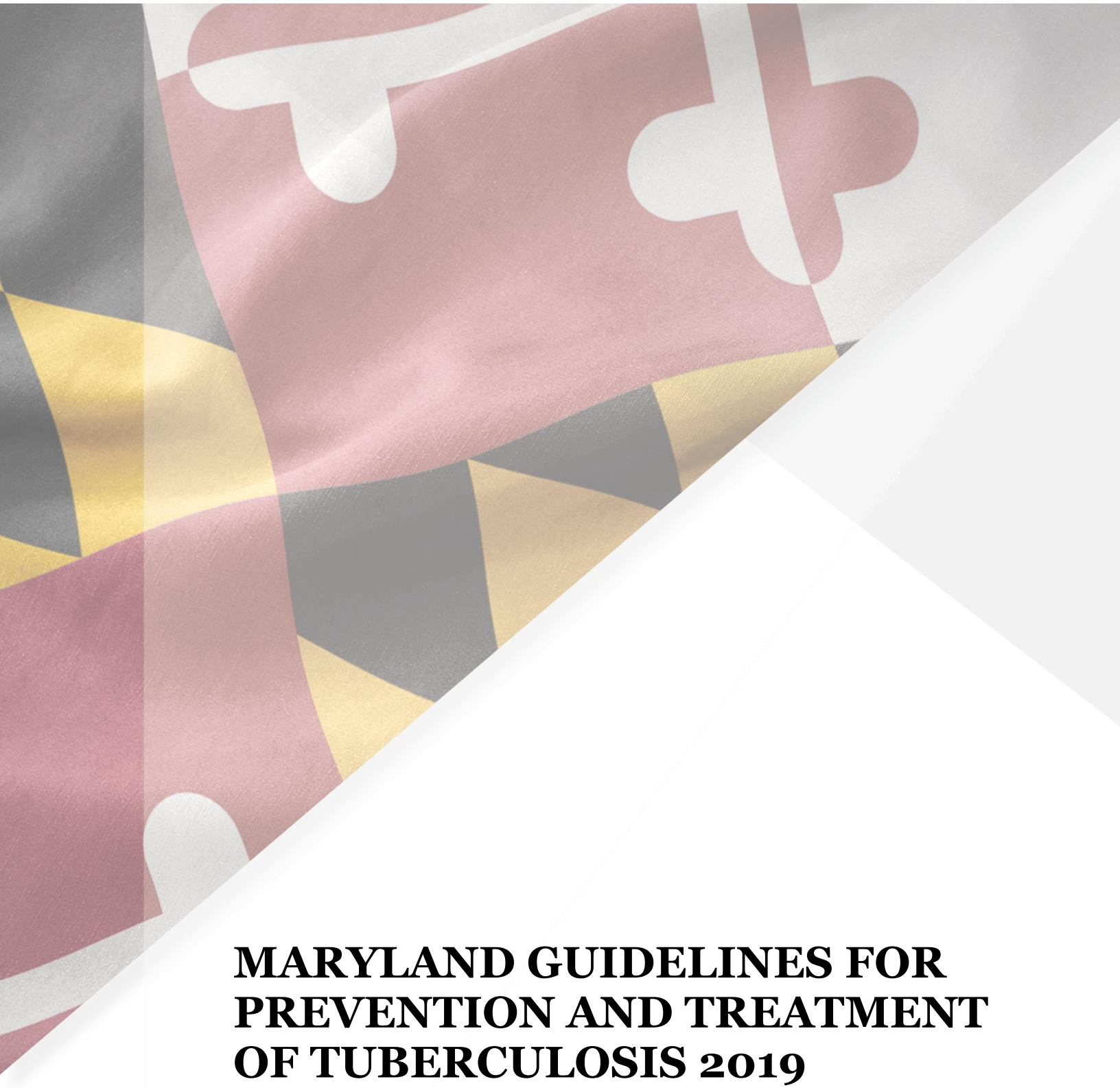


MARYLAND GUIDELINES FOR PREVENTION AND TREATMENT OF TUBERCULOSIS 2019

3rd Edition, revised

Maryland Department of Health
Prevention and Health Promotion Administration
Center for TB Control and Prevention

Development of this document was funded, in part, by the Maryland Tuberculosis Elimination and Laboratory CDC Cooperative Agreement 6 NU52PS910211

MDH, 201 W. Preston Street · Baltimore, MD 21201 · health.maryland.gov · Toll Free: 1-877-463-3464 · TTY: 1-800-735-2258

The use of trade names in this document is for identification purposes only and does not imply endorsement by the U.S. Public Health Service, the U.S. Department of Health and Human Services, the U.S. Centers for Disease Control and Prevention (CDC) or the Maryland Department of Health.

The services and facilities of the Maryland Department of Health (MDH) are operated on a non-discriminatory basis. This policy prohibits discrimination on the basis of race, religion, color, sex, or national origin and applies to the provisions of employment and granting of advantages, privileges, and accommodations.

The Department, in compliance with the Americans with Disabilities Act, ensures that qualified individuals with disabilities are given an opportunity to participate in and benefit from MDH services, programs, benefits, and employment opportunities.

Maryland Guidelines for Prevention and Treatment of Tuberculosis
2019 Table of Contents

FIGURES

TABLES

APPENDICES

Recommendations made by Maryland TB Expert Panels 2001, 2003, and 2006 were acknowledged and incorporated into the previously published Maryland Guidelines for Prevention and Treatment of Tuberculosis 2nd edition, 2007.

The Maryland Department of Health, Center for TB Control and Prevention gratefully acknowledges the contributions of the many nurses, clinicians, epidemiologists, support staff and others who have willingly shared their knowledge, expertise, time, and resources in the development of these guidelines.

This page intentionally left blank.

I. INTRODUCTION

The Maryland Department of Health **Guidelines for Prevention and Treatment of Tuberculosis** are provided as a resource for Maryland healthcare providers and local health departments (LHD). They are based upon Centers for Disease Control and Prevention (CDC) Guidelines, recommendations and guidelines from various professional organizations (e.g., the American Thoracic Society) and have been reviewed and approved by TB experts and practicing TB clinicians within Maryland. These are minimum recommendations. A local health officer or the medical director of an institution may establish more stringent guidelines for defined populations. The guidelines are meant to be a "living" document and in addition to annual reviews may be updated periodically when necessary. Notification and highlights of major changes will be posted on the Maryland Department of Health website when they occur.

Prevention and control activities for TB in Maryland are based upon the following key principles:

- All confirmed and suspected TB cases and diagnoses of latent TB infection (LTBI) must be reported to the Local Health Department (LHD) of the jurisdiction in which the individual resides within 24 hours of diagnosis. (*Maryland COMAR regulations 10.06.01.20.*)
- All Maryland TB cases are managed directly by or co-managed with the LHD of the jurisdiction in which the individual resides, (*Maryland Health General §§ 18 324-325*).
- Four-drug antibiotic therapy (isoniazid, rifampin, pyrazinamide, and ethambutol) is the standard of care for initial treatment of all TB cases and suspected TB cases in the U.S.
- Drug susceptibility testing must be obtained on all initial isolates.
- Directly observed therapy (DOT) for TB medication administration is the standard of care in Maryland for all TB cases and suspected TB cases and may be provided by or coordinated through LHDs. (*Maryland COMAR regulations 10.06.01.20 A.*)
- Only high-risk populations identified by local and state epidemiology are targeted for TB screening via risk assessment followed by testing for TB if warranted. Screening and testing programs must include plans for the medical evaluation and treatment of newly identified persons with latent TB infection or active disease.
- HIV testing should be done on any individual diagnosed with latent TB infection or TB disease regardless of age, as well as high or medium-priority contacts to tuberculosis cases.
- HIV testing should be considered a routine part of any initial medical evaluation for TB.
- Serum drug level monitoring is recommended for diabetic and other high- risk patients to assess that levels of prescribed TB medications are therapeutic.

Strict adherence to the clinical standards and recommendations outlined in these guidelines will result in successful treatment of most patients. This document does not provide detailed answers to complex case management or contact investigation questions that may arise from a clinical or a public health perspective. Co-morbidities and social determinants often make TB diagnosis and treatment extremely challenging and require expert consultation on issues not fully addressed or referenced in this document. General information on medications and possible adverse reactions are summary references only. Consult pharmacy texts and manufacturers' literature as necessary. Consultation is available through LHDs and the Center for Tuberculosis Control and Prevention (CTBCP), Maryland Department of Health. Comments or questions regarding these Guidelines should be directed to:

Maryland Department of Health, Center for TB Control and Prevention,
201 W. Preston St. Room 335
Baltimore, Maryland 21201 Telephone: (410) 767-6698 FAX: (410) 767-5972
WEB Site: https://phpa.health.maryland.gov/OIDPCS/CTBCP/pages/Home.aspx

II. ROLE OF THE LOCAL HEALTH DEPARTMENT IN TUBERCULOSIS CONTROL

Local health departments (LHD) in Maryland are responsible for ensuring the identification and treatment of patients with tuberculosis (TB) disease, conducting contact investigations, treating, or consulting on treatment of latent TB infection and providing local community outreach. Each local health department has a designated TB Coordinator.

Individual programs vary in terms of numbers of staff and dedicated resources depending on local epidemiologic trends and health department resources. Although private providers may be involved in TB diagnosis and treatment, and often assume direct responsibility for treatment of TB infection, the LHD is responsible for ensuring that basic standards of care, including directly observed therapy (DOT) are being met, and that communication from the private provider to the LHD occurs on a regular basis throughout the course of treatment. Legal and regulatory governance of TB in Maryland is discussed more fully in Section VIII, Legal Aspects of TB Control *(page 57)*.

A TB case is officially "counted" for state and national surveillance purposes in the jurisdiction where the patient resides at the time of the TB diagnosis. The LHD in the counting jurisdiction is responsible for that case and any associated contact investigation and follow-up, even if the patient moves to another jurisdiction prior to completion of treatment or the contact investigation expands to other jurisdictions. Local health department responsibilities cover several key areas essential to program success and are detailed in the sections that follow.

Reporting of Cases

Health care providers must report all confirmed and clinically suspected TB cases to the local health department within 24 hours of identification [(36)]. The LHD is responsible for verifying the diagnosis. The local health department electronically submits a *Report of Verified Case of Tuberculosis* (RVCT) to the Maryland Department of Health (MDH) Center for TB Control and Prevention (CTBCP) for each confirmed and suspected case of TB within 7 days of starting therapy. It is important that RVCT data be completed accurately and timely, as this data is also transmitted to the Centers for Disease Control and Prevention (CDC) via the National Electronic Data Surveillance System (NEDSS) to become part of national TB surveillance data. This data is used to evaluate program performance by CDC, a primary funding source for this program. Data is also used to inform state and local health department administrations. Data reported to CDC are reviewed at least weekly by CTBCP surveillance staff and periodically by the Maryland TB Program Evaluation Team as part of an ongoing quality assurance process.

Training on the surveillance definitions used in completing the RVCT, electronic completion of the various components of the RVCT form, and basic instruction on using the National Electronic Data Surveillance System (NEDSS) is provided periodically to accommodate new LHD staff. NEDSS is one national surveillance data reporting platform used by the state of Maryland to submit data to CDC.

Priorities of LHD TB Control Programs

The primary goal of the CTBCP and all LHD TB Control programs is to decrease the incidence of new TB cases in Maryland. This is achieved by meeting the following general objectives, listed in order of priority.

1. Prompt identification and treatment of patients with clinically active TB.
2. Prompt identification, evaluation, and treatment of high-priority contacts to TB cases.
3. Initiation and completion of treatment of latent TB infection in high-risk individuals.
4. Targeted testing and treatment of high-risk populations within the community.

Successful treatment of TB cases is the single most important TB control strategy employed to

achieve a decline in TB incidence. Treatment of TB disease not only cures the patient of TB, but also interrupts transmission of *M. tuberculosis*, thus decreasing the pool of infected patients who contribute to future cases. Complete treatment of TB cases utilizing directly observed therapy (DOT) is the top priority for all Maryland LHD TB Control programs.

The prevention of disease in persons living with HIV, close contacts, and other high-risk individuals is the second priority for LHD TB programs, followed by targeted TB screening and testing of local high-risk populations and treatment of those infected. Testing of low-risk populations for TB is not recommended. Assistance with assessment of local TB epidemiology and discussion of local TB Control and Prevention plans is available through the CTBCP.

General community outreach activities remain important but are addressed only if the priorities noted above are well managed. Two key exceptions to this general rule are the critical outreach LHD TB Control programs provide to their local hospital and nursing home Infection Preventionists/Infection Control Practitioners and to the local detention center. Assisting with facility TB risk assessments and facility TB infection control plans is an important function of the LHD. Establishing relationships with key providers who serve high-risk populations within the community is also highly recommended.

With limited public health resources, funding should be allocated and prioritized to best serve the health of the general public. (*Table 1, Priorities for Local Health Department Resource Allocation, page 5*). Regular review of these priorities in evaluating local TB control activities helps determine if resources are being appropriately allocated.

Nurse Case Management

Nurse case management is an integral part of TB control in the United States and in Maryland. LHD nurses are responsible for the case management and follow-up of all TB cases counted in their respective jurisdictions, including patients whose treatment is being directed by private practice clinicians. Regardless of the size of the LHD or the number of cases, each TB case should have an assigned nurse case manager. Case managers must be registered nurses (RN), who may direct the activities of licensed vocational or practical nurses, nursing assistants, and outreach workers. Delegation of case management activities must be done in accordance with Board of Nursing regulations. https://mbon.maryland.gov/Pages/nurse-practice-act.aspx

Case management begins with the first patient contact, often in the hospital setting, and continues until treatment is complete. Nurse case managers facilitate and monitor treatment and assess the patient's physical, psychosocial, socioeconomic, and other needs throughout the course of treatment to identify barriers to care and factors which may affect adherence to treatment. Local health departments developing TB case management procedures and protocols are encouraged to consult with the CTBCP.

Assessment of the patient's clinical status, including the degree of infectiousness, risk factors for drug resistance, potential difficulty adhering to treatment protocols, and HIV infection or the presence of another chronic condition such as diabetes, allows for the development of an individualized treatment plan, and implementation of therapeutic interventions, e.g., enablers and incentives, which assist in achieving treatment completion using the least restrictive measures impacting personal lifestyle, as appropriate for the patient.

Periodic ongoing assessments over the entire course of treatment allow for detection of potential barriers to treatment completion and alteration of interventions if the patient's health status or lifestyle changes. All assessments should consider any economic concerns, environmental factors and social determinants affecting the patient’s health in terms of any actual or potential impact they may have on the person’s ability to complete treatment. Ongoing consultation with CTBCP nurse and physician consultants is available through telephone

consultations, formal and informal case consultations and scheduled case/cohort reviews.

In addition to developing a comprehensive treatment plan with input from the patient/family as appropriate, it is the responsibility of the nurse case manager to ensure patient education (both written and verbal) is ongoing and appropriate to the patient's age, language, literacy level, culture and beliefs. A trained medical interpreter is necessary when the patient and health care provider do not speak the same language. If the LHD does not have an interpreter available, a telephone interpreter should be utilized. The Maryland state government contracts with language service providers that LHDs can utilize. Some LHDs also contract directly with language interpretation and translation service providers.

Use of a family member, friend of the patient or others e.g., clergy for interpretation/ translation is not appropriate due to legal protections regarding the patient's confidentiality and privacy. Even voluntary community organization members or other LHD staff should be used for interpretation with caution and only if they have been appropriately trained (and preferably certified) in medical interpretation and applicable confidentiality protocols.

LHD staff unfamiliar with working with interpreters either in person or via the telephone should attend available training opportunities to increase their skills if working with limited-English speaking individuals. Numerous TB educational materials have been translated into multiple languages, as have certain recommended patient care documents, and can be accessed through the MDH website or by contacting CTBCP.

LHD programs are encouraged to use translated materials that have been appropriately processed to ensure they meet national standards for accurate translation of medical terms, appropriate use of language structure and have been professionally vetted and approved. LHDs should contact CTBCP for references to access patient-oriented TB materials or may refer to sites like the NIH library site which may have materials that could be useful [62.] Other states with large TB populations born outside the U.S. also have vetted materials that can be shared. The CDC and Southeastern TB Center of Excellence have excellent ethnographic cultural guides for several countries available that may be helpful.
https://www.cdc.gov/tb/publications/guidestoolkits/ethnographicguides/default.htm
https://sntc.medicine.ufl.edu/home/index#/products

Use of general non-certified computer-based programs for translated medical and educational materials is not recommended.

Communication and coordination of services between different health care providers, different states and even different countries may be required of the nurse case manager to ensure treatment completion and appropriate follow-up for both cases and high-priority contacts. Consultation and assistance can be provided by CTBCP staff.

Tuberculosis is an air-borne infectious disease; therefore, the responsibility of completing TB treatment does not rest with the patient ultimately, but with the provider and public health program as noted in the CDC statement below. The nurse case manager is critical in ensuring that this provider responsibility can be met through judicious implementation of a coordinated plan of care and patient support that ensures adherence to that plan.

Provider Responsibility

"Treatment of tuberculosis benefits both the community as a whole and the individual patient; thus, any public health program or private provider (or both in a defined arrangement by which management is shared), undertaking to treat a patient with tuberculosis, is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed." [7]

Table 1. Priorities for Local Health Department Resource Allocation

Activities are listed in descending priority order. Each succeeding activity should be undertaken only when all activities above it on the list are fully implemented. Local programs unable to effectively handle major priorities should consult with CTBCP.

Priority 1: Tuberculosis (TB) Treatment

a. AFB smear-positive pulmonary TB confirmed and clinically suspected cases.
b. All children < 5 years of age regardless of AFB smear status.
c. All other pulmonary TB confirmed and clinically suspected cases.
d. All other confirmed and clinically suspected TB cases.

Priority 2: Contact Investigations and Follow-Up

a. Contact investigations in order of priority:
    1. AFB smear-positive, culture-positive pulmonary cases.
    2. AFB smear-negative, culture-positive pulmonary cases.
    3. Source case investigations for all children < 5 years of age regardless of smear-status or site of disease.
    4. All other cases as appropriate and as resources permit.
b. Treatment of contacts:
    1. HIV-infected and other immune compromised contacts.
    2. Contacts age < 5 years.
    3. All other high-risk contacts with positive TST/IGRA (*Table 2, page 12).*

Priority 3: Treatment of Other Individuals with Latent TB Infection

a. HIV infected and other immune compromised individuals.
b. Injection drug users.
c. Non-US-born individuals from TB endemic countries.
d. Other high-risk persons (*Table 2, page 12*).

Priority 4: Targeted Testing

Testing should be targeted toward high-risk population groups and should only be performed when priorities 1-3 can be handled effectively and timely within the local program, there is local capacity for medical evaluation of all positive tests, and completion of treatment for latent infection is likely to occur.

Testing of individuals at low-risk for TB infection based on risk assessment screening is not recommended and local health departments should make efforts to eliminate this activity.

USPSTF Recommendations for Health Care Providers on Screening for Latent TB Infection

In September 2016 the U.S. Preventive Services Task Force issued new recommendations for health care providers stating that providers should screen all individuals 18 years of age and older for TB and test those found to be at risk. *U.S. Preventive Service Task Force Latent Tuberculosis Infection: Screening Recommendations. September 2016* [(6)]
https://jamanetwork.com/journals/jama/fullarticle/2547762

These are grade B recommendations and screening results leading to positive PPD or IGRA tests should be followed up with an appropriate treatment regimen for latent TB infection once active disease has been ruled out.

Directly Observed Therapy (DOT)

DOT is the *observation* by a trained health care worker of every dose of medication taken by the patient. All patients with TB disease in Maryland are required to be on DOT as defined in COMAR regulations 10.06.01.20 (5). "*A health care provider shall place individuals with tuberculosis and clinically suspected tuberculosis on a tuberculosis treatment regimen that is in accordance with current national and State standards of care, and that provides for direct observation by a trained health care worker of ingestion of each dose of medication"* [(37)].

Research has shown that widespread use of DOT results in a significant reduction in TB case rates compared to similar jurisdictions not using DOT [(8)]. It is well documented that roughly a third of all patients under medical care for any reason fail to follow medical advice, that it is impossible to predict compliant behavior on the basis of age, sex, race, educational background or socioeconomic situation, and that education about a disease does not necessarily alter an individual's behavior.

DOT significantly increases TB treatment completion rates and reduces acquired drug resistance. It is now the standard for TB treatment throughout the world. Considering that compliance with treatment cannot be predicted across populations or population sub-groups, universal DOT is a non-discriminatory way to assure TB treatment completion.

Local health departments must determine their own policies and procedures as to who may perform DOT within their jurisdictions. A LHD worker who has a basic knowledge of TB and has received approved DOT training signed off by an authorized health department nurse is able to perform DOT. An online DOT training program can be found on the Curry International Tuberculosis Center of Excellence website containing a trainer's guide, participant workbook, slides and references that can be used to develop individualized training options for LHD TB Control programs. http://www.currytbcenter.ucsf.edu/products/directly-observed-therapy-training-curriculum-tb-control-programs

DOT is labor intensive, but far less costly than treatment failure which can result in ongoing transmission, acquired drug-resistance or even death. LHD programs should explore options within the local community for providing DOT when appropriate. TB programs across the country have successfully utilized school health programs, dialysis centers, substance abuse treatment centers, emergency/medical service providers, pharmacists, and others to assist with DOT provision.

Video DOT (VDOT)

Video DOT (VDOT) guidance is available from the CTBCP and summarized in *Appendix G. Video/ Electronic Directly Observed Therapy (VDOT).* LHD staff may utilize the guidance provided in *Appendix G* to develop local policies/protocols in which DOT can be observed via technology, such as a computer with a camera or a smart phone. This allows for greater flexibility in treating TB patients. VDOT may be considered for treatment of both TB infection and disease.

Case Reviews

Prospective **case reviews are conducted on all individual confirmed and clinically suspected TB cases during the intensive phase of treatment** to facilitate discussion that may improve case and contact investigation outcomes. Case reviews compliment the daily ongoing monitoring of NEDSS data and daily/weekly consultations with LHD TB Coordinators and case managers. Formal case review calls are held with CTBCP TB nurse and physician consultants and other LHD staff. LHD TB staff not presenting cases are encouraged to listen and participate in the reviews as an ongoing educational opportunity.

Case reviews are mandatory and conducted on all patients (confirmed and clinically suspected cases) started on treatment within the two months prior to the month of the review. A line list is sent to LHDs prior to the review with confirmed and clinically suspected cases that have been reported to CTBCP and are due for

review. Case managers should complete the case/cohort review forms and return to CTBCP. The Case/Cohort Review form can be found on the CTBCP website. https://phpa.health.maryland.gov/OIDPCS/CTBCP/pages/Forms.aspx

The secured fax number is 410-767-5972. LHD case managers should include any additional patients not on the original line list that are being treated as presumptive TB cases. Information submitted on the Case/Cohort Review forms, information in NEDSS and information obtained during routine communications with LHDs form the basis for selection of cases for discussion.

Cases of interest to the larger MD TB community or cases requested for presentation by a local program are selected for discussion by the CTBCP consulting staff and may be reviewed with respective LHD case managers in advance of the case review call.

Cases can be presented by either LHD or CTBCP staff and should include a *brief overview* of the case and associated contact investigation, followed by discussion focusing on identified issues of interest and/or concern. Nurses and clinicians from other programs are encouraged to ask questions, offer suggestions, and share expertise and lessons learned from handling similar cases as part of this review process. Recommendations made during the case reviews are documented and sent to the LHD presenting the case after the review.

Program Evaluation and Cohort Review

All Maryland LHD TB programs must participate in the program evaluation cohort review process. This process is based on CDC guidelines for cohort review that have been adapted for Maryland.

Cohort review is a standardized, *retrospective* review of the management of patients with TB disease and their contacts. A "cohort" is a group of TB cases counted over a specific period of time and may be drawn from one or multiple jurisdictions. Details of each case and associated contacts are evaluated according to specific standard outcomes as determined by the CDC National Tuberculosis Indicators Project (NTIP) which identified key TB prevention and control objectives and measures state performance outcomes against national targets. https://www.cdc.gov/tb/publications/factsheets/statistics/ntip.htm

Data are reviewed in a group setting, with information on individual cases usually presented by the respective case managers. Local physicians and outreach staff that provide DOT and/or assist with contact investigations are encouraged to participate. After presentation of the cases, a summary of the data as it relates to NTIP goals and objectives is discussed and provided to all participants. The cohort review process can increase individual staff accountability for patient treatment outcomes and contact investigations, and can also reveal program weaknesses that need correcting, e.g., clinic policies that impede patient ability to schedule appointments, or training and education needs of staff. These reviews also provide opportunities to discuss program strengths and best practices that should be shared with others.

Maryland jurisdictions have participated in the cohort review process since 2012. Data and comments from cohort reviews are summarized and reviewed periodically by the state TB Program Evaluation Team, comprised of TB Coordinators and/or representatives from across the state to include all jurisdictions. The evaluation team uses this information to assess overall TB program control and prevention efficacy and make recommendations for further study, changes in practice, education and training needs and additional resources needed.

LHDs should refer to the *Maryland Guidelines for Cohort Review* posted on the MDH website and/or contact the state CTBCP with questions regarding the statewide cohort review schedule and process.

Contact Investigations

Contact investigations are an integral part of any TB program and are conducted to evaluate individuals who may have been exposed to an infectious TB case. A contact investigation shall be initiated on all pulmonary TB cases. (*Table 1, page 5*). Contact investigations are also strongly recommended for household members of extrapulmonary cases from high-incidence countries listed in *Appendix B*. Consult with CTBCP if unsure whether a contact investigation is warranted. Goals of a contact investigation include a) ensuring there are no more active cases of TB as a result of the index case, b) finding source cases, and c) evaluating and treating infected contacts to prevent future disease and transmission.

The contact investigation initiated as a result of a TB diagnosis in a child, if there is no identified source of infection, is referred to as a "source case" investigation. TB in children ≤ 4 years of age and LTBI in children ≤ 2 years of age indicates recent transmission which implies a "source case" exists who transmitted TB to the child and possibly others. If there is no known exposure to an infectious TB case, a source case investigation may help find the person with undiagnosed TB disease who had contact with the child and is potentially continuing to infect others. Source case investigations may occur as part of larger contact investigations.

The jurisdiction that counts a TB case is also responsible for the associated contact investigation. Often during a contact investigation, contacts, or sites of possible TB transmission in other jurisdictions, such as work sites, are identified. The jurisdiction responsible for the TB case is also responsible for notifying the appropriate LHDs if contacts are identified in other jurisdictions. The jurisdiction counting the index case is also responsible for collecting and reporting all data obtained during the contact investigation to the CTBCP, including data from other jurisdictions. Contact investigation data reported to CTBCP is summarized and reported to CDC in *Aggregate Report of Program Evaluation* (ARPE) summaries.

Identification and testing of contacts at any site as part of the contact investigation is the responsibility of the LHD in the jurisdiction where the site is located. There are situations where some steps of the contact investigation can be designated to entities outside of the LHD but it is the responsibility of the health department to collect and report the data. In these situations, the outside entity should report contact investigation outcomes to the health department. The LHD located within the jurisdiction of the TB case residence is responsible for reporting of ***all*** contact investigation data to the CTBCP. LHDs are encouraged to discuss cross-jurisdictional contact investigations with each other and with CTBCP so that appropriate coordination of effort and communication with various authorities occurs. CTBCP must be notified of contact investigations that involve out- of- state or out- of- country investigations. Some contact investigations (workplaces, schools, etc.) require careful planning, can be very resource intensive, and may generate media attention. LHDs are asked to inform CTBCP staff well in advance of any planned large contact investigation prior to its initiation.

Interjurisdictional Referrals

LHDs can work directly with other local health departments to assure appropriate treatment continues when the patient moves to another jurisdiction. If a patient moves to another jurisdiction within the state, please notify the respective CTBCP nurse consultant that a change of residence has occurred. If a patient changes permanent residence to another state or to the District of Columbia, a copy of the interjurisdictional form should be faxed to CTBCP indicating that a referral has taken place. When a patient moves outside of Maryland or the U.S. all interjurisdictional referrals must go through the CTBCP.

For transfer within the U.S. a fillable pdf Interjurisdictional form can be found on the NTCA website at http://www.tbcontrollers.org/docs/resources/IJN_Form_May2015.pdf

Standard forms used to report international interjurisdictional referrals to CTBCP are available on the CDC website. https://www.cdc.gov/tb/programs/international/default.htm

CTBCP can assist with international referrals to programs, such as CureTB and Migrant Clinicians Network (MCN), that can facilitate and support continuity of care for transitory TB patients. Details about MCN can be found at http://www.migrantclinician.org/services/network/tbnet.html

Cure TB, in collaboration with the CDC's Division of Global Migration and Quarantine and the County of San Diego's TB Control Program, helps to connect TB patients to healthcare services as they move between the United States and other countries. https://www.cdc.gov/usmexicohealth/curetb.html

When a TB patient moves to another jurisdiction, either within the state or to another state, it is the responsibility of the jurisdiction in which the patient was diagnosed (the "counting" jurisdiction) to obtain all information necessary to complete all required variables and sections of the RVCT, including treatment completion data. CTBCP will assist with obtaining information from other states if assistance is needed and other countries to the extent that information is available.

Airline Contacts

Three large international airports are located in the central Maryland, northern Virginia, and District of Columbia metropolitan region; one (Dulles International) a designated CDC Division of Global Migration and Quarantine (DGMQ) site. Reports of airline contacts are received from DGMQ through the CDC national Epi-X notification system.

When CTBCP/LHD receives notice that Maryland residents traveled on a flight in a seat near a person who was subsequently diagnosed with TB disease, it is the responsibility of the LHD to locate, evaluate and treat those contacts and to provide any follow-up information to CTBCP, including patients who cannot be located. This information is then forwarded to DGMQ. If it is discovered that a TB case in Maryland traveled by plane during the infectious period, it is the responsibility of the LHD to contact CTBCP, so the appropriate information can be forwarded to DGMQ. Questions about airline investigations should be referred to CTBCP.

Travel Restrictions

LHDs must notify CTBCP if a TB patient has intentions of traveling while still infectious. If the LHD believes the individual will be noncompliant with recommendations against travel, CTBCP can request DGMQ to issue a "do not board" order and the infectious patient will not be issued a boarding pass and therefore not allowed on the plane even if they have already purchased tickets for a flight.

Should a LHD believe a "do not board" order is warranted, representatives of the LHD TB program and administration will be asked to participate in a conference call with CTBCP, the state medical epidemiologist and DGMQ. The case manager should be prepared to provide identifying demographic, clinical and possible travel/ticket information on the patient and state the reasons to justify the request. If the decision to issue a "do not board order" is reached, DGMQ is responsible for notifying the airlines and other government agencies, as appropriate. The LHD assumes responsibility for notifying the patient that such an action has been taken. CTBCP assumes the responsibility for notifying DGMQ when a patient is considered safe to resume air travel based on LHD consultation and recommendations.

On rare occasions a clinically suspected or known infectious TB patient may travel significant distances within the U.S. via bus, train, ship, or car. LHDs should notify CTBCP of such patients and should be prepared to conference with the state medical epidemiologist, CDC, and possibly other agencies/jurisdictions regarding any perceived exposure risk to others and any appropriate actions required specific to

a) identifying and evaluating contacts already exposed and b) the appropriateness of the individual continuing further travel.

Surveillance

CTBCP provides real time surveillance data to CDC which is used to monitor the achievement of goals as defined by NTIP (National TB Indicators Project). Additional information on genotyping and contact investigation is also provided to CDC. These reports include incidence rates for specific populations and achievement of goals related to case management of patients and contact investigations as defined, measured and reported via NTIP (National TB Indicators Project).

All LHD TB programs are responsible for completion of the RVCT form and entry of local data into NEDSS (National Electronic Data Surveillance System) for *all confirmed and clinically suspected TB cases initiating treatment* in their respective jurisdictions (*Reporting TB Suspects in NEDSS, internal communication, June 2016*) This data serves as the basis for all CDC national TB surveillance reporting, program evaluations and national TB funding formula applications.

It is ***extremely*** important that NEDSS data, both new cases and updates to existing cases, be entered accurately and timely. The data is used to track state and local progress toward achieving national TB program objectives and is also used to determine funding allocations from the CDC. NEDSS TB data is downloaded by the CDC into the national TB NTIP (National Tuberculosis Indicators Project) database. NTIP is a monitoring system for tracking the progress of states, CDC-designated "big" cities, and local jurisdictions toward achieving standard national TB program objectives.

Program objectives and performance targets are also set by the state to align with or compliment the national targets. NTIP provides reports to state and some local TB programs which help prioritize prevention and control activities, as well as direct program evaluation efforts. Currently LHDs within Maryland with average annual case counts of ≥ 15 can access NTIP directly with authorization from CTBCP. LHDs with smaller annual case counts may request similar data from CTBCP if they wish to compare local data with national outcomes.

Contact investigation data is collected and submitted to CTBCP on all respiratory cases of TB using the state *Contact Investigation Summary* form sent quarterly to each LHD for initiation and follow-up. LHDs are responsible to keep accurate data on every contact investigation, complete all required forms, and return them to CTBCP by the date requested. These data are summarized and submitted to CDC in aggregate as part of the national evaluation of Maryland's overall TB prevention and control efforts. Contact investigation objectives are also included as part of NTIP evaluations. Training on entering TB surveillance data into the NEDSS system is available through CTBCP and MDH.

TB Research

Maryland is one of multiple sites (10) nationwide comprising the TB Epidemiologic Studies Consortium (TBESC), designed to conduct research that will lead to improvements in TB prevention and control activities within the United States. The Maryland MDH CTBCP has formal relationships with both the Johns Hopkins University (JHU), the University of Maryland (UMD) and CDC as part of this consortium. Past consortium studies in Maryland have been related to contact investigations, latent TB infection, new diagnostics, TB among non-U.S.-born populations and diagnosis delays. The 2011-2021 TBESC is focused largely on quicker and better diagnosis and treatment of latent TB infection, as well as risk factors that lead to development of disease once infected.

All TBESC studies receive Internal Review Board (IRB) approval through CDC, MDH, JHU, UMD and in some cases, by LHD IRBs. Research activities are performed by TBESC staff, with the cooperation of LHD case managers and staff as necessary.
Research data and outcomes for posters, publications and any other uses must be defined and negotiated with consortium partners and

LHDs, as appropriate, prior to use.

LHDs are sometimes asked to participate in TB focused research activities originating from organizations outside TBESC or CTBCP, e.g. university schools of public health. The decision to participate is made by the LHD, but CTBCP requests notification of such participation as a general courtesy.

Partnering with Others

As changes to health care practice and policies continue to occur, it will become increasingly necessary for LHD TB programs to partner (formally or informally) with other health care providers and organizations to ensure patients receive the necessary care and adequate support they require to compete treatment. Such partnerships and collaborations are encouraged; however, all LHDs need to be cognizant of their own *non-transferable* legal responsibilities for TB prevention and control as codified in Maryland regulation (COMAR 10.06.01) and statute (Annotated Code of Maryland, Health-General §§ 18-324,325).

III. PATHOGENESIS OF TB

Tuberculosis (TB) is usually transmitted through an airborne route when an individual with active pulmonary or laryngeal TB coughs, sneezes, speaks or sings. Infection with TB usually (but not always) requires relatively prolonged contact with an infectious person in an enclosed space.

Approximately 5% of infected individuals develop active TB disease within the first 2 years after infection. Another 5% will develop disease later in life (*Figure 1*). The majority of those who become infected never develop active disease.

Latent TB infection (LTBI) is diagnosed by a positive tuberculin skin test (TST) or positive interferon-gamma release assay (IGRA) test, **PLUS** a negative chest radiograph (CXR).

Certain medical conditions increase the risk that TB infection will progress to disease *(Table 2*), e.g., diabetes (approximately 3 times greater) or HIV infection (more than 100 times greater). Individuals from countries where TB is endemic are more likely to have been exposed and infected. Individual risk may change over time.

Figure 1. Pathogenesis of TB in Untreated Immune-Competent Individuals Exposed to TB

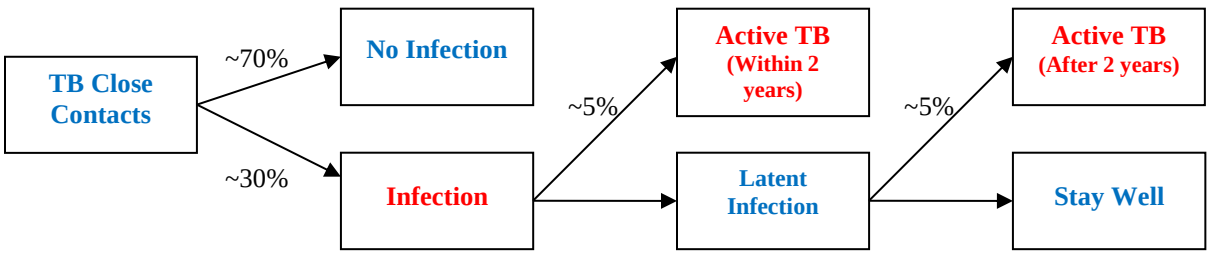


Table 2. TB Risk Factors

- Close contact to infectious TB case
- Foreign born from high-incidence countries (*Appendix B*)
- Injection and non-injection drug users
- Excessive alcohol users
- Residents/Employees of:
  - prisons and jails
  - long-term care facilities
  - hospitals/health care facilities
  - homeless shelters
- Mycobacteriology laboratory personnel
- Children exposed to adults at high risk for TB (e.g., HIV-infected adults)
- Persons living with HIV
- TST or IGRA convertors/recently infected
- Individuals with fibrotic changes on chest radiograph consistent with old-healed TB or history of inadequately treated TB
- Patients with certain clinical conditions:
  - organ transplant
  - immunosuppressed patients (equivalent to > 15 mg/day of prednisone for > 1 month)
  - Patients on immune-suppressive drugs such as tumor necrosis-alpha (TNF-ά) antagonists e.g., infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®)
  - silicosis
  - diabetes mellitus
  - chronic renal failure
  - certain hematologic disorders (leukemia, lymphomas)
  - carcinomas of the head and neck, or lung
  - underweight (> 10% under ideal body weight)
  - gastrectomy, jejunoileal bypass
- History of smoking

IV. TUBERCULOSIS TESTING

National tuberculosis (TB) guidelines emphasize targeted testing of high-risk populations who would benefit from treatment of latent TB infection (TLTBI) [6,10]. Tables 3 and 4 *(pages 17-18)* outline priority risk groups for targeted testing and the recommended testing frequency for these groups. Targeted testing programs should be developed utilizing available local surveillance and population data to identify local populations at high risk for TB.

Targeted testing programs for LTBI should be implemented only when the following criteria can be met: a) the individual or group can be successfully tested b) those with positive tests can be medically evaluated, and c) completion of a full course of treatment is feasible.

In general, "A decision to test is a decision to treat." High risk individuals are candidates for treatment regardless of age. The use of age cut-points to determine eligibility for treatment for LTBI is no longer recommended.

Testing of low-risk populations is generally ***not*** recommended. A substantial proportion of TST (tuberculin skin test) or IGRA (interferon-gamma release assay)-positive persons from low-risk populations with no other identified risk factors will have false-positive tests. The estimated true prevalence of TB in the general population is ~ 5% overall, an estimate that has not changed significantly over the past two decades.[11,12] Testing of groups or individuals without a known or likely exposure to TB is not recommended.

The primary reason to test a low-risk person should be to establish a baseline prior to employment or residence in a high-risk setting (e.g., corrections or certain health care settings) or as the result of a risk assessment placing an individual at high-risk. Testing is discouraged unless a plan has been developed for medical evaluation of the TST or IGRA-positive persons and for treatment of latent TB infection (TLTBI). As a general rule, once a person has had a positive TST or IGRA test, the test is not

repeated. However, when verification of a prior positive test is needed, and no records are available, the TST or IGRA test can be repeated; the exception being a person with a history of a vesiculating or anaphylactic reaction to a previous TST. In such cases, one would verify TB infection status using an IGRA.

TB testing requirements differ from state to state and between local jurisdictions. In Maryland, local school boards, in collaboration with local health departments, determine TB testing requirements for the local school district. These requirements do vary depending on local TB epidemiology and may change over time.

Universal testing of school children is not recommended. Jurisdictions with large non-U.S. born populations are encouraged to consider using risk assessments to determine the need to test, and/or strategic testing of school children at specific intervals (e.g., school entry, high school, etc.). Consult with CTBCP as needed.

Administering and Reading TB Tests

Both the Mantoux TST and IGRA blood test are used to diagnose TB infection. IGRA is the *preferred* method for individuals who are not likely to return for TST reading and for those who have received Bacille Calmette-Guérin (BCG) who are over the age of one. IGRA tests can be used under the same circumstances as TST. **IGRAs should not be routinely used to confirm TST test results but may be used under some circumstances when confirmation of an individual's TB infection status is critical to diagnostic or treatment decisions.** The use of multiple puncture tests (such as the tine test) is not recommended.

Mantoux Tuberculin Skin Test (TST)

The Mantoux TST is subject to variability and should be administered and read by a trained health-care worker. For information about the ***Maryland Tuberculin Skin Test Training Program***, call 410-767-6698 or visit https://phpa.health.maryland.gov/OIDPCS/CTBCP
The Mantoux TST is administered by injecting 0.1 ml (5 tuberculin units) of purified protein derivative (PPD) solution intradermally into the palm-side surface of the forearm. A tense white wheal ≥ 5 mm in diameter should appear. If not, the test should be repeated immediately at least 2 inches away from the first injection site. By convention, tests are generally placed on the left arm. Do not use band-aids. Instruct patient not to rub or scratch the site. Record manufacturer, lot number, expiration date of PPD solution used, date placed, and date results are read.

TSTs are read within 48-72 hours after administration, measuring the transverse diameter of the induration across the forearm. If greater than 72 hours have elapsed since placement the TST should be repeated, unless the individual has a positive reaction which is measurable up to 7 days after the TST was placed. Record all results in millimeters (mm) of induration (not erythema); record the absence of a reaction as "0 mm." Documenting TST results as "positive" or "negative" without numerical results is not acceptable.

Interpreting TST Reactions

Three cut-points for TST reaction size (≥ 5 mm, ≥ 10 mm, ≥ 15 mm) have been recommended for defining a positive reaction based on risk factors for TB infection. Tables 3, 4 and 5 *(pages 17 and 18*) delineate TST cut-points based upon risk factors and age. With the exception of young children, the cut-point for low-risk individuals (for whom testing is generally not recommended) is 15 mm.

Inaccurate results can occur because of inappropriate placement or reading of the TST or clinical characteristics of the person being tested. False-negative results can occur by injecting the PPD solution too deep, presence of over-whelming infection (including active TB disease), anergy, and recent (within one month) live virus vaccination. False-positive results can occur because of infection with mycobacteria other than *M. tuberculosis* and prior BCG vaccination.

Booster Phenomenon and Two-Step TST

Some individuals infected with *M. tuberculosis* may have an initial negative TST when tested many years after first being infected with TB. This initial skin test, however, may stimulate or "boost" the immune system's ability to react to the PPD solution, causing a positive reaction to

subsequent TSTs. The booster phenomenon can be induced more than a year after an initial test. Two-step testing is a technique used to help distinguish between "boosted" reactions and reactions due to new infection. It is recommended for individuals who will be subjected to repeat TSTs (e.g., health-care workers, correctional workers) and as a baseline test for residents in long term care facilities and those who will begin medication or treatment that can cause immunosuppression. After the initial two-step baseline test, all subsequent testing consists of one test only. Individuals who have had a documented (in millimeters) negative TST within the previous 12 months need only a single TST to complete the 2-step process.

Two-Step Procedure

If the initial TST reaction is negative, a second test should be placed 1 to 3 weeks later. If the second TST is also negative, the person is considered uninfected, and any subsequent positive TST would be considered new infection (skin test conversion). If, however, the second TST is positive, the person should be classified as infected (a TST reactor) and evaluated further.

Interferon-Gamma Release Assay (IGRA)

The Food and Drug Administration (FDA) has approved the use of two different IGRA tests QuantiFERON® - TB Gold Plus (QFT-Plus) (recently replacing QuantiFERON-TB Gold In-Tube® (QFT-G) and T-SPOT●TB® (T-SPOT) to aid in the diagnosis of latent TB infection (LTBI) and active TB disease. Both IGRA tests detect increases in interferon-gamma and can be used in all circumstances in which the TST is used; e.g., contact investigations, evaluation of non-U.S.-born individuals who have had BCG vaccination, and TB screening of health-care workers and others undergoing serial testing. Both IGRA tests are blood tests and LHD staff utilizing IGRA tests should be trained in the appropriate handling of the blood tubes required for the specific IGRA test being utilized. No second visit by the patient is required to read the test, and 2-step testing is not necessary.

IGRA tests are not affected by BCG vaccination and a positive IGRA in a BCG vaccinated person indicates TB infection.

IGRA testing in Maryland via QFT -Plus is currently available through most LHDs and the state MDH TB laboratory. The manufacturers of both IGRA tests may be able to assist LHDs with large scale contact investigations. Check with the Center for TB Control and Prevention for more information. Detailed information on the two FDA approved tests in the U.S. can be accessed at the respective company websites listed below.

QIAGEN (manufacturer of QFT-Plus)
https://www.qiagen.com/us/

T-SPOT®●TB
http://www.oxfordimmunotec.com/north-america/

Interpreting IGRA test results

QFT–Plus results are reported out as positive or negative. QFT-Plus results are reported out for two antigen containing tubes: TB1 (elicitation of CD4+ T-helper lymphocyte response) and TB2 (CD8 cytotoxic T-lymphocyte response). The results are reported as either positive or negative. *A positive result for either <u>one</u> of the tubes (TB1 or TB2) is considered a positive result for the test.* Both tubes do not have to be positive. An indeterminate result is considered invalid and the test should be repeated A "positive" QFT-Plus should be interpreted as "likely TB infection." *(9)*

At the MDH Laboratory, every positive QFT-Plus is repeated on the same blood sample to assist in verification of the final result. QFT-Plus is not a test intended to diagnose the presence or absence of other mycobacteria, nor should it be used to "confirm" TST results.

T-SPOT●TB measures the number of interferon-γ producing white blood cells within a specific range and is interpreted as positive, negative, borderline, or invalid based on the number of cells or "spots" counted. It is recommended the test be repeated for both borderline and invalid results. A fair number of

"borderline" patients will test positive on repeat testing.

In situations that require evidence of testing for TB infection (i.e., school entry) LHDs and health care facilities may accept documentation of a positive or negative commercial IGRA test or a TST as provided. There is no need to repeat testing simply because the test is different from the one routinely used in an organization or facility. It is important to remember there is NO "gold-standard" test for LTBI and individual patient risk should always be considered before any LTBI test is administered. Use of repeated testing to "confirm" IGRA or TST results is generally not recommended.

"Convertor" vs. "Reactor"

A TST or IGRA *reactor* is anyone who has a positive test for TB. A reactor is a high-priority candidate for treatment of LTBI if they have other TB risk factors.
For those with negative TST/IGRA results who undergo repeat testing (e.g., health care workers) an increase in reaction size of ≥ 10 mm for a TST or a negative to positive IGRA result within a period of two years should be considered a *conversion* indicative of recent infection with *M. tuberculosis*. When evaluating conversions, risk factors for TB should be considered, but all convertors are high-priority candidates for TLTBI, regardless of age[2].

Special Situations (Testing)

Children

Routine testing of children in the U.S. is NOT recommended. Guidelines for targeted testing of children are summarized in Table 4 *(page 18)*.
A "yes" answer to any of the following questions may be an indication for a TST/IGRA.

1) Has the child ever had contact with a known TB case?

2) Was the child or any current household member born in, or traveled to or resided ≥ 1 month in any country other than the United States, Canada, Australia, New Zealand, countries of western Europe, or Japan?

A list of countries where TB case rates are ≥ 15 cases/100,000 population (which CTBCP considers significant) can be found in *Appendix B*. TB incidence by country as determined by WHO may be found at https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&lan=%22EN%22&iso2=%22US%22or

3) Does the child have regular (e.g., daily, or at least 8 cumulative hours per week) contact with an adult at high-risk for TB (e.g., untreated HIV-infection, homelessness, recent incarceration, illicit drug use)?

4) Does the child have any immunosuppressive condition (current or planned)? This includes HIV infection, organ transplant recipient, treatment with a TNF-alpha antagonist medication (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥ 2 mg/kg/day, or ≥ 15 mg/day for ≥ 2 weeks) or any other immunosuppressive medication.

5) Has the child ever had raw milk or un - pasteurized cheese?

If TB testing is deemed appropriate secondary to travel, testing can take place 8-10 weeks after the child has returned to the U.S. and/or potential exposure risk has ended. If children are deemed to be at low-risk, *"not indicated"* can be recorded on health forms which require reporting of TB testing results, with a reference to this document if necessary.

Live-virus Vaccinations

Live-virus vaccinations (e.g., measles, mumps, rubella, varicella, Flu-Mist) can be administered simultaneously with a TST; however, if administered at different times, a TST should *not* be placed until at least four weeks after a live-virus vaccine has been administered. Until further research is performed, follow the same guidelines when using an IGRA to test for *M.tb.*

Pregnancy

Pregnancy is not a contraindication for a TST or IGRA test. No adverse effects on the fetus have ever been demonstrated following the use of PPD solution for TB testing. Pregnant women should be screened for risk factors and tested if risk factors for TB are present. Pregnancy alone is not considered a risk factor for acquiring TB infection or disease, although once infected with

TB stress and other factors secondary to the pregnancy may increase the risk of progression to active disease.

HIV Infection

When HIV infection is first identified, the patient should receive a TST or IGRA regardless of age. Both the TST or an approved IGRA test are appropriate for TB screening among individuals living with HIV in the United States. Using IGRAs to "confirm" TST results is generally not recommended in the United States as a routine practice. Retesting may be considered for HIV-positive individuals whose initial TST or IGRA is negative and whose immune function has subsequently improved in response to treatment, i.e., CD4+ cells/µl increase to >200 and the patient has other risks for TB. Annual testing is recommended for all HIV-positive individuals who have ongoing risk of TB exposure. Anergy testing for individuals living with HIV with negative TST results is no longer recommended.

Individuals Born Outside the US

The general TST cut-point for individuals born in or who have visited a high incidence country for ≥ 1 month is ≥ 10 mm, regardless of BCG history.

The "low-risk" cut-point of ≥ 15 mm should be used for individuals born in United States, Canada, Australia, New Zealand, countries of western Europe, or Japan and who have not visited a high incidence country for ≥ 1 month. If the individual has other TB risk factors which place them at higher TB risk (i.e., HIV infection or evidence of old healed TB on chest x-ray) then use the ≥ 5 mm cut-point.

Individuals with LTBI, who have emigrated from countries with high TB incidence are at high risk of developing TB disease during the first 5 years after arrival in the U.S., with the greatest risk during the first 2 years after arrival. However, in recent years 40% of non-U.S.-born TB cases in Maryland were in the country for 10 years or more before breaking down with active TB; many had histories of untreated LTBI, and many were elderly with likely declining immune systems. Students from high TB incidence countries are also at relatively high risk for developing active TB if infected and should be tested upon arrival and offered TLTBI if infected. Some immigrants (not all) and all refugees entering the U.S. are required to undergo a medical health examination, including evaluation for TB as part of the visa process.

Table 3. Adult Risk Groups for Targeted Testing and Treatment of LTBI with TST Cut Points or IGRA Positive Results and Recommended Testing Frequency

TST or IGRA Positive	*Risk Group*	*Testing Frequency*
TST ≥ 5 mm OR IGRA positive	**HIV infection** (human immunodeficiency virus)	At diagnosis/annually (if person has other risk factors for tuberculosis), with immune reconstitution (CD4+ > 200 cells/µl)
	Recent contacts of TB case patients	Baseline, and repeat if TST negative, 8-10 weeks after exposure ends. Two-step testing NOT required for IGRA if performed 8-10 weeks **after** end of exposure [49]
	Fibrotic changes on chest radiograph consistent with prior TB	At time of chest radiograph
	Radiographic or clinical findings suggesting TB	Immediately
	Immunosuppressed patients (organ transplants or those receiving equivalent of ≥ 15 mg/day of prednisone for 1 month or more)	Two-step TST testing prior to transplant or immunosuppressive therapy. Two-step testing NOT required for IGRA.
	Individuals taking anti-TNF-alpha inhibiters	Two-step TST testing prior to starting treatment. Two-step testing NOT required if using IGRA.
TST ≥ 10 mm OR IGRA positive	**Non-US-born individuals (**within the last 5 years) from high-incidence countries *(Appendix B).*	Upon arrival,< 5 years are highest priority.
	Injection drug users	Annually
	Residents of long- term care facilities and assisted living facilities	Two-step TST baseline upon admission only. Two-step testing NOT required for IGRA. No repeat testing necessary for re-admissions unless recently exposed or away > 12 months.
	Prison, jail, and detention center inmates	Test according to facility risk
	Homeless individuals / Migrant farm workers	Only test if it is likely that the person can complete a full course of TLTBI, person is a known TB contact, or is symptomatic for active TB; refer migrants to TB-NET or Cure-TB if travel is expected prior to treatment completion.
	Employees of: • prisons/ jails / homeless shelters • long-term care facilities • hospitals and other health-care facilities • residential facilities /rehabilitation centers	Two-step TST at baseline; thereafter test according the section **"**Recommendations for Screening, Testing and Treatment of Health Care Personnel" on Page 66. *(*Two-step testing NOT required for IGRA. For pre-employment testing of employees previously at low risk, use a ≥ 15 mm cut-point.
	Volunteers of long-term and other health care or day care facilities	Same as employees if spending 8 or more cumulative hours at facility per week.
	Mycobacteriology laboratory personnel	Two-step TST at baseline; then annually Two-step testing NOT required if using IGRA.
	Patients with the following: • silicosis • diabetes mellitus • chronic renal failure • some malignancies (e.g., leukemia, lymphomas, carcinoma of the head, neck, lung) • underweight (≥ 10% under ideal body weight) • gastrectomy and jejunoileal bypass	At diagnosis
TST ≥ 15 mm OR IGRA positive	**Low-risk adults; includes pre-employment screening if no other risk factors apply**	Not recommended unless needed for employment or some school programs requiring a clinical practicum in high-risk settings (e.g., nursing students)

Table 4. Pediatric Risk Groups for Targeted Testing and Treatment of LTBI with TST Cut-Points or IGRA Positive Results and Recommended Testing Frequency		
TST or IGRA Positive	***Risk Group***	***Testing Frequency***
TST ≥ 5 mm OR IGRA Positive	**Children living with HIV** or children who have other immunosuppressive conditions or are taking immune-modulating medications (equivalent of prednisone ≥ 2 mg/kg/day, or ≥ 15 mg/day for ≥ 2 weeks).	At diagnosis, annually if HIV-positive or if immune - compromised for other reasons and TB risk factors are present; with immune reconstitution (defined as CD4+ > 200 cells/µl)
	Contacts of patients with confirmed or clinically suspected TB	At baseline, and if TST or QFT is negative, repeat 8-10 weeks after exposure end.
	Radiographic or clinical findings suggesting TB	Immediately
	Age < 1 year	Not recommended unless risk factors present
TST ≥ 10 mm OR IGRA Positive	**Children** ≥ 6 months who were born in or traveled to or lived ≥ 1 month in high incidence country (defined in MD as ≥ 15 cases/ 100,000persons. (*Appendix B.)*	Additional testing based upon screening evaluation.
	Non US-born children from high incidence countries who do not have documented prior TST results in the U.S.	Upon school entry; periodic testing may be required depending on assessed risk. (LHDs should work with local school boards to determine policy).
	Children with the following medical conditions (e.g., diabetes mellitus, lymphoma, chronic renal failure, ≥ 10% below ideal body weight, leukemia and other malignancies)	At diagnosis; thereafter based on exposure risk
	Children ≥ 6 months of age **upon entry into the foster care system**	Prior to foster placement, perform risk assessment and test if indicated. Additional testing should be based on subsequent risk screening.
	Adoptees if no testing done within 6 months prior to arrival.	Upon entry into the U.S. Repeat at age 6 months if first test administered prior to 6 months of age
	Children consistently exposed to high-risk adults (regular contact [e.g., daily] with adults who are HIV infected, homeless, incarcerated, migrant farm workers or illicit drug users)	Test every 2-3 years
	Incarcerated adolescents	Test according to facility risk (*page 65*).
	Age 1-4 with no risk factors	Not recommended
TST ≥ 15 mm OR IGRA Positive	**Age ≥ 5 with no risk factors**	Not recommended

Table 5. TST Cut-Points by Age for Low-Risk Persons		
Adults		**15 mm**
Children	**Ages 5-18**	**15 mm**
	Ages 6 months – 4	**10 mm**

Bacille Calmette-Guérin (BCG) Vaccination

BCG is a vaccine used in many countries to protect children against severe forms of TB disease. However, its efficacy in preventing TB in adults is variable and controversial. IGRA tests for TB are not affected by BCG, but BCG vaccination can produce a false-positive reaction to the TST. Although BCG usually causes a TST < 5 mm there is no way to distinguish a positive reaction due to BCG vaccination from one due to TB infection. Sensitivity to TSTs in BCG-vaccinated individuals is highly variable and tends to wane over time.

BCG vaccination is not a contraindication for TST and any BCG-vaccinated person who is a recent arrival from a high incidence country *(Appendix B)* is high priority for testing. A positive TST (≥ 10 mm) in a BCG- vaccinated person originating from a high incidence country is considered indicative of TB infection. After active TB has been ruled out, the person should be evaluated and treated for LTBI. For BCG-vaccinated individuals from low incidence countries (e.g., Canada, England,) without other risk factors, a 15 mm cut-point should be used.

Immunosuppressive Treatment

TB disease is a potential adverse sequela of treatments that suppress the immune system in patients with latent TB infection. New treatments are being approved for autoimmune diseases (i.e. rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and plaque psoriasis). These drugs include the tumor necrosis factor-alpha (TNF-α) antagonists such as infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), or certolizumab pegol (Cimzia®) which work by blocking TNF-α, an anti-inflammatory cytokine. The Centers for Disease Control (CDC) has released recommendations for patients taking these drugs *(see adjoining box).*

Treatment with other immune suppressants such as T-cell co-stimulatory blockade agent batacept (Orencia®) has also resulted in opportunistic infections such as TB. All patients receiving immune suppressive treatment should be screened for risk factors for *M. tuberculosis* and tested for infection before initiating immunosuppressive therapy. If using a TST, two-step baseline testing is recommended with a ≥ 5 mm induration cut-point for TST positivity.

The evolution of new mediations to treat diseases affecting the immune system is an ongoing process and rapidly changing. LHDs are encouraged to work closely with prescribing physicians treating patients (adults and children) with immune modulating mediations and to consult with CTBCP when coordinating treatment for TB or LTBI.

Screening, Diagnosis and Treatment of LTBI And TB Disease in Patients Receiving TNF-α Antagonists

- Screen patients for risk factors for *M. tuberculosis* and test them for infection before initiating immunosuppressive therapies.
- If using TST, a two-step test is recommended.
- Exclude TB disease before starting treatment for LTBI.
- Start treatment for LTBI before commencing TNF-α blocking agents. Short course treatment regimens may be considered; consultation with CTBCP is recommended.
- Consider treatment for LTBI in patients who have negative TST results but whose epidemiologic and clinical circumstances suggest a probability of LTBI.
- Consider TB disease as a potential cause of febrile or respiratory illness in immunosuppressed patients, including those receiving TNF-α blocking agents.
- ***Consider postponing TNF-α antagonist therapy until the conclusion of treatment for LTBI or TB disease. Utilize short-course LTBI regimens if able. Consult with CTBCP.***

LTBI Reporting in Maryland

A diagnosis of latent TB infection (LTBI) is reportable in Maryland by regulation (effective July 1, 2018). For reporting purposes, a diagnosis of LTBI is defined as:

(a) A positive result on an Interferon-Gamma Release Assay, or Tuberculin Skin Test, or any other test indicating TB infection, *and*
(b) Confirmed or clinically suspected tuberculosis has been ruled out via laboratory and radiograph testing.

LTBI should be reported using the LTBI reporting form available on the CTBCP website or the MDH 1140 morbidity report form; both available on the MDH website.
https://phpa.health.maryland.gov/OIDPCS/CTBCP/pages/Home.aspx

https://phpa.health.maryland.gov/Documents/DHMH-1140_MorbidityReport.pdf

Individuals diagnosed with LTBI should be offered treatment to prevent active disease and further transmission of TB. Tables 3, 4 and 5 summarize adult and pediatric risk groups appropriate for testing for latent TB infection and standard cut-points used with TST *(pages 17 and 18)*. Table 6 *(page 26)* summarizes approved medication regimens for the treatment of LTBI in the United States.

V. TREATMENT OF LATENT TUBERCULOSIS INFECTION

Treatment of latent tuberculosis infection (TLTBI) will decrease the likelihood that an individual with latent TB infection (LTBI) will progress to TB disease. TLTBI should be targeted to individuals in high-risk groups regardless of patient age. Tables 3 and 4 *(pages 17-18)* outline the risk groups which should be targeted. The highest risk groups for progression to TB disease once infected are:

- High-priority contacts to sputum AFB smear-positive cases
- Individuals living with Human immunodeficiency virus (HIV)/TB
- Patients taking immunosuppressive drugs
- Tuberculin skin test (TST) or immune gamma release assay TB test (IGRA)-positive **Non-US-born individuals** in the U.S. < 5 years
- TST or IGRA positive children ≤ 4 years of age

TLTBI for a low-risk individual with a positive TST is generally not recommended. When an individual at low-risk for TB infection presents with a positive TST (≥ 15 mm), the person should be advised that because they are at low-risk for TB, their TST may be falsely positive. After active disease has been ruled out, the person should be given the option for TLTBI with an explanation of possible future risks for developing active TB and the risks and benefits associated with the treatment. Individuals who decline treatment as "low-risk" should be told that any changes in personal risk factors should be discussed with their physician and that TLTBI can occur at any time in the future as long as active TB continues to be ruled out.

Medical Evaluation for a Positive TST/IGRA

Individuals with a positive TST or IGRA should be examined by a provider to rule out TB disease and be evaluated for TLTBI. The evaluation consists of a TB symptom review, chest radiograph, HIV test, and evaluation of other medical conditions. An assessment should be made to determine the need for laboratory testing prior to starting or throughout TLTBI.

Chest Radiographs

Chest radiographs (CXR) are performed to rule out pulmonary TB disease. Children younger than 5 years old should undergo both a posterior-anterior (PA) and a lateral CXR. All others should initially receive a PA view. A CXR does not need to be repeated for asymptomatic individuals who received a CXR within 3 to 6 months if HIV-negative, or within one month prior to the TST/IGRA if HIV-positive, unless otherwise medically warranted. Repeat chest radiographs **for employment purposes** (e.g., annual), are not needed if documentation is available showing a previous negative CXR and there are no current symptoms that could be attributed to TB.

HIV Testing

HIV testing, regardless of age, is the standard of care for all confirmed and clinically suspected TB cases and is recommended for all contacts to cases.[7] A person with LTBI who is HIV infected is at high risk of developing active TB and high priority for TLTBI. HIV testing should be considered for all individuals who have LTBI, regardless of age.

Diabetes Screening and Testing

Diabetic screening is the standard of care for all confirmed and clinically suspected TB cases in Maryland and screening should be considered for all LTBI patients. A diabetic patient co-infected with LTBI is at high risk of developing active TB. Diabetic patients co-infected with TB are 3 times more likely to develop active disease than those who are not diabetic. Patients with a positive diabetic screening test should be referred for further medical evaluation. See Table *7 (page 33-34) Components of a Tuberculosis Diagnostic Work-Up* for further diabetic screening guidance.

Pregnancy

A CXR should be done with appropriate shielding immediately during the first trimester for pregnant women who:

- Have symptoms suggestive of TB disease,
- Are HIV-positive and are a contact to a TB case regardless of TST or IGRA results, or
- Are TST or IGRA-positive and are a close contact to a smear-positive or cavitary case.

A CXR is recommended for lower-risk TST or IGRA positive pregnant women after the first trimester, utilizing lead shielding.

Pregnancy/Post-Partum

In most pregnant women, TLTBI should be delayed until 2 to 3 months after delivery, even though no harmful effects of INH on the fetus have been documented. There are key exceptions to this general rule, however, and the following groups of pregnant women should be considered for TLTBI:

- **First trimester** for TST-positive (≥ 5 mm) or IGRA positive women who are HIV positive, have behavioral risk factors for HIV and refuse HIV testing, or who are close contacts to smear-positive, pulmonary TB cases (at physician discretion).
- **After the first trimester** if documented conversion within the past 2 years.

Delaying TLTBI for two to three months after delivery for all other pregnant women at high-risk for TB is acceptable. In general, TLTBI should be discontinued if a woman becomes pregnant while on treatment (unless the woman is HIV-infected, a close contact to a smear-positive case or has had a TST/IGRA conversion within 2 years).

Medication Regimens for TLTBI

There are three medication regimen options for TLTBI. Currently, the *preferred* regimens for most individuals are short course, ranging from 3-4 months. Decisions about which regimen to use should be based upon the likelihood that they will comply with a particular regimen and the possibility for medication interactions and/or side effects. See Table 6 *(page 26)* for a summary of approved regimens.

Medication Interactions

Rifamycin based regimens can affect the metabolism of many other mediations from multiple drug classes (e.g., contraceptives, some anti-retroviral drugs, and warfarin). Medication history and patient education are critical; consult with CTBCP physician staff.

Preferred LTBI Regimens:

- **Isoniazid (INH) and Rifapentine (RPT)** once weekly INH-RPT for 3 months (3HP)/12 weeks is a preferred regimen for individuals ≥ 2 years of age and those with HIV/AIDS on ART with no presumed or previously clinically significant reactions to Rifampin (RIF) or RPT.[19] Notify CTBCP if the patient has missed 2 consecutive doses (2 consecutive weeks) of treatment. This regimen may be administered via DOT or self-administered therapy (SAT).

- **Rifampin (RIF)** for 4 months (daily) (4R) is a preferred regimen for individuals who are not taking medications known to have interactions with RIF. RIF for four months is a preferred regimen for children and other individuals exposed to INH-resistant cases. DOT is recommended for children less than 5 years of age who were exposed to an infectious TB case.

Alternative LTBI Regimens:

- **Isoniazid (INH) and Rifampin (RIF)** for 3 months (daily) (3HR).

- **Isoniazid (INH)** for 6 months (daily) (6H).
- **Isoniazid (INH)** for 9 months (daily) (9H). This regimen is one that many people find difficult to complete.

A previously approved regimen for LTBI based on 2 months of RIF and pyrazinamide (PZA) is no longer recommended by the CDC due to several severe hepatotoxic reactions.

DOT is recommended for ALL children less than 5 years of age who were exposed to a TB case.

If a contact has an exposure to a confirmed multidrug resistant (MDR) or extensively drug resistant (XDR TB) case, consultation with a TB expert is required regarding preventive treatment.

Intermittent regimens are not recommended by CTBCP. If an intermittent regimen is used (e.g., thrice weekly), it should be provided using DOT. VDOT is acceptable to use for TLTBI.

Children

All CDC approved LTBI regimens may be used with children as of changes to recommendations made in 2018 and outlined in the American Academy of Pediatrics 2018 edition of the Red Book [(15)]. DOT is still recommended for children who are close contacts to infectious cases. School health programs are often able to assist with DOT for students. VDOT may be an acceptable DOT alternative for some children based on case manager assessment and parental consent. (*See Table 6 for LTBI treatment recommendations, page 26*).

Breast Feeding

Breast feeding should not be discouraged for HIV-negative women placed on INH; however, the low concentration of antituberculosis medications in breast milk should not be considered effective treatment for a nursing infant with TB disease or LTBI.

Supplementary pyridoxine (8 mg pyridoxine/100 mg INH) is recommended by CDC for breast feeding infants on INH or whose mothers are on INH. A regular vitamin supplement appropriate for the infant's age provides adequate pyridoxine and is preferred over the use of pyridoxine alone by Maryland TB expert panel physicians. Supplementary pyridoxine should not be given to infants in addition to a regular vitamin supplement without consulting a TB expert.

HIV Infection

Due to the frequent advances being made in antiretroviral (ART) therapy, consultation with a TB/HIV expert for patients living with HIV on TLTBI is strongly recommended.

HIV infection is the single greatest risk factor for development of TB disease if a person is infected. *A preferred regimen for TLTBI is 9 months of INH*, however, shorter regimens may be considered. Once weekly INH-RPT for 3 months can be used with some antiretroviral medications (e.g. efavirenz, raltegravir). RIF is contraindicated with many antiretroviral therapy regimens, but a 4-month course can be considered as an alternative regimen if there are no drug interactions. Additionally, if compatible with current ART therapy, rifabutin may be substituted for RIF in adults.

Renal Insufficiency/ End-Stage Renal Disease

TST or IGRA-positive patients with renal insufficiency or on renal dialysis are very high priority for treatment. INH can be administered daily or thrice (3x) weekly after dialysis. Often arrangements can be made with the dialysis center to administer the medication. Consult with CTBCP regarding any patient requiring hemodialysis or peritoneal dialysis.

Contacts to Active TB Cases

Contacts of patients with drug susceptible TB who have positive TST reactions (≥ 5 mm) or positive IGRA tests should be treated regardless of age. Some TST/IGRA-negative high-risk contacts should also be considered for treatment. See *page 60* for further information regarding the testing and treatment of contacts.

Patients with Fibrotic Lesions

TLTBI is recommended for some TST or IGRA-positive patients with CXR demonstrating

previous, healed TB and no history of treatment. Dense pulmonary nodules, with or without visible calcifications, and fibrotic lesions (usually with sharp margins) may contain slowly multiplying tubercle bacilli with substantial potential for future progression to TB disease. Once TB disease is ruled out (with a symptom review and sputum specimens for smear and culture), a preferred LTBI regimen (found on page 21) can be used for treatment.

Suspected TB Disease Ruled Out

Patients who begin multidrug therapy for confirmed and clinically suspected TB disease, but are subsequently determined to have LTBI (i.e., sputum cultures are negative and CXRs are stable), may be considered to have completed TLTBI if they have:

- Positive TST or IGRA,
- No evidence of active TB on CXR,
- No history of previous TB treatment, and
- At least 2 months of treatment with a regimen that included RIF and PZA with at least one other mediation.

A two-month regimen using *only* RIF and PZA should never be used for TLTBI.

Pyridoxine Supplements (Vitamin B_6)

Adults

Some adults should receive pyridoxine (vitamin B_6) supplements while on INH. Patients with the following conditions should take pyridoxine when taking INH:

- Presence of paresthesia
- Pregnancy
- Conditions where neuropathy is common
  - Diabetes
  - Malnourishment (>10% below ideal body weight)
  - Alcoholism
  - Cancer
  - Chronic liver disease
  - HIV infection

The dose should be 25 mg B_6 for each 300 mg of INH daily or 50 mg for twice or thrice weekly therapy, depending on the dosing schedule being utilized. Pregnant women should take 50 mg daily.

Children

Routine administration of pyridoxine is not recommended for children taking INH except for breast feeding infants, children and adolescents who have milk and meat deficient diets or nutritional deficiencies, including all symptomatic children infected with HIV and pregnant adolescents and women. For breast feeding infants the dose should be 8 mg pyridoxine/100mg INH. A regular vitamin supplement appropriate for the child's age that provides adequate pyridoxine is preferred over the use of pyridoxine alone. Supplemental pyridoxine should not be given to infants in addition to a regular vitamin supplement without consulting a TB expert.

Monitoring LTBI Treatment

Monthly in-person clinical evaluations (including monthly weight checks) should be conducted by a licensed clinician (MD, PA, NP, RN, LPN) for all patients on TLTBI. This includes a monthly review with patients about the symptoms and signs that can be associated with adverse effects of the drugs prescribed and the need for prompt cessation of treatment and clinical evaluation should any of the following occur:

- Unexplained anorexia
- Nausea with or without vomiting
- Dark urine
- Jaundice/Icterus
- Rash
- Persistent paresthesia of hands and feet
- Persistent fatigue
- Weakness
- Fever lasting 3 or more days
- Abdominal tenderness right upper quadrant
- Easy bruising or bleeding
- Malaise
- Arthralgias

To prevent severe hepatitis, instruct the patient to STOP taking ALL medications immediately and call their provider if any hepatitis symptoms occur.

Medication fact sheets for patients are available on the CDC website, in addition to a medication "tracker" which may be helpful to use with patients or parents/guardians of young children on the 12 dose 3 HP regimen which no longer requires the medication be given DOT. https://www.cdc.gov/tb/publications/pamphlets/12-doseregimen.htm

Laboratory Monitoring TLTBI

Baseline

Baseline laboratory monitoring is not routinely indicated for all patients at the start of TLTBI. Children under age 18 do not need baseline blood work unless risk factors for hepatitis or HIV infection are present. Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurement of serum aspartate aminotransferase (AST, formerly known as serum glutamic oxaloacetic transaminase [SGOT]) and/or alanine aminotransferase (ALT, formerly known as serum glutamate pyruvate transaminase [SGPT]) and bilirubin. Baseline testing is also indicated for the following patients:

- Patients living with HIV
- Pregnant women
- Women ≤ 3 months postpartum
- Patients with a history of alcohol abuse or injection drug use
- Patients who currently use alcohol regularly
- Others at risk for chronic liver disease.

Baseline liver function tests are no longer routinely indicated in patients over age 35. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are contraindications for TLTBI.

Ongoing/ Routine

During TLTBI, more frequent laboratory monitoring is indicated for patients whose baseline liver function tests are abnormal and for other patients at risk for hepatic disease. In addition, laboratory testing should be used to evaluate possible adverse effects that occur.

Withhold LTBI treatment if transaminase levels exceed 3 times normal in symptomatic patients or 5 times normal is asymptomatic patients with no risk factors for hepatic disease and notify the Center for TB Control and Prevention (CTBCP). Serious adverse events associated with TLTBI (hospitalization, permanent disability, or death) should be promptly reported to CTBCP, and the Food and Drug Administration's (FDA) MedWatch program by phone, 1-800-FDA-1088, fax 1-800-FDA-0178 or internet www.fda.gov/medwatch.

Managing Interruptions in LTBI Treatment

The Maryland TB Expert Panel recommends that interruptions in treatment due to either nonadherence or drug intolerance be handled as follows: If 50% or less of doses have been missed within the intended treatment period, add doses on to the end of treatment. If greater than 50% of doses have been missed, restart therapy. If treatment is interrupted for more than 2 months, the patient should be re-evaluated to rule out TB disease. For patients on 3HP CTBCP should be notified if ≥ 2 consecutive doses are missed.

Table 6 *(pages 26-28)* summarizes the different LTBI regimens approved for use by CDC with medical monitoring recommendations. ***The shortest course regimen that can be utilized to treat LTBI successfully is recommended.*** The use of 3 months of INH/RPT for both adults and children 2 years of age and older is now considered the regimen of choice if not contraindicated for other reasons. Reducing the pool of potential active cases by successfully treating the large numbers of individuals with LTBI is critical to the elimination of TB.

Providers are encouraged to contact their local health departments or CTBCP for consultation if they have questions. Please note that local health departments have different programs for LTBI referrals and treatment depending on local resources. Referrals for assessment and/or treatment of LTBI should be made *only after consultation* with the local health department in the jurisdiction in which the patient resides. Local TB programs do retain the responsibility for ensuring treatment of LTBI in high-risk contacts to cases and for immigrants/refugees with B-waiver status.

This space intentionally left blank.

Table 6. Regimens for Treatment of Latent TB Infection and Recommended Monitoring

Medication	Interval	Dose	Medical Monitoring	
Isoniazid and Rifapentine (3HP) for 3 months ***Patients should not be given or prescribed more than a one-month supply at a time***	Once weekly DOT or self-administered therapy (SAT) Ideally doses are taken the same day/time each week until treatment is complete. If doses must be rescheduled be sure there is at least 72 hours between doses **Notify CTBCP if patient misses ≥ 2 consecutive doses**	INH 15 mg/kg rounded up to the nearest 50 or 100 mg in patients >11 years (Max 900 mg) 25 mg/kg rounded to the nearest 50/100 mg in patients 2–11 years RPT dosing via weight range in kg (Max 900 mg) 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	**Pretreatment assessment:** • H/O previous TB treatment • H/O liver disease, injection drug use, alcohol abuse (if yes, obtain blood for LFTs) • HIV status (obtain HIV test if status unknown, if HIV positive obtain blood for LFTs) • Allergies • Pregnant or ≤ 3 mos. postpartum (if yes, obtain blood for LFTs, but generally hold treatment until >3 mos. postpartum *(see page 20)* • Current medications, both prescription (Rx) and over-the-counter (OTC). RIF and RPT have significant interactions with many drugs • Consider results of Diabetic Screening	**Monthly assessment**: • Symptoms of hepatitis (anorexia, nausea, vomiting, abdominal pain, dark urine, jaundice, scleral icterus, rash, fatigue) • Other side effects (fever, flu-like syndrome, CNS effects, thrombocytopenia, renal failure) • Paresthesia (if on INH, may need supplemental B_6) • Any new medications (prescribed or OTC) • Evaluate adherence to prescribed regimen • Obtain LFTs if baseline tests elevated, history or risk of hepatitis, pregnant or postpartum, or symptomatic for hepatitis • *The need for baseline blood work in children should be based on assessed need. Monitor adolescents as adults*
	Treatment Completion 12 doses administered *once per week* within a 16-week period; either directly observed therapy DOT or self-administered therapy (SAT)		Parents may administer to children if educated on the doses and the need to administer them via a set schedule. Parents should also be taught about symptoms of possible hepatitis and instructed to stop all medications and contact the health care provider immediately should they occur. Both medications can be crushed and mixed with small amounts of soft foods (pudding, ice cream, etc.) for young children. Tools such as medication logs for parents to record doses taken may be helpful. VDOT may be used. Monthly "in-person" monitoring is strongly recommended. https://www.cdc.gov/tb/publications/pamphlets/12-doseregimen.htm A 3 HP provider's guide developed by the clinician group of the National TB Controllers Association, 2018, is available at http://www.tbcontrollers.org/docs/resources/3hp/NTCA_Provider_Guidance_3HP_11918.pdf	

Table 6. Regimens for Treatment of Latent TB Infection and Recommended Monitoring *(continued)*

Medication	Interval	Dose	Medical Monitoring
Rifampin (RIF) 4 months ***Patients should not be given or prescribed more than a one-month supply at a time.*** In 2018 both CDC and the American Academy of Pediatrics (in the 2018 edition of its "Red Book") agreed that 4 months of RIF was adequate TLTBI for children.	Daily	**Adults** RIF 10mg/kg (Max.600 mg) **Children** RIF 15-20 mg/kg* (Max 600 mg)	Medical monitoring and monthly assessment same as for INH /RPT based on patient age and history. Rifabutin may be used as a substitute for RIF (5 mg/kg). Rifabutin is not recommended for children <2. For more information on interactions with antiretrovirals see: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm *This regimen is **not recommended*** for: - patients who are presumed infected with RIF-resistant TB **OR** - patients on ART with possible RIF interactions
	Treatment Completion 120 doses within six months		
Isoniazid (INH) and Rifampin (RIF) 3 months ***Patients should not be given or prescribed more than a one-month supply at a time.*** In 2018 both CDC and the American Academy of Pediatrics (in the 2018 edition of its "Red Book") agreed that 4 months of RIF was adequate TLTBI for children.	Daily	**Adults** INH 5 mg/kg (Max: 300 mg) RIF 10mg/kg (Max.600 mg) **Children** INH 10-20 mg/kg (Max 300 mg) RIF 15-20 mg/kg (Max 600 mg)	Medical monitoring and monthly assessment same as for INH/ RPT based on patient age and history.
	Treatment Completion 90 doses within six months		

Table 6. Regimens for Treatment of Latent TB Infection and Recommended Monitoring *(continued)*			
Medication	**Interval**	**Dose**	**Medical Monitoring**
Isoniazid (INH) for 9 months or 6 months ***Patients should not be given or prescribed more than a one-month supply at a time***	**9 months** Daily	**Adults** INH 5 mg/kg (Max: 300 mg) **Children** INH 10-20 mg/kg (Max 300 mg)	Medical monitoring and monthly assessment same as for INH/ RPT based on patient age and history. <u>*This regimen is **not recommended***</u> for: - patients who are presumed infected with INH-resistant TB. <u>*The 9-month regimen is considered more efficacious than the 6-month regimen and is preferred for:*</u> -Patients living with HV/AIDS on ART who are at risk for significant drug interactions with weekly RPT or daily RIF regimens.
	Twice Weekly *must be DOT*	**Adults** INH 15 mg/kg (Max. 900 mg) **Children** INH 20-40 mg/kg (Max 900 mg)	
	6 months Daily	INH 5 mg/kg (Max: 300 mg) **Children** INH 10-20 mg/kg (Max 300 mg)	
	Twice Weekly *must be DOT*	**Adults** INH 15 mg/kg (Max. 900 mg)	
	Treatment Completion **9- month regimen):** Daily = 270 doses within 12 months Twice weekly DOT = 76 doses within 12 months **6 -month regimen:** Daily = 180 doses within nine months Twice weekly DOT = 52 doses within nine months		

*The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers. [15]

VI. DIAGNOSIS OF TUBERCULOSIS DISEASE

Pulmonary

The symptoms of pulmonary tuberculosis (TB) include cough, chest pain and hemoptysis; the specific symptoms of extrapulmonary TB depend on the site of disease. Systemic symptoms of TB disease include fever, chills, night sweats, fatigue, loss of appetite and weight loss. Patients infected with human immunodeficiency virus (HIV) often have atypical symptomatic and radiographic presentation.

Components of a TB diagnostic work-up include a medical history, physical exam, interferon-gamma release assay (IGRA) TB test or tuberculin skin test (TST), chest x-ray (CXR) and bacteriology. If there is a history of a prior positive test or TB is culture confirmed at time of diagnosis, the TST or IGRA is not needed. Components of the diagnostic work-up are listed in Table 7 *(pages 33-34).*

HIV testing (regardless of age) should be considered the standard of care for all clinically suspected and/or confirmed TB cases and should be considered for high-risk contacts to cases.

Knowledge of HIV status is critical as a) the presentation of TB in persons living with HIV can differ from that in immunocompetent persons, b) TB treatment regimens are often adjusted depending on the CD4+ cell/µl counts, and c) antiretroviral medications are required to support successful TB treatment. Screening for diabetes is done because those diagnosed with both TB and diabetes are at much higher risk of treatment failure and death.

Delays in diagnosis of greater than 2 months after reporting TB symptoms to a health care provider is not uncommon in Maryland. These delays are often associated with diagnoses of community acquired pneumonia with serial prescriptions for antibiotics. In a patient with repeat respiratory infections whose CXR and/or clinical course is consistent with pulmonary TB, an appropriate diagnostic work-up (including submitting sputum specimens) should be done promptly, preferably before initiating antibiotics.

Extrapulmonary

In 2017 38% of Maryland TB cases (with or without pulmonary involvement) were extrapulmonary. Extrapulmonary TB should be considered in the differential diagnosis of persons at risk for TB with site specific and/or systemic symptoms. The diagnostic work-up is dependent on the suspected disease site and any evidence of necrotizing or caseating granuloma on a pathology report is presumed TB until proven otherwise. Co-existent pulmonary disease should always be ruled out in all cases of extrapulmonary disease. The more common forms of extrapulmonary TB include:

- **TB Meningitis.** Infants and children ≤ 4 years of age are very susceptible to this disease manifestation. Diagnostic work-up should include examination of the cerebrospinal fluid, especially if symptomatic.

- **Disseminated (miliary) TB.** Disseminated TB is suspected in the presence of miliary appearing infiltrates on CXR. In addition to sputum, urine and blood cultures may yield *M. tuberculosis.*

- **Lymphatic TB.** The diagnosis is established by culture of *M. tuberculosis* from lymph node biopsy or aspirate. Presumptive diagnosis is often made with demonstration of acid-fast bacilli (AFB) in tissue or pathologic evidence of caseating granuloma.

- **Skeletal TB.** (bones and joints). Skeletal TB most commonly occurs in the spine (Pott's disease) and in the weight-bearing joints. It is diagnosed by radiograph and/or Computed Tomography (CT) of the involved joint, followed by specimen collection and culture.

- **Pleural TB.** AFB stains are seldom positive and cultures only positive in 25% to 30% of cases following thoracentesis and specimen collection. A transthoracic needle pleural biopsy supports a diagnosis of pleural TB based upon demonstration of caseating granuloma on pathology report.

- **Abdominal TB.** Diagnosis occurs after other causes of severe pain are ruled out; *M. bovis* should be considered in individuals (and especially children) from households where unpasteurized milk products are consumed.

- **Ocular TB/ TB of Reproductive Organs.** Although not common in Maryland, cases have been diagnosed, usually after ruling out other more common diagnoses. TB of the eyes and reproductive organs is more common in other countries and TB should be considered as part of the differential diagnosis in high-risk individuals from TB endemic countries.

Chest X-ray Manifestations of TB

Typical radiographic features of pulmonary TB often described in radiology reports include:

- **Location:** apical and/or posterior segment of right upper lobe (RUL), anterior-posterior segment of left upper lobe (LUL) or superior segment of either lower lobe.
- **Infiltrate:** fibro-nodular, variable coalescence and cavitation.
- **Cavities:** thick, moderately irregular walls; air-fluid levels uncommon.
- **Volume:** progressive, often rapid loss of volume with the involved segment(s) or lobe(s).
- **Adenopathy:** hilar adenopathy is a common presentation in persons living with HIV and young children.

Persons living with HIV and other immunocompromised persons can present with non-descript CXRs and still have infectious pulmonary TB. A good reference on radiographic manifestations of TB is available at https://www.currytbcenter.ucsf.edu/products/view/radiographic-manifestations-tuberculosis-primer-clinicians-second-edition

Diagnostic Specimens / Laboratory Testing

Sputum

Individuals with suspected pulmonary TB should have at least 3 sputum specimens examined for AFB smear and culture. Specimens should be obtained at 8-24-hour intervals, with one specimen collected in the early morning. Sputum specimens should be clearly labeled with patient identifying information and the date and time collected. Sputum specimens must be refrigerated if stored overnight but should be shipped within 24 hours whenever possible. Collection containers for sputum submission to the MDH TB Laboratory may be obtained by calling the Outfit Department at (443) 681-3776.

Other laboratories may have different criteria for acceptable specimen containers and should be contacted before submission. At a minimum, sputum collection containers must be sterile and have a leak-proof screw cap lid. Take care to ensure any collection container is sealed tightly and correctly before submission, as leaking specimens are generally unacceptable for testing and will be rejected by the laboratory.

TB patients often do not have purulent sputum. Watery specimens after several deep coughs are acceptable. Sputum induction with hypertonic saline or bronchoscopy may be done to obtain specimens from an individual who cannot produce sputum when there is reasonable suspicion of TB disease.

Nebulized specimens should be obtained in a sputum induction booth or airborne infection isolation room with staff using appropriate respiratory protection. If a portable nebulizer is taken to a patient's home, it is preferable to collect the specimen outdoors. Specimens should be clearly labeled "induced sputum".

Tissue

Tissue specimens for the culture of *M. tuberculosis* should be placed in sterile saline and delivered promptly to the laboratory. Do NOT place in formalin or encase in paraffin. Consult with CTBCP or the Maryland Laboratory Administration if you have questions.

Gastric aspiration is occasionally used in young children to obtain specimens of swallowed bacilli when the susceptibility results of the source case are unknown. The procedure is uncomfortable, invasive and results are often inconclusive. It is recommended that this procedure be done in a hospital setting. Specimens should be obtained in the early morning. Seek consultation with a TB expert prior to obtaining gastric aspirates.

AFB Smear

Smear examination permits only a presumptive diagnosis of TB because the AFB (acid-fast bacilli) on the smear may be mycobacteria other than *M. tuberculosis*. Many patients with active TB disease have negative AFB smears. Positive AFB smears are often used as a proxy measure for infectiousness, but do not differentiate between live and dead organisms. TB treatment is often initiated prior to confirmatory culture results and should not be delayed if TB is suspected, even with negative AFB smears.

Nucleic Acid Amplification (NAA) Test

This is a test that can detect the presence of *M. tuberculosis* DNA or RNA in sputum within 24 hours from receipt of the specimen in the laboratory. The test should only be performed prior to initiation of TB treatment because it cannot distinguish between dead and live bacilli. It is licensed for use on AFB smear-positive and smear-negative respiratory specimens from untreated patients. Sensitivity for AFB smear-positive specimens is > 95% and as low as 50% for smear-negative specimens. Specificity for both is 98%.

At the MDH TB laboratory, the GeneXpert, (a nucleic acid amplification test) is routinely done on all initial pulmonary AFB smear-positive specimens. Because of the low sensitivity, GeneXpert tests are not routinely performed on AFB smear-negative specimens. The treating physician can request a GeneXpert test/retest on pulmonary AFB smear-negative patients.

1. Smear-negative specimens will only be tested if accompanied by a written request on the lab requisition form. It is helpful to call the laboratory to provide notification when requesting NAAT regardless of smear status but is not required.

2. A single NAAT will be performed per patient. A second NAAT may be considered for extrapulmonary patients to rule out pulmonary TB; additional NAATs will require CTBCP approval.

3. If a NAAT was performed on a smear-negative specimen, a second test will be performed automatically if a subsequent specimen yields a positive smear result.

GeneXpert testing is not licensed for diagnostic use on extrapulmonary specimens. When submitting a tissue specimen for GeneXpert testing, mark the box for NAA in the Mycobacteriology section of the Infectious Agents requisition form. Tissue specimens that are fixed in formalin or paraffin are NOT accepted for testing but may be referred to the Infectious Disease Pathology Branch of the CDC for identification and drug resistance testing. These specimens should be submitted through the MDH TB Laboratory and require approval from the CDC based on clinical information and patient history indicating Mycobacterial disease. The MDH TB Laboratory can also assist in facilitating the delivery of extrapulmonary specimens to a reference laboratory for NAA testing when necessary. For further information, contact the MDH TB Laboratory at (443) 681-3944.

AFB Culture

Cultures should be obtained for all specimens, regardless of AFB smear results. Liquid media methods generally yield positive AFB culture results in 8 to 21 days and should be considered the standard of practice for processing suspected TB specimens. AFB culture requires at least 6 weeks of incubation to yield a negative result.

AFB Culture Identification

Once an AFB culture grows it is necessary to identify the organism. This is generally done using nucleic acid probes, high performance liquid chromatography (HPLC) (2-8 hours), or DNA sequencing. Anytime a laboratory report indicates "Positive AFB Culture", further testing is necessary to identify which acid-fast organism is growing.

Treatment for tuberculosis should be initiated based on clinical signs and symptoms while awaiting culture results. A report of "*M. tuberculosis* complex" (MTBC) indicates the presence of one of several organisms (*M. tuberculosis, M. canetti, M. africanum, M. microti, M. bovis, M. mungi, M. suricattae, M. pinnipedii, M. caprae*, and *M. orygis*). If a laboratory report states "*M. tuberculosis* complex" it should be assumed that the patient has tuberculosis and the patient should be treated accordingly.

Further biochemical testing can be performed on initial *M. tuberculosis* complex isolates to determine a final identification when speciation is deemed necessary. A final report will identify the isolate as *M. tuberculosis* or another organism as appropriate. A final report of *M. tuberculosis* confirms the TB diagnosis.

Drug Susceptibility/Sensitivity Testing

Obtain drug susceptibilities on all initial *M. tuberculosis* culture-positive isolates. The MDH State laboratory automatically tests initial positive cultures for drug susceptibility. Some commercial laboratories require a separate physician request before doing susceptibilities. After receipt of a positive *M. tuberculosis* culture result from a private laboratory, contact the laboratory to assure that susceptibility testing is being done. If payment is an issue, have the cultures sent to MDH TB laboratory for testing.

It is critical to detect drug resistance as early as possible to ensure appropriate treatment. Drug susceptibility testing should be repeated on all positive cultures that have not converted to negative within the first two-three months of treatment. Therapeutic drug monitoring should be considered. Isolate sensitivity determines the frequency of repeat testing, and consultation with CTBCP or a TB expert is recommended. All initial isolates are tested for susceptibility to isoniazid, streptomycin, rifampin, ethambutol, and pyrazinamide. Testing for susceptibility to second-line drugs is performed only when drug resistance to initial first-line drugs is found or upon physician request.

Molecular Detection of Drug Resistance (MDDR)

CDC offers a service for the molecular detection of drug resistance (MDDR) to rapidly identify multidrug-resistant TB. This service utilizes DNA sequencing for detection of mutations most frequently associated with RIF and INH drug resistance. Additional testing is conducted to identify mutations associated with resistance to the other second-line drugs; fluoroquinolones, amikacin, kanamycin, and capreomycin. MDDR does not take the place of conventional culture and drug susceptibility testing (DST) for TB. MDDR testing should be considered for INH resistant patients. Please consult with CTBCP.

Submission Criteria for MDDR

Isolates of MTBC and NAA positive processed sputum sediment specimens may be submitted by U.S. Public Health Laboratories for MDDR if one of the following criteria is met:

- By patient history, there is a high-risk of RIF resistance or MDR-TB (including those previously treated for TB, a contact of drug resistant TB, are non-U.S.-born from an area with high rates of MDR-TB).
- Known RIF resistance (by rapid test or by culture-based DST).
- Patients where the result of drug resistance will predictably have a high public health impact (e.g., daycare workers, nurses).
- Patient is known to have certain adverse reactions to critical antituberculosis drug (e.g., allergy to RIF).
- Mixed or non-viable cultures.
- Isolates which fail to grow in DST medium.
- Other situations considered on case by case basis, including certain INH-resistance patterns.

Standard of care testing (i.e., smear, culture, and DST) should be performed in the submitting laboratory when NAA (+) sputum sediments are submitted for MDDR testing. **The MDH TB Laboratory automatically refers any specimens for MDDR where GeneXpert testing indicates the presence of mutations associated with rifampin resistance.** Please contact the CTBCP or the state laboratory for additional instructions regarding the process for submitting diagnostic specimens for MDDR.

Genotyping

The main purpose of genotyping is to identify or confirm TB outbreaks and to detect unsuspected transmission between cases. If 2 or more cases have the same *M. tuberculosis* strain (“clustered”), transmission between the cases may have occurred if supported by local epidemiology (e.g., cases know each other or have been in the same place at the same time).

Genotyping of *M. tuberculosis* isolates from culture-positive patients has been used in Maryland since 1996. CDC provides genotyping on one isolate from each culture positive TB patient. Tests are PCR-based and include spoligotyping and MIRU-VNTR.

Maryland isolates are sent to a CDC reference laboratory in Michigan to perform whole genome sequencing. Whole genome sequencing (WGS) analyzes the entire TB genome compared to the current method which looks at only a small segment. WGS is being used to support outbreak detection and surveillance of drug resistance. For additional information see: https://www.cdc.gov/tb/programs/genotyping/default.htm (TB Genotyping)

https://www.cdc.gov/amd/project-summaries/tuberculosis-surveillance.html(TB WGS)

The MDH TB Laboratory sends all isolates for genotyping, including cultures performed at other laboratories. Private laboratories are required to submit one initial isolate from all Maryland TB patients to the MDH TB Laboratory. Results are maintained in a national database (TB-GIMS). When 3 or more cases are clustered CTBCP may contact the local health department and request a cluster investigation be done, which entails discussions with case managers, review of patient records, and sometimes re-interviewing patients to determine whether they were in the same place at the same time. LHD staff may also request genotyping results from CTBCP when they are concerned about possible transmission.

Genotyping can be used to determine whether a TB patient who has completed treatment and is re-diagnosed with active disease has relapsed with the same *M. tuberculosis* organism or has been newly infected with a different organism. Exogenous reinfection in low incidence countries like the U.S is rare.

Genotyping is also used to assess if laboratory contamination has occurred when a culture-positive patient's disease is not consistent with TB. This should be suspected when there is a negative AFB smear, a single positive culture, a low colony count on conventional media and a clinical presentation uncharacteristic of TB. Notify CTBCP immediately if laboratory contamination is suspected.

Table 7. Components of a Tuberculosis (TB) Diagnostic Work-Up

Medical History	TB History	History of extensive foreign travel, TB exposure, prior TST/IGRA results, prior TB infection or disease, risk factors for drug resistant TB (history of incomplete treatment, foreign birth, incarceration).
	Demographics	Country of origin, occupation, incarceration history and other factors that might increase the person's risk of TB.
	Medical conditions	Conditions which increase risk for developing TB if infected *(Table 2, TB Risk Factors, page 12)* or may affect ability to tolerate TB treatment.
	TB symptom history	Fever, weight loss, cough, hemoptysis, chest pain, night sweats.
Physical Exam	Cannot be used to confirm or rule out a TB diagnosis but can provide valuable information about the person's overall health status.	
TST/IGRA	Obtain if no documented history of prior testing. Tests can be negative in the presence of active TB disease or HIV infection. Not needed if disease already confirmed with a positive culture.	
CXR	Posterior/anterior (P/A) view initially, others as appropriate. Children should routinely have a lateral view in addition to a P/A.	

Table 7. Components of a Tuberculosis (TB) Diagnostic Work-Up (*continued)*	
HIV	Because HIV infection can impact TB diagnosis and treatment, HIV counseling and testing is the standard of care for the initial work-up for all clinically suspected of TB cases regardless of age. If HIV-positive, obtain CD4+ count and viral load.
Diabetes	Diabetes can significantly impact TB treatment outcomes. A blood glucose or glycemic control test (HgA1c) at the time of treatment initiation is the standard of care for the initial work-up for all persons suspected of TB. **Known diabetics:** Review HgA1c levels. If no recent HgA1c level is available obtain the test. If HgA1c > 7% pursue therapeutic drug monitoring 2-3 weeks after TB treatment initiation and refer for diabetic follow-up. **All Others:** Suspect diabetes if blood test results are: ≥ 126 mg/dl for a fasting blood glucose ≥ 200 mg/dl for a non-fasting or "casual" blood glucose HgA1c is ≥ 6.5% If HgA1c > 7% pursue therapeutic drug monitoring 2-3 weeks after TB treatment initiation and ensure appropriate referrals for diabetes evaluation and follow-up.
AFB Smears, NAA Tests, Cultures and Sensitivities	**Positive AFB smear:** indicates mycobacterial infection which may or may not be *M. tuberculosis*. **Nucleic Acid Amplification Test (NAA):** should be done for *M. tuberculosis*. on all AFB smear-positive sputum specimens, and treatment started if positive. MDDR testing should also be considered as indicated. Bacteriologic culture confirms the diagnosis of TB, but clinicians should not wait for culture results before initiating therapy if they suspect TB disease. (see data on abacillary TB in Maryland, page 34).
Histology	Pathology reports indicate caseating or necrotizing granuloma that are presumed to be TB unless proven otherwise.

Culture negative (abacillary) TB in Maryland
Between 20% and 25% (23% in 2014 and 2015) of Maryland TB cases had culture negative (abacillary) pulmonary TB. A negative culture for *M. tuberculosis* does ***not*** rule out a diagnosis of pulmonary TB. Patient with negative cultures but with abnormal CXRs and symptom histories compatible with TB should be treated presumptively. Individuals on antituberculosis treatment with CXR/symptom improvement and negative cultures are considered to have abacillary or culture negative TB and are counted as cases.

VII. TREATMENT OF TUBERCULOSIS DISEASE

General Principles

The goal of tuberculosis (TB) treatment is to interrupt transmission, prevent acquisition of drug resistance and cure the patient. The following general principles form the basis of TB treatment in Maryland.

- **Four antituberculosis medications must be included in the initial treatment regimen for all TB patients, regardless of culture or clinical status.** The purpose of a four-drug regimen is to prevent acquisition of drug resistance. Adjustments to the regimen can be made after drug susceptibility results are known.

- **Standard initial treatment consists of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) or RIPE** (rifampin, isoniazid, pyrazinamide, ethambutol)**.** The only routine exceptions to this standard regimen are infants and very young children who cannot perform visual acuity testing *(may* exclude EMB) and pregnant women (*may* exclude PZA),

- **Directly observed therapy (DOT) is the standard of care for treatment of TB disease worldwide and is codified into regulation in Maryland.** DOT is the direct *observation* by a trained health-care worker of every TB medication dose administered. DOT should be used with both pulmonary and extrapulmonary TB patients and is also recommended for high-risk contacts to infectious cases. DOT may be done in person or via an approved electronic device. *(see Appendix G)*

- **A single drug is never added to a failing regimen.** Doing so can lead to acquired drug resistance.

- **Patients are managed in the least restrictive manner possible.** An important programmatic goal is to identify strategies tailored to the individual patient which will lead to treatment adherence and avoid the need to invoke more restrictive measures to assure treatment completion.

Promoting Adherence to Treatment

Treatment adherence is promoted through comprehensive and consistent nurse case management which includes identification of barriers to treatment, working with the patient to eliminate barriers, DOT, referrals to appropriate sources of assistance if needed and the use of incentives and enablers. At the beginning of treatment, patients are asked to sign the Maryland Tuberculosis Patient/ Provider Agreement. This document advises patients of their legal responsibility to take medications and follow LHD directions regarding isolation, DOT, appointments, and testing. It also details the responsibilities of the LHD to the patient. It is available in multiple language translations at https://phpa.health.maryland.gov/OIDPCS/CTBCP/Pages/PatientProvider-Agreements.aspx

Failure of patients to comply with TB treatment plans can result in legal action secondary to the potential or actual risk they may pose to the health of the community. This form should be utilized for all TB patients, regardless of site of disease. Signed copies may be shared with private providers if a case is being co-managed with the LHD. Translations of the form in 20 languages are available on the CTBCP website.

Ultimately the responsibility for completion of treatment rests with the local health department (LHD), not the patient.

Nurse Case Management

This is an essential component of Maryland LHD TB control services. The nurse case manager, in conjunction with the clinician and other appropriate individuals, works with the patient and family to develop a treatment plan, identify barriers to treatment, and work with the patient/family to overcome them. Patient-centered case management is often key to treatment adherence and starts with the initial

visit made to the newly diagnosed TB case, both confirmed and clinically suspected.

This initial visit should take place within one business day of the LHD receiving notification of the diagnosis and frequently takes place in the hospital setting. This initial visit (although sometimes difficult to schedule) can be critical in the establishment of a relationship between the case manager and the patient that leads to successful treatment outcomes.

A recent publication on TB nurse case management from the Rutger's Global TB Center of Excellence covers basic TB case management responses to special situations (e.g., homelessness), and can be found at http://globaltb.njms.rutgers.edu/products/TB%20Nurse%20Case%20Management/Nurse%20Case%20Management%20Guide.pdf

Directly Observed Therapy (DOT)

DOT is the standard of TB care in Maryland and is written into the Maryland Code of Regulation (COMAR 10.06.01.20). All Maryland LHDs must provide DOT to confirmed and clinically suspected TB cases. DOT can be provided through co-management with private providers if the LHD is not the primary provider for the patient. All intermittent TB treatment (including for LTBI) MUST be administered DOT. LHDs are encouraged to explore alternate methods of DOT using electronic devices (e.g., mobile phones, computers with cameras, etc.) for high-risk clients for whom such devices could be utilized safely. LHDs are also encouraged to explore options that may be available such as school health, FQHCs and others to assist with DOT.

Video/Electronic Directly Observed Therapy

Video or electronic DOT (VDOT) is a strategy used to remotely observe patients taking their medications in their homes or other agreed upon locations. This observation may be done "live" or in "real-time" or may be done via approved "asynchronous" recorded interactions. VDOT is an additional tool for health department staff to utilize to enhance TB control and prevention efforts. Established CTBCP guidance for VDOT can be found in *Appendix G (Video/Electronic Directly Observed Therapy (DOT))* and on the CTBCP website. VDOT may also be referenced in the literature as mDOT (mobile DOT) or eDOT (electronic DOT) or by other abbreviations, all referring to some type of remote DOT.

Enablers and Incentives

The use of enablers and incentives *(Table 8)* can improve adherence to TB treatment and improve TB treatment completion rates. Enablers help the patient complete therapy. Incentives motivate the patient, generally tailored to individual patient wishes and need. CTBCP has, on occasion, limited funds to supplement LHD efforts to provide enablers and incentives. Requests are considered on a case-by-case basis and are always contingent on availability of funds. Exploration of local resources/programs that may be available to patients is encouraged.

Table 8. Examples of Enablers and Incentives

Enablers	Incentives
• Transportation vouchers/bus tokens • Convenient clinic location/hours • Bilingual staff (in appropriate languages) • Social service assistance • Housing or short-term rent assistance • Groceries • Short-term utility assistance	• Small toy (for a child) or book • Congratulations card/party at treatment milestone • Money • Gift card (local businesses, phone card) • Clothes, scarf, hat, gloves • Specific to patient (pet food, personal care items, special food)

CTBCP Patient Consultations

The following types of cases must be submitted for CTBCP Nurse Consultant/Medical review:

Upon Identification of the following using CTBCP consultation form:

- No culture conversion by 2 months.
- Reported INH or RIF resistance.
- Evidence of non-adherence.
- Evidence of delayed or missed TB diagnosis.
- Unusual presentation of TB with the exception of lymphadenitis or pleural TB. Examples include ocular, bone/joints, meningitis, peritoneal.
- Unusual response to treatment including unexplained fever, rash with fever and/or mucosal involvement, CBC abnormalities, uric acid abnormalities or symptoms of gout; AST or ALT three times (3x) the upper limit of normal or higher *with* associated symptoms, or five times (5x) the upper limit of normal or higher *without* symptoms.
- Signs of treatment failure.
- Initial drug regimen other than RIPE.

Weekly (CTBCP consultation form or secured e-mail to CTBCP nurse consultant):

- Patients housed at any state patient care facility, including Deer's Head and Western Maryland Medical Centers.
- Incarcerated patients who are suspected of having TB or have been diagnosed with TB.
- MDR-TB cases until documented culture conversion defined as 2 consecutive negative cultures obtained at least one month apart.
- Patients with either INH or RIF mono-resistant TB until deemed stable by CTBCP consultants.
- Patients with significant adverse drug reactions until deemed stable by CTBCP consultants.

Monthly (CTBCP consultation form or secured e-mail to Nurse Consultant):

- Children <5 years of age.
- RIF mono-resistant cases.
- MDR-TB cases once established on adequate regimen and clinically stable.
- Patients receiving non-standard treatment regimens.
- Patients living with HIV on ART.

Pertinent laboratory reports, prior and current radiographic images/reports and other clinical information are important and must be available at the time of any scheduled consultation session. Information and reports may be sent to CTBCP via secured e-mail/ fax or courier. Consultation forms and consultation time/location information can be found on the CTBCP website. https://phpa.health.maryland.gov/OIDPCS/CTBCP/pages/Home.aspx

Additional TB related consultations may be requested whenever nurse or physician TB recommendations are needed. LHD staff are invited to participate in the consultative process by phone if they desire. Arrangements can be made in advance for anyone who would like to attend an in-person consultation at the CTBCP. Medical consultations can also be made available outside the standard schedule for any unanticipated questions/concerns and are arranged through the CTBCP nurse consultant staff. Please call 410-767-6698 to schedule any consultation outside of the standard schedule.

It is recognized that the complexity of TB cases, especially those with co-morbidities, may necessitate multiple consultations with TB experts from several venues. It is important that LHD and CTBCP staff be informed of such consultations, recommendations made, and any actions taken. The treating LHD physician will email/notify CTBCP Nurse Consultant within 1

week for any consultation performed outside of CTBCP to include:

- Name of provider consulted,
- Recommendation(s) made by the consultant, and
- Actions taken.

CTBCP Physician Consultants will notify CTBCP Nurse Consultants by phone or e-mail of any *informal* consultation request from LHD staff or other provider (i.e., corrections, state medical center) and any recommendations made.

Case and Cohort Reviews

All TB cases are reviewed by the CTBCP nurse and physician consultant team at approximately 2 months into treatment (case reviews) and upon treatment completion (cohort reviews). LHDs are asked to participate in these formal reviews which comprise a major part of the MDH state TB program evaluation and quality monitoring efforts. Contact CTBCP for details regarding this process and schedules.

CDC Centers of Excellence

The former CDC Regional Training and Medical Consultation Centers (RTMCCs) are now referred to as Centers of Excellence with four regional sites providing medical and nursing education, educational materials, consultation services and training. For more information contact CTBCP or CDC at https://www.cdc.gov/tb/education/tb_coe/default.htm

Medical consultations provided by the Centers of Excellence consultants on Maryland cases are summarized and sent to CTBCP for reference.

Tuberculosis Treatment Regimens

In 2016 the American Thoracic Society (ATS), CDC and Infectious Disease Society of America (IDSA) jointly released a set of guidelines on the treatment of drug-susceptible TB which was endorsed by several other international and national organizations, including the U.S. National Tuberculosis Controllers Association (NTCA). Targeted to well-resourced countries, this document represents the first major comprehensive TB treatment guideline targeted to this specific audience in many years and is the basis for many of the following recommendations [(43)].
https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

Treatment of TB is focused on both curing the individual of his/her TB and minimizing transmission to others, thus protecting the community at large. Multiple antituberculosis antibiotics are used. Treatment is focused on achieving three core primary objectives;

- To rapidly reduce the TB bacillary population resulting in reduced disease severity and/or death and halting further transmission to others,
- To eradicate persisting bacilli resulting in durable cure after completion of treatment (prevent relapse), and
- To prevent acquisition of drug resistance during treatment. [(43)]

The standard treatment regimen for TB patients consists of two phases; a 2-month initiation or intensive phase and a 4-month continuation phase. To reduce the risk of relapse, extending the continuation phase of treatment an additional 3 months is recommended for individuals who have cavitation on initial chest x-ray *and* also remain culture positive at the completion of the intensive phase.

Recommended treatment regimens in Maryland are based on published guidelines and scientific studies and are periodically reviewed and updated by recognized TB experts within the state via TB Expert Panels convened for this purpose. Deviations from the MDH TB guidelines should be made only after consultation with CTBCP or a recognized TB expert clinician.

Regular consultation with CTBCP is required for any patient prescribed a medication regimen other than RIPE.

Intensive Phase

The standard intensive phase of treatment in the U.S. consists of INH, RIF, PZA and EMB until initial drug sensitivity results indicate there is no resistance to INH *or* RIF, at which time EMB may be dropped from the regimen. This 4-drug combination is frequently referred to as RIPE (**r**ifampin, **i**soniazid, **p**yrazinamide, **e**thambutol). Under most circumstances treatment should be initiated as soon as TB becomes a suspected diagnosis, which may be prior to completion of all confirmatory radiographic and laboratory testing.

Medications should be taken once daily 7 days per week throughout the intensive phase of treatment for a total of 56 doses over a period of 8 weeks DOT. Weekend, holiday, or travel doses are not "counted" toward completion of the intensive phase of treatment unless verified by some form of DOT or other CTBCP approved patient/provider arrangement for verifying that doses have been taken as prescribed. Any type of TB medication provided by the LHD for patient use must be done in accordance with Maryland Board of Nursing regulations.

While acknowledging that DOT 5 days/week dosing has been successfully used by many clinicians for years during the intensive phase, this regimen has not been compared directly with 7 days per week dosing in clinical trials. The 2016 CDC/ATS/ISDA recommendations do acknowledge the opinion of many TB clinical experts that dosing 5 days/week via DOT is an acceptable alternative to 7 days per week dosing and that both regimens meet the definition of "daily dosing" [(43)]. It is noted, however, that this assumption of "dosing equivalence" is becoming increasingly controversial.

Note: 7 day per week dosing

The 2017 Maryland TB Expert Panel felt strongly that based on both published and unpublished data currently available, every effort should be made to dose the patient 7 days per week throughout treatment.

CTBCP should be consulted regarding intensive phase regimens based on dosing schedules other than 7 days/week. *(Table 9, page 48).*

Continuation Phase

After completion of the intensive phase of TB treatment and confirmation of drug sensitivities, the regimen is changed to INH and RIF for a total of 126 doses administered daily over a period of 18 weeks DOT. Treatment should be extended in specific circumstances *(see Table 10, page 49)* and when DOT requirements cannot be met. Weekend and holiday/travel doses not taken DOT cannot be counted toward completion of the continuation phase of treatment unless an alternate arrangement for verifying the dosing has been approved in advance by CTBCP.

Rifapentine/INH during continuation phase:
A regimen comprised of once weekly INH and Rifapentine (RPT) previously approved for use during the continuation phase of treatment ***is no longer recommended and should not be used.*** This regimen has been associated with unacceptably high rates of disease relapse.

Follow-up Sputum Examination

Sputum smear status:
Sputum AFB smear status (positive or negative) is used as a proxy measure of a person's infectious status or ability to transmit TB to others. Negative AFB sputum smears are generally required to release an individual from isolation or allow a person to return to work or school.

Sputum specimens should be collected every 2 weeks once TB treatment has started until all 3 in one set are AFB smear-negative (a set is defined as 3 specimens obtained at least 8 hours apart to include one early morning specimen). Thereafter, specimens should be collected every 4 weeks until all 3 in a single set are culture-negative. Finally, collect one sputum specimen at the end of treatment. S*putum may be collected more frequently if smear status is critical to determine return to work, school, or to discontinue isolation.*

Sputum Culture Conversion:
Sputum culture conversion is considered the **initial collection date** (not the result date) of the *first consecutive series of negative sputa*. This specimen set must be obtained at **least seven (7) days after the last positive culture.**
For example, if one of the 3 specimens in a set is culture positive on days 48, 49 and/or 50 an additional 7 days must pass before collecting the next set of specimens starting on day 58. It is important that sputum specimens are obtained after the start of treatment and that sputum conversion is documented within 60 days of treatment initiation.

The 60-day conversion date is used to determine if an individual is progressing satisfactorily on the current treatment regimen or if other options need to be considered e.g., changes in the regimen and extension of treatment in the continuation phase beyond the planned 126 doses over 18 weeks. If an individual has not converted his/her culture and remains culture positive at 60 days therapeutic drug monitoring should be considered and CTBCP notified.

Medication Administration
General Principles
All medication doses for both children and adults should be calculated based upon weight *(Tables 11-12 page 50-55) (Appendix E)*. In general, use the lowest possible dose for an individual's weight and adjust doses if the weight changes. Although rare, for obese patients, dosing is generally based on ideal body weight to avoid toxicity. Consult with a TB expert as needed.

Count only observed doses toward treatment completion. If provided, weekend and/or holiday/travel doses are not counted toward the final dose count unless provided via some form of DOT. They should be documented as self-administered doses on the patient's medication record if not observed.

In general, doses should not be split over the course of a day. Administration of the medications at one time facilitates maximum peak serum concentration and assists with DOT scheduling. Bioavailability of most antituberculosis medications (except RPT) increases when given on an empty stomach, however, many patients cannot tolerate this, and for small children it is often not practical. Case managers must work with each individual patient to determine the best way medications can be taken and tolerated.

Intermittent dosing regimens must be approved by CTBCP. If CTBCP has approved the use of a thrice (3x) weekly dosing regimen there should be at least 48 hours between doses and all doses must be DOT. If doses are missed, they should be added on to the end of therapy.

In the rare event that medication is routinely self-administered (with explicit approval by the LHD and CTBCP), it *must* be administered daily and combination drugs e.g., Rifater (rifampin, isoniazid and pyrazinamide) or Rifamate (rifampin, isoniazid) should be considered to prevent acquired drug resistance due to self-selection of medications ingested.

Medication Interactions
Drug-drug interactions can result in changes in concentrations of one or both drugs involved. In the case of antituberculosis drugs, there are relatively few interactions that substantially change the concentrations of the antituberculosis drugs; much more often these medications cause clinically relevant changes in the concentrations of other drugs. Most interactions are associated with rifampin. Some of the more common interactions are described below and should be discussed with patients and other providers.

Methadone
Because of the interaction between RIF and methadone, TB patients on methadone will require up to a 50% increase in their methadone dose while on TB treatment to prevent and control withdrawal symptoms. In consultation with an addiction's treatment expert, increase the methadone dose by 5 mg every other day to a maximum of a 50% increase over the original dose. Careful monitoring is required.

Hormone-based Contraceptives

RIF reduces the contraceptive effect of hormone- based contraceptives such as pills, injections, or vaginal rings. When a TB patient is on hormonal contraceptives, she should be advised to use a barrier method while on TB treatment.

Antiretroviral Therapy (ART)

Anti-Retroviral Therapy (ART) is recommended for all patients living with HIV and TB. A consultation with CTBCP at the time of diagnosis should be performed to assist with ART decisions. Individuals with a low CD4 count and TB had a mortality benefit with early (2 weeks) ART initiation, but also had higher rates of immune reconstitution inflammatory syndrome (IRIS). In some instances, IRIS can have severe manifestations and unfavorable outcomes.

In general, for patients not currently on treatment for HIV, ART should be started within 2 weeks after TB treatment initiation in those with CD4 count <50 cells/mm^3, **except in the instance where TB meningitis is confirmed or suspected**. For patients with confirmed or suspected TB meningitis and a low CD4 count, ART initiation should be delayed to avoid severe adverse effects related to IRIS. In addition, the risks and benefits related to early ART initiation in patients with multi-organ involvement or other forms of disseminated TB should be discussed with CTBCP.

If the patient's CD4 count is >50 cells/mm^3, ART should be initiated within 8 weeks of starting anti-TB treatment. If a patient is currently on ART when diagnosed with TB, the ART regimen should be reviewed to assure no drug-drug interactions exist. Rifamycin-associated drug interactions must be considered, as ART frequently needs to be modified due to these interactions. Close collaboration between HIV and TB care providers/programs is required to assure appropriate monitoring, patient support and adherence services.

Other Medication Interactions

The rifamycins interact with several other classes of drugs, including anti-coagulants such as Coumadin, and can reduce blood levels of anticonvulsants, cardiovascular agents, bronchodilators, oral hypoglycemics, immunosuppressants (such as cyclosporine), antifungals and some psychotropic drugs. It is critical to monitor all medications and any over-the-counter and herbal supplements a patient might be taking. Patients should be asked monthly about any medicines they are taking in addition to the prescribed TB medications.

Laboratory Monitoring

Baseline liver function tests (LFTs) and a chemistry panel including creatinine, uric acid, and complete blood count (CBC) and platelets should be done for all adult patients at the start of treatment. Monthly LFTs should be done for those with:

- Abnormal baseline LFTs.
- Development of hepatitis symptoms.
- Excess alcohol use.
- Injection drug use.
- Documented Hepatitis B or C co-infection.
- HIV co-infection.
- Pregnancy or ≤ 3 months post-partum.

Children under age 18 do not routinely need baseline blood work; however, baseline and monthly LFTs should be considered for children with any of the conditions noted above and/or:

- Severe TB disease (especially meningitis or disseminated disease).
- Concurrent liver or biliary disease.
- Pregnancy or delivery within 6 weeks of diagnosis.
- Clinical evidence of hepatotoxicity or recent medical treatment for same.
- Concurrent use of other hepatotoxic drugs (e.g., anticonvulsant or HIV agents).

Therapeutic Drug Monitoring (TDM)

TDM should be strongly considered within 2-3 weeks of treatment initiation for any TB patient if one or more of the following conditions are present:

- HIV
- Diabetes

- Severe TB disease with cavitation and high bacillary load indicated on AFB smear
- Evidence of relapse or treatment failure
- Evidence of malnutrition or malabsorption (e.g., abnormally low BMI, abnormal serum albumin levels, previous diagnosis of Crohn's or another GI disease)
- "Slow Responder" (indicated by delayed clinical or microbiological response to treatment e.g., failure to convert cultures within 60 days)

If indicated, perform a 2-hour TDM test unless otherwise requested by a TB consultant. Established MDH Laboratory recommendations and guidelines for obtaining TDM specimens can be found in *Appendix F* and on the CTBCP website. **Consult with CTBCP or TB Expert regarding any TB medication dosage changes based on the results of TDM.**

6-hour TDM monitoring for TB patients can be used to help differentiate between malabsorption and slow absorption of medications. A 6-hour test is *not* recommended for initial TDM monitoring and should only be performed after consultation with a TB expert.

Monitoring Treatment of TB Disease

At minimum, monthly in-person clinical evaluations (including a monthly weight check) should be conducted with all patients being treated for TB disease. Patients should also receive a general assessment during DOT visits. At every encounter, patients should be assessed for hepatotoxicity and other medication side effects including:

- Unexplained anorexia
- Nausea or vomiting
- Dark urine
- Icterus
- Itching or rash
- Persistent paresthesia of hands or feet
- Persistent weakness or fatigue
- Fever lasting 3 or more days
- Abdominal tenderness
- Easy bruising or bleeding
- Arthralgias

Patients should be instructed at every visit to immediately report the occurrence of any of these symptoms. Table 14 *(page 56)* outlines monitoring of TB treatment with first-line antituberculosis drugs. Second-line drugs have the potential for multiple adverse reactions and toxicity. Consultation with CTBCP is recommended regarding second-line medication side effects.

Managing Adverse Reactions

Treatment with antituberculosis medications is associated with occurrence of adverse effects, ranging from mild to serious, requiring consultation with a TB Expert. Some of the more common adverse reactions are summarized in this section of the guidelines.

Gastrointestinal (GI)

GI symptoms are common, particularly during the first few weeks of therapy. If GI symptoms occur, medications should be stopped, and serum AST and bilirubin measured. If the AST is ≥ 3 times normal the symptoms may represent hepatic toxicity and the patient should be evaluated as described in the following section on hepatitis. If the AST is < 3 times normal, the symptoms are presumed not to be due to hepatotoxicity. The initial approach in this instance is to change the hour of medication administration and/or to administer the drugs with food.

Rash

Rash can be caused by all antituberculosis drugs. Treatment depends on the severity of the rash and the patient's coping response. A minor rash, affecting a limited area and predominantly manifested as itching can be treated with oral antihistamines for symptomatic relief while continuing all antituberculosis medications. For generalized rash, especially one associated with fever, all medications should be stopped immediately. Seek expert consultation and restart medications one at a time at intervals of 2 to 3 days (usually RIF first, then INH, followed by EMB and then PZA) to attempt to identify the offending drug. Petechial rashes can be due to RIF-related thrombocytopenia. Platelets should be checked and, if low, the RIF stopped.

Hepatitis
Three of the first-line drugs, INH, RIF, and PZA, can cause drug-induced liver injury. It is important to note that an asymptomatic increase in AST occurs in nearly 20% of patients treated with the standard four-drug regimen. If AST levels are ≥ 5 times the upper limits of normal (with or without symptoms) or ≥ 3 times normal in the presence of symptoms, stop all an antituberculosis medications and evaluate the patient for liver damage.

Assess for risk factors for viral hepatitis, and perform serologic testing for Hepatitis A, B and C, if indicated. Once liver enzymes return to normal (or near baseline level in patients with preexisting liver disease), drugs should be restarted one at a time (usually with RIF first, followed by INH and then PZA) at weekly intervals with close monitoring of symptoms and AST levels. Regularly check patients' sclera and nail beds for signs of jaundice. Patients should be educated on signs and symptoms of hepatotoxicity and instructed to contact the LHD immediately if they occur.

Serious adverse events associated with TB treatment (hospitalization, permanent disability, or death) must be promptly reported to CTBCP. In case of death, a copy of the death certificate and patient record will be requested for review. An excellent reference on side-effects and drug-resistant TB treatment can be found at https://www.currytbcenter.ucsf.edu/products/view/nursing-guide-managing-side-effects-drug-resistant-tb-treatment

Managing Interruptions in Treatment

When patients miss doses, either because of non-adherence or problems with adverse reactions, continuing or re-starting treatment depends upon the duration of the interruption, the patient's clinical presentation and the current bacteriological status of the patient. The following are general TB expert recommendations that may be considered. Consult with CTBCP to verify treatment restart/continuation plan and to determine remaining number of doses required for completion of treatment.

Restart treatment if:
- Interruption ≥ 14 days during the intensive phase of treatment, or
- Interruption ≥ 3 months in the continuation phase and the patient has received less than 80% of total doses prescribed.

Continue treatment if:
- Interruption < 14 days during the intensive phase of treatment, or
- Interruption < 3 months during the continuation phase and the patient has received at least 80% of total doses prescribed.

Consultation with a TB expert is recommended when significant interruptions in treatment occur. If treatment is interrupted for more than 2 months, the patient *must* be re-evaluated with CXR and sputum specimen collection for culture and drug susceptibility testing. Individuals who experience significant or repeated interruptions in treatment are at greater risk for relapse and treatment failure.

Drug Resistance or Intolerance

Consultation from a TB expert is recommended for all patients with drug resistance or drug intolerance. Regular consultation with CTBCP is required for all multi-drug resistant (MDR) TB and extensively drug resistant (XDR) TB cases. General recommendations to consider when resistance and/or drug intolerance present include the following:

Regimens lacking INH: Treat for a total of 6 months with a regimen of RIF, PZA and EMB and a later-generation fluoroquinolone (i.e. moxifloxacin or levofloxacin). A GeneXpert must be performed to assess for RIF resistance. 1st and 2nd line phenotypic drug susceptibility testing (DST) is recommended. Additional molecular DST may be considered.

When INH resistance is identified, EMB must be continued for the duration of treatment.

The duration of pyrazinamide can be shortened to 2 months in selected situations (i.e., noncavitary and lower burden disease or toxicity from pyrazinamide).

Please note that an alternative regimen may be needed in cases of unknown RIF susceptibility, known or suspected fluoroquinolone intolerance or resistance, known or suspected risk for QT-prolongation, or possibility of pregnancy.

Regimens lacking PZA: Treat for a total of 9 months with a regimen of INH and RIF.

Regimens lacking RIF: Treat for 12-18 months with INH, PZA EMB and a fluoroquinolone (levofloxacin or moxifloxacin).

Regimens lacking INH/RIF: Treatment of MDR and XDR- TB using regimens lacking INH/RIF must be closely managed in consultation with CTBCP utilizing multiple second-line drugs to which the organism is sensitive. All-oral regimens are preferred to ones containing injectables. Treatment duration is at least 18 to 24 months *after* culture conversion, although recent clinical trials and other studies are supporting the efficacy of shorter regimens for drug-resistant cases. MDR- and XDR-TB cases are managed in consultation with CTBCP and TB experts who are experienced in treating such cases and their contacts.

Regular consultation with CTBCP is required for any patient prescribed a medication regimen other than RIPE.

Pyridoxine (B_6) Supplementation

Adults

Adults with the following conditions should take pyridoxine (vitamin B_6) when taking INH:

- Presence of paresthesia
- Pregnancy
- Conditions where neuropathy is common
  - Diabetes
  - Malnourishment (>10% below ideal body weight)
  - Alcoholism
  - Cancer
  - Chronic liver disease
  - HIV infection

The dose should be 25 mg for each 300 mg of INH daily or 50 mg for thrice weekly therapy, depending on the dosing schedule being utilized. Pregnant women should take 50 mg daily or the equivalent in a prenatal vitamin supplement.

Children

Routine administration of pyridoxine is not recommended for children taking INH except for breast feeding infants, children, and adolescents with diets likely to be deficient in pyridoxine, and children who experience paresthesia while taking INH. For breast feeding infants the dose should be 10-25mg/day of pyridoxine.

A regular vitamin supplement appropriate for the infant's age generally provides adequate pyridoxine and is preferred over the use of pyridoxine alone. Supplemental pyridoxine should not be given to infants in addition to a regular vitamin supplement without consulting a TB expert.

Treatment Duration

In certain instances, treatment is prescribed beyond the standard 6 months. The minimum months of treatment for specific disease characteristics is listed in Table 10 *(page 49).* Case managers are advised to discuss treatment duration in terms of general goals and guidelines, emphasizing that each patient is unique and responds to the medications differently which may impact the total length of treatment required. Avoid discussing specific "end" dates as regimens can change.

Treatment Completion

To determine if a patient has completed therapy, count the total number of doses received and compare it to the total which is recommended for that frequency and phase of treatment including the total number of DOT doses for each phase of treatment. At the end of therapy, the patient should undergo a medical evaluation (including CXR and sputum specimen for pulmonary TB cases) to document response to TB treatment. Patients should be provided a summary of their TB treatment.

Special Situations

Cavitary TB with Positive *M. tuberculosis* Cultures at 60 Days

Patients who present with cavitary disease and whose sputum cultures remain positive after 60

days of treatment have been demonstrated to have very high rates of relapse and therefore it is recommended that the continuation phase in such patients be extended by 3 months for a total of 9 months treatment.

Extrapulmonary TB
Extrapulmonary TB is treated according to standard TB guidelines using DOT. For TB meningitis, miliary and bone/joint TB treatment is extended to a minimum of 9 months and many clinicians prefer treating for 12 months depending on the extent of disease. For any form of extrapulmonary TB treatment may be extended based upon clinical response.

Culture-Negative (abacillary) Pulmonary TB
All patients must be started on a **four-drug regimen** regardless of initial smear and culture status. Culture-negative, pulmonary TB is diagnosed when there are CXR and clinical signs consistent with TB that improve with antituberculosis treatment, but sputum cultures are negative for TB. Therapy may be shortened to four (4) months in *some* patients with documented culture-negative TB; however, *most* culture negative pulmonary TB patients **are not eligible** for four-month treatment. Individuals with abacillary TB that must receive 6 months of treatment include the following:

- HIV co-infection
- Children (defined as < 18 years of age)
- Extrapulmonary TB (including pleural TB)

Individuals with conditions that compromise successful outcomes if less than 6 months of treatment is provided and require CTBCP consultation if considering a 4-month treatment regimen include the following:

- Diabetes mellitus
- Renal failure and on dialysis
- Malignancy
- Current immunosuppressive therapy
- Lung cavitation or extensive pulmonary lesions, including bilateral disease
- TB treatment initiated before specimen collection for culture
- Known exposure to fluoroquinolones or other antibiotics active against TB for 7 days or more within one month, or any exposure within one week prior to specimen collection for culture
- Less than 100% DOT provided during the intensive phase of treatment

For patients without any of the above diseases and conditions, shortening the continuation phase of standard TB treatment may be considered. Shortening the treatment consists of four drugs for two months (RIPE) followed by two drugs for two months (INH/RIF). Given the risk to the patient of treatment for only 4 months if a short regimen is really not appropriate, consultation with CTBCP or a local TB expert is strongly recommended and should be clearly documented in the medical record.

Children
Because of the potential for rapid progression of TB disease, children suspected of having TB disease should be started on therapy as soon as possible. Children generally tolerate anti-tuberculosis medications very well. Routine laboratory monitoring is not recommended in children under age 18 unless there are presenting co-morbidities such as HIV infection or diabetes or other high-risk factors i.e., alcohol abuse.

Follow recommendations for standard therapy with dosing based on the child's weight *(Appendix E)*. A pediatric pharmacist may be needed to assist in dosage recommendations and medication formulations for very small children and infants. Weight changes in young children will affect the concentrations of the medications and weight needs to be monitored and discussed as appropriate as doses of medications may need to be changed as a child responds to treatment.

EMB has generally been avoided in children too young to perform visual acuity testing; however, some clinicians have successfully used EMB (15 mg/kg) in consultation with an ophthalmologist when the source case drug sensitivities show resistance or are of unknown status with a high likelihood of drug resistance.

Pregnancy
In almost all situations, a pregnant woman with a positive *M. tuberculosis* culture or who is

suspected of having TB disease should be treated without delay. HIV testing is essential. Treatment regimen recommendations for pregnancy previously excluded the use of PZA, however the new ATS/CDC recommendations now indicate it may be used safely. It has been used in many high-burden countries safely for years and is recommended by WHO as part of the standard regimen in pregnancy. Expert opinion considers HIV co-infection, extrapulmonary or severe disease as reasons to strongly consider utilizing PZA in the regimen. Clinicians who are interested in including PZA in the intensive phase of treatment during pregnancy should educate the patient about the benefits of including PZA in the regimen, potential side effects and potential risk. Treatment for 9 months with INH, RIF *and* EMB is required if PZA is not included in the regimen. Consultation with a TB Expert is necessary for pregnant women who require second-line drugs secondary to drug resistance or intolerance which precludes use of the standard regimen. Pregnant women on INH should be prescribed pyridoxine (vitamin $B_{6)}$) unless already taking the equivalent in a prenatal vitamin.

Congenital TB
Congenital TB is extremely rare in the U.S. but can be life-threatening to the infant. Consult with CTBCP if you are treating a pregnant woman with active TB who may deliver during treatment. Consultation with local and national TB experts who have experience with pre- and post-natal care of the mother, and care of the newborn will be arranged.

Breastfeeding
Only small concentrations of antituberculosis medications are passed to the nursing infant in breast milk, therefore breastfeeding should not be discouraged in women being treated for TB disease who are non-infectious. Consultation with experts in the field of TB and pregnancy is recommended regarding breastfeeding while still smear and/or culture positive. Supplemental pyridoxine is recommended for a nursing mother prescribed INH. Breastfeeding is generally not routinely recommended for women who are on fluoroquinolones or other second-line drugs to prevent TB in infants whose mothers are newly diagnosed with infectious pulmonary TB, bottle feeding by other family members (pumped breast milk or formula) may be preferable to breastfeeding until the infectious period is over, depending on the potential risk to the infant and the mother's ability to follow required infection control measures. The concentrations of drugs in breast milk are not sufficient to treat a nursing infant for either TB disease or infection. Clinicians are encouraged to consult with CTBCP or a TB expert with experience in TB and pregnancy. The American Academy of Pediatrics recommends giving an infant who is exclusively breastfed supplemental pyridoxine (1-2 mg./kg/day) regardless of whether or not the infant has been placed on INH. Case managers need to review all vitamins and other supplements of both mother and infant to ensure safe dosing of any vitamin is maintained.

Renal Insufficiency/End-Stage Renal Disease
Renal insufficiency complicates the treatment of TB due to prescribed medications that are cleared through the kidneys. Management may be further complicated if the individual is receiving hemodialysis. For patients with a creatinine clearance < 30 ml/min or are on hemodialysis, the alternate mediation dosing schedule outlined in Table 13 *(page 56)* should be utilized. Mediations are given 3 times/week *after* dialysis. Often arrangements can be made with the dialysis unit to provide for DOT of anti-tuberculosis medications. Follow these same guidelines for a person receiving peritoneal dialysis.

HIV Co-infection and Dosing Schedules
All confirmed and clinically suspected TB cases, regardless of age, need to be assessed for HIV infection at the time of TB diagnosis. The treatment of HIV, if infected, is critical to the success of any TB treatment.

Treatment recommendations for individuals co-infected with HIV follow the same principles as for patients without HIV co-infection. TB/HIV co-infection can pose significant treatment challenges and consultation with a TB/HIV expert is critical. Drug interactions between the

rifamycins and many of the antiretroviral (AVR) agents in use can occur when treatment for both HIV and TB is administered, resulting in increased metabolism and sub-optimal levels of antiretroviral medications.

Rifabutin (RBT) is an alternative to RIF and can be administered with certain ARVs with appropriate dose adjustments. New ART combination formulations are being developed frequently and recommendations on managing drug/drug interactions change rapidly. Always seek consultation with a TB expert for TB/HIV co-infected patients who are initiating or changing either TB or HIV treatment regimens. *(5, 32, 33, 34, 35)*.

Refer to Page 41 for information regarding when to initiate ART.

Immune Reconstitution Inflammatory Syndrome (IRIS)

TB/HIV co-infected patients on antituberculosis treatment may have temporary exacerbation of TB symptoms, signs, or radiographic manifestations up to several months after beginning antiretroviral therapy. These reactions presumably develop as a consequence of reconstitution of an individual's immune responsiveness brought on by the ARTs or by the individual's response to the TB treatment itself.

If signs of clinical worsening on treatment occur, such findings should be attributed to IRIS *only* after a thorough evaluation has excluded other possible causes (e.g., drug-resistant TB, poor absorption of TB drugs, another infectious or malignant process).

Despite development of IRIS, antituberculosis medications should not be discontinued without consultation. Paradoxical worsening also occasionally occurs in HIV-negative patients after initiating TB treatment. Consultation is required to discuss the patient's individual response and any adjustments to therapy that may be recommended.

MEDICATION REFERENCE TABLES FOR TB TREATMENT

Tables 9-14 (*pages 48-56)* are designed to facilitate medical management of TB cases based on the 2016 ATS/CDC/IDSA recommendations *(43)*. *Appendices C and D* contain commonly reported adverse reactions to first and second-line TB medications. These are summary reference tables only. Tuberculosis is complex to treat successfully under the best of circumstances. Providers are encouraged to contact CTBCP consultant staff when questions arise and should always refer to pharmaceutical texts, manufacturer product information and published research for detailed information on specific medications.

Table 9. Approved Dosing Regimens for Treatment of Drug Susceptible TB - Maryland

Initiation Phase [d]			Continuation Phase) [d]		
Options	**Drugs**	**Interval and Dose (minimum duration)**	**Options**	**Drugs**	**Interval and Dose (minimum duration)**
Option 1 ***Preferred***	**INH RIF [a] PZA EMB [b]**	**7 days/week for a minimum of 8 weeks (56 doses DOT [c])**	**INH RIF**	**Option 1** ***Preferred***	**7 days/week for a minimum of 18 weeks (126 doses DOT [c])**
Option 2	**INH RIF [a] PZA EMB [b]**	**7 days/week for a minimum of 8 weeks (40 doses DOT [c] plus 16 doses self administered)*** *Option 2 is typically provided as 5 days/week DOT, plus self-administered doses on weekends to equal 56 total doses. Self-administered doses are not counted without consultation with CTBCP.	**INH RIF**	**Option 2**	**7 days/week for a minimum of 18 weeks (90 doses DOT [c] plus 36 doses self administered)*** *Option 2 is typically provided as 5 days/week DOT, plus self-administered doses on weekends to equal 126 total doses. Self-administered doses are not counted without consultation with CTBCP.

INH = isoniazid RIF = rifampin PZA = pyrazinamide EMB = ethambutol

[a] **Patients Infected with HIV** on certain antiretroviral drugs may need medication adjustment because of drug interactions with rifampin. Consultation with an experienced HIV clinician may be required.

[b] **EMB** can be discontinued (prior to 8 weeks) once sensitivity to INH, RIF and PZA are known.

[c] **All regimens must be DOT.** DOT may be administered in person or via secured video or other computer or mobile monitoring device that provides view of patient preparing and swallowing medications and is HIPAA compliant.

[d] **Treatment should be extended in certain circumstances** (*see Table 10*).

Note: Intermittent regimens such as thrice weekly therapy are described in the 2016 ATS/CDC/IDSA guidelines [43] as possible alternatives to daily therapy but may not be appropriate for use with patients with certain co-morbidities or health problems, including diabetes, renal disease and malabsorption problems. The Maryland 2017 TB Expert Panel felt overwhelmingly that daily dosing should be used throughout the entire course of treatment whenever possible.

There is evidence that in some patients, appropriate concentrations of the antituberculosis medications are not reached, resulting in sub-optimal dosing and risk of delayed culture conversions, acquired drug resistance and/or treatment relapse. Please consult with CTBCP if considering treatment with intermittent dosing schedules so that appropriate monitoring plans can be discussed.

A formerly recommended regimen for the continuation phase of treatment using weekly INH and Rifapentine is no longer recommended for use.

Table 10. Minimum TB Treatment Duration by Case Characteristics	
TB Diagnosis	**Months of Treatment** (minimum)
Standard drug sensitive TB disease	6
Culture negative (abacillary) pulmonary TB disease	4
Drug resistance / Intolerance	
Without INH	6
Without PZA (pregnancy and M. *bovis*)	9
Without RIF	12-18
Without INH / RIF ± other drugs	18 to 24 after culture conversion
Culture positive after 60 days of treatment	
Cavitary disease	9
Extensive pulmonary disease	9
Extrapulmonary TB disease, treatment	
Central nervous system	9-12
Bone/joint	9-12
Miliary	9
Other extrapulmonary TB	6

Note: **The months of treatment outlined in the table above are estimates only.**

Completion of treatment is ultimately based on the total number of doses taken DOT over an acceptable length of time considered appropriate for the drug sensitivity pattern, type of TB diagnosed and assessment of the clinical response to treatment within expected parameters (i.e., culture conversion within 2 months of initiating treatment).

It is recommended that patients be given only approximate times for length of treatment when initiating therapy as many factors may change over the course of treatment which may lead to decisions to extend treatment beyond the initial estimates. Patents who understand this are far less likely to be disappointed or frustrated when temporary interruptions or delays in treatment occur.
Patients also need to understand that while TB is curable, it involves multiple antibiotics and individual responses to these medications may require adjustments or even temporary suspension of treatment (i.e., a "drug holiday"). These setbacks are often associated with physical discomfort and disappointment, requiring intense nurse case management support.

Table 11. Doses [a] of First-Line Antituberculosis Drugs for Adults and Children [b]

Drug	Formulation	Population	Daily	Once Weekly	2 Times/Week	3 Times/ Week
Isoniazid (INH)	**Tablets** (50 mg, 100mg, 300 mg) **Elixir** (50 mg/5ml) **Aqueous solution** (100 mg/ml) for intravenous(IV) or intramuscular (IM). Pyridoxine (vitamin B6) 25–50 mg/day, is given with INH to all patients at risk of neuropathy (e.g., pregnant women, patients with HIV, diabetes, renal failure, alcoholism, malnutrition, elderly, breastfeeding infants) For patients with peripheral neuropathy experts recommend increasing dose to 100 mg/day.	**Adults** **Children**	5 mg/kg (300 mg) 10-15 mg/kg	15 mg/kg (900 mg) ----------	15 mg/kg (900 mg) 20-30-mg/kg	15 mg/kg (900 mg) ---------- [b)]
Rifampin (RIF)	**Capsule** (150 mg, 300 mg). Powder may be suspended for oral administration. Aqueous solution for IV available.	**Adults** [c)] **Children**	10mg/kg (600 mg) 10-20mg/kg	---------- ----------	10mg/kg (600 mg) 10-20mg/kg	10mg/kg (600 mg) ---------- [b)]
Rifabutin (RBT)	**Capsule** (150 mg)	**Adults** [d)] **Children**	5 mg/kg (300 mg) Appropriate dosing for children unknown. Estimated at 5 mg/kg.	----------	Not Recommended	Not Recommended
Rifapentine (RPT)	**Tablet** (150 mg. coated)	**Adults** **Children**	---------- Use adult dosing for children with active TB ≥ 12 years of age. Not FDA approved for children < 12 years old.	10-20 mg/kg [e)]	----------	----------

Table 11. Doses [a] of First-Line Antituberculosis Drugs for Adults and Children [b] (continued)						
Drug	**Formulation**	**Population**	**Daily**	**Once Weekly**	**2 Times/Week**	**3 Times/Week**
Pyrazinamide (PZA)	**Tablet** (500 mg scored) Doses for adults are based on estimated lean body weight. Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest weights in the weight band. Optimal doses for obese patients are not calculated.	**Adults** 40-55 kg 56-75 kg 76-90 kg **Children**	1000 mg (18.2-25.0) 1500 mg (20.0–26.8) 2000 mg (22.2–26.3) 35 (30-40) mg/kg	---------- ---------- ---------- ----------	2000 mg (36.4–50.0) 3000 mg (40.0–53.6) 4000 mg (44.4–52.6) 50 mg/kg	1500 mg (27.3–37.5) 2500 mg (33.3–44.6) 3000 mg (33.3–39.5) ---------- [b)]
Ethambutol (EMB)	**Tablet (**100 mg; 400 mg) Suggested doses based on use of whole tablets. Doses for adults are based on estimated lean body weight. Numbers in parentheses are the calculated mg/kg doses for patients at the highest and lowest weights in the weight band. Optimal doses for obese patients are not calculated.	**Adults** 40-55 kg 56-75 kg 76-90 kg **Children** [f)]	800 mg (14.5–20.0) 1200 mg (16.0–21.4) 1600 mg (17.8–21.1) 20 (15–25) mg/kg	---------- ---------- ---------- ----------	2000 mg (36.4–50.0) 2800 mg (37.3–50.0) 4000 mg (44.4–52.6) 50 mg/kg	1200 mg (21.8–30.0) 2000 mg (26.7–35.7) 2400 mg (26.7–31.6) ---------- [b)]

a) Dose based on actual weight for patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. A modified IBW (IBW + [0.40 × (actual weight – IBW)]) as done for initial aminoglycoside doses may be used. Therapeutic drug monitoring to ensure adequate dosing may be needed.
b) For purposes of this document, **adult dosing begins at age 15 years or at a weight of > 40 kg in younger children unless otherwise noted**. The optimal doses for thrice-weekly therapy in children and adolescents have not been established. Some experts use the same doses as recommended for adults, and for younger children the same doses as recommended for twice-weekly therapy.
c) Higher doses of rifampin, currently as high as 35 mg/kg, are being studied in clinical trials.
d) Rifabutin dose may need to be adjusted if also using protease inhibitors or nonnucleoside reverse transcriptase inhibitors.
e) TBTC (Tuberculosis Trials Consortium) Study 22 used rifapentine (RPT) dosage of 10 mg/kg in the continuation phase of treatment for active disease, however, other studies have safely used higher dosages of RPT, administered once weekly. Daily doses of 1200 mg RPT are being studied in clinical trials for active tuberculosis disease.
f) To avoid EMB ocular toxicity, a 3-drug regimen (INH, RIF, and PZA) in the initial 2 months of treatment for children who are not HIV-infected, have no prior TB treatment history, are living in an area of low prevalence of drug-resistant TB, and have no exposure to individuals from an area of high prevalence of drug-resistant TB has been routinely used. However, because the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the American Academy of Pediatrics and most experts include EMB as part of the intensive-phase regimen for children with tuberculosis.

Table 12. Doses [a] of Second-Line Antituberculosis Drugs for Adults and Children [b]						
Drug	**Formulation**	**Population**	**Daily**	**Once Weekly**	**2 Times/Week**	**3 Times/Week**
Cycloserine Experts suggest starting with 250 mg once daily and gradually increasing as tolerated. Serum concentrations can be helpful. Few patients tolerate 500 mg twice daily.	**Capsule** (250 mg)	**Adults** **Children**	10–15 mg/kg total (250–500 mg once or twice daily) 15–20 mg/kg total (divided 1–2 times daily)	There is no adequate data to support intermittent dosing for either adults or children.		
Ethionamide Experts suggest starting with 250 mg once daily and gradually increasing as tolerated. Serum concentrations may be helpful. Few patients tolerate 500 mg twice daily.	**Tablet** (250 mg) Can be given at bedtime or with a main meal to reduce nausea. Pyridoxine (Vitamin B6) should be administered with ethionamide.	**Adults** **Children**	15–20 mg/kg total (250–500 mg 1-2 times daily) 15–20 mg/kg total (divided 1–2 times daily)	There is no adequate data to support intermittent dosing for either adults or children.		
Streptomycin WHO and TB experts no longer recommend the use of injectables for treating drug resistant strains of TB. Consult with CTBCP. [d)]	**Aqueous solution** (1 g vials) for IM or IV use Patients with decreased renal function may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance.	**Adults** **Children**	15 mg/kg 15–20 mg/kg *(46)*	--------- ---------	---------- 25–30 mg/kg	25 mg/kg (preferred by some clinicians) ----------

Table 12. Doses [a] of Second-Line Antituberculosis Drugs for Adults and Children [b] (continued)						
Drug	**Formulation**	**Population**	**Daily**	**Once Weekly**	**2 Times/Week**	**3 Times/Week**
Amikacin/ Kanamycin WHO and TB experts no longer recommend the use of injectables for treating drug resistant strains. Consult with CTBCP. [d]	**Aqueous solution** (500 mg or 1 g vials) for IM or IV use Patients with decreased renal function may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance	**Adults** **Children**	15 mg/kg 15–20 mg/kg (46)	--------- ----------	---------- 25–30 mg/kg	25 mg/kg (preferred by some clinicians) ----------
Capreomycin Although referenced in the 2016 ATS statement **Capreomycin is no longer recommended** . Consult with CTBCP.	**Aqueous solution** (1 g vials) for IM or IV use Patients with decreased renal function may require the 15 mg/kg dose to be given only 3 times weekly to allow for drug clearance	**Adults** **Children** [c] Use serum drug levels to guide dosing.	15 mg/kg 15–20 mg/kg (46)	--------- ----------	---------- 25–30 mg/kg	25 mg/kg (preferred by some clinicians) ----------
Para-amino salicylic acid	**Granules** (4 g packets) can be mixed and ingested with soft food. **Should not be chewed.** T**ablets** (500 mg) still available in some countries, but not in U.S. **IV solution o**nly available in Europe.	**Adults** **Children**	8–12 g total (4000 mg 2–3 times daily) 200–300 mg/kg total (divided 100 mg/kg given 2-3 times daily)	There are inadequate data to support intermittent administration.		

Table 12. Doses [a] of Second-Line Antituberculosis Drugs for Adults and Children [b] (continued)						
Drug	**Formulation**	**Population**	**Daily**	**Once Weekly**	**2 Times /Week**	**3 Times /Week**
Levofloxacin	**Tablets** (250 mg, 500 mg, 750 mg); **aqueous solution** (500 mg vials) IV	**Adults** **Children** Optimal dose is not known	500–1000 mg Clinical data suggest 15–20 mg/kg *(46)*	There are inadequate data to support intermittent administration.		
Moxifloxacin	**Tablets** (400 mg); **aqueous solution** (400 mg/250 mL) IV Lack of different formulations makes such titration challenging	**Adults** **Children** Optimal dose is not known	400-800 mg daily 10 mg/kg daily has been used by experts.	There are inadequate data to support intermittent administration. [c] *(46)* Aiming for serum concentrations of 3-5 µL/mL 2 h post dose in children is proposed by experts as a reasonable target.		
Bedaquiline	Tablets: 100 mg.	**Adults** **Children**	⟹ ⟹	400 mg daily for 2 weeks then 200 mg thrice daily for 22 weeks for total of 24 weeks. Based strictly on weight, estimated pediatric doses would be 6 mg/kg daily for 14 days, followed by 3 mg/kg 3times weekly for 22 weeks http://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_chap5_medications.pdf WHO approved for use in MDR/RR-TB for children > 6 years of age https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf		
Linezolid	**Tablets (coated):** 400 and 600 mg; **aqueous solution:** 2 mg/ml: 100, 200, or 300 mg bags. **Oral powder for suspension:** 100 mg/5 ml	**Adults** **Children**	600 mg. daily 10 mg/kg every 12 hours	Doses may be decreased because of peripheral neuropathy and cytopenias. Optic and peripheral neuropathy – may be irreversible. http://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_chap5_medications.pdf		

Table 12. Doses [a] of Second-Line Antituberculosis Drugs for Adults and Children [b] (continued)						
Drug	**Formulation**	**Population**	**Daily**	**Once Weekly**	**2 Times /Week**	**3 Times /Week**
Pretomanid ***NEW*** **Approved 2019** by FDA for MDR-TB patients on a 3-drug regimen that includes bedaquiline and linezolid.	Tablets: 200 mg Pretomanid Tablets used ONLY in combination with bedaquiline and linezolid ***MUST* Consult with CTBCP**	**Adults** 200 mg orally (1 tablet) **Children** Not approved for use in children	200 mg orally (1 tablet of 200 mg), once daily, for 26 weeks.	Antimycobacterial to be used ONLY as part of a combination regimen with bedaquiline and linezolid for the treatment of adults with pulmonary extensively drug resistant (XDR) OR treatment-intolerant or nonresponsive multidrug-resistant (MDR) tuberculosis (TB). Not indicated for patients with: drug-sensitive tuberculosis, LTBI, extra-pulmonary TB, MDR-TB that is responsive to standard therapy. Safety and effectiveness of Pretomanid Tablets have not been established for its use in combination with drugs other than bedaquiline and linezolid as part of the recommended dosing regimen. Interreacts with other medications including rifamycins.		
Clofazimine	**Capsules:** 50 and 100 mg. capsules	**Adults** **Children**	100 mg daily 1 mg/kg daily	Some experts have started with 200 mg as daily dose. Limited data regarding children.		
Delamanid	**Tablets:**50 mg. coated ***MUST* Consult with CTBCP**	**Adults** **Children**	100 mg. BID 50-100 mg BID by age	Although approved by regulatory bodies in Europe, Japan, and the World Health Organization, **Delamanid is not yet approved for routine use in the United States.** There have been rare instances of the drug being approved for "compassionate" use with severely ill XDR-TB patients.		
Meropenem and imipenem	**For IV administration only**	**Adults** **Children**	No data specific to TB	Shows *in vitro* activity against TB but limited clinical experience. Both drugs must be administered with Augmentin (amoxicillin / clavulanate) 1000/125 mg every 12 hours. Consult with TB expert.		

a) Dose based on actual weight for patients who are not obese. For obese patients (>20% above ideal body weight [IBW]), dosing based on IBW may be preferred for initial doses. A modified IBW (IBW + [0.40 × (actual weight – IBW)]) as done for initial aminoglycoside doses may be used. Therapeutic drug monitoring to ensure adequate dosing may be needed.

b) For purposes of this document, **adult dosing begins at age 15 years or at a weight of >40 kg in younger children unless otherwise noted.** The optimal doses for thrice-weekly therapy in children and adolescents have not been established. Some experts use the same doses as recommended for adults, and for younger children the same doses as recommended for twice-weekly therapy.

c) RIFAQUIN trial studied a 6-month regimen. Daily isoniazid was replaced by daily moxifloxacin 400 mg for the first 2 months, followed by once-weekly doses of moxifloxacin 400 mg and RPT 1200 mg for the remaining 4 months. Two hundred twelve patients were studied (each dose of RPT was preceded by a meal of 2 hard-boiled eggs and bread). This regimen was shown to be noninferior to a standard daily administered 6-month regimen [(43)].

d) The World Health Organization and TB experts globally are now recommending that any MDR and any rifampin resistant TB strain be treated with a longer MDR/ RR-TB regimen that does NOT include injectables if at all possible. A TB expert should be consulted and **in Maryland no injectables should be prescribed without consultation with CTBCP**. A pre-finalized report of the new recommendations, including supporting research is available at https://www.who.int/tb/publications/2018/WHO.2018.MDR-TB.Rx.Guidelines.prefinal.text.pdf

Table 13. Dosing Recommendations for Patients with Reduced Renal Function		
Drug	**Daily Dose (maximum)**	**Thrice Weekly Dose (maximum)**
INH	5 mg/kg (300 mg)	15 mg/kg (900 mg)
RIF	10 mg/kg (600 mg)	10 mg/kg (600 mg)
PZA	not recommended	25-35 mg/kg
EMB	not recommended	15-25 mg/kg

Table 14. Monitoring for Treatment Response and Adverse Reactions (baseline and monthly)	
Treatment Response	
Vital signs/weight	Weight gain is often a critical measure of treatment response.
TB signs and symptoms	Check for cough, hemoptysis, chest pain, fever, night sweats, fatigue, malaise, no clinical improvement.
Sputum specimens	Obtain specimens monthly until sputum culture conversion (consecutive negative cultures at least 7 days after last positive culture). Timely specimen collection is needed in order to show culture conversion by treatment day 60. To document conversion of AFB smear (for return to work/school), obtain every 2 weeks. At end of treatment obtain one specimen if patient able to produce sputum. Collect all specimens in sets of 3, 8-24 hours apart with at least one morning specimen.
Adherence	Evaluate adherence to prescribed regimens and medical care.
Chest radiograph (CXR)	After initial CXR, repeat only if clinically indicated. With clinically suspected culture-negative TB obtain CXR at 2 months on treatment to evaluate for CXR improvement. For pulmonary cases, a CXR should be obtained at treatment completion.
Adverse Reactions	Nausea, vomiting, abdominal pain, decreased appetite, fatigue, jaundice (sclera and nail beds), dark urine, itching, rash, joint pains, peripheral neuropathy, flu-like syndrome, photosensitivity.
Vision	While on ethambutol, check visual acuity (Snellen) and color (Ishihara) at baseline/monthly.
Audiometry	Only for patients on aminoglycosides (streptomycin, capreomycin, etc.). Test at baseline and if symptoms of eighth nerve toxicity occur.
Blood Work	**Adults:** Baseline liver function tests, uric acid, complete blood count including platelets, and chemistry panel including creatinine should be done for all adult patients. Monthly LFTs should be done only for those with: • Abnormal baseline LFTs • Development of hepatitis symptoms • HIV infection • History of heavy alcohol use, liver disease or chronic hepatitis • Pregnant and postpartum women (up to 2 months after delivery) • Injection drug users or documented Hepatitis B or C infection **Children:** Those under age 18 do not routinely need baseline blood work. Baseline and monthly LFTs should be considered for those with: • Severe TB disease (especially meningitis or disseminated disease) • Concurrent liver or biliary disease or use of other hepatotoxic medications • Pregnancy or recent delivery (within past 6 weeks) • Clinical evidence of hepatotoxity • History or indications of substance abuse, hepatitis, HIV risk behaviors

VIII. LEGAL ASPECTS OF TB CONTROL

General Principles

The goal of the Maryland Center for TB Control and Prevention (CTBCP) is to treat TB patients in the least restrictive manner possible. Lengthy TB therapy can pose challenges in compliance with isolation directives, medication adherence and keeping clinical appointments. Factors that may be associated with incomplete treatment include diagnosis in and subsequent release from a correctional facility, excess drug and alcohol use, and homelessness. Measures to promote adherence begin with the first patient contact by the case manager and continue throughout the entire course of treatment.

The statutes and regulations that govern tuberculosis (TB) are Health-General Ann. §§ 18-324 and 18-325 and Maryland COMAR 10.06.01. Maryland COMAR 10.06.01.20 also directs local health department actions regarding the isolation of infectious TB patients, the clinical examination of patients, use of appropriate treatment regimens, release from hospital isolation, hospital discharge and control and evaluation of contacts to tuberculosis cases *(Appendix J).*

References to TB isolation and quarantine often utilize the terms interchangeably and many older laws and regulations do the same or use the term quarantine implying physical isolation from the general society. This document refers to both the physical isolation of patients while infectious as well as to the removal of a patient from the general society via what in Maryland statute is described as "quarantine."

Maryland regulations provide for the quarantine of both a) infectious patients and b) non-infectious patients who are considered a potential threat to the health of the public if they do not comply with the treatment regimen ordered and are considered a real or potential public health risk. An example of a non-infectious patient who could rapidly become infectious and jeopardize the general public if not compliant with medications would be a severely immunocompromised individual with cavitary disease and MDR-TB who only recently converted from AFB smear positive to smear negative and is now refusing treatment.

Health department personnel should completely document all specific instances of noncompliance, the barriers identified, implementation of measures to alleviate barriers, promote adherence, and the outcomes achieved. This documentation is critical in supporting LHD attempts to support a patient in the completion of treatment through the least restrictive means possible should later more restrictive measures be required.

The progressive steps described below should be followed in order. Progression to the next step in the event of nonadherence to the treatment plan should not occur until all efforts to resolve the compliance concerns have been exhausted. LHDs are encouraged to consult with CTBCP as soon as concerns about patient adherence are identified. Each patient situation is unique and therefore recommendations for pursuing legal actions leading to restriction of patient freedoms are unique as well.

Legal Steps

1. Tuberculosis Patient/Provider Agreement for Treatment (MDH Form 4511)

At the beginning of treatment, the patient's legal responsibility to comply with treatment should be fully explained and documented by having the patient/guardian and case manager sign the "Tuberculosis Patient / Provider Agreement" (MDH Form 4511). This document outlines the responsibilities of both the patient/guardian and the LHD. It serves as notification that the patient is required by Maryland law to take TB medication and that failure to comply will result in more restrictive measures. This document serves as the basis for all further legal action. *The patient/provider agreement forms have been translated into several languages and are available on the MDH/CTBCP website.* On-site interpreters should be used, as appropriate.

The patient/provider agreement form, and any subsequent order will ask for the patient to sign that the contents of the document have been explained. If a patient refuses to sign this should be noted on the document and in the patient's medical record. The patient should be provided a copy. Translation and/or interpreter services *must* be provided for the patient or guardian when needed.

At the beginning of care, the nurse case manager should work with the patient to identify potential barriers to completing treatment and enablers and incentives that will allow and encourage the patient to continue therapy. If appropriate, include other household members in the process if they are able to offer support. Incentives (small rewards that motivate patients) and enablers (things that allow patients to overcome barriers) can be very effective if they are tailored to the individual's needs and interests *(Table 8, page 36*).

LHD TB case managers should explore options within the LHD and the larger community that might be available to assist patients who present other needs that could affect the ability to adhere to a lengthy TB regimen e.g., linkage to care for mental health or substance abuse counseling, HIV care services, housing assistance, etc. Being aware of these services and reaching out for assistance may be helpful in avoiding pursuing legal alternatives. Case managers should also be prepared to deal with changes in what motivates or helps the individual over time; especially if the patient is dealing with an especially long treatment regimen. If use of incentives and enablers does not improve treatment adherence and all other options have been explored, the nurse case manager should discuss with CTBCP and the LHD administration the potential need to move forward with the next step of legal actions.

2. Health Officer Order for Appropriate TB Treatment and Medical Care

A Health Officer order for appropriate TB treatment and medical care serves as legal notification that the patient is required to be compliant with requests for medical evaluation and follow-up, adherence to the medication plan, etc. The title and exact wording of the order may vary depending on the notice being served to the patient, but it should include that failure to comply will result in more restrictive measures, e.g., quarantine to home or a state facility. This type of order is generally issued by the LHD and is signed by the Health Officer, the nurse case manager, and the patient. These orders are specific to the issuing jurisdiction and are issued under that jurisdiction's authority. The patient should be provided information as to who to contact in the jurisdiction if there are questions/concerns about the order.

Samples of this type of order can be obtained from CTBCP. For example, a patient who has consistently missed DOT appointments after provision of enablers and/or incentives can be issued an order to take all TB medications and keep all TB-related medical appointments. The order must include information on the patient's TB symptoms, diagnosis, and treatment, and describe specific incidents when non-compliance occurred. It is strongly recommended that ***all*** orders be reviewed by CTBCP prior to being issued. Arrangements can be made to have the MDH Office of the Attorney General review the order as well.

If the LHD is aware of a person who is suspected of having TB disease and who refuses to comply with requests to complete an evaluation for TB, the LHD may require that person to be examined. The tests covered under this order must be non-invasive (CXR and sputum specimens). COMAR regulations also permit a Health Officer to require that a contact to an infectious case be examined as well, although the examination may not require any invasive testing. However, in the case of a contact to an infectious case or any high-risk contact (e.g., HIV infection or young child) at least active TB disease can be ruled out with CXR and sputum specimens as appropriate.

Children under 5 years of age are especially susceptible to TB meningitis and are at very high risk for developing active TB. Local jurisdictions may need to request the assistance of other local agencies, e.g., child protective services if parents/guardians refuse to have children identified as contacts evaluated and/or

placed on "window prophylaxis" if recommended.

3. Health Officer or Secretary of MDH Order for Isolation/Quarantine

An order for isolation/quarantine is served only after the patient fails to comply with the order for appropriate treatment/medical care. Orders for isolation/quarantine order the patient to a specific location or facility which can include a health-care facility, the patient's home, or any setting in which appropriate TB treatment and follow-up care can be provided. This order is written by the LHD in collaboration with CTBCP, but usually signed by the Secretary of MDH to avoid jurisdictional concerns which can occur with placement outside the patient's home jurisdiction. As with a treatment order, an order for isolation/quarantine should be sent to CTBCP for review by the MDH Office of the Attorney General prior to signature of the Secretary.

Planning by the LHD in collaboration with CTBCP is often required with other agencies and facilities (i.e., Deer's Head Medical Center or DPSCS (Department of Public Safety and Correctional Services) should more restrictive measures be needed. The LHD of the jurisdiction in which the patient resides remains the LHD of record (including discharge plans) regardless of where a patient might be placed

4. Violation of Order for Quarantine

If a patient violates the Order for Isolation/Quarantine a misdemeanor has been committed which can result in criminal prosecution and incarceration. Prosecution must be done by the local state's attorney's office of the jurisdiction in which the violation occurred and should involve consultation with the MDH Office of the Attorney General, LHD, and CTBCP. A quarantine order cannot be issued referencing CTBCP or MDH without review. A quarantine order must include specific documentation of how the patient may challenge the quarantine that is approved by the MDH Office of Attorney General.

Once a person is placed in a facility under a quarantine order, they cannot be released unless all signatories to the order agree that releasing the person from quarantine would not jeopardize completion of treatment and thus pose additional risk to the citizens of the state. Alternate options for less restrictive supervised confinement *may* be determined with input from all parties, including the patient and the courts. Any decision to impose measures that do not involve incarceration is based primarily on the ability of the state to ensure the protection of other citizens from TB, as well as appropriately considering the rights of the patient.

As soon as a serious pattern of non-compliance is identified, contact CTBCP (410-767-6698) to coordinate an appropriate management plan. Samples of *Orders for Appropriate Treatment/ Medical Care* and for *Isolation/ Quarantine* are available from CTBCP. Every patient presents with unique challenges and issues, so orders may vary significantly in terms of content; but do need to be specific (i.e. dates, medication names and doses missed, efforts to assist the patient, etc.) so that anyone reviewing the document is clear as to what the patient did or did not do, and what the health department attempted to do to assist the patient's adherence with the agreed upon treatment plan. They also need to be written in an approved legal format.

HIPAA (Health Insurance Portability and Accountability Act)

Local Health Departments may require medical documents from other health care facilities regarding the care and treatment of TB patients; access to such documents is permitted under Annotated Code of Maryland, Health-General Article, §§2-104, 18-101, 18-201, 18-202 and 18-205 along with the Code of Maryland Regulations (COMAR) 10.06.01.

National guidance and HIPAA resources can be found at http://www.cdc.gov/mmwr/preview/mmwrhtml/m2e411a1.htm

IX. CONTACT INVESTIGATIONS AND TREATMENT OF CONTACTS

The goal of a tuberculosis (TB) contact investigation is twofold: 1) to identify other active cases of TB to initiate treatment and prevent further transmission, and 2) to identify and completely treat individuals with new latent TB infection (LTBI), who are at particularly high-risk for developing active disease. TB contact investigations are required and should begin within 3 working days for all pulmonary and laryngeal TB cases in Maryland and are coordinated by the local health department (LHD) in the county where the TB case resides. The need for contact investigations for pleural TB cases should be discussed with CTBCP. (*See Figure 2, page 65).*

Notify the Center for TB Control and Prevention (410-767-6698) when planning for any large institutional investigation or other contact investigation that may trigger media interest.

Decision to initiate a tuberculosis (TB) contact investigation

Prioritization

Prioritization of contacts is necessary to ensure no individuals are missed who should be evaluated due to exposure to an infectious case and to ensure appropriate utilization of LHD resources. The LHD of the jurisdiction in which the TB case resides is responsible for the outcome and evaluation of a contact investigation even when working with private providers, employers, other health care facilities and/or other health departments. Consultation with CTBCP is recommended.

TB Cases Priority for Investigation

When a report of a TB case is received by the LHD, an evaluation should be done immediately to determine its priority for a TB contact investigation. Table 15 (*page 63)* outlines the priority of a case for investigation based upon clinical characteristics of the case. The highest priority cases for investigation are confirmed and clinically suspected pulmonary TB cases with positive acid-fast bacillus (AFB) smears and/or cavitation on chest radiograph (CXR). *Each of these cases should have at least 3 identified contacts.* Contact investigations are not a top priority for extrapulmonary TB cases for which pulmonary TB has been ruled out unless there are high-risk contacts within the household.

Priority for Evaluation of TB Contacts

Contacts to AFB smear-positive or cavitary cases should be assessed based upon both a) the likelihood that a contact will be infected and, b) the risk of TB disease if infected. Table 16 *(page 64)* outlines contact characteristics by their priority for evaluation. Contacts who are living with HIV and children under age 5 are always the highest priority for evaluation because of their high risk for rapid progression to TB disease.

Planning the Investigation

The "concentric circle approach" (a method formerly used by TB programs to plan contact investigations using household infection rates to determine if the investigation needed to be expanded) is no longer recommended. In general, the contacts an individual spends the most time with on a consistent basis (those with the greatest duration and intensity of exposure) are tested first. These "close" contacts may be individuals identified from school, work, or social settings where the cumulative exposure risk is much greater than any person(s) residing in the same household as the TB case.

It is possible that the initial investigation will exclude some of the "high-priority" contacts listed in Table 16 *(page 64)* if there are a significant number of contacts with greater exposure than others. Only when there is evidence of TB transmission among close contacts is the investigation expanded to contacts with less exposure to the index case. Characteristics to consider include:

- Likelihood of transmission,

- Contact risk factors for development of TB disease if infected, and
- Environment where exposure occurred.

Every effort should be made to *avoid* testing individuals who are at low risk of infection.

Contact Investigation Procedures

1. **Collect Data.** Data collection and documentation should begin as soon as the LHD receives notification of a confirmed or clinically suspected TB case. Medical and social history of the index case can be obtained from the reporting facility or physician. Information should include the TB disease site, AFB smear/culture results, CXR results and nature and duration of TB symptoms, as well as demographic information.

2. **Interview Case.** The index patient should be interviewed within 1-3 business days of notification of the case. More than one interview of the TB case or proxy should be conducted. Establish rapport with the client and provide education on TB. Describe the contact investigation process and assure that every effort will be made to protect the patient's confidential information. Identify the infectious period and obtain locating and demographic information on individuals who were in contact with the case during the infectious period. Specifically ask about any contacts who are young children or HIV positive. When necessary, utilize an interpreter to communicate with the client.

3. **Identify Infectious Period.** A date must be identified for both the start and end of the infectious period. See Table 17 *(page 64).*

   Start of the infectious period: The start of the infectious period is determined by clinical characteristics of the index patient. If TB symptoms are present, then the period of infectiousness begins 3 months prior to symptom onset. If no symptoms are present, the period of infectiousness begins 3 months prior to the first positive finding consistent with TB disease.

   End of the infectious period: The infectious period is closed when the case has been on appropriate TB treatment for ≥ 2 weeks, there is clinical improvement, and sputum smears are AFB-negative. The infectious period is also closed when a hospitalized patient is admitted to airborne infection isolation (AII).

4. **Perform Field Investigation.** The field investigation is a mandatory component of the contact tracing process. A personal visit to the case's home, worksite, etc. provides important additional information about the case, locations where exposure occurred and often results in additional contacts being identified. Contact testing can also be conducted in the field.

5. **Evaluate High and Medium Priority Contacts.** Utilizing the prioritization scheme outlined in Table 17, determine the priority for evaluation of contacts. Evaluation of contacts, including symptom **r**eview and tuberculin skin test (TST) or interferon-gamma release assay (IGRA) test should occur within 7 days of identification for high priority contacts, and within 14 days for medium priority contacts.

6. **Determine Infection rate.** The infection rate is calculated as follows:

   $$\frac{\text{Total TST/IGRA (+) (not including prior +)}}{\text{Total Tested (not including prior +)}}$$

   Example: Of 23 contacts identified in a given investigation, 20 receive TST and 5 are positive, one has a prior positive TST, and 2 are never evaluated.

   $$\text{Infection Rate} = \frac{5 \text{ TST (+)}}{20 \text{ tested}} = 25\%$$

7. **Determine Need to Expand Investigation**. Testing results for contacts should determine the need to expand a contact investigation. Criteria include an unexpectedly high rate of infection, evidence of second-generation transmission, TB disease in any contacts assigned low priority, infection in any contacts age < 5 years, or contacts with

change in TST/IGRA from negative to positive.

Medical Evaluation of High and Medium Priority Contacts

Contacts should be assessed for symptoms of TB, history of positive TST/ IGRA, history of TB disease and TB exposure, HIV status, country of origin and other risk factors for TB. Because management of patients living with HIV differs from HIV-negative contacts, **HIV testing is recommended for all contacts.**

Routine contact evaluation for individuals with no history of prior positive TST/IGRA or prior treatment consists of the following:

- TB symptom assessment and TST/IGRA at the time contact is identified, and (if this test is negative and no symptoms present),
- TB symptom assessment and TST/IGRA 8-10 weeks after exposure ended.
- CXR for those with symptoms consistent with TB disease or those with a positive TST (> 5 mm) or positive IGRA.
- Once TB disease is ruled out, evaluate for treatment of latent TB infection (TLTBI).

Treatment of Contacts

Contacts who test positive during a contact investigation who have either a history of previous negative test (TST or IGRA), or who have no history of a previous test are considered recently infected and are high priority for TLTBI. Contacts to patients with drug resistant TB are treated on a case by case basis. See pages 20-21 and Table 6 starting on page 26 for LTBI treatment recommendations.
All children diagnosed with latent TB who are under the age of 5 and identified as a close contact of a pulmonary TB case need to complete LTBI treatment using DOT if able. LHDs may have to intervene with social services and others in the event parents/guardians and other health care providers do not understand the high risk presented to their children if they are not treated. Consult with CTBCP as appropriate.

Contacts 6 months to 2 years of age

Children under 2 years of age who are close contacts to infectious cases should receive a TST and CXR and be started on window prophylaxis, using DOT when possible, as described above. If the initial TST is negative, a repeat TST and CXR should be done at least 8-10 weeks after exposure ended. Infants should be at least 6 months old before the second TST. Window prophylaxis should be continued until the child receives the second TST. If the second TST is positive, treatment should continue for a full course of TLTBI. Window prophylaxis is considered a national standard of TB care.

Contacts 2- 4 years of age

Children ages 2- 4 who are close contacts of infectious cases should receive a TST or IGRA and both PA and lateral CXR to rule out active TB disease. If the initial TST is < 5mm or IGRA is negative, child is asymptomatic, CXR is negative, and exposure occurred < 8 weeks prior, window prophylaxis with INH is recommended. DOT is strongly recommended to ensure the child is receiving the required medication and to monitor for any adverse effects. If the second test administered 8-10 weeks after exposure has ended is negative, treatment is discontinued. If the second test is positive, a full course of treatment is completed.

Documented prior positive TST or IGRA test, or history of TB disease

If the contact has a history of a positive TST/IGRA and has no TB symptoms, no further evaluation is needed.

Contacts with Immunosuppression

Contacts with immunocompromising conditions such as HIV, organ transplant recipients, and those taking immunosuppressive drugs, should receive a TST or IGRA, CXR and symptom review. If the person is asymptomatic and CXR is negative, a full course of TLTBI should be given, regardless of TST/IGRA result, and prior history of infection or treatment. Those with a negative TST should have it repeated 8-10 weeks after exposure ended.

Source Case Investigation

When a child under age 5 is diagnosed with TB disease, a source investigation is required to try to identify the source case as TB in young children indicates recent transmission. Although uncommon, young children and infants can transmit TB under certain conditions. Consult with CTBCP.

Source case investigations should also be done for TST-positive children ≤ 2 years of age unless the child has a known risk of TB infection (i.e., foreign adoptees). Close contacts are evaluated with a TST/IGRA and symptom screening. Everyone (adults and children) who had close contact with the child should be evaluated.

Confidentiality

A general principle when implementing TB contact investigations is to protect the confidentiality of the index case (unless the case chooses independently to inform contacts of the TB diagnosis). Contacts are informed that they may have been exposed to a recent active TB case without revealing the identity of the case. When there is a large institutional investigation the only way to identify exposed contacts may be to inform an appropriate administrator(s) of the identity of the index case. LHDs ca assist the organization in addressing privacy concerns.

Table 15. Priorities for Initiation of TB Contact Investigations [5]

Disease Site/Characteristics	Priority for Investigation
Pulmonary/Laryngeal Disease	
AFB Smear-positive	
GeneXpert or other NAA test (+) or not done	High
GeneXpert or other NAA test (-)	Not indicated
AFB Smear-negative	
Cavitary disease	High
CXR non-cavitary consistