biopsy of lung, lymph nodes, or other specimens

Providers must report a suspected or confirmed case of TB disease within 24 hours of diagnosis by telephone or in writing submitted electronically or by fax using the Health Department Universal Reporting

Form (URF). (See *Appendix Q: New York City Health Department Universal Reporting Form*.) Information reported must be as complete as possible and include the following:

- Information needed to identify and locate the individual (name, telephone number, address, and date of birth)
- Provider information (physician's name, email, telephone number, and reporting facility)
- Results of AFB smear culture (including date specimen obtained and accession number, if available)
- Results of any chest radiographs (CXR)

To obtain free copies of the URF, call toll free 866-NYC-DOH1 (866-392-3641) or access the form at nyc.gov/health and search for "URF." Providers have 4 options for submitting the URF:

1. **ELECTRONICALLY (preferred method): Complete the URF electronically using the Reporting Central online via NYCMED within 24 hours at nyc.gov/health and search for "NYCMED"**
   - ›› **A NYCMED account must be set up to access and submit the form. Assistance is available if needed by calling 888-NYC-MED9 or 347-396-2400, or by email at nycmed@health.nyc.gov**
2. **TELEPHONE: Call the TB HOTLINE at 844-713-0559 within 24 hours. Mail a completed URF within 48 hours to the address below.**
3. **FACSIMILE: Fax the URF to BTBC at 844-713-0557 within 24 hours. Mail a completed URF within 48 hours to the address below.**
4. **MAIL: Express or overnight mail the URF, ensuring it will arrive within 24 hours to:**
   New York City Department of Health & Mental Hygiene
   49-02 28th Street, CN#72, Long Island City, NY 11101

REPORTING OF CHILDREN YOUNGER THAN FIVE YEARS OF AGE WITH A POSITIVE TEST FOR TUBERCULOSIS INFECTION

Medical providers are required to report any child younger than five years of age (up to the day of their fifth birthday) who has a positive tuberculin skin test (TST) or a positive blood-based interferon gamma release assay (IGRA) test for TB infection, regardless of whether the child has received BCG vaccination [NYC Health Code §11.03(a) and §11.21].

For any child younger than five years of age (up to the day of their fifth birthday) with a positive TB test, providers must also report qualitative and quantitative TB test results (including induration [in millimeters (mm)] for TST), radiography results (CXR, computed tomography [CT], and magnetic resonance imaging [MRI]), and any prophylactic medication initiated for latent TB infection (LTBI).

In addition, laboratories are required to report positive results for TB infection obtained from a blood based test (e.g., IGRA) or other laboratory test when performed on children younger than five years of age [NYC Health Code §13.03(b)(1)].

REPORTING PATIENT TREATMENT PLANS AND PATIENT STATUS

Medical providers or heads of treatment facilities who treat active TB patients are required to do the following [NYC Health Code § 11.21(a)(1-3)]:

- Submit a treatment plan to the patient's case manager for all newly diagnosed cases within one month of treatment initiation. This plan must include at least:
  - The name of the healthcare provider who has assumed responsibility for TB treatment
  - Names and duration of prescribed anti-TB drugs
  - Anticipated date of treatment completion
  - A plan for promoting treatment adherence
- Submit to BTBC monthly clinical status reports for active TB disease patients, which must include at least:
  - The name, address, and telephone number(s) of the patient
  - Whether treatment is still ongoing
  - The stage, clinical status, and treatment being provided
  - Dates and results of sputum and CXR exams
- Provide any other information required by the Health Department.
- Report to BTBC when treatment ceases and the reason for the cessation.

To facilitate the submission of mandatory monthly patient status reports, the Health Department has created the REPORT OF PATIENT SERVICES FORM (TB 65), available at nyc.gov/health and search for "TB provider resources." This form, or other report containing the same information, must be submitted to the patient's case manager. (See *Appendix R: Report of Patient Services Form*.)

REPORTING HOSPITAL DISCHARGE OF AN INFECTIOUS TUBERCULOSIS PATIENT

Medical providers are required to obtain discharge approval from the Health Department prior to discharging an infectious TB patient from inpatient care. The Health Department will respond to discharge approval requests within one business day and will either approve the discharge or request additional information or actions [NYC Health Code § 11.21(a)(4)]. (See *Chapter 9: Tuberculosis Reporting and Surveillance*.)

All requests for inpatient discharge approval must be made using the HOSPITAL DISCHARGE APPROVAL REQUEST FORM (TB 354). All forms must be submitted at least 72 hours prior to planned discharge. To submit by fax, send to 844-713-0557.

To assist in discharge planning, providers should use the HOSPITAL DISCHARGE PLANNING CHECKLIST for TB Patients. Both forms are available at nyc.gov/health; search for "TB provider resources." (See *Appendix S: Hospital Discharge Approval Form*.)

If there is a concern that an infectious patient who does not meet discharge criteria may leave the hospital without authorization, healthcare providers should contact the Health Department immediately, 24 hours a day, seven days a week at:

- BTBC **TB HOTLINE** at **844-713-0559** (regular business hours)
- Poison Control Center at **212-POISONS** (212-764-7667) (after hours/weekends/holidays)

REPORTING OUTBREAKS AND UNUSUAL MANIFESTATIONS OF DISEASE

Healthcare providers must immediately report by telephone a suspected TB outbreak among three or more persons or animals, and any unusual manifestation of disease in an individual [NYC Health Code §§ 11.03(c)(1), 11.25(a)(4), 13.03(a); 10 NYCRR § 2.10]. An outbreak may be detected based on clinical, laboratory, or epidemiologic evidence. Telephone reports must be followed up in writing within 24 hours [NYC Health Code §§ 11.03(c)(1), 11.25(a)(4), 13.03(a)]. The Health Department has a duty to immediately report any outbreak to the NYS Department of Health (NYS DOH) [10 NYCRR §§ 2.1(b)-(c), 2.16].

Reports of suspected TB outbreaks or unusual manifestations of TB disease must be made immediately by calling the following numbers and asking to speak to the Health Department doctor on-call:

- **Business Hours (Monday through Friday 9 AM to 5 PM): Call the TB HOTLINE at 844-713-0557**
- **Non-Business Hours (nights, weekends, and holidays): Call the Poison Control Center at 212-POISONS (212-764-7667)**

A written report must be submitted in addition to telephone notification unless the Health Department explicitly instructs otherwise. The report must be submitted within 24 hours by fax, electronically, or by mail [NYC Health Code §§ 11.03(c)(1), 13.03(a)].

REPORTING CONTACTS

If a healthcare provider examines any contacts to a patient with infectious TB disease, the results of the examination must be reported when requested by the Health Department [NYC Health Code § 11.21(b)]. Suspected or confirmed cases of active TB disease among contacts must be reported in the same manner as with the initial case. There is no requirement to report all persons who test positive for TB infection (as opposed to active TB disease), except when the person is younger than five years of age, the Health Department is investigating outbreaks, or otherwise requests such information.

MICROBIOLOGY AND PATHOLOGY LABORATORIES: TESTING AND REPORTING

NYC Health Code §§ 13.03(a) and (b)(1) require laboratories testing specimens submitted for NYC resident patients to report the following to the Health Department, whether confirmed or presumptive, for patients alive or deceased, within 24 hours of obtaining test results (see *Chapter 9: Tuberculosis Reporting and Surveillance*):

- AFB-positive smears (from any anatomic site)
- Cultures positive for *M. tuberculosis* complex (including *M. tuberculosis*, *M. africanum*, *M. bovis-BCG*, *M. caprae*, *M. canettii*, *M. microti*, *M. pinnipedii*, *M. bovis*)
- NAA test results that identify *M. tuberculosis* complex (e.g., Roche's COBRAS®AMPLICOR, the Gen-Probe® Amplified™ MTD Test, Xpert MTB/RIF assay)
- Results of drug-susceptibility tests (DSTs) performed on *M. tuberculosis* complex cultures on a drug-specific basis
- Biopsy, pathology, and autopsy findings consistent with TB, including the presence of AFB or granulomas
- Any culture result associated with an AFB-positive smear, including negatives and species identification, even if negative for *M. tuberculosis* complex
- All subsequent laboratory TB tests (negative or positive) on samples collected within one year from patients with a prior AFB-positive smear or positive test for *M. tuberculosis* complex [also § 13.05(b)(8)]
- All results including negative and indeterminate results of blood-based or other later-developed laboratory tests for tuberculosis infection

All reports by laboratories to the Health Department must contain all of the information required by the reporting form including:

- The full name, date of birth, and address of the patient, as well as the patient's email, mobile phone number, race, ethnicity, and sex if known
- The specimen source and the collection date
- The medical record number if known, and any other assigned patient identifiers
- The name, address, and telephone number of the physician, facility, and/or laboratory that submitted the specimen, as well as the submitting provider's email, fax number, mobile phone number, and National Provider Identification (NPI) number (and facility NPI) if known
- The name and address of the laboratory
- The date the test results were first available
- The name(s) of the tests performed [NYC Health Code § 13.03(a)]

In addition to the above reporting requirements, the NYC Health Code requires laboratories to:

- Adhere to the following testing schedule (or, if unable to do so, send specimens to another laboratory within 24 hours after receipt of the specimen [§ 13.05(b)(5)]):
  - Examine smears performed to detect AFB within 24 hours of receipt [§ 13.05(b)(1)].
  - Initiate conventional cultures of clinical specimens within 24 hours of receipt, and examine for growth at least once each week after inoculation and, upon observing adequate suspicious growth, perform acid fast smear examination [§ 13.05(b)(2)].
  - Complete cultures of clinical specimens within 15 working days after growth is first indicated [§ 13.05(b)(3)].
  - Identify the presence or absence of *M. tuberculosis* complex within four working days after adequate suspicious growth is first detected [§§ 13.05(b)(2), (3)].
  - If direct DST is performed, initiate test within 24 hours of the next scheduled work day after obtaining the smear-positive for AFB; if indirect DST of pure cultures is performed, initiate as soon as growth typical of *M. tuberculosis* is observed [§ 13.05(b)(4)].
  - For other laboratory techniques, adhere to the methodologies and examination schedules recommended by the manufacturer [§ 13.05(b)(6)].
- Perform NAA testing on all positive AFB smears from patients not previously diagnosed with TB disease, or send such specimens to the Health Department for testing if the facility lacks NAA testing capabilities [§ 13.05(b)(1)].
- Submit, within 24 hours of observing growth of a culture or subculture of *M. tuberculosis* complex, a portion of the initial culture from any specimen to the Health Department for deoxyribonucleic acid (DNA) or other molecular analysis (a specimen submitted to Health Department for DST meets this requirement unless Health Department notifies otherwise) [§ 13.05(a)].
- Report any results of TB-related tests to the physician or other person authorized to order such tests within 24 hours of test results or findings, whether positive or negative [§§ 13.05(b)(1) and (b)(7)].

Laboratories must report the above listed findings via the ELECTRONIC CLINICAL LABORATORY REPORTING SYSTEM (ECLRS), the mandatory method of laboratory reporting in NYC [NYC Health Code §§ 13.03(c)]. Access to ECLRS is available through the NYS Health Commerce System (formerly the Health Provider Network) at https://commerce.health.state.ny.us/public/hcs_login.html

Laboratories must submit positive *M. tuberculosis* cultures for DNA analysis to the Health Department Public Health Laboratory within 24 hours of observing growth:

New York City Health Department Public Health Laboratory
455 First Avenue, Room 136
New York, NY 10016

VETERINARIAN AND ANIMAL CARE INSTITUTIONS: REPORTING ANIMALS INFECTED WITH TUBERCULOSIS

A confirmed diagnosis of TB disease in an animal must be reported to the Health Department by veterinarians, veterinary technicians, persons who work at an animal hospital or other facility providing or responsible for animal care or treatment (e.g., animal shelters, zoos), and veterinary diagnostic laboratories [NYC Health Code §§ 11.25(a) (2), (b)(1)].

Diseases in animals raised as food sources must be reported to the NYS Department of Agriculture and Markets via fax, mail, or in an electronic transmission acceptable to the Health Department.

Reports must be made within 24 hours of laboratory diagnosis by telephone or in writing by submission of an "Animal Disease Case Report" form via fax, mail, or in an electronic transmission acceptable to the Health Department. This form can be found at nyc.gov/health; search for "Animal Disease Case Report" [NYC Health Code §§ 11.25(a) (2), (b)(1)]. Reports must contain all information available concerning the disease and the infected animal and its owner, including the species and location of the animal, and the name, telephone number, and address of the owner [NYC Health Code § 11.25(b)(3)].

See "Reporting Outbreaks and Unusual Manifestations of Disease" subsection for information regarding reporting suspected or confirmed outbreaks or unusual manifestation of disease in animals.

Laboratory confirmed cases of TB disease in animals must be reported to Health Department Bureau of Communicable Disease within 24 hours by telephone or in writing:

TELEPHONE: Business Hours (Monday through Friday 9 AM to 5 PM): Call the Bureau of Communicable Disease at 347-396-2600; Non-Business Hours (nights, weekends, and holidays): Call the Poison Control Center at 212-POISONS (212-764-7667)

MAIL: New York City Health Department Bureau of Communicable Disease; 42-09 28th Street, CN22A, Long Island City, New York 11101

TABLE 17.1: Summary of mandatory tuberculosis reporting requirements[1]

REPORTER(S)	REQUIREMENT [APPLICABLE NYC HEALTH CODE CITATION]
Non-laboratory healthcare providers (e.g., treating physician, hospital, or clinic)	• Report cases of suspected or confirmed TB disease for patients alive or deceased to the Health Department within 24 hours [§§ 11.03(a), (b)(2); 10 NYCRR §§ 2.10, 2.11]. • Report any child younger than 5 years of age who has a positive test result for TB infection, regardless of whether the child had a BCG vaccination, to the Health Department within 24 hours [§ 11.03(a)]. • Use the URF for reporting suspected or confirmed cases of TB to the Health Department [§ 11.05(b)]. • Submit an initial treatment plan [§ 11.21(a)(2)]. • Obtain consent from the Health Department at least 72 hours before discharging a patient with infectious TB via the "Hospital Discharge Approval Request" Form (TB 354) [§ 11.21(a)(4)]. • Report patient treatment plans and outcomes monthly via the "Report of Patient Services" Form (TB 65) or other means [§§ 11.21(a)(1)-(3)]. • Evaluate contacts to a TB patient, or refer such contacts to the Health Department for examination [§ 11.21(b)]; suspected or confirmed TB cases among contacts must be reported in the same manner as the initial case. • Report results of contact investigations to the Health Department as requested [§ 11.21(b)]. • Immediately report suspected TB outbreaks (3 or more cases) and unusual manifestations of disease to Health Department by phone, followed by written notification within 24 hours [§ 11.03(c)(1); 10 NYCRR § 2.10].
Laboratories	• Report the following to the Health Department within 24 hours of a confirmed or presumptive finding: AFB-positive smears; cultures or NAA test positive for *M. tuberculosis* complex; DST results; and any other biopsy, pathology, or autopsy finding consistent with TB [§§ 13.03(a), (b)(1)]. • Report TB test results (positive or negative) for a patient testing positive for TB within the last year to the Health Department within 24 hours [§§ 13.03, 13.05(b)(8)]. • Include in reports to the Health Department specific, detailed information regarding the patient, provider(s), and specimen [§ 13.03(a)]. • Use the NYS ECLRS for all TB-related reporting to the Health Department [§§ 13.05(a), (c)]. • Report results of TB-related tests to the patient's provider within 24 hours [§§ 13.05(b)(1), (7)]. • Perform NAA testing on all AFB-positive smears from patients not previously diagnosed with TB [§ 13.05(b)(1)]. • Adhere to a specific testing schedule, and send specimens to another laboratory if unable to do so [§ 13.05(b)]. • Submit positive *M. tuberculosis* cultures for DNA analysis to the Health Department Public Health Laboratory within 24 hours of observing growth [§ 13.05(a)]. • Immediately report suspected TB outbreaks (3 or more cases) and unusual manifestations of disease to the Health Department by phone, followed by written notification within 24 hours [§ 13.03(a); 10 NYCRR § 2.10]. • Report positive results for TB infection obtained from a blood based test (e.g., IGRA) or other laboratory test when performed on children younger than 5 years of age [NYC Health Code §13.03(b)(1)].

TABLE 17.1: Summary of mandatory tuberculosis reporting requirements (*continued*)[1]

REPORTER(S)	REQUIREMENT [APPLICABLE NYC HEALTH CODE CITATION]
Veterinary and animal care facilities	• Report all animals infected with TB, alive or deceased, to the Health Department within 24 hours of diagnosis by telephone or in writing [§ 11.25(a)(2)]. • Include in report specific, detailed information regarding the animal, its owner, and test results [§ 11.25(b)(3)]. • When making a written report to the Health Department, use the "Animal Disease Case Report" form [§ 11.25(a)(2)]. • Immediately report suspected TB outbreaks (3 or more animals) and unusual manifestations of disease to Health Department by phone, followed by written notification within 24 hours [§ 11.25(a)(3)]. • Report diseases in animals used as food sources to NYS Department of Agriculture and Markets.
Persons in charge of other institutions (e.g., schools, child day care centers, camps, hotels, shelters, correctional facilities)	• If no healthcare provider is in attendance, report an individual likely to be infected with TB [§ 11.05(c); 10 NYCRR § 2.12].

[1]All citations are to the NYC Health Code unless otherwise indicated

Abbreviations Used: AFB=acid-fast bacilli; BCG=bacille Calmette-Guérin; BTBC=Bureau of Tuberculosis Control; DNA=deoxyribonucleic acid; DST=drug-susceptibility test; ECLRS=Electronic Clinical Laboratory Reporting System; IGRA=interferon gamma release assay; *M. tuberculosis*=*Mycobacterium tuberculosis*; NAA=nucleic acid amplification; NYC=New York City; NYCRR=New York Compilation of Codes, Rules and Regulations; NYS=New York State; TB=tuberculosis; URF=universal reporting form

INVESTIGATION, ISOLATION, EXCLUSION REQUIREMENTS, AND ENFORCEMENT MECHANISMS FOR NON-ADHERENT PATIENTS

Healthcare providers who come in contact with a suspected or confirmed case of TB disease are required to minimize the risk of transmission to others, including advising contacts on their risk and need for evaluation, isolating infectious patients, and providing information to infectious patients and their contacts regarding TB transmission and prevention. Every effort should be made to secure voluntary compliance with these measures, and to identify and remove any barriers to testing, isolation, and treatment.

The Health Department can require examination of suspected cases and isolation of infectious patients until they are no longer infectious when the patient's presence in the community constitutes a danger to any person or the public's health. Patients who are non-adherent with TB evaluation or treatment and who may pose a danger to public health must be evaluated for appropriate regulatory action if voluntary compliance or other less restrictive measures of securing compliance have been unsuccessful or were considered and rejected. (See *Chapter 10: Case Management for Patients with Tuberculosis*.)

DUTY TO INVESTIGATE CONTACTS AND OTHER SUSPECTED TUBERCULOSIS CASES

The Health Department must investigate all reported suspected or confirmed TB cases to verify diagnosis (including collecting laboratory specimens for testing), ascertain the source of infection, and discover contacts and unreported cases [10 NYCRR §§ 2.6(a), 2.6(b), 2.7(a), 43-1.2]. If a patient with suspected TB disease is being treated by a private physician, the Health Department must ascertain whether the physician is maintaining proper sanitary supervision [10 NYCRR § 2.7(b)]. The Health Department is required to maintain supervision of every suspected and confirmed case of TB in a NYC resident until the patient has completed treatment and is no longer a public health risk.

Healthcare providers must examine all household contacts, or refer contacts to the Health Department for examination, and report results to the Health Department if requested [NYC Health Code § 11.21(b)]. The Health Department may require any contact to be examined, and re-examined as necessary, referring patients with suspected or confirmed TB disease for further examination or treatment [NYC Health Code § 11.21(b)]. Such examination must include any necessary tests for TB [NYC Health Code § 11.21(b); 10 NYCRR § 2.5]; suspected or confirmed TB cases among contacts must be reported pursuant to regular reporting requirements (see *Summary of Reporting Requirements*).

DUTY TO ISOLATE, EXCLUDE, AND INFORM SUSPECTED AND CONFIRMED TUBERCULOSIS PATIENTS AND THEIR CONTACTS

Physicians and persons in charge of medical facilities and nursing homes have a duty to isolate any patient with suspected or confirmed TB disease using recognized infection control principles until the Health Department can evaluate the patient's risk to public health [NYC Health Code § 11.17(a), 10 NYCRR §§ 2.27, 2.29]. Facilities that cannot implement appropriate isolation precautions, such as schools, day care facilities, camps, homeless shelters, correctional facilities, or other congregate residential settings, must provide the patient with a mask to wear as necessary, and separate them from others until transfer to an appropriate medical facility [NYC Health Code § 11.17(c)].

An individual with infectious TB disease must be excluded from attending work, school, or any location where TB transmission can occur (as determined by the Health Department) [NYC Health Code § 11.21(c)] (see *Schools, Childcare Services, and Other Children's Facilities* for requirements specific to these institutions).

Physicians who attend a patient with suspected or confirmed TB disease must inform the patient and any contacts regarding applicable isolation, exclusion, quarantine, screening, and treatment requirements [NYC Health Code § 11.13]. Physicians, or the Health Department if no physician is attending the patient, must also advise members of the patient's household regarding the risks of personal contact with the patient and specific precautions to be taken to prevent the spread of TB [10 NYCRR §§ 2.7(b), 2.27; Public Health Law § 2222(1); NYC Health Code § 11.13]. All patient and contact education should be documented.

Every effort should be made by healthcare providers and the Health Department to identify, address, and remove barriers to outpatient TB treatment and to document such efforts before considering imposing compulsory measures. It is also necessary to document evaluations showing that in some rare cases it is necessary to impose compulsory measures without undertaking less restrictive alternatives.

NYC Health Code § 11.21(d) authorizes the Commissioner of Health to exercise a range of enforcement options (i.e., to issue "any orders he or she deems necessary to protect the public health or the health of any other person") to control TB in patients who are non-adherent with evaluation or treatment and whose presence in the community constitutes a danger to an individual's or the public's health. These enforcement options may be issued without obtaining judicial review, and include an order:

- **Authorizing the removal to or detention in a hospital or other treatment facility of a person with confirmed or suspected active TB disease for examination [§11.21(d)(1)];**
- **Requiring a person with active TB disease to complete prescribed treatment and follow required infection control precautions [§ 11.21(d)(2)];**
- **Requiring a person with active TB disease who is unwilling or unable to complete an appropriate treatment course to follow directly observed therapy (DOT) [§ 11.21(d)(3)];**
- **Authorizing the removal to or detention in a hospital or other treatment facility of a person who has, or is substantially likely to have, active TB disease that is infectious, where there is a substantial likelihood of TB transmission because of the patient's inadequate separation from others [§ 11.21(d)(4)];**
- **Authorizing the removal to or detention in a hospital or other treatment facility of a person who has active TB disease, or who has been reported to the Health Department as having active TB disease with no report to the Health Department of treatment completion, where such person cannot be relied upon to participate in or complete treatment or follow infection control precautions as evidenced by past or present non-adherent behavior [§ 11.21(d)(5)].**

NOTICE OF OBLIGATION TO ISOLATE

Sometimes an infectious TB patient will not or cannot adhere to hospital isolation procedures or threatens to leave the hospital without a suitable discharge plan. When a provider believes that a patient with suspected or confirmed TB disease will leave the hospital against medical advice, BTBC must be contacted immediately. When this happens a Notice of Obligation to Isolate (NOI) will be faxed to the provider to remind them of their obligation to isolate a patient until BTBC evaluates the patient's risk to public health and makes a determination regarding detention.

Upon receiving the NOI, the hospital or other healthcare provider must continue to take all necessary measures to prevent the patient from leaving the hospital including placing security staff outside the patient's room if necessary. If, after evaluation of the circumstances, the Health Department agrees that detention is necessary, a Commissioner's Order for Detention will be faxed to the hospital within 24 business hours of the issuance of the NOI [Involuntary Isolation and Detention (New York City Health Code § 11.21(d)(1), (4), and (5) Orders)].

REGULATORY ORDERS

The Health Department may order removal and/or detention in a medical facility and outpatient examination and treatment of non-adherent patients [NYC Health Code §§ 11.17(d), 11.21(d)]. Detention orders may require infectious patients to remain in hospital isolation, or be admitted to a hospital for examination or treatment of TB [NYC Health Code § 11.21(d)]. Involuntary detention should only be sought where voluntary detention is not possible.

The Commissioner of Health does not have authority to order forcible administration of medication; a court order must be obtained by the hospital in order to do so [NYC Health Code § 11.21(i)].

Constitutional due process safeguards for detained patients are required by NYC Health Code §§ 11.21(e), (f), and (g). The patient ordered detained is personally served with the detention order by the Health Department or hospital staff.

Each order includes:

- The legal authority for the order
- An individualized assessment of the patient's circumstances and/or behavior constituting the basis for the order
- The less restrictive means that were attempted but unsuccessful, or that were considered and rejected with the reason for rejection
- The purpose of the detention
- How to request release from detention
- How to obtain judicial review
- The right to be represented by counsel
- The right to notify family and friends regarding the detention

The law provides for mandatory judicial review of detention orders when the patient requests release or will be detained for more than 60 days:

- When a patient requests release, the application for a court order must be filed within three business days (or within one business day following a Saturday, Sunday, or legal holiday accompanied by a request for an expedited hearing) and the detention will not continue for more than five business days after the request if there is no court order issued.
- If the patient will be detained for more than 60 days, further court review is required; additional court review is required every 90 days thereafter [NYC Health Code § 11.21(e)].

If a hearing is required, the detainee has a right to be represented by counsel; counsel must be provided free of charge upon request [NYC Health Code § 11.21(e)]. At any hearing, the hospital or the Health Department will provide the necessary infection control measures to protect the health of all participants in attendance. Evidence will be presented by representatives of the Health Department and by the patient

and their lawyer. The burden of proof rests with the Health Department, which must provide "clear and convincing evidence" supporting the detention [NYC Health Code § 11.21(e)]. The judge then determines whether the patient will be released or remain in detention based on the evidence.

Detention must end when:

- An individual detained pursuant to § 11.21(d)(1) has been examined and a determination made regarding whether the patient has active TB disease or is infectious; further detention requires issuance of another Commissioner's Order for Detention [NYC Health Code § 11.21(g)(1)].
- An individual detained pursuant to § 11.21(d)(4) can be adequately isolated from others in a location of preference while still infectiousness [NYC Health Code § 11.21(g)(2)].
- An individual detained pursuant to § 11.21(d)(5) has completed an appropriate prescribed course of medication [NYC Health Code § 11.21(g)(3)].

Inquiries regarding requests for Notices of Obligation to Isolate and Commissioner's Orders for individual patients including requests for detention may be made to the Health Department at:

Business Hours (Monday through Friday 9 AM to 5 PM): Call the TB HOTLINE at (844) 713-0559.

At all other times (nights, weekends, or holidays): Call the Poison Control Center at 212-POISONS (212-764-7667).

SCHOOLS, CHILDCARE SERVICES, AND OTHER CHILDREN'S FACILITIES*

**All citations in this section are to the NYC Health Code*

The NYC Health Code regulates schools, childcare services, and other children's facilities. Article 45 includes general health provisions for all elementary schools, junior high schools (including kindergartens that are part of an elementary school operated by the Board of Education), children's institutions, and some regulations for high schools (only §45.09 (b) through (d) apply to high schools). Other NYC Health Code articles provide additional requirements specific to school-based programs for children ages three through five years (Article 43); elementary and junior high schools, as well as kindergartens attached to elementary schools operated by the Department of Education (Article 49); and high schools (Article 49, § 49.15(d)). Article 47 regulates all childcare facilities for children under six years of age except those programs provided by schools for children aged three to five years, which are regulated by Article 43. Camps are regulated under Article 48.

TUBERCULOSIS TESTING OF CHILDREN AND STAFF

There is no longer any NYC requirement that all children and staff be tested for TB infection prior to entering a school or other children's facility. The Health Department has broad authority, however, to test any person for TB in public or private elementary and junior high schools as necessary for "epidemiological or other public health purposes" [§ 49.06]. Likewise, the Health Department may require TB testing of

any person (child or staff) in a school-based program for children ages three to five years [§ 43.11(d)]; elementary, junior high, and high schools; children's institutions [§ 45.09(c)]; and child care facilities [§ 47.33(d)] for "epidemiological investigation" as necessary. Staff of summer camps, however, must undergo TB testing at intervals prescribed by the Health Department [§§ 48.17(g)]. This is because camps are also regulated by the State Sanitary Code, which mandates testing in this setting.

While TB testing is no longer specifically mandated for school entry, requirements for staff employment and student medical examination help identify medical issues, including TB.

EXCLUSION AND ISOLATION OF TUBERCULOSIS-INFECTED PERSONS FROM SCHOOLS AND OTHER CHILDREN'S FACILITIES

NYC Health Code § 11.21(c) requires that persons with infectious TB disease (both staff and students) be excluded from schools and other places where they can transmit TB infection. This requirement is reinforced elsewhere in the NYC Health Code, which prescribes exclusion requirements for children and staff at schools, children's institutions, camps, and other childcare facilities [§§ 43.11(a), 43.19(f), 45.09(b), 47.27(f), 47.33(a), 49.15(d)].

Additionally, persons in charge of elementary schools, junior high schools, and children's institutions must isolate cases and carriers of communicable diseases (both children and staff), including active TB disease, and provide facilities for their isolation pursuant to NYC Health Code § 11.57 [§ 45.17(b)]. There is also a duty to isolate any child or staff member suspected of having a communicable disease, including TB disease, in summer and overnight camps [§ 48.17(k)].

Staff or students returning to a public or private elementary, junior high, or high school, and staff returning to a children's institution after being infectious with TB disease must obtain a certificate of recovery from the Health Department before being permitted to return [§§ 45.09(b)(1), 49.15(d)(1)]. Staff or students returning to a school or non-school-based childcare program for children five years and under after being infectious with TB disease must obtain a written statement of recovery from a healthcare provider before being permitted to return [§§ 43.11(a), 43.19(f), 47.27(f), 47.33(a)]. In the case of returning children, the statement of recovery must state that the child is no longer infectious and that the period of isolation or exclusion pursuant to Article 11 has ended [§§ 43.19(f), 47.27(f)].

SPECIAL RULES FOR FACILITIES WITH CHILDREN FIVE YEARS OF AGE AND YOUNGER

Rules for reporting and monitoring TB in schools and childcare facilities are more stringent for facilities where children five years of age and younger are in attendance.

All teachers and assistant teachers employed by childcare facilities for children under three years of age (school and non-school based), and non-school based facilities for children three to five years of age, must receive training in infection control and reporting infectious diseases [§§ 47.37(b), (d)(1)].

Further, absences due to TB must be reported by parents to facilities serving children aged five and under within 24 hours, and facilities are responsible for reminding parents of this requirement at the beginning of each school year [§§ 43.19(d), 47.27(d)]. Once notified, the person in charge of the facility must report the case to the Health Department by telephone within 24 hours [§§ 43.19(e), 47.27(e)].

Additionally, childcare facilities for children under three years of age (school and non-school based), and non-school-based facilities for children three to five years of age can be asked to immediately remove a worker or close a facility, suspending its permit, if a worker with infectious TB disease has remained at work [§§ 47.01(k)(14), 47.77(a)]. Any facility so cited must submit a corrective action plan to the Health Department within five business days for review and approval [§ 47.21(a)]. The plan must include an assessment of the risk to children and must "clearly and convincingly" demonstrate that there is no danger to any child or any other person [§§ 47.21(b)]. School-based facilities for children three to five years of age must similarly submit a corrective action plan if a worker with infectious TB disease was allowed to remain at work [§§ 43.15(a)(3),(b)].

PAYMENT FOR TUBERCULOSIS SERVICES

Public Health Law (PHL) section 2202(1) (e) prohibits patients from being charged for TB healthcare services received in a licensed Article 28 facility or from a Certified Home Health Agency. Consistent with PHL section 2202(1) (e), NYS DOH regulations (10 NYCRR Section 43-1.10) prohibit providers from requesting or requiring a patient or their responsible relative to pay for TB services provided in these settings. Therefore, no provider can request or require payment from a patient or their legally responsible relative for TB care provided in or by a facility listed above, which includes co-payments and deductibles.

- Medical providers are eligible for payment by a patient's health insurance carrier or other third-party payer with no out-of-pocket payment(s) from the patient
- If the patient does not have health insurance, a provider claim can be submitted to the NYC Health Department for reimbursement at the Medicaid rate
- A provider can submit a claim to the NYC Health Department if the payment received from the patient's insurer or other third-party payer was below the Medicaid rate
- If TB healthcare services are provided in a facility other than an Article 28 facility or Certified Home Health Agency, providers may bill the patient's health insurance carrier or other third-party payer as well as the patient.

KEY SOURCES

INQUIRIES AND FORMS TO REPORT SUSPECTED OR CONFIRMED TUBERCULOSIS CASES AND FOR TUBERCULOSIS CASE MANAGEMENT:

To inquire about reporting procedures, please call the TB Hotline at 844-713-0559.

The ECLRS can be accessed at https://commerce.health.state.ny.us/public/hcs_login.html (providers need to create a username and password). Additional information regarding ECLRS can be found at https://www.health.ny.gov/professionals/reportable_diseases/eclrs/

The URF can be obtained by calling 866-NYC-DOH1 (866-392-3641) or at nyc.gov/health; search for "URF"

NYCMED Reporting Central for electronic submission of the URF can be accessed at nyc.gov/health; search for "NYCMED"

The Report of Patient Services Form (TB 65) can be obtained by calling 844-713-0559 or at nyc.gov/health; search for "TB provider resources"

The Hospital Discharge Approval Request Form (TB 354) can be obtained by calling 844-713-0559 or at nyc.gov/health; search for "TB provider resources"

The Hospital Discharge Planning Checklist can be found at nyc.gov/health; search for "TB provider resources"

The Animal Disease Case Report form can be obtained by calling 347-396-2600 or at nyc.gov/health; search for "Animal Disease Case Report"

FEDERAL LAW:

A free text version of HIPAA can be found at: https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/combined/hipaa-simplification-201303.pdf or http://www.ecfr.gov/cgi-bin/ECFR?page=browse.

Additional information regarding HIPAA can be found at: http://www.hhs.gov/ocr/privacy/

NEW YORK LAW:

The NYS Public Health Law can be found at http://public.leginfo.state.ny.us/LAWSSEAFcgi?QUERYTYPE=LAWS+&QUERYDATA=@LLPBH+&LIST=LAW+&BROWSER=BROWSER+&TOKEN=17718570+&TARGET=VIEW

The NYS Codes, Rules and Regulations can be found at http://government.westlaw.com/linkedslice/default.asp?SP=nycrr-1000, and also at http://w3.health.state.ny.us/dbspace/NYCRR10.nsf/Full+Directory?OpenView

The NYC Health Code can be found at nyc.gov/health; search for "NYC Health Code"

***NOTE:** The laws and regulations in these links might not be the current law and should be used as a starting point only. If you have any questions about the application of any of these laws, speak to a supervisor, who can contact the NYC Health Department Office of the General Counsel.

APPENDICES

APPENDIX A: INTERNATIONAL CLASSIFICATION OF TUBERCULOSIS[1]

CLASS	TYPE	DESCRIPTION	FOLLOW-UP ACTION
0	No history of TB exposure; Not infected	• Negative result on IGRA or TST • No history of TB exposure • No evidence of LTBI or disease	None
I	TB exposure; No evidence of TB infection or disease	• History of exposure to person with *M. tuberculosis* • Negative result on IGRA or TST (given at least 8 to 10 weeks after exposure [post-window period])	None
II	TB infection; No disease	• Positive results on IGRA or TST • No clinical or radiographic evidence of active TB disease • Calcified granuloma on CXR • Negative bacteriological studies (smears and cultures) for TB if performed	Classify as contact, medical, population, or administrative risk Treat for LTBI, if indicated
III	Current TB disease	• Positive culture for *M. tuberculosis* and/or • Clinical, bacteriological, or radiographic evidence of current active TB • With or without a positive result on IGRA or TST	Treat for TB disease
IV	Previous TB disease	• Positive result on IGRA or TST • History of active TB in past or abnormal but stable or fibrotic radiographic findings • Negative bacteriologic studies (if done) • No clinical or radiographic evidence of current active TB disease	Conduct patient evaluation and consider re-treatment, as indicated
V (high)[2]	Current TB disease suspected	• Current TB symptoms[3] • Diagnosis pending • Expected to be Class III	Conduct patient evaluation and reclassify patient within two months
V (low)[2]	Previous TB disease suspected	• Diagnosis pending • Expected to be Class IV or abnormality unrelated to TB	Conduct patient evaluation and reclassify patient within two months

Adapted from: *Centers for Disease Control and Prevention. (2013). Core curriculum on tuberculosis: what the clinician should know. Atlanta, Georgia: United States Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention; Division of Tuberculosis Elimination. Retrieved from https://www.cdc.gov/tb/education/corecurr/pdf/corecurr_all.pdf.*

1. The International Classification of TB has been modified for use by BTBC. 2. The division of Class V into "high" or "low" categories is intended to improve case management and is specific to the BTBC; it is not part of the International Classification of TB. 3. Current TB symptoms or CXR findings consistent with active TB.

Abbreviations Used: BTBC=Bureau of Tuberculosis Control; CXR=chest radiograph; IGRA=interferon gamma release assay; LTBI=latent tuberculosis infection; *M. tuberculosis*=*Mycobacterium tuberculosis*; NYC=New York City; TB=tuberculosis; TST=tuberculin skin test

APPENDIX B: TUBERCULOSIS RISK ASSESSMENT TOOL

This tool helps you identify asymptomatic adults and children at risk for latent tuberculosis infection (LTBI).

- Do not repeat testing unless there are new risk factors since the last test for TB infection.
- Do not treat for LTBI until active TB disease has been excluded.[1]

Testing for TB infection[2] is recommended if your patient meets ANY of the below criteria:

○ **HAVE THEY LIVED WITH OR SPENT TIME WITH ANYONE WHO HAD OR MAY HAVE HAD TB?**

Notify the New York City Department of Health and Mental Hygiene (NYC Health Department) if your patient has had close contact with anyone with TB disease. Call the **TB HOTLINE** at **(844) 713-0559**, available 24 hours a day, seven days a week.

○ **DO THEY HAVE HIV/AIDS, CANCER, OR AN IMMUNE DISORDER?**

Immunosuppression[3] includes the following: HIV infection, cancer, prolonged corticosteroid use (equivalent to 15 milligrams/day or more of prednisone for one month or more), other immunosuppressive treatments (for example, TNF- α antagonists, JAK Inhibitors, IL-1 receptor antagonists, chemotherapy, organ transplant medications).

○ **WERE THEY BORN OUTSIDE OF THE U.S. IN A HIGH TB INCIDENCE AREA, SUCH AS AFRICA, ASIA, MEXICO, CENTRAL OR SOUTH AMERICA, THE CARIBBEAN, OR EASTERN EUROPE, OR HAVE THEY TRAVELED TO OR LIVED IN A HIGH TB INCIDENCE AREA FOR MORE THAN ONE MONTH?**

If your patient was born outside of the U.S. in a high TB incidence area —or—traveled or lived outside the U.S. for one consecutive month or more in a high TB incidence area, they may be at greater risk of infection.

If the TB test result is positive and TB disease is ruled out,[1] treatment for LTBI is recommended.

1. Evaluate, by medical history and physical examination, all people with TB symptoms, positive TB test results or abnormal chest radiographs (CXRs) consistent with TB disease. Following NYC Health Code Article 11, report all people with potential or confirmed TB disease and children younger than 5 years of age diagnosed with LTBI to the NYC Health Department. For more information, visit: www.nyc.gov/health/tb.
2. Interferon Gamma Release Assays (IGRAs) are preferred for people age 2 years and older, particularly those who have previously received the Bacille Calmette-Guérin (BCG) vaccine since IGRAs do not cross-react with BCG; some experts recommend using IGRAs for people of all ages.
3. IGRA results may be indeterminate and may need to be repeated. IGRA results may be negative and unless indicated by clinical judgment (for example, clinical suspicion of TB disease, immunosuppression), no further evaluation is needed.

APPENDIX C: ADMINISTERING THE TUBERCULIN SKIN TEST

FIRST STEPS:

1. Gather your equipment
   - Gloves
   - Alcohol pads or alternative skin cleanser
   - Disposable 26-gauge syringe needle
   - Tuberculin syringe (do not pre-draw tuberculin into syringes prior to test)
   - Purified protein derivative (PPD)
   - Sharps container
2. Check PPD vial's expiration/opening date
3. Explain to patient why test is being done and how it will be performed

PREPARATION:

1. Wash hands and put on gloves
2. Place patient's arm on a flat surface, exposing the volar (inside) surface of the forearm
3. Locate site for the injection (two to four inches below elbow, where no scars, bumps or veins are located)
4. Clean the injection site with an alcohol swab
5. Wipe the top of the PPD vial with a second alcohol swab and place the vial on a flat surface
6. Prepare the syringe by inserting it into the vial. Inject 0.1 milliliters (ml) of air into the airspace in the vial. Do not inject air into the PPD solution. Invert the vial, keeping the needle tip below fluid level. Pull back on the plunger of the syringe and draw slightly more than 0.1 ml of PPD solution. Remove the syringe from the vial and tap the syringe lightly to dispel air bubbles. Hold the syringe point up and expel air and/or excess fluid, leaving exactly 0.1 ml of PPD solution in the syringe
7. Return the PPD vial to the refrigerator when not in use and place on a cooling pad when in use

INJECTION:

1. Stretch the skin of the injection site with the thumb of the non-dominant hand (e.g., left hand for right-handed persons)
2. Hold the syringe between the thumb and forefinger of the dominant hand (e.g., right hand for right-handed persons) with the bevel of the needle pointing upward
3. Insert the needle intradermally (just under the top layer of skin) at a 5°-15° angle
4. Inject the PPD solution slowly. A firm resistance should be felt as the tuberculin solution enters the skin. Ensure that the entire needle bevel lies just under the skin
5. Release the stretched skin and remove the needle from the injection site (DO NOT RECAP). Discard the syringe immediately in a sharps container

6. Ensure that a discrete skin elevation (wheal), six to 10 mm in diameter, has been formed (measure wheal using a tuberculin skin test [TST] ruler). If the injection angle was too deep, no wheal will appear. If the angle was too shallow, fluid may leak. Be sure to check for leakage at the insertion site.
7. Repeat injection two inches (five cm) from site, or on opposite arm, if wheal is smaller than six mm or if less than 0.1 ml was injected (both tests need to be documented; [see below]). If, after a second injection, the wheal is still less than six mm or not enough fluid is injected, clinic staff should speak with a supervisor

POST-INJECTION:

1. Educate the patient on the possible reactions to the TST (e.g., mild itching, swelling, irritation)
2. Instruct patient not to rub, scratch, or put an adhesive bandage or lotion on the test site. The area may be washed and patted dry
3. Document the test in the patient's chart (including second test if done)
4. Schedule reading date and explain the importance of the patient returning for reading in 48 to 72 hours

READING THE TUBERCULIN SKIN TEST REACTION:

The test result should be read only by a trained healthcare worker. Patients should never be allowed to read their own reaction.

1. Read the result 48 to 72 hours after administering the test. A test result that has a palpable induration can still be read up to 96 hours
2. Inspect the injection site for raised areas. Palpate the arm for a hard, dense, and raised area known as an induration. Feel the edges of the induration with the index finger
3. Mark the two edges of the induration with a dot, using a black, watermark pen, if available
4. Measure the induration (not redness) at its widest point transversely, from one marked edge to the other, using a flexible TST ruler. If the reading is between two points, the lower value should be used. Swollen areas, if they feel hard (but not red areas), should be palpated and included in the measurement
5. Record the size in mm and not simply as "positive" or "negative." If there is no induration, record the result as "00 mm"
6. Interpret the reaction as positive or negative based on both the size of the induration and the individual's risk factors. (See *Table 2.4: Criteria for Determination of a Positive Tuberculin Skin Test Result.*)
7. Explain the meaning of a positive or negative reaction to the individual and refer for follow-up evaluation, if needed. Provide appropriate literature
8. Document results in the patient's chart

APPENDIX D: THE USE OF BACILLE CALMETTE-GUÉRIN VACCINE

Bacille Calmette-Guérin (BCG) vaccine[1] is a live, attenuated strain of *Mycobacterium bovis* (*M. bovis*). In most parts of the world, BCG vaccine is used routinely to prevent serious complications of tuberculosis (TB), such as miliary TB and central nervous system (CNS) TB, in infants and children and in healthcare workers with frequent exposure to individuals with infectious TB disease.

Although the evidence is conflicting, a large body of research indicates that BCG vaccination does not completely prevent TB infection or pulmonary TB disease. Some studies suggest that BCG vaccination lessens the likelihood of disseminated TB and TB meningitis, especially in infants.

In the United States, BCG vaccination is not recommended routinely for children or used as a control strategy against TB. Specifically, it is not recommended as a general preventive strategy for healthcare workers because it complicates the interpretation of tuberculin skin test (TST) reactions and because it has not been proven effective in preventing TB infection.

BCG is not recommended for children or adults with human immunodeficiency virus (HIV) infection; HIV testing must be performed before BCG is administered. Similarly, active TB disease must be ruled out before BCG can be given. Nonetheless, BCG vaccine may be considered in very specific circumstances. These circumstances include instances in which infants and children are close household contacts of an individual with persistently untreated or ineffectively treated smear-positive TB disease, especially MDR-TB.

As of January 2018, TICE BCG (Manufacturer: MERCK) is available through Cardinal Health as a special order item. All requests for BCG must be discussed with the Bureau of Tuberculosis Control (BTBC); BTBC can be contacted via the TB Hotline at 844-713-0559.

1. INDICATIONS AND CONTRAINDICATIONS FOR BACILLE CALMETTE-GUÉRIN VACCINE

Before deciding to give BCG vaccine to a contact of an individual with persistently untreated or ineffectively treated smear-positive TB disease, every effort should be made to (1) ensure that the inadequately treated individual with infectious TB disease is treated properly, and (2) separate the individual with TB and the exposed contact(s).

If this is not possible, giving BCG vaccine may be considered if the contact meets **ALL** of the following criteria:

- The contact has a negative test for TB infection
- The contact is repeatedly exposed to an individual with persistently untreated or ineffectively treated smear-positive multidrug resistant TB (MDR-TB)
- The contact does not have HIV infection (in some situations, however, BCG vaccine may be given to infants who have a positive HIV antibody as below)

BCG vaccine should **NOT** be given to the following individuals:

- Persons with a documented history of a positive reaction to a test for TB infection
- Persons with HIV infection or persons who are otherwise immunosuppressed

There have been no reports of harmful effects of BCG vaccine on the fetus. Nevertheless, giving BCG vaccine should be avoided in pregnant patients, unless there is an unusual risk of unavoidable exposure to infectious MDR-TB.

2. SPECIAL CONSIDERATIONS FOR INFANTS

At least two other factors must be weighed before a decision is made to give BCG vaccination to a newborn or infant younger than nine months old:

- Because an infant may not be able to mount a cellular immune response to infection with *Mycobacterium tuberculosis* (*M. tuberculosis*), a TST may not be a reliable indicator of infection. Thus, there may be instances where an infant with a negative TST may receive BCG vaccine even though they may be infected with *M. tuberculosis.*
- The blood of some infants born to mothers with HIV infection may show the presence of HIV antibodies for a number of months after birth, even if the infant is not infected with HIV. Because HIV infection cannot be excluded in this situation, BCG vaccine could be considered only if the infant is otherwise healthy, especially if the evaluation of other close contacts reveals a high rate of documented TST conversions and if all other efforts to prevent transmission have failed. Such an infant needs to be followed by a specialist until HIV infection is ruled out based on the most current recommendations.

3. EVALUATION AND FOLLOW-UP

- An individual who is being considered for BCG vaccination who cannot document a history of a previous positive TST reaction should have a TST, using five tuberculin units of purified protein derivative (PPD). A blood-based test is not recommended.
- An individual who is being considered for BCG vaccination should be offered HIV counseling and testing if they have risk factor(s) for HIV infection.
- If the individual being considered for BCG vaccination is an infant or child, the parent or legal guardian must be interviewed and must agree. This must be documented in the chart.
- Eight weeks after the administration of BCG vaccine, the individual should have a repeat TST performed to document any reaction. If the contact's TST is less than five millimeters (mm), the BCG vaccination should be repeated.
- There is no evidence that revaccination with BCG later in life affords any additional protection and therefore revaccination is not recommended.

NOTE: Product names are provided for identification purposes only; their use does not imply endorsement by the New York City Health Department.

APPENDIX E: INSTRUCTIONS FOR PERFORMING SPUTUM INDUCTION

Sputum induction is the procedure for obtaining sputum from patients who have difficulty producing it spontaneously. In this procedure, patients inhale a mist of nebulized, sterile water (many facilities use hypertonic saline), which irritates their airways, causing them to cough and produce respiratory secretions.

EQUIPMENT

In order to appropriately and safely conduct sputum induction, the following equipment is required:

- A room, booth, or enclosed area that meets environmental control standards for high-risk procedures, including:
  - Negative air pressure relative to other areas (air flow must be from the corridor into the sputum induction room or booth; from there it should be exhausted to the outside or appropriately filtered and safely discharged by a mechanical ventilation system)
  - 12 or more complete air changes per hour
  - For rooms, ultraviolet germicidal irradiation (UVGI) must be used

All Bureau of Tuberculosis Control (BTBC) sputum induction rooms are fully equipped with the following:

- Nebulizer and table to support nebulizer
- Disposable tubing with cup and lid
- Sterile sputum collection jar, properly labeled
- Mycobacteriology forms
- Clear plastic biohazard specimen bag and paper bag
- Paper tissues and bag for disposal of tissues
- Sterile water
- Distilled water
- Solution of 10% bleach, 90% water
- Disposable gloves
- Disposable drinking cups

PREPARING EQUIPMENT AND THE SPUTUM INDUCTION ROOM

Once all equipment has been collected, BTBC staff prepare the room and supplies as follows:

- Assemble and organize the following equipment in quantities sufficient for the anticipated number of patients to be seen that day:
  - Sputum jars
  - Plastic biohazard bags and brown paper bags
  - Disposable plastic nebulizer tubing with cup and lid
  - Sterile water
  - Distilled water
  - 10% bleach solution, mixed at the start of the shift in an amount sufficient for that shift only
  - Disposable drinking cups

- Check that the ultraviolet light and exhaust fan are on and functional
- Prepare the nebulizer:
  - Inspect it for cleanliness
  - If necessary, wipe the nebulizer surfaces with 10% bleach solution
  - Place distilled water in the nebulizer chamber to the level marked on the chamber
  - Place a small amount of sterile water in the cup portion of the disposable nebulizer tubing
  - Insert the cup into the nebulizer
  - Test to make sure the nebulizer is functional by turning it on and checking to see whether it produces a mist
- Before beginning sputum induction:
  - Label the sputum jar in pencil with the patient's name and address, and the date
  - Place the completed Mycobacteriology form in the lab slip pocket of a biohazard bag with the patient's name facing out
- Include the TB Registry number of patients with confirmed TB disease or signs and symptoms consistent with TB disease on the mycobacteriology form

PREPARING THE PATIENT

The attending BTBC staff member prepares the patient for sputum induction:

- Explain the purpose of the procedure
- Orient the patient to the nebulizer and demonstrating how it functions
- Show patient the sputum jar and instruct them not to open the jar until ready to expectorate into it and to close the jar tightly as soon as the specimen is collected
- Provide sterile or bottled water and ask the patient to rinse their mouth prior to the procedure
- Explain not to begin the sputum induction procedure until the staff member has left the room and the door is firmly closed
- Telling the patient to:
  - Inhale the aerosol by taking three or four deep, slow breaths through the mouth without placing their mouth on the tubing (the patient is not to demonstrate deep breathing during the instruction)
  - Cough vigorously if they do not cough spontaneously in response to the mist
- Ask the patient to cover their mouth with a tissue when coughing unless expectorating into the sputum jar
  - Continue trying to cough and to expectorate after inhaling the mist
  - Expectorate all sputum into the sputum jar, without spilling it outside the jar
  - Cover the jar tightly after 5-10 milliliters (ml) of sputum from deep in the lung are in the jar

- Place sputum specimens in the biohazard bag, then the brown paper bag, and give the plastic to the TB clinic staff
- Stay in the sputum induction room, remaining in the anteroom until coughing has completely stopped
- Shut the door after leaving the sputum induction room

ROLE OF TUBERCULOSIS CLINIC STAFF DURING THE INDUCTION PROCEDURE

BTBC staff remain near, but not inside, the sputum induction room during the procedure in order to be available to assist patients if necessary and to ensure that patients remain in the sputum induction room until coughing has stopped. If a staff member must enter the sputum induction room during the procedure, a properly fitted, National Institute for Occupational Health and Safety (NIOSH)-approved respirator (e.g., respirator type N95) is worn.

HANDLING OF SPECIMENS

While in the sputum induction room or booth, patients place the sputum jar in the Ziploc section of the biohazard bag and put the biohazard bag in a brown paper bag. The patient gives the brown paper bag to clinic staff, who place the bag in the refrigerator until it is delivered to the laboratory.

- BTBC staff put on a properly fitted, NIOSH-approved N95 particulate respirator and disposable gloves before entering the sputum induction room
  - The respirator is not removed until after leaving the room
  - The door is closed after entering the sputum induction room
- BTBC staff remove nebulizer tubing with cup and lid and discard it into the disposal bag for biohazardous waste
- BTBC staff wipe the nebulizer and table surfaces clean with a 10% bleach solution and discard any litter in the treatment area
- Staff remove gloves, wash hands, and prepare the equipment for the next patient

SPUTUM INDUCTION ROOM CLEARANCE TIMES

Each sputum induction room has an individually calculated clearance time that is determined by the size of the room, the air changes per hour (ACH), and the air mixing factor. NYC Health Department TB clinic sputum induction rooms' clearance times are as follows:

- **Corona TB Clinic:** 15 minutes
- **Fort Greene TB Clinic:** 10 minutes
- **Morrisania TB Clinic:** 15 minutes
- **Washington Heights TB Clinic (3rd Floor):** 13 minutes
- **Washington Heights TB Clinic (2nd Floor):** 15 minutes

Clearance times are determined by qualified Bureau staff and calculated as follows:

- Determine the cubic volume of the room: **Cubic volume = length x width x height**
- Calculate ACH: **ACH = (cubic feet per minute x 60) / cubic volume**
- Determine air mixing factor: Isol-Aide sputum induction booths/rooms have an effective mixing factor of 1.81 as determined by the manufacturer.
- Extrapolate clearance time from Centers for Disease Control and Prevention's "Guidelines for Preventing the Transmission of *Mycobacterium Tuberculosis* in Health-Care Facilities, 2005," available at **www.cdc.gov**

CARE OF ROOM AND NEBULIZER AT THE END OF THE DAY

At the end of the day, staff restore the nebulizer and the sputum induction room as follows:

- Before entering the sputum induction room, wait at least 10 minutes after the last patient leaves
- Put on disposable gloves and a properly fitted, NIOSH-approved particulate respirator prior to entering
- Close the door after entering
- Remove and discard the nebulizer tubing with cup and lid
- Empty the nebulizer chamber
- Clean the nebulizer chamber and all exposed surfaces with a 10% bleach solution and wipe the chamber dry
- Discard the bleach solution
- Remove and discard the disposable gloves and wash hands
- Leave the ultraviolet light and the fan on
- Remove the personal N95 particulate respirator after leaving the room

APPENDIX F: POTENTIAL DRUG INTERACTIONS WITH ISONIAZID AND RIFAMYCIN MEDICATIONS

DRUG INTERACTIONS WITH RIFAMYCIN MEDICATIONS[1]

DRUG INTERACTION	EFFECTS
Angiotensin Converting Enzyme Inhibitors	Decreases angiotensin converting enzyme levels
Angiotensin Receptor Blockers	Decreases angiotensin receptor blocker levels
Antianxieties	Decreases antianxiety effect
Anticoagulants	Decreases anticoagulants effect
Antidepressants (TCA)	Decreases antidepressant effect
Antiplatelet Agents	Increases antiplatelet effect
Antipsychotics	Decreases level of antipsychotic and may increase clearance of some
Azole Antifungals	Decreases azole antifungal effect
Beta-Blockers	Decreases beta blockade; RIF has more of an effect than RBT
Barbiturates	Decrease barbiturate effect
Benzodiazepines	Decreases benzodiazepines effect that undergo oxidative oxidation
Calcium Channel Blockers	Decreases calcium channel blocker effect
Chloramphenicol	Decreases chloramphenicol effect
Contraceptives	Decreases contraceptive effect
Corticosteroids	Marked decrease in steroid effect
Cyclosporine	Decreases cyclosporine effect, increases RIF effect
Delavirdine	Marked decrease in delavirdine effect
Digoxin	Decreases digoxin effect; decreases RIF level
Dilantin	Decreases dilantin effect
Dipeptidyl Peptidase IV Inhibitors	Decreases dipeptidyl peptidase IV inhibitor effect
Efavirenz	Slight decrease in efavirenz effect
Glipizide and Metformin	Decreases glipizide effect, no effect on metformin
Glyburide and Metformin	Decreases glyburide effect, no effect on metformin
Haloperidol	Decreases haloperidol effect
HMC CoA Inhibitors (Statins)	Decreases statin levels
Macrolide antibiotics	Decreases macrolide effect; increases RBT toxicity
Meglitinide Analogue	Decreases meglitinide analogue
Methadone	Decreases methadone effect
Protease Inhibitors	Marked decrease in activity of protease inhibitors, increases RIF effect
Sitagliptin and Metformin	May decrease sitagliptin levels, no effect on metformin
Sulfonylurea	Decreases sulfonylurea effect

DRUG INTERACTIONS WITH ISONIAZID

DRUG INTERACTION	EFFECTS
Acetaminophen	Increases hepatotoxicity
Alcohol	Increase incidence of hepatitis; possible decreased INH effect
Anticoagulants	Increases anticoagulant effect
Benzodiazepine	Increases benzodiazepine toxicity
Carbamazepines	Increases toxicity of both carbamazepines and INH
Disulfiram (Antabuse)	Potential for psychotic episodes
Halpendol	Increases halpendol toxicity
Hypoglycemics	Monitor glucose, decreases effect (may cause hyperglycemia)
Ketoconazole	Decreases ketoconazole effect
Phenytoin	Increases phenytoin toxicity
Theophylline	Increases theophylline toxicity

Adapted from: Heartland National TB Center. Tuberculosis Medication Drug and Food Interactions. Retrieved from www.heartlandntbc.org/assets/products/tuberculosis_medication_drug_and_food_interactions.pdf.

1. Rifabutin is a weaker inducer of the cytochrome P450 system, potentially interacting with some of the same medications as RIF

Abbreviations Used: CNS=central nervous system; RBT=rifabutin; RIF=rifampin; TB=tuberculosis

APPENDIX G: DOSAGES, ADVERSE REACTIONS, AND MONITORING FOR FIRST-LINE MEDICATIONS USED TO TREAT TUBERCULOSIS*

DRUG *ROUTE OF ADMINISTRATION* MODE OF ACTION	DAILY DOSE [MAX]	THREE TIMES PER WEEK DOSE [MAX]	TWO TIMES PER WEEK DOSE [MAX]*	MAJOR ADVERSE REACTIONS	RECOMMENDED REGULAR MONITORING	COMMENTS
INH *Oral/ Intramuscular* Bactericidal	Children: 10-15 mg/kg Adults: 5 mg/kg [300 mg]	Children: 20-30 mg/kg Adults: 15 mg/kg [900mg]	Children: 20-30 mg/kg Adults: 15 mg/kg [900mg]	Hepatic enzyme elevations, hepatitis, rash, peripheral neuropathy, CNS effects, increased phenytoin levels, possible interaction with disulfiram (Antabuse®)	• Monthly clinical evaluation • LFTs[1]	• Vitamin B6 (pyridoxine) 25 mg/day may decrease peripheral neuritis and CNS effects and should be used in patients who are abusing alcohol, pregnant, breastfeeding infants on INH, malnourished, or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy • Aluminum-containing antacids reduce absorption • Drug interactions with several agents
RIF *Oral/Intravenous* Bactericidal	Children: 10-20 mg/kg Adults: 600 mg (range: 8-12 mg/kg) [600 mg]	Children: 10-20 mg/kg Adults: 600 mg (range: 8-12 mg/kg) [600 mg]	Children: 10-20 mg/kg Adults: 600 mg (range: 8-12 mg/kg) [600 mg]	Hepatic enzyme elevations, hepatitis, rash, fever, thrombocytopenia, influenza-like syndrome, reduced levels of many drugs, including methadone, warfarin, hormonal forms of contraception, oral hypoglycemic agents, theophylline, dapsone, ketoconazole, PIs and NNRTIs	• Monthly clinical evaluation • CBC including platelets and LFTs as indicated[1]	• Orange discoloration may occur in contact lenses and body secretions such as tears and urine • Patients receiving methadone will need their methadone dosage increased, by an average of 50%, to avoid opioid withdrawal • Interaction with many drugs leads to decreased levels of the co-administered drug • May make glucose control more difficult in people with diabetes • Contraindicated for patients taking most PIs and NNRTIs • Patients should be advised to use barrier contraception
RBT[2] *Oral* Bactericidal	Children: 5 mg/kg Adults: 5 mg/kg [300 mg]			Rash, hepatitis, fever, neutropenia, thrombocytopenia, reduced levels of many drugs, including PIs, NNRTIs, dapsone, ketoconazole and hormonal forms of contraception	• Monthly clinical evaluation • CBC including platelets and LFTs as indicated[1]	• Orange discoloration may occur in contact lenses and body secretions, such as urine and tears • If taken concurrently with PIs or NNRTIs, adjust dose of RBT and monitor for decreased ART activity and for RBT toxicity • Contraindicated for patients taking single PI, ritonavir/saquinavir, or delaviridine based ART regimens • Methadone dosage generally does not need to be increased • Patients should be advised to use barrier contraception

APPENDIX G: DOSAGES, ADVERSE REACTIONS, AND MONITORING FOR FIRST-LINE MEDICATIONS USED TO TREAT TUBERCULOSIS (CONTINUED)*

DRUG *ROUTE OF ADMINISTRATION* MODE OF ACTION	DAILY DOSE [MAX]	THREE TIMES PER WEEK DOSE [MAX]	TWO TIMES PER WEEK DOSE [MAX]*	MAJOR ADVERSE REACTIONS	RECOMMENDED REGULAR MONITORING	COMMENTS
PZA *Oral* Bacteriostatic	Children: 35 mg/kg (range: 30-40 mg/kg) Adults: 25 mg/kg (range: 20-30 mg/kg) [2000 mg for children and adults]	Children: 50 mg/kg (range: 40-60 mg/kg) Adults: 35 mg/kg (range: 30-40 mg/kg [3000 mg for children and adults]	Children: 50 mg/kg (range 40-60 mg/kg) Adults: 50 mg/kg (range 40-60 mg/kg) [3500 mg for children and adults]	GI upset, hepatotoxicity, hyperuricemia, gout (rarely), arthralgias, rash	• Monthly clinical evaluation • LFTs as indicated[1]	• Hyperuricemia can be used as indicator of adherence • Treat increased uric acid only if symptomatic • May complicate management of diabetes mellitus • Allopurinol increases level of PZA by inhibiting xanthine oxidase resulting in failure of allopurinol to lower serum uric acid
EMB *Oral* Bacteriostatic	Children: 20 mg/kg (range: 15-25 mg/kg) [1500 mg] Adults: 15-25 mg/kg [2000 mg]	Children: 50 mg/kg [2500 mg] Adults: 30 mg/kg (range: 25-35 mg/kg) [2800 mg]	Children: 50 mg/kg [2500mg] Adults: 45 mg/kg (range: 40-50 mg/kg) [3600 mg]	Decreased red-green color discrimination, decreased visual acuity, skin rash	• Monthly clinical evaluation • Check color vision and visual acuity monthly	• Optic neuritis may be unilateral; check each eye separately. If possible, avoid in children too young to undergo vision testing • If patient develops visual complaints, refer for prompt ophthalmologic evaluation. May need to discontinue EMB while awaiting evaluation
SM *Intramuscular/ Intravenous* Bactericidal	Children: 15-20 mg/kg Adults: 15 mg/kg [1000 mg]	Children: 25-30 mg/kg Adults: 15 mg/kg [1000 mg]	Children: 25-30 mg/kg Adults: 15 mg/kg [1000 mg]	Auditory toxicity, renal toxicity, hypokalemia, hypomagnesemia	• Monthly clinical evaluation • Audiometry, renal function, electrolytes, including magnesium	• Ultrasound and warm compresses to injection site • Patients with decreased renal function may require the 15 mg/kg dose to be given only 3 times per week to allow for drug clearance

Source: Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. Clin Infect Dis. 2016 Oct 1;63(7):e147-e195.

* All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts. Use of brand names is for informational purposes only and does not imply endorsement by the New York City Health Department.

♦ Daily or three times per week therapy are the preferred treatment regimens compared to twice weekly therapy.

1. LFTs are indicated if baseline is abnormal or patient has risk factors for toxicity.

2. Not FDA-approved for the treatment of TB.

Abbreviations Used: ART=antiretroviral therapy; ATS=American Thoracic Society; CBC=complete blood count; CDC=Centers for Disease Control and Prevention; CNS=central nervous system; DOT=directly observed therapy; EMB=ethambutol; FDA=Food and Drug Administration; GI=gastrointestinal; HIV=human immunodeficiency virus; IDSA=Infectious Disease Society of America; INH=isoniazid; IUATLD=International Union against Tuberculosis and Lung Disease; kg=kilograms; LFT=liver function test; mg=milligrams; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitors; PZA=pyrazinamide; RBT=rifabutin; RIF=rifampin; SM=streptomycin; TB=tuberculosis; WHO=World Health Organization

APPENDIX H: DOSAGES, ADVERSE REACTIONS, AND MONITORING FOR ADDITIONAL MEDICATIONS USED TO TREAT TUBERCULOSIS*

DRUG *ROUTE OF ADMINISTRATION* MODE OF ACTION	DAILY DOSE [MAX]	MAJOR ADVERSE REACTIONS	RECOMMENDED REGULAR MONITORING	COMMENTS
AK *Intramuscular/ Intravenous* Bactericidal	Children: 15–30 mg/kg Adults: 15 mg/kg [1000 mg]	Auditory toxicity, renal toxicity, vestibular toxicity (rare), hypokalemia, hypomagnesemia	• Monthly clinical evaluation • Audiometry, renal function, electrolytes, including magnesium	• Ultrasound and warm compresses to injection site may reduce pain and induration • PICC line may need to be used • AK levels are commercially available and should be followed • Patients with decreased renal function may require 15 mg/kg dose to be given only 2-3 times per week to allow for drug clearance
BDQ *Oral* Bactericidal	Children: 5 years of age and older weighing 15-29 kg: 200 mg x 2 wks, then 100 mg 3x/wk x 22 wks Children weighing > 30 kg: Dose same as adults Adults: 400 mg x 2 wks, then 200 mg 3x/wk x 22 wks	QT prolongation, hepatotoxicity, nausea, loss of appetite, abdominal pain, arthralgia, hemoptysis, rash	• Monthly clinical evaluation • Complete blood count, chemistry including K^{+}, Ca^{+2}, Mg^{+2}, and LFTs • FDA requires monitoring EKG at baseline then at 2 wks, 12 wks, and 24 wks	• Approved for pulmonary MDR-TB • Part of combination regimen for MDR-TB • Duration is 24 wks total; longer duration could be considered on a case-by-case basis especially when there are limited treatment options • BDQ's half-life is 4-5 months; consider discontinuing BDQ 4–5 months prior to discontinuing other drugs in the treatment regimen to reduce or avoid an extended period of exposure to low levels of BDQ • Should not be used with CYP3A4 inducers, i.e., rifampin and efavirenz • There may be cross resistance between BDQ and CFZ • Can be taken with food • Must be given under DOT • For children who cannot swallow, disperse tablets in water and mix with beverage or soft food or crush the tablet and mix with soft food
CFZ *Oral* Bactericidal	Children: Limited data, but doses of 2-5 mg/kg/day have been given Adults: 100 mg	Pink or red discoloration of skin and body fluids discoloration; gastrointestinal intolerance; hepatotoxicity; photosensitivity; rash, pruritus, dry skin, ichthyosis; retinopathy; severe abdominal symptoms, bowel obstruction, gastrointestinal bleeding	• Monthly clinical evaluation • Baseline and monthly EKGs to assess QT interval • Monitor complete blood count, chemistry including K^{+}, Ca^{+2}, Mg^{+2}, and LFTs	• Needs an IND from the FDA and coordination with Novartis • Skin discoloration is reversible but may take a long time • Can prolong the QT interval especially if given with BDQ and other QT prolonging agents • Each dose should be taken with food and on DOT • There may be cross resistance between BDQ and CFZ
CM *Intramuscular/ Intravenous* Bactericidal	Children: 15–20 mg/kg Adults: 15 mg/kg [1,000 mg]	Auditory, vestibular, and renal toxicity; eosinophilia, hypokalemia, hypomagnesemia	• Monthly clinical evaluation • Audiometry, renal function, electrolytes, including magnesium	• Ultrasound and warm compresses to injection site may reduce pain and induration • Patients with decreased renal function may require 15 mg/kg dose to be given only 2-3 times per week to allow for drug clearance

APPENDIX H: DOSAGES, ADVERSE REACTIONS, AND MONITORING FOR ADDITIONAL MEDICATIONS USED TO TREAT TUBERCULOSIS (CONTINUED)*

DRUG *ROUTE OF ADMINISTRATION* MODE OF ACTION	DAILY DOSE [MAX]	MAJOR ADVERSE REACTIONS	RECOMMENDED REGULAR MONITORING	COMMENTS
CS *Oral* Bacteriostatic	Children: 15–20 mg/kg Adults: 500–1000 mg, divided doses [1000 mg]	Psychosis, seizures, headache, depression, suicide, other CNS effects, rash, increased phenytoin levels	• Monthly clinical evaluation • Assess and monitor mental status	• Increase gradually, checking serum levels • Pyridoxine hydrochloride (vitamin B6) may decrease CNS effects (use 50 mg for each 250 mg of CS)
ETA *Oral* Bacteriostatic	Children: 15–20 mg/kg Adults: 500–1000 mg, divided doses [1000 mg]	Nausea, vomiting, diarrhea, abdominal pain, bloating, hepatotoxicity, hypothyroidism (especially when administered with PAS), metallic taste	• Monthly clinical evaluation • LFTs (if baseline abnormal) • Thyroid function periodically, especially if also on PAS	• Antacids/anti-emetics and lying supine for 20 minutes after dose may help tolerance • Start with 250 mg daily and increase as tolerated
LFX[1] *Oral/Intravenous* Bactericidal	Children: 6 months to under 5 years of age: 10 mg/kg two times per day 5 years and older: 10 mg/kg once per day Adults: 500–1000 mg in one dose	Nausea, vomiting, diarrhea, abdominal pain, tremulousness, insomnia, headache, dizziness, lightheadedness, photosensitivity, tendonitis, tendon rupture, possible hypo- and hyperglycemia hypersensitivity	• Monthly clinical evaluation • Monitor blood sugar	• Our clinical experience shows safety with long-term use • Dose should be adjusted to 3 times per week in renal failure
LZD *Oral/intravenous* Bacteriostatic[2]	Children: Under 12 years of age: 10-15 mg/kg per day, based on weight 12 years of age and older: 10 mg/kg [600 mg/day] Adults: 600 mg	Myelosuppression, hemolytic anemia, peripheral and optic neuropathy, nausea, vomiting, diarrhea, LFT elevations, tongue discoloration	• Monthly clinical evaluation, BP, screening for optic and peripheral neuropathy • Complete blood count initially 1-2 wks, then monthly, chemistry, and LFTs	• Available in an oral suspension 100mg/5ml • Drug-drug interactions with tyramine containing foods (e.g., cured meats), SSRIs, and MAOIs • Risk of serotonin syndrome • Can cause lactic acidosis
MFX[1] *Oral/Intravenous* Bactericidal	Children: 10-15 mg/kg Adults: 400 mg[3]	Similar to LFX	• Monthly clinical evaluation • Monitor blood sugar	• More active than LFX against *M. tuberculosis*. • Avoid in patients with prolonged QTc interval and those receiving class Ia or III antiarrhythmic agents

APPENDIX H: DOSAGES, ADVERSE REACTIONS, AND MONITORING FOR ADDITIONAL MEDICATIONS USED TO TREAT TUBERCULOSIS (CONTINUED)*

DRUG *ROUTE OF ADMINISTRATION* MODE OF ACTION	DAILY DOSE [MAX]	MAJOR ADVERSE REACTIONS	RECOMMENDED REGULAR MONITORING	COMMENTS
PAS *Oral* Bacteriostatic	Children: 200-300 mg/kg total (usually divided 100 mg/kg given two times per day) Adults: 4000 mg two times per day [12,000 mg]	Nausea, vomiting, diarrhea, abdominal pain, hypersensitivity, hepatoxicity, hypothyroidism (especially when administered with ETA), decreased digoxin levels, increased phenytoin levels, PAS levels decreased by diphenhydramine	• Monthly clinical evaluation • Thyroid function periodically especially if also on ETA	• Begin gradually and increase dosage as tolerated • May cause hemolytic anemia in patients with glucose 6-phosphate dehydrogenase deficiency
Pretomanid *Oral* Bactericidal	Children: Not established Adults: 200 mg per day for 26 wks	Optic and peripheral neuropathy, myelosuppression, hepatotoxicity[4]	• Monthly clinical evaluation • Baseline and monthly EKGs to assess QT interval[5] • Monitor complete blood counts, chemistry including K^{+}, Ca^{+2}, Mg^{+2}, and LFTs • Monitor for visual changes and neuropathy	• Pretomanid must be used in combination with BDQ and LZD for treatment of pulmonary XDR-TB and treatment intolerant or nonresponsive MDR-TB (BPaL regimen); regimen must be given as specified[6] • Pretomanid is contraindicated in patients for whom BDQ and/or LZD are contraindicated • Most of the adverse reactions observed in the BPaL regimen were noted when pretomanid was given with BDQ and LZD and may be attributed to those drugs • Tablets should be taken whole and can be given with food • Should not be used with CYP3A4 inducers, i.e., rifampin and efavirenz • Avoid organ anion transport substrates (OAT3) • Testicular atrophy and male infertility in animal studies

Source: Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. Am J Respir Crit Care Med. 2019;200(10):e93-e142.

* All toxicities are not listed here. Full prescribing information should be checked in the package insert or pharmacology texts. Use of brand names is for informational purposes only and does not imply endorsement by the New York City Health Department.

1. Although FQNs are not approved for use in children in most countries, the benefit of treating children with MDR-TB with a FQN may outweigh the risk in many instances. 2. May be bactericidal when combined with other agents in the treatment of MDR-TB. 3. Higher MFX doses have been used safely when the isolate is resistant to ofloxacin and the minimum inhibitory concentration for LFX or MFX suggests higher doses may overcome resistance. Higher doses also are used in cases of malabsorption. 4. List of adverse reactions when pretomanid is used combined with LZD and BDQ. 5. When used in combination with BDQ and LZD, the BDQ package insert recommends EKGs at baseline, and then at 2, 12, 24 wks after starting medications. Some experts recommend monthly EKG monitoring. 6. BPAL regimen: pretomanid 200 mg orally x 26 wks, BDQ 400 mg orally x 2 wks, then 200 mg 3x/wk for 24 wks, and LZD 1200 mg orally for 26 wks, with dose adjustments after the first month.

Abbreviations Used: AK=amikacin; BDQ=bedaquiline; BTBC=Bureau of Tuberculosis Control; CFZ=clofazimine; CM=capreomycin; CNS=central nervous system; CS=cycloserine; ETA=ethionamide; FQN=fluoroquinolone; kg=kilograms; LFX=levofloxacin; LZD=linezolid; MAOI=monamine oxidase inhibitors; *M. tuberculosis*=*Mycobacterium tuberculosis*; MDR-TB=multidrug-resistant tuberculosis; MFX=moxifloxacin; mg=milligrams; PAS=para-aminosalicylic acid; PICC=peripherally inserted central catheter; SSRI=selective serotonin reuptake inhibitors; TB=tuberculosis; wk=week; XDR-TB=extensively drug-resistant tuberculosis

APPENDIX I: THE USE OF ANTI-TUBERCULOSIS DRUGS AND PREGNANCY, BREASTFEEDING, TUBERCULOSIS MENINGITIS, AND RENAL AND HEPATIC FAILURE[1]

DRUG	SAFETY IN PREGNANCY[2]	SAFETY IN BREASTFEEDING	CNS PENETRATION[3]	DOSAGE IN RENAL INSUFFICIENCY[4]	DOSAGE IN HEPATIC INSUFFICIENCY
Isoniazid	Has been used safely[3]	Safe	Good (20-100%)	No change[5]	No change, but use with caution
Rifampin	Has been used safely (isolated reports of malformations)	Safe	Fair (inflamed meninges) (10-20%)	No change	No change, but use with caution
Rifapentine	Safety not established	No data	Not established	Not established; Use with caution	No change, but use with caution
Rifabutin	Use with caution (limited data on safety)	No data	Good (30-70%)	No change	No change, but use with caution
Pyrazinamide	Recommended by WHO (not FDA)	Moderately safe	Good (75-100%); Use with caution	Decrease dosage; Increase interval; Use with caution	No change, but use with caution
Ethambutol	Has been used safely	Safe	Inflamed meninges only (20-30%)	Decrease dosage; Increase interval[4]	No change
Aminoglycosides (streptomycin, kanamycin, amikacin)	Avoid[6] (associated with ototoxicity in fetus)	Safe	Poor[7] (10-20%)	Decrease dosage; Increase interval[4,8]	No change
Capreomycin	Avoid[6] (limited data on safety)	No data	Poor (10-20%)	Decrease dosage; Increase interval[4,8]	No change
Levofloxacin	Use if benefit outweighs risk	Moderately safe	Good (70-80%)	Increase interval	No change, but use with caution
Moxifloxacin	Use if benefit outweighs risk	Moderately safe	Good (70-80%)	No change, but use with caution	No change, but use with caution, esp-ecially with severe hepatic insufficiency
Cycloserine	Use with caution (limited data on safety)	Moderately safe	Good (50-100%)	Decrease dosage; Increase interval[4,5]	No change
Ethionamide	Do not use (premature labor, congenital malformation)	No data	Good (100%)	No change, but use with caution	No change, but use with caution

APPENDIX I: THE USE OF ANTI-TUBERCULOSIS DRUGS AND PREGNANCY, BREASTFEEDING, TUBERCULOSIS MENINGITIS, AND RENAL AND HEPATIC FAILURE (CONTINUED)[1]

DRUG	SAFETY IN PREGNANCY[2]	SAFETY IN BREASTFEEDING	CNS PENETRATION[3]	DOSAGE IN RENAL INSUFFICIENCY[4]	DOSAGE IN HEPATIC INSUFFICIENCY
Para-aminosalicylic acid	Has been used safely	Moderately safe	Inflamed meninges only	No change, but use with caution	No change, but use with caution
Linezolid	Use only if the potential benefit justifies the risk	Limited data	Good (30-70%)	No change, but use with caution[4]	No change, but use with caution
Bedaquiline	Use only if the potential benefit justifies the risk	Limited data; if needed, monitor infants for signs of BDQ toxicity	Limited data	No change, but use with caution	No change, but use with caution
Clofazimine	Use only if the potential benefit justifies the risk	Should not be used unless clearly indicated	Limited data	Limited data	Limited data
Pretomanid[9]	No data	No data	No data	No data	No data

1. This table presents a consensus of published data and recommendations.

2. As with all medications given during pregnancy, anti-TB medications should be used with extreme caution. The risk of TB to the fetus far outweighs the risk of most medications. Data are limited on the safety of anti-TB medications during pregnancy.

3. Steroid treatment appears to improve outcome in TB meningitis, particularly in patients with altered mental status.

4. If possible, monitor serum drug levels of patients with renal insufficiency.

5. Supplement with pyridoxine hydrochloride (vitamin B6), 25 mg per day for INH, 50 mg per day for each 250 mg per day of cycloserine.

6. If an injectable medication must be used during pregnancy, streptomycin is the preferred agent if the organism is susceptible.

7. Has been used intrathecally: efficacy not documented.

8. If possible, avoid injectable agents in patients with reversible renal damage.

9. Pretomanid is used as part of a regimen that includes linezolid and bedaquiline.

Abbreviations Used: CNS=central nervous system; FDA=Food and Drug Administration; mg=milligrams; TB=tuberculosis; WHO=World Health Organization

APPENDIX J: RECOMMENDATIONS FOR PATIENTS TO ASSIST WITH TAKING TUBERCULOSIS MEDICATIONS

DRUG	RECOMMENDATION
Isoniazid	• Avoid alcohol and acetaminophen-containing medications • Take 1 hour before or 2 hours after meals • May take with small snack if needed • Take 1 hour before or 2 hours after antacids • Supplement Vitamin B6 as needed (25-50 mg) • Avoid food and drinks that contain tyramine including hard cheeses, smoked or cured meats, and soy products
Rifampin	• Avoid alcohol • Take 1 hour before or 2 hours after meal • May take with small snack if needed • Take 1 hour before antacids
Ethambutol	• May be taken with food
Moxifloxacin and Levofloxacin	• Take 2 hours before or after aluminum-, magnesium-, or calcium-containing antacids; iron; vitamins; sucralfate; milk-containing products; and food supplements
Pyrazinamide	• May be taken with food
Ethionamide	• Avoid alcohol • Take with or after meals
Amikacin	• Increase fluid intake, if allowed
Streptomycin	• Increase fluid intake, if allowed • May affect the taste of food
Capreomycin	• May need to increase intake of foods high in potassium, if instructed • Increase fluid intake, if allowed
Para-aminosalicylic acid	• Take with or immediately following meals • Increase fluid intake • Take with yogurt, applesauce, or acidic foods
Cycloserine	• Avoid alcohol • Supplement vitamin B6 as directed
Linezolid	• May be taken with food • Avoid food and drinks that contain tyramine including hard cheeses, smoked or cured meats, and soy products • Do not use with pseudoephedrine, selective serotonin reuptake inhibitors, and other antidepressants

Adapted from: *Heartland National TB Center. Tuberculosis Medication Drug and Food Interactions.* Retrieved from www.heartlandntbc.org/assets/products/tuberculosis_medication_drug_and_food_interactions.pdf.

APPENDIX K: PROCEDURES FOR THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) should be done when there is a clear indication for it. Routine monitoring of antituberculosis drug levels is not recommended in clinical practice. The significance of low serum levels of antituberculosis drugs in relation to clinical response has not been demonstrated. Studies have shown that as many as 60% of tuberculosis (TB) patients had low serum levels of isoniazid or rifampin. However, the clinical response to TB therapy did not differ in those with low drug levels when compared to those with normal levels.

Nonetheless, some patients will fail to respond to antituberculosis treatment despite documented adherence to the medications and absence of drug resistance. Some of these patients may have malabsorption syndromes that prevent them from achieving therapeutic levels of these drugs. Diseases such as human immunodeficiency virus (HIIV) infection, cystic fibrosis, diabetes, and sprue have been implicated in malabsorption of antituberculosis drugs.

A select number of patients with drug susceptible TB will therefore require drug level testing at some point during their treatment for tuberculosis. Patients with drug-resistant TB are more likely to require drug level testing.

In order to optimize the treatment of patients with TB while maintaining the highest levels of sound medical practice, the Bureau of Tuberculosis Control (BTBC) recommends that TDM be used in the following circumstances:

- Lack of clinical response (i.e., culture conversion) while on appropriate drugs and doses, on directly observed therapy (DOT) for at least two months and in the absence of drug resistance
- Lack of clinical response from second-line drugs with a narrow therapeutic window, such as cycloserine, when alternative drugs are limited, and when plans are in place to increase the dose of the drug should levels be low
- Patients with few effective drugs in their regimen, in order to optimize the effect of available drugs
- Lack of clinical response (i.e., lack of culture conversion at two months) in a patient with known or suspected malabsorption syndrome
- Patients with renal insufficiency and who have multidrug-resistant tuberculosis (MDR-TB) or are on certain drugs such as ethambutol
- Patients who relapse with active TB despite appropriate therapy

If drugs levels are low and doses are increased, clinical monitoring should be used to judge the response; repeat TDM should only be done when there is no clinical response after a reasonable amount of time.

Patients with pansensitive, cavitary, or otherwise very extensive disease tend to have a delayed clinical response to treatment even when adherence is documented (under DOT). In most cases these patients will respond if given enough time, usually in the third month of therapy. All patients with a delayed response (i.e., lack of culture conversion at two months) should be treated for nine months instead of six months.

In order to obtain accurate TDM results, BTBC staff must adhere strictly to the guidelines on specimen procurement and handling. Failure to do so will lead to inaccurate results, which may ultimately harm the patient. The following sections delineate procedures for obtaining and handling specimens for TDM.

PHYSICIANS

1. Request New York State (NYS) Clinical Laboratory Evaluation Program (CLEP) pre-approval for TDM through the Office of Medical Affairs, who will fax the NYS non-permitted lab test request to NYS CLEP. Approval is usually received within 1-2 days of submission of the request at the BTBC and the Bureau of Public Health Lab (PHL).
2. Schedule blood drawing on Monday or Tuesday to ensure delivery of the specimen to the Advanced Diagnostic Laboratories National Jewish Health (ADx-NJH) by Thursday. Since the serum must be frozen immediately after centrifugation, arrange immediate delivery of the serum on dry ice to the PHL if a freezer is unavailable at the chest center.
3. Order blood drawing for approximately 2 hours after an observed dose of antituberculosis medications for most medications. When testing levels for linezolid, blood should be drawn just before ingestion of the scheduled dose to obtain the trough level. After the observed ingested dose, blood should be drawn again in 2 hours to obtain the peak level. Additional information on the number of hours after administration of the drug/s dose to collect peak concentration is available on the ADx-NJH Pharmacokinetics Laboratory Requisition (https://www.nationaljewish.org/NJH/media/ADX/Requisitions/ADx700-Pharmacokinetics_Req_10-2018.pdf).
4. For most drug assays, continue all other antituberculosis medication as usually given. For streptomycin, inquire if patient is taking ampicillin and record this on ADX-NJH Pharmacokinetic Laboratory requisition.

PHLEBOTOMISTS

1. Communicate with PHL at (212) 447-6745 to inform them about the scheduled blood draw for TDM at the clinic and to arrange dry ice for specimen delivery back to the PHL.
2. Complete ADX-NJH pharmacokinetic laboratory requisition and PHL requisition to accompany the serum sample to the PHL.
3. Draw blood 2 hours or as applicable after an observed dose of anti-tuberculosis medication(s). Use two 5mL serum separator tubes (SST) or Northwell Lab gold top tubes to draw 5 mL of blood in each tube for one drug assay. Allow blood to clot for 30 minutes before centrifuging specimen to separate serum from cells. Label the cryovial to be used for aliquoting serum with the patient's name, DOB, the date and time of the blood draw, and the name of the drug(s) to be assayed.
4. Centrifuge blood tubes and aliquot serum from each 5mL tube into a separate 2 mL labeled cryovial. ADx-NJH requires at least 2mL of serum per test. Allow room for expansion of the serum inside the tube.

5. Freeze serum in the cryovial immediately and contact PHL to have the frozen serum picked up and transported to them on dry ice.

BUREAU OF PUBLIC HEALTH LABORATORY

1. At PHL, the sample will be frozen overnight at −70° C; the next day it will be packed in dry ice and labeled as specified in full compliance with the shipper and guidelines on handling of dry ice and potentially infectious materials. The ADx-NJH Pharmacokinetic Laboratory requisition sent with the specimen will be included in the shipping package.
2. PHL staff will call the shipper to pick up and deliver the samples.

ADVANCED DIAGNOSTIC LABORATORIES NATIONAL JEWISH HEALTH

1. TDM reports will be delivered from ADx-NJH to the BTBC Office of Medical Affairs. Assays may require up to seven business days for completion.
2. ADx-NJH will bill the BTBC and the bill will go directly to Internal Accounting.
3. The Office of Medical Affairs will notify the staff taking care of the patient of the results. The results will be attached in the surveillance system and the electronic medical record.

APPENDIX L: INITIAL PATIENT INTERVIEW TOPICS

1. Educate the patient about tuberculosis (TB), debunking any misconceptions about the disease. The case manager should determine the most appropriate educational intervention and provide appropriate literature. The educational content should include information about:
   - TB transmission and pathogenesis
   - Preventing TB
   - Distinguishing infection from disease
   - How drug resistance develops
   - Length of treatment needed for sensitive vs. drug-resistant TB (DR-TB)
   - Standard TB medications, including names, dosages, actions, and side effects
   - Directly observed therapy (DOT) program and free New York City (NYC) Health Department services for TB
2. Establish long-term plans for treatment (including DOT).
3. Determine whether the patient will stay in NYC during TB treatment.
4. Inquire about contacts and emphasize to the patient why it is important that contacts be identified and evaluated as soon as possible.
5. Establish a trusting relationship, as this determines how well the patient views the role of the case manager and the healthcare establishment.
6. Obtain and document locating information and agree with the patient on a mode of communication (e.g., cell phone, home/work number, significant other). Identify who will always know where to find the patient.
7. Educate family and identified contacts about TB and the importance of getting evaluated.
8. Assess social needs such as access to social services to resolve issues with child care, housing, employment, substance abuse, and (if appropriate) legal or immigration issues (tell the patient that all services are provided irrespective of immigration status) and refer patient to social worker.
9. If the patient is diagnosed with TB while in a hospital, plans for follow-up care upon discharge must be initiated at the onset of hospitalization and not on the day before discharge. These plans must address issues that will ensure adherence with the treatment regimen.

APPENDIX M: DIRECTLY OBSERVED THERAPY AGREEMENT FORM

NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
Dave A. Chokshi, MD MSc
Commissioner

BUREAU OF TUBERCULOSIS CONTROL (BTBC)
DIRECTLY OBSERVED THERAPY (DOT) AGREEMENT FORM

For Office Use Only:

Patient Name:_____

EMR ID (DOHMH): _____ TB Registry ID: _____

Patient's telephone number: ( ) _____ VDOT telephone number: ( ) _____

This is an agreement between the Bureau of Tuberculosis Control and _____to enroll into the Directly Observed Therapy program for: [ ] myself or [ ] _____ of who I am the legal guardian.

It has been explained to me that the most effective way to treat and prevent tuberculosis (TB) is by taking prescribed anti-TB medication and having a trained health care worker observe the ingestion of all oral medication doses. This observation can be done face to face or virtually by the use of a video-enabled device also known as video DOT (VDOT).

PATIENT/GUARDIAN AGREEMENT

I am enrolling [ ] myself [ ] my ward (e.g. minor child) in:

(1) Face to Face DOT: (a) _____ clinic (b) _____community

(2) Video DOT: (a) _____live video (LVDOT) (b) _____Recorded video (RVDOT)

Therefore, I, _____, agree to the following:
Name of patient /guardian

- I will take or ensure that _____(ward) takes his/her medication under direct observation either face to face in the clinic or the community or by video-enabled device, e.g., phone, tablet, or computer, in my home or secure location of my choice.
- I will or ensure that _____(ward) attends <u>all</u> clinic appointments until the doctor tells me that treatment is completed or is removed from the DOT program.
- If I or _____(ward) cannot make an appointment, I will call to reschedule it as soon as I know I cannot make it:
  - For VDOT appointments, I will call: _____ at _____
    Name of VDOT supervisor Telephone Number
  - For Chest Center appointments, I will call: _____ at _____
    Name of Clinic Nurse Telephone Number
  - For home/community provider appointments, I will call: _____ at _____
    Name of DOT case manager Telephone Number
- I understand that I may transfer between DOT options at any time during the course of the treatment.

APPENDIX M: DIRECTLY OBSERVED THERAPY AGREEMENT FORM (CONTINUED)

- If I or _____ (ward) attends a DOHMH clinic and enrolled in VDOT and decides to withdraw for any reason, I will immediately return unused medication to the clinic so that a new treatment plan can be made by my doctor. I will not give (ward) medication on my own without permission from the treating physician or designee.

Participants who selected VDOT, please initial beside each statement below to indicate that you understand and agree:

- If using my own equipment:
  _____ I understand that standard rates apply. I understand that the DOHMH is not responsible for any data, wireless, or other charges that may occur due to the use of the free VDOT software.

- If I am loaned a DOHMH videophone equipment:
  _____ I understand that the videophone equipment is the property of the DOHMH, and I am responsible for its care, maintenance, and return to the DOHMH upon completion or discontinuation of the VDOT program.

  _____ I will only use the equipment for VDOT and for communication directly related to my TB care.

BUREAU OF TUBERCULOSIS CONTROL (BTBC) AGREEMENT

I have explained the importance of TB treatment and DOT to the patient/guardian. Therefore,

I, _____, as a representative of the BTBC, agree to the following:
Name/title of Nurse/Case Manager/DOT Observer

- BTBC staff will meet _____ at _____AM/PM in person or by video conferencing.
  Name of Patient/ward

- BTBC staff will notify the patient and or guardian as quickly as possible if there is a scheduling conflict by phone at:
  _____ or _____.
  Home Number Mobile Number

- BTBC staff will assist the patient in maintaining his/her DOT and clinic appointments.

- BTBC staff will respond to all questions, concerns, and needs raised by the patient or guardian to the best of his/her capacity, including referrals for social services.

By signing below, we agree to be responsible for the above statements:

_____ Date____/____/____
Signature of Patient/Guardian

_____ Date____/____/____
Signature of Case Manager/DOT Observer/Nurse

If you have any questions, concerns, suggestions or complaints about any aspect your care, please contact:

_____ at _____
Name/Title Telephone Number

Last updated: March 2019

APPENDIX N: HOME ISOLATION AGREEMENT

NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
Dave A. Chokshi, MD MSc
Commissioner

HOME ISOLATION PATIENT AGREEMENT

I _____ acknowledge that I have active infectious tuberculosis,
(Patient's full name)
and that I must separate myself from others in order to prevent other from being exposed to my tuberculosis disease.
I have discussed this agreement with _____
(Full name of DOHMH employee)
a _____ at the Department of Health and Mental Hygiene
(Job title)
(DOHMH), who has answered my questions about home isolation fully to my satisfaction. I further acknowledge that if I am unable or unwilling to observe any of the conditions of this agreement, while my tuberculosis remains infectious, I represent a danger to the health of others and I am subject to removal to a hospital for respiratory isolation either voluntarily or by order of the Commissioner of Health.

In return for being allowed to remain in my home while my tuberculosis is infectious, I agree to all of the following conditions.

- I will take all my prescribed anti-tuberculosis medications in a program of daily directly observed therapy (DOT) as directed by my physician or the Commissioner of Health.
- I will entertain no visitors in my home and will not visit other persons' home.
- I will cover my mouth and nose whenever I cough, sneeze, or hack while indoors or outdoors in the presence of other people.
- I will not use any public (bus, train, taxi, subway, airplane) or private (automobile) transportation unless absolutely necessary to obtain medical attention, and then only using the mask which my physician has prescribed for me.
- I will not visit enclosed public spaces such as theaters, shopping malls, department, supermarket or other stores; but I may spend time in open spaces such as parks, backyards or public streets which are not crowded.
- I will not care for or spend time with children of any age or work outside my home without permission from my physician and the DOHMH.
- I will not leave New York City for any reason without the DOHMH and my physician's permission and under such conditions as are prescribed.
- I have received a copy of the instructions entitled "Instructions for Patients with Potentially Infectious TB"
- Any additional conditions:

_____
_____
_____

If I have any further questions about how to comply with this agreement, I will telephone
_____ at _____
(Full name and title of contact person at DOHMH) (Telephone number with area code)

Date: _____ _____
(Patient's signature)

Date: _____ _____
(Staff signature)

Revised: July 2006

APPENDIX O: INSTRUCTIONS FOR PATIENTS WITH POTENTIALLY INFECTIOUS TB

NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
Dave A. Chokshi, MD MSc
Commissioner

Instructions for patients with potentially infectious TB

You are being discharged from the hospital although your sputum tests indicate that you may still infect other people with TB or you are advised to be evaluated as an outpatient while you may have infectious TB.

You are being discharged because you said that either you live alone or will be going back to a living arrangement where the other people living there are healthy and wish to have you home. We are required by law to notify them that they have been exposed to TB and to evaluate them.

You may have been placed on medication to treat TB already or are waiting to start medications after you have been evaluated as an outpatient.

The following instructions will help reduce the spread of TB germs to other people and you should follow them carefully:

- If you return to a home that has other people, you should always:
  - Limit the time spent in common household areas (such as bathroom or kitchen) and keep your bedroom door closed
  - Wear a surgical mask when spending time in a space that is also used by others to reduce the number of TB germs that you put in the air when you cough or talk.
- You should always cover your mouth when coughing or sneezing
- You should not be around infants, young children or, to the best of your knowledge, persons who have weakened immunity such as people with HIV/AIDS. (If there are young children at home, you may still be discharged to the home if the children have been evaluated for latent TB infection and are on "preventive" medication, as determined by their physician)
- You should participate in a program of directly observed therapy (DOT), about which you have been educated by an employee of the NYC health department
- You should avoid going to public places or return to work or school until your doctor, working with the health department, says it is OK for you to do so
- You should keep your doctor's or clinic appointments to ensure that treatment for TB is not interrupted
- Some of these restrictions will be removed once your physician, along with the health department, determines that you are no longer infectious
- Your TB treatment and DOT will continue even after these restrictions are removed.

Following these instructions will help in limiting the spread of TB germs to your family and others. If you have questions about your treatment please call your physician or health department at 311.

You can also find more information about TB on our website at nyc.gov/health/tb.

APPENDIX P: INFORMATION FOR PERSONS WHO LIVE WITH PATIENTS WITH TB

NEW YORK CITY DEPARTMENT OF
HEALTH AND MENTAL HYGIENE
Dave A. Chokshi, MD MSc
Commissioner

Information for persons who live with patients with TB

A family member or someone in your household was recently diagnosed with or is suspected of having active TB. TB is a preventable and treatable disease. TB is transmitted through the air when a patient with the disease coughs or sneezes without covering his or her mouth. People with the active form of the disease must take their medication and must follow certain rules to prevent the spread of TB germs to people they live or work with. ***We are required by state law to inform you of this information.***

If there are children in your home they should be evaluated by their doctor and they should be placed on "preventive" therapy if appropriate. They can also be evaluated and treated at the health department's chest centers.

If a family member or someone in your household has been diagnosed with TB:

- You should get tested to see if you have already been infected with the germs that cause TB
- If you have been infected with the germs that cause TB, you should have a medical evaluation and a chest x-ray to make sure that you have not progressed to active TB
- If you have TB infection, you should take medicine to prevent the development of active TB.
- **The member of your household with TB should stay at home until his or her physician and the health department says he/she can go out.**
- He/she should not go to work or school during this time period and should avoid going to any public areas during this time period.
- Please assist the TB patient by doing their errands, such as grocery shopping.
- Your household member with TB should cover his/her mouth with a tissue whenever he/she coughs or sneezes; he/she should put the used tissue in the regular garbage.
- When around other people, the patient should wear a surgical mask that covers the nose and mouth.
- While at home, limit your contact with the TB patient as much as possible; the patient should sleep in a separate room until advised by their physician.
- It is OK to share eating utensils (spoons, forks, cups or glasses) and other household items.

Following these instructions will help in limiting the spread of TB germs to your family and others.
If you have questions about your treatment please call your physician or health department at 311.
You can also find more information about TB on our website at nyc.gov/health/tb.

APPENDIX Q: NEW YORK CITY HEALTH DEPARTMENT UNIVERSAL REPORTING FORM

NYC Health

New York City Department of Health and Mental Hygiene

Universal Reporting Form

To report an **immediately notifiable** disease or condition, an outbreak among three or more persons or an unusual manifestation of any disease or condition, or any newly apparent or emerging disease or syndrome, call the Provider Access Line at **866-692-3641**.

Diseases and conditions in green and marked with * are **immediately notifiable**; those marked with † are immediately notifiable if case meets the risk group criteria on page 2. Report by calling **866-692-3641**.

For all other diseases and conditions, report using Reporting Central online via NYCMED at **www.nyc.gov/health/nycmed**, mail this form to the NYC Department of Health and Mental Hygiene, 42-09 28th Street, CN-22, Long Island City, NY 11101, or call **866-692-3641** for the appropriate fax number.

Go to **www.nyc.gov/health/diseasereporting** for more information.

Patient Information

Patient Last Name	First Name	Middle Name	DATE OF REPORT
Patient AKA: Last Name	AKA: First Name	AKA: Middle Name	_____/_____/_____
Age / Date of Birth _____/_____/_____	Country of Birth	Social Security Number	DATE OF DIAGNOSIS
If patient is a child, Guardian Last Name	Guardian First Name	Guardian Middle Name	_____/_____/_____
Medical Record Number	Medicaid Number		DATE OF ILLNESS ONSET
Patient Home Address	City / State / Zip Code		_____/_____/_____
Country	Borough: ☐ Manhattan ☐ Bronx ☐ Brooklyn ☐ Queens ☐ Staten Island ☐ Unknown ☐ Not NYC		
Email Address	Mobile Phone	Home Phone	☐ Homeless

Sex: ☐ Male ☐ Female ☐ Transgender MTF ☐ Transgender FTM ☐ Unknown

Race: ☐ Black ☐ White ☐ American Indian/Alaska Native ☐ Native Hawaiian/Pacific Islander ☐ Asian ☐ Other: _____ ☐ Unknown

Ethnicity: ☐ Hispanic ☐ Non-Hispanic ☐ Unknown

Is patient alive? ☐ Yes ☐ No ☐ Unknown
If no, date of death: _____/_____/_____

Is patient pregnant? ☐ Yes ☐ No ☐ Unknown
If yes, due date: _____/_____/_____

Is case suspected to be due to healthcare associated transmission? ☐ Yes ☐ No ☐ Unknown

Was patient admitted to hospital? ☐ Yes ☐ No ☐ Unknown
Admission date: _____/_____/_____
Discharge date: _____/_____/_____

Is patient a newborn infant? ☐ Yes ☐ No ☐ Unknown
If yes, name of hospital where infant was born _____
Name of facility where infant's mother obtained prenatal care _____

Foreign travel

Countries _____ **Date returned to U.S.** _____/_____/_____

Other Information

REPORTER	Name of Person Reporting Disease	Email address	Phone	
	Name of Facility of Person Reporting Disease	National Provider Identifier (NPI) Code	Permanent Facility Identifier (PFI) Code	
	Facility Street Address	City	State	Zip Code
FACILITY	Name of Hospital/Healthcare Facility Providing Care for Patient	Facility National Provider Identifier (NPI) Code	Permanent Facility Identifier (PFI) Code	
	Facility Street Address	City	State	Zip Code
LAB	Name of Testing Laboratory	Phone	CLIA Number	
	Laboratory Street Address	City	State	Zip Code
PROVIDER	Name of Provider Caring for Patient	National Provider Identifier (NPI) Code	Fax	
	Email address	Phone	Mobile	
	Provider Street Address	City	State	Zip Code

Form PD-16 (Rev. 3/2017)

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APPENDIX Q: NEW YORK CITY HEALTH DEPARTMENT UNIVERSAL REPORTING FORM (CONTINUED)

Patient Last Name	First Name	Medical Record Number

Diseases and conditions in green and marked with * are immediately notifiable; those marked with † are immediately notifiable if case meets the risk group criteria at the bottom of the page. Report by calling **866-692-3641**.

For all other diseases and conditions, report using Reporting Central online via NYCMED at **www.nyc.gov/health/nycmed**, mail this form to the NYC Department of Health and Mental Hygiene, 42-09 28th Street, CN-22, Long Island City, NY 11101, or call **866-692-3641** for the appropriate fax number.

Go to **www.nyc.gov/health/diseasereporting** for more information.

- ☐ **Amebiasis†**
- ☐ **Anaplasmosis** (Human granulocytic anaplasmosis)

  Animal bite – see Environmental Conditions section on page 3. See rabies if potential for exposure.
- ☐ **Anthrax***
- ☐ **Arboviral infections,** acute*

  Specify which virus: _____
  If Chikungunya, Dengue, West Nile, Yellow Fever or Zika report as such.
  Attach copies of diagnostic laboratory results if available.
- ☐ **Babesiosis**
- ☐ **Botulism***
  ○ Foodborne ○ Infant ○ Wound
- ☐ **Brucellosis***
- ☐ **Campylobacteriosis†**

  Carbon Monoxide poisoning* – see Poisonings section on page 3

  Chancroid – see STD section on page 4
- ☐ **Chikungunya**

  Chlamydia – see STD section on page 4
- ☐ **Cholera***

  Creutzfeldt-Jakob disease – see Transmissable spongiform encephalopathy
- ☐ **Cryptosporidiosis†**
- ☐ **Cyclosporiasis†**
- ☐ **Dengue**
  Attach copies of dengue diagnostic laboratory results if available.
- ☐ **Diphtheria***

  Drownings – see Environmental Conditions section on page 3
- ☐ **Ehrlichiosis** (Human monocytic ehrlichiosis)
  If human granulocytic anaplasmosis report as anaplasmosis.
- ☐ **Encephalitis**
  If Jul.1–Oct. 31 consider and test for West Nile virus. If due to another reportable disease (e.g. Lyme, West Nile, arbovirus), report under the other disease.
- ☐ **Escherichia coli** O157:H7 infection†

  Falls from windows – see Environmental Conditions section on page 3
- ☐ **Food poisoning** in a group of 2 or more individuals*
- ☐ **Giardiasis†**
- ☐ **Glanders***

  Gonorrhea – see STD section on page 4

  Granuloma inguinale – see STD section on page 4
- ☐ **Haemophilus influenzae** (invasive disease)†

  Test type:
  ○ Culture ○ Antigen
  ○ PCR ○ Gram stain
  ○ Other _____

  Specimen Source:
  ○ Blood ○ CSF ○ Unknown
  ○ Other _____

  Specify Serotype:
  ○ Type B ○ Not typeable
  ○ Not tested ○ Unknown
  ○ Other _____
- ☐ **Hantavirus disease***
- ☐ **Hemolytic uremic syndrome**

FOR ALL HEPATITIS REPORTS

Jaundice ○ Yes ○ No ○ Unknown
ALT (SGPT) value:_____ ○ Unknown
Lab reference range:_____ ○ Unknown

- ☐ **Hepatitis A†**
  Total Ab to Hepatitis A is NOT reportable.
  IgM anti-HAV: ○ Pos ○ Neg ○ Unknown
- ☐ **Hepatitis B†**
  Report at least one positive hepatitis B test result. Total Ab to Hepatitis B is not reportable.
  IgM anti-HBc: ○ Pos ○ Neg ○ Unknown
  HBsAg: ○ Pos ○ Neg ○ Unknown
  HBeAg: ○ Pos ○ Neg ○ Unknown
  HBV Nucleic Acid: ○ Pos ○ Neg ○ Unknown

  If IgM is positive, describe symptoms and risk in comments box on last page.

  Hepatitis B in pregnancy
  Report cases in Reporting Central or fax IMM-5 form to 347-396-2558. For more information, call 347-396-2403.
- ☐ **Hepatitis C†**
  Check all that apply:
  ○ EIA pos
  ○ HCV Nucleic Acid (e.g.PCR) pos

  Is this an acute infection?
  ○ Yes
  ○ No
  ○ Unknown

Herpes, neonatal – see STD section on page 4

HIV/AIDS
Report using the New York State Provider Report Form (PRF). Call 518-474-4284 for forms or 212-442-3388 for more information.

Influenza
- ☐ Suspected novel viral strain with pandemic potential (e.g., avian H5N1 or H7N9)*
- ☐ Death in a child aged 18 or younger

Lead poisoning – see Poisonings section on page 3

- ☐ **Legionellosis†**

  Specify positive test:
  ○ Culture ○ Urine antigen
  ○ DFA ○ Serology
  ○ NAAT or PCR
- ☐ **Leprosy** (Hansen's disease)
- ☐ **Leptospirosis**
- ☐ **Listeriosis†**
- ☐ **Lyme disease**

  Erythema migrans present?
  ○ Yes ○ No ○ Unknown
- ☐ **Lymphocytic choriomeningitis virus**

  Lymphogranuloma venereum – see STD section on page 4
- ☐ **Malaria†**

  Select at least one of the following:
  ○ falciparum ○ vivax ○ malariae
  ○ ovale ○ undetermined

  Complete Foreign Travel section on page 1.
- ☐ **Measles** (rubeola)*
- ☐ **Melioidosis***
- ☐ **Meningitis,** bacterial

  Specify bacteria identified _____
- ☐ **Meningococcal disease,** invasive (including meningitis) *

  Test type/Specimen source:
  ○ Blood culture ○ CSF culture
  ○ Antigen test from CSF ○ Gram stain
  ○ PCR ○ Other _____
- ☐ **Monkeypox***
- ☐ **Mumps†**
- ☐ **Paratyphoid fever†**
- ☐ **Pertussis** (whooping cough)†
- ☐ **Pesticide poisoning** - see Poisonings section on page 3
- ☐ **Plague***

  Poisoning – see Poisonings section on page 3
- ☐ **Poliomyelitis***
- ☐ **Psittacosis**
- ☐ **Q Fever***
- ☐ **Rabies** and **exposure to rabies*** – see animal bites in Environmental Conditions section on page 3
- ☐ **Ricin poisoning***
- ☐ **Rickettsialpox**
- ☐ **Rocky Mountain spotted fever**
- ☐ **Rubella** (German measles)*
- ☐ **Rubella syndrome,** congenital
- ☐ **Salmonellosis†**

  Serogroup: _____
  If due to Salmonella typhi or paratyphi, select Typhoid or Paratyphoid Fever.
- ☐ **Severe or novel coronavirus** (e.g., SARS or MERS-CoV)*
- ☐ **Shiga-toxin** producing Escherichia coli (STEC) infection†
- ☐ **Shigellosis†**
- ☐ **Smallpox** (variola)*
- ☐ **Staphylococcal enterotoxin B poisoning***
- ☐ **Staphylococcus aureus,** vancomycin intermediate (VISA) and resistant (VRSA)*

  Source: _____
  MIC (µg/ml): _____
- ☐ **Streptococcus** (Group A and B) invasive†

  Specify Source: ○ Blood ○ CSF ○ Unknown
  ○ Other, Specify:_____

  Syphilis, including congenital – see STD section on page 4
- ☐ **Tetanus**
- ☐ **Toxic shock syndrome**
- ☐ **Trachoma**
- ☐ **Transmissible spongiform encephalopathy** (Creutzfeldt-Jakob disease and variants)

  Testing done: _____
  (e.g. 14-3-3 on CSF, brain biopsy, autopsy, EEG/MRI)
- ☐ **Trichinosis**

  Tuberculosis – see Tuberculosis section on page 3
- ☐ **Tularemia***
- ☐ **Typhoid fever†**
- ☐ **Vaccinia disease** (adverse events associated with smallpox vaccination)*
- ☐ **Vibrio species,** non-cholera

  Specify species:_____
- ☐ **Viral hemorrhagic fever***
- ☐ **West Nile** fever and viral neuroinvasive disease (e.g., meningitis and encephalitis)

  Attach copies of diagnostic laboratory results if available.
- ☐ **Yellow fever***

  Attach copies of diagnostic laboratory results if available.
- ☐ **Yersiniosis,** non-plague†
- ☐ **Zika**

*Report suspected and confirmed cases immediately to 1-866-692-3641 †If case meets any of the risk group criteria below, report immediately to 1-866-692-3641

Risk Groups for Disease Exposure/Transmission Complete this section for diseases marked with † and if case meets any criteria, report it immediately to 1-866-692-3641.

Patient works in:
☐ Childcare ☐ Health care facility ☐ Long-term care facility/Nursing home ☐ Clinical/Research laboratory
☐ Unknown ☐ Food service ☐ Correctional facility ☐ Position with routine animal contact ☐ Other _____

Patient attends/resides in:
☐ Assisted living facility ☐ School ☐ Dormitory ☐ Long-term care facility/nursing home
☐ Unknown ☐ Correctional facility ☐ Shelter ☐ Day care/group baby-sit ☐ Other congregate living facility (specify: _____)

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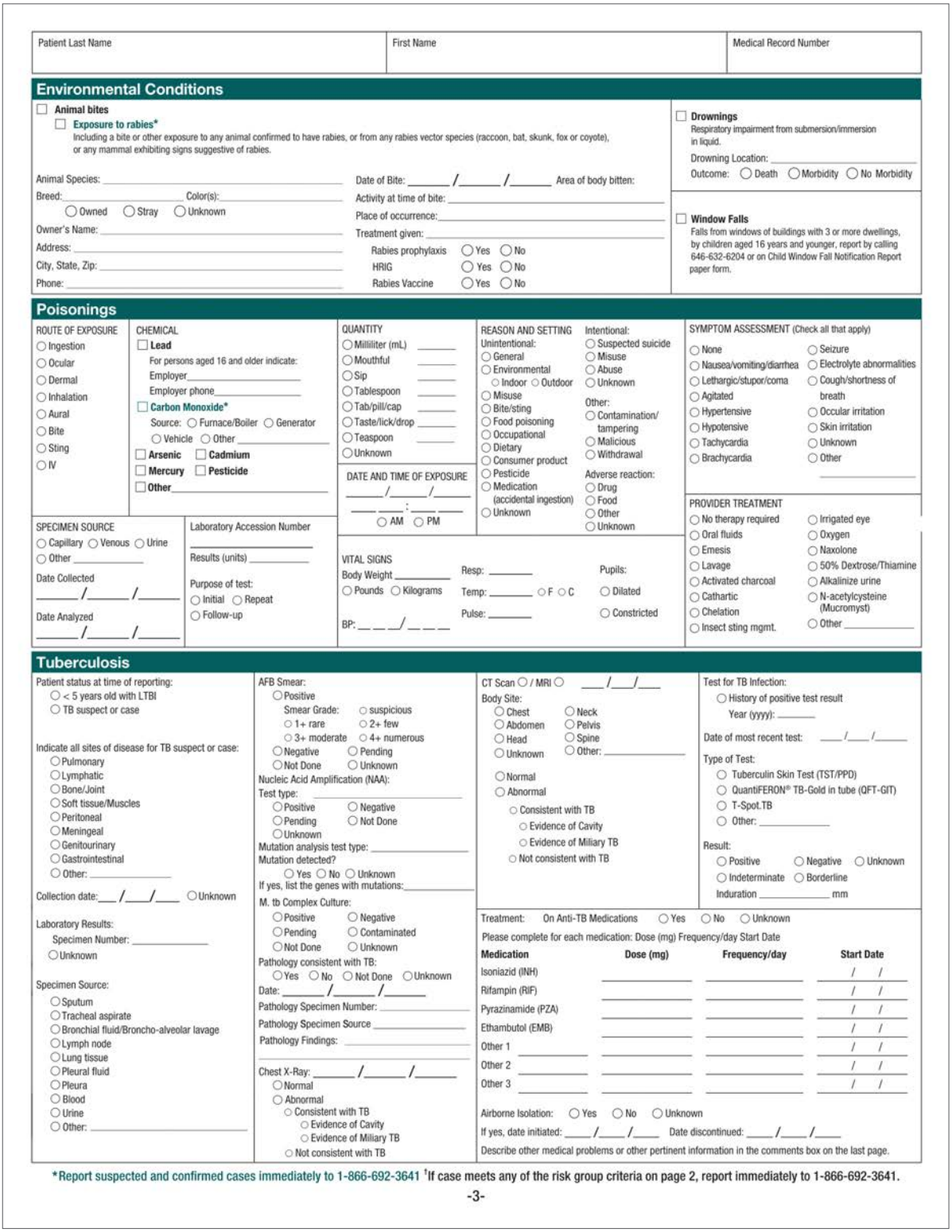
APPENDIX Q: NEW YORK CITY HEALTH DEPARTMENT UNIVERSAL REPORTING FORM (CONTINUED)



Patient Last Name | First Name | Medical Record Number

Environmental Conditions

☐ **Animal bites**

☐ **Exposure to rabies***
Including a bite or other exposure to any animal confirmed to have rabies, or from any rabies vector species (raccoon, bat, skunk, fox or coyote), or any mammal exhibiting signs suggestive of rabies.

Animal Species: _____
Breed: _____ Color(s): _____
○ Owned ○ Stray ○ Unknown
Owner's Name: _____
Address: _____
City, State, Zip: _____
Phone: _____

Date of Bite: ____/____/____ Area of body bitten:
Activity at time of bite: _____
Place of occurrence: _____
Treatment given: _____
Rabies prophylaxis ○ Yes ○ No
HRIG ○ Yes ○ No
Rabies Vaccine ○ Yes ○ No

☐ **Drownings**
Respiratory impairment from submersion/immersion in liquid.
Drowning Location: _____
Outcome: ○ Death ○ Morbidity ○ No Morbidity

☐ **Window Falls**
Falls from windows of buildings with 3 or more dwellings, by children aged 16 years and younger, report by calling 646-632-6204 or on Child Window Fall Notification Report paper form.

Poisonings

ROUTE OF EXPOSURE
○ Ingestion ○ Ocular ○ Dermal ○ Inhalation ○ Aural ○ Bite ○ Sting ○ IV

CHEMICAL
☐ **Lead**
For persons aged 16 and older indicate:
Employer_____
Employer phone_____
☐ **Carbon Monoxide***
Source: ○ Furnace/Boiler ○ Generator ○ Vehicle ○ Other _____
☐ **Arsenic** ☐ **Cadmium** ☐ **Mercury** ☐ **Pesticide** ☐ **Other**_____

QUANTITY
○ Milliliter (mL) _____ ○ Mouthful _____ ○ Sip _____ ○ Tablespoon _____ ○ Tab/pill/cap _____ ○ Taste/lick/drop _____ ○ Teaspoon _____ ○ Unknown

DATE AND TIME OF EXPOSURE
____/____/____
____ : ____
○ AM ○ PM

REASON AND SETTING
Unintentional:
○ General ○ Environmental ○ Indoor ○ Outdoor ○ Misuse ○ Bite/sting ○ Food poisoning ○ Occupational ○ Dietary ○ Consumer product ○ Pesticide ○ Medication (accidental ingestion) ○ Unknown
Intentional:
○ Suspected suicide ○ Misuse ○ Abuse ○ Unknown
Other:
○ Contamination/tampering ○ Malicious ○ Withdrawal
Adverse reaction:
○ Drug ○ Food ○ Other ○ Unknown

SYMPTOM ASSESSMENT (Check all that apply)
○ None ○ Nausea/vomiting/diarrhea ○ Lethargic/stupor/coma ○ Agitated ○ Hypertensive ○ Hypotensive ○ Tachycardia ○ Brachycardia ○ Seizure ○ Electrolyte abnormalities ○ Cough/shortness of breath ○ Occular irritation ○ Skin irritation ○ Unknown ○ Other _____

PROVIDER TREATMENT
○ No therapy required ○ Oral fluids ○ Emesis ○ Lavage ○ Activated charcoal ○ Cathartic ○ Chelation ○ Insect sting mgmt. ○ Irrigated eye ○ Oxygen ○ Naxolone ○ 50% Dextrose/Thiamine ○ Alkalinize urine ○ N-acetylcysteine (Mucromyst) ○ Other _____

SPECIMEN SOURCE
○ Capillary ○ Venous ○ Urine ○ Other _____
Date Collected ____/____/____
Date Analyzed ____/____/____

Laboratory Accession Number _____
Results (units) _____
Purpose of test:
○ Initial ○ Repeat ○ Follow-up

VITAL SIGNS
Body Weight _____ ○ Pounds ○ Kilograms
BP: ___ ___/___ ___
Resp: _____
Temp: _____ ○ F ○ C
Pulse: _____
Pupils:
○ Dilated ○ Constricted

Tuberculosis

Patient status at time of reporting:
○ < 5 years old with LTBI ○ TB suspect or case

Indicate all sites of disease for TB suspect or case:
○ Pulmonary ○ Lymphatic ○ Bone/Joint ○ Soft tissue/Muscles ○ Peritoneal ○ Meningeal ○ Genitourinary ○ Gastrointestinal ○ Other: _____
Collection date: ___/___/___ ○ Unknown

Laboratory Results:
Specimen Number: _____
○ Unknown

Specimen Source:
○ Sputum ○ Tracheal aspirate ○ Bronchial fluid/Broncho-alveolar lavage ○ Lymph node ○ Lung tissue ○ Pleural fluid ○ Pleura ○ Blood ○ Urine ○ Other: _____

AFB Smear:
○ Positive
Smear Grade: ○ suspicious ○ 1+ rare ○ 2+ few ○ 3+ moderate ○ 4+ numerous
○ Negative ○ Pending ○ Not Done ○ Unknown
Nucleic Acid Amplification (NAA):
Test type: _____
○ Positive ○ Negative ○ Pending ○ Not Done ○ Unknown
Mutation analysis test type: _____
Mutation detected?
○ Yes ○ No ○ Unknown
If yes, list the genes with mutations: _____
M. tb Complex Culture:
○ Positive ○ Negative ○ Pending ○ Contaminated ○ Not Done ○ Unknown
Pathology consistent with TB:
○ Yes ○ No ○ Not Done ○ Unknown
Date: ____/____/____
Pathology Specimen Number: _____
Pathology Specimen Source _____
Pathology Findings: _____

Chest X-Ray: ____/____/____
○ Normal
○ Abnormal
○ Consistent with TB
○ Evidence of Cavity
○ Evidence of Miliary TB
○ Not consistent with TB

CT Scan ○ / MRI ○ ___/___/___
Body Site:
○ Chest ○ Abdomen ○ Head ○ Unknown ○ Neck ○ Pelvis ○ Spine ○ Other: _____
○ Normal
○ Abnormal
○ Consistent with TB
○ Evidence of Cavity
○ Evidence of Miliary TB
○ Not consistent with TB

Test for TB Infection:
○ History of positive test result
Year (yyyy): _____
Date of most recent test: ___/___/___
Type of Test:
○ Tuberculin Skin Test (TST/PPD)
○ QuantiFERON® TB-Gold in tube (QFT-GIT)
○ T-Spot.TB
○ Other: _____
Result:
○ Positive ○ Negative ○ Unknown
○ Indeterminate ○ Borderline
Induration _____ mm

Treatment: On Anti-TB Medications ○ Yes ○ No ○ Unknown
Please complete for each medication: Dose (mg) Frequency/day Start Date

Medication	Dose (mg)	Frequency/day	Start Date
Isoniazid (INH)			/ /
Rifampin (RIF)			/ /
Pyrazinamide (PZA)			/ /
Ethambutol (EMB)			/ /
Other 1			/ /
Other 2			/ /
Other 3			/ /

Airborne Isolation: ○ Yes ○ No ○ Unknown
If yes, date initiated: ___/___/___ Date discontinued: ___/___/___
Describe other medical problems or other pertinent information in the comments box on the last page.

*Report suspected and confirmed cases immediately to 1-866-692-3641 †If case meets any of the risk group criteria on page 2, report immediately to 1-866-692-3641.

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APPENDIX Q: NEW YORK CITY HEALTH DEPARTMENT UNIVERSAL REPORTING FORM (CONTINUED)

Patient Last Name	First Name	Medical Record Number

Sexually Transmitted Diseases

For All STD Reports

As of the date of this report,

Were any of this patient's sex partners notified of possible exposure to an STD? (Check all that apply)
- ◯ Yes, our office notified the partner(s)
- ◯ Yes, the patient was asked to notify partner(s)
- ◯ No
- ◯ Unknown

Did you provide treatment for any of this patient's partners? (Check all that apply)
- ◯ Yes, I saw the sex partner(s) in my office
- ◯ Yes, I gave extra medication for ___(#) partner(s)
- ◯ Yes, I wrote a prescription for ___(#) partner(s)
- ◯ Yes, some other way (specify):_____
- ◯ No
- ◯ Unknown

Is the patient on pre-exposure prophylaxis (PrEP) to prevent HIV infection?
- ◯ Yes, started PrEP at time of current STD diagnosis
- ◯ Yes, already on PrEP at time of current STD diagnosis
- ◯ No
- ◯ Unknown

Please indicate gender of sexual partners in the past year: (Check all that apply)
- ◯ Males
- ◯ Females
- ◯ Transgender Male to Female
- ◯ Transgender Female to Male
- ◯ Unknown

☐ **Chancroid**
Specify type of specimen:
◯ Penile ◯ Vaginal ◯ Endocervical ◯ Anorectal ◯ Oropharyngeal ◯ Other: _____
Specimen collection date: ____/____/____
Treatment: _____
Treatment date: ____/____/____ ◯ Unknown

☐ **Granuloma inguinale**
Specify type of specimen:
◯ Penile ◯ Vaginal ◯ Endocervical ◯ Anorectal ◯ Oropharyngeal ◯ Other _____
Specimen collection date: ____/____/____
Treatment: _____
Treatment date: ____/____/____ ◯ Unknown

☐ **Lymphogranuloma venereum**
Clinical Presentation (Check all that apply)
◯ Proctitis ◯ Lymphadenopathy ◯ Buboe ◯ Skin lesion ◯ Other: _____
Specimen collection date: ____/____/____
Treatment: _____
Treatment date: ____/____/____ ◯ Unknown

Syphilis Test Types: (Check all that apply)

1. Serologic tests for syphilis

A. Non-treponemal Test
◯ RPR ◯ Reactive ◯ Non-reactive
Titer _____
◯ VDRL ◯ Reactive ◯ Non-reactive
Titer _____
Specimen collection date: ____/____/____

B. Treponemal Test
◯ TP-PA/MHA-TP ◯ Reactive ◯ Non-reactive
◯ FTA ◯ Reactive ◯ Non-reactive
◯ Treponemal IgG ◯ Reactive ◯ Non-reactive
Specimen collection date: ____/____/____

2. Cerebrospinal fluid tests
◯ CSF VDRL ◯ Reactive ◯ Non-reactive
◯ CSF FTA ◯ Reactive ◯ Non-reactive
◯ Other Test: _____ Result _____
Specimen collection date: ____/____/____
◯ Elevated CSF protein ◯ Yes ◯ No
◯ Elevated CSF leukocytes ◯ Yes ◯ No
Specimen collection date: ____/____/____

3. Organism visualization
◯ Darkfield ◯ Positive ◯ Negative
◯ Other Test: _____ Result _____
Specimen collection date: ____/____/____

☐ **Chlamydia** (CT)
Specify type of specimen:
◯ Endocervical ◯ Urethral ◯ Anorectal ◯ Oropharyngeal ◯ Urine ◯ Other: _____
Specify test type:
◯ Culture ◯ Nucleic acid amplification ◯ Nucleic acid hybridization ◯ EIA ◯ DFA ◯ Other: _____
Specimen collection date: ____/____/____
Treatment: _____
Treatment date: ____/____/____ ◯ Unknown

☐ **Herpes, neonatal**
Herpes simplex virus infection in infants aged 60 days and younger.
◯ Clinical diagnosis
◯ Lab confirmed diagnosis
◯ Culture ◯ PCR ◯ Other _____
Herpes type: ◯ Type 1 ◯ Type 2 ◯ Not typed
Clinical Syndrome (Check all that apply)
◯ Skin, eye, mucous membrane infection
◯ CNS involvement
◯ Disseminated disease
Herpes lesions present?
◯ Yes, anatomic site _____
◯ No
◯ Unknown
Specimen collection date: ____/____/____
Treatment for infant: _____
Treatment date: ____/____/____ ◯ Unknown
Mother's Name: _____
Mother's DOB: ____/____/____
Birth Hospital _____
Mother's Labor and Delivery Medical Record No: _____

☐ **Syphilis****
Stage:
◯ Congenital
◯ Primary, chancre present (Check all that apply)
◯ Penile ◯ Vaginal ◯ Endocervical ◯ Anorectal ◯ Oropharyngeal ◯ Other: _____
◯ Secondary (Check all that apply)
◯ Alopecia ◯ Condylomata ◯ Mucous patches ◯ Rash
◯ Early Latent
no symptoms, infection ≤ 1 year duration
◯ Late Latent
no symptoms, infection of > 1 year duration
◯ Tertiary, gumma or cardiovascular
Neurologic symptoms present?
◯ Yes ◯ No ◯ Unknown
Ocular symptoms present?
◯ Yes ◯ No ◯ Unknown
Otic symptoms present?
◯ Yes ◯ No ◯ Unknown
Treatment – list medication and dosage below:
_____
_____
_____
Treatment date: ____/____/____ ◯ Unknown
Continue to next column

☐ **Gonorrhea*** (GC)
Specify type of specimen:
◯ Endocervical ◯ Urethral ◯ Anorectal ◯ Oropharyngeal ◯ Urine ◯ Other: _____
Specify test type:
◯ Culture ◯ Nucleic acid amplification ◯ Nucleic acid hybridization ◯ Other: _____
Specimen collection date: ____/____/____
Treatment 1*: _____ mg/gram
Treatment 2*: _____ mg/gram
Treatment date: ____/____/____ ◯ Unknown

* For uncomplicated gonococcal infections of the cervix, urethra, anorectum or pharynx, CDC recommends dual therapy (irrespective of concurrent chlamydial infection) using BOTH Ceftriaxone 250mg IM AND Azithromycin 1g PO.

** Licensed health care providers can access current and historical syphilis test results and treatment information in the New York City Syphilis Registry to inform the diagnosis and management of syphilis in their patients. For more information, see the Syphilis Registry check at: http://www1.nyc.gov/assets/doh/downloads/pdf/std/hcp-syphilis-registry-check.pdf, or call 347-396-7201

Comments:

APPENDIX R: REPORT OF PATIENT SERVICES FORM

NYC Health

Bureau of Tuberculosis Control
42-09 28th Street, Box 72
Long Island City, N.Y. 11101
844-713-0559/ FAX: 844-713-0557

REPORT OF PATIENT SERVICES

Please print firmly and legibly

By law this form must be submitted for every monthly visit of patients with active tuberculosis.

TB Registry Number _____ Social Security Number ___ ___ _____ Chart Number _____

Patient Name: _____ (Last) _____ (First) _____ (M.I.)

Address _____ Apt. # _____ Zip Code _____

Daytime Phone ( ) ___ _____ Evening Phone ( ) ___ _____ Date of Birth ____ (Month) / ____ (Day) / ____ (Year)

❑ If patient missed appointment, check here and go to box at bottom of page. (Date of missed appointment ____ (Month) / ____ (Day) / ____ (Year))

TB Site of Disease (check all that apply):

- ❑ Pulmonary
- ❑ Other (Specify)
- ❑ Pleural _____
- ❑ Lymphatic _____
- ❑ Meningeal _____

Latest chest X-ray: ____ (Month) / ____ (Day) / ____ (Year)

- ❑ Normal
- ❑ Abnormal-noncavitary (including adenopathy)
- ❑ Abnormal-cavitary

Findings: _____

If prior films available; is this film

- ❑ Stable ❑ Worsening ❑ Improving

Most recent bacteriology:

Date specimen collected: ____ (Month) / ____ (Day) / ____ (Year)

Source of Specimen: _____

Smear:	Culture:
❑ Positive	❑ Positive
❑ Negative	❑ Negative
❑ Pending	❑ Pending

If culture positive:

❑ M.tb ❑ Other _____

Was susceptibility ordered? ❑ Yes ❑ No

Medications prescribed at this visit?

❑ Yes ❑ No Reason: _____

Medication regimen changed this visit?

❑ Yes ❑ No Reason: _____

Is patient on Directly Observed Therapy?

❑ Yes ❑ No Reason: _____

Frequency of DOT:

- ❑ Daily
- ❑ 2x per week
- ❑ 3x per week
- ❑ 5x per week
- ❑ once a week

Drugs and dosages:

❑ INH ____ mg	❑ RIF ____ mg	❑ PZA ____ mg
❑ EMB ____ mg	❑ SMN ____ mg	❑ PAS ____ mg
❑ Ethio ____ mg	❑ CYC ____ mg	❑ Kana/AMI ____ mg
❑ RPT ____ mg	❑ Levo ____ mg	❑ Capreo ____ mg
❑ RBT ____ mg	❑ Other ____	❑ MOXI ____ mg

Services provided
Check all that apply:

- ❑ Doctor visit
- ❑ Nurse visit
- ❑ X-ray
- ❑ Sputum sample
- ❑ Audiometry
- ❑ Liver enzymes
- ❑ Vision testing
- ❑ Other

Date of this visit: ____ (Month) / ____ (Day) / ____ (Year) Date of next visit: ____ (Month) / ____ (Day) / ____ (Year)

Management Course/Outcome:

- ❑ Completed treatment
- ❑ Expired – was cause of death TB? ❑ Yes ❑ No
- ❑ Moved/transferred (where): _____
- ❑ Rehospitalized (where): _____
- ❑ Other _____

M.D. Name: _____ M.D. License # _____

Facility: _____ Prepared by: _____ Phone: ( ) ___ _____

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COPIES: White–DOHMH; Yellow–Chart; Pink–Clinic Records

APPENDIX S: HOSPITAL DISCHARGE APPROVAL FORM

NYC Health

NEW YORK CITY DEPARTMENT OF HEALTH AND MENTAL HYGIENE
BUREAU OF TUBERCULOSIS CONTROL

HOSPITAL DISCHARGE APPROVAL REQUEST FORM

Please complete this form in entirety and fax to 844-713-0557 (toll-free)

SECTION A: Patient Contact Information

Patient name: _____ DOB: ____/____/____ (mm/dd/yyyy)

Tel. #: (1) (____)_____–_____ (2) (____)_____–_____

Address: _____ Apt.: _____ City: _____ State: _____ Zip: _____

Emergency contact name: _____ Relationship to patient: _____ Tel. #: (____)_____–_____

SECTION B: Discharge Information

Discharging facility: _____ Discharging facility tel. #: (____)_____–_____

Address: _____ Fl.: _____ City: _____ State: _____ Zip: _____

Patient medical record #: _____ Date of admission: ____/____/____ (mm/dd/yyyy) Planned discharged date: ____/____/____ (mm/dd/yyyy)

Discharged to: ☐ Home (if not the same address as above, fill in address below)

☐ Shelter ☐ Skilled nursing facility ☐ Jail/Prison ☐ Residential facility ☐ Other facility

Name of facility: _____ Tel. #: (____)_____–_____

Address: _____ Apt./Fl.: _____ City: _____ State: _____ Zip: _____

Is patient scheduled to travel outside of NYC? ☐ Yes ☐ No If yes, specify date/destination: _____

SECTION C: Patient Follow-Up Appointment

Patient follow-up appointment date: ____/____/____ (mm/dd/yyyy)

Physician assuming care: _____ Tel. #: (____)_____–_____ Cell. #: (____)_____–_____

Address: _____ City: _____ State: _____ Zip: _____

Potential barriers to TB therapy adherence: ☐ None ☐ Adverse reactions ☐ Homelessness

☐ Physical disability (*specify*) _____ ☐ Medical condition (*specify*) _____

☐ Substance use (*specify*) _____ ☐ Mental disorder (*specify*) _____ ☐ Other _____

SECTION D: Laboratory Results

Dates of three most recent acid fast bacilli (AFB) smears	Specimen source	Acid fast bacilli (AFB) smear results
____/____/____	_____	☐ Positive Grade: _____ ☐ Negative
____/____/____	_____	☐ Positive Grade: _____ ☐ Negative
____/____/____	_____	☐ Positive Grade: _____ ☐ Negative

SECTION E: Treatment Information

Date TB therapy initiated: ____/____/____ (mm/dd/yyyy) Interruption in therapy? ☐ Yes ☐ No If yes, state the reason and duration of the interruption? _____

TB medications at discharge: ☐ INH ____ mg ☐ RIF ____ mg ☐ PZA ____ mg ☐ EMB ____ mg ☐ SM ____ mg ☐ Vitamin B_6 ____ mg

☐ Injectables (*specify*) _____ ☐ Other TB meds (*specify*) _____

Frequency: ☐ Daily ☐ 2x weekly ☐ 3x weekly ☐ Other _____

Was a central line (i.e. PICC) inserted on the patient? ☐ Yes ☐ No

Number of days of medications supplied to patient at discharge _____ Patient agreed to be on DOT? ☐ Yes ☐ No

Print name of individual filling out this form: _____ Date: ____/____/____ (mm/dd/yyyy)

Name of responsible physician at the discharging facility: _____ License #: _____

Signature of responsible physician at the discharging facility: _____ Tel. #: (____)_____–_____

COMPLETED BY THE HEALTH DEPARTMENT **BTBC NUMBER:** _____

Discharge approved: ☐ Yes ☐ No Action required before discharge: _____

Reviewed by: _____ (NAME OF HEALTH OFFICER/DESIGNEE) Date: ____/____/____ (mm/dd/yyyy)

TB 354 (11/10)

APPENDIX S: HOSPITAL DISCHARGE APPROVAL FORM (CONTINUED)

Guidelines for How to Complete and Submit the Mandatory TB Hospital Discharge Approval Request Form (TB 354)

As of June 16, 2010, Article 11 of the New York City Health Code mandates health care providers to obtain approval from the New York City Department of Health & Mental Hygiene (DOHMH) before discharging infectious TB patients from the hospital.

Discharge of an Infectious (sputum smear positive) Tuberculosis Patient

Health care providers must submit a Hospital Discharge Approval Request Form (TB 354) at least 72 hours prior to the anticipated discharge date. The DOHMH will review the form and approve or request additional information before the patient can be discharged from the health care facility.

Weekday (non-holiday) Discharge: The written discharge plan should be submitted by fax to the Bureau of TB Control between 8am-5pm. Bureau of TB Control staff will review the discharge plan and, within 24 hours, notify the provider of approval or inform the provider of any additional information/actions required for approval prior to discharge.

Weekend and Holiday Discharge: All arrangements for discharge should be made in advance when weekend or holiday discharge is anticipated.

For detailed information about hospital admission and discharge of TB patients, please refer to the New York City DOHMH Bureau of TB Control Policies and Protocols manual available online at http://www1.nyc.gov/site/doh/health/health-topics/tb-hosp-manual.page

Instructions for Completing the Hospital Discharge Approval Request Form (TB 354)

Section A Patient contact information: Provide the patient's contact information including patient's name, a verified address and telephone numbers. In addition, include a name of an emergency contact, the contact's relationship to the patient and the contact's verified phone number.

Section B Discharge information: Provide the name and phone number of the discharging facility, the medical record number of the patient at the facility, date the patient was admitted, planned discharge date, and the location to which the patient is being discharged. If the patient will be discharged to a location other than the patient's address listed in Section A, a facility name (if applicable), address and phone number must be provided. If the patient plans to travel, provide the date and destination.

Section C Patient follow-up appointment: Provide the patient's follow-up appointment date, as well as the name and contact information of the provider who is assuming patient care. Check all potential obstacles that may affect TB therapy adherence.

Section D Laboratory results: Report the results of the three most recent acid fast bacilli (AFB) smears including the date of specimen collection, specimen source, and AFB smear results and/or grade.

Section E Treatment information: Fill in the date TB treatment was initiated. If there were any treatment interruptions, indicate the reason and number of days treatment was stopped. Check the box next to each prescribed drug and state dosages for each drug. Write in drugs and dosages for drugs not specified. Specify the treatment frequency by checking one of the three boxes, or writing in a different treatment schedule. State whether the patient will have a central line inserted at the time of discharge. If TB medication will be supplied to the patient at discharge, write the number of days for which the medication will be supplied. State whether the patient agreed to be on directly observed therapy (DOT).

After Section E, the name of the person completing the form should be printed and the authorized physician at the discharging facility must print and sign their name, and provide their medical license number and telephone number.

Forms should be faxed to the DOHMH at 844-713-0557 (toll-free).

If you have questions about completing the form, please call 311 and ask to speak to a Bureau of TB Control physician.

To fulfill State requirements for communicable disease reporting, health care providers must report all suspected or confirmed TB cases to the DOHMH via Reporting Central (formerly Universal Reporting Form (URF)). Instructions for reporting a case of TB can be found at http://www1.nyc.gov/site/doh/providers/reporting-and-services/hcp-urf.page

NOTE: A discharge approval request form does not substitute required case reports.

TB 354 (11/10)


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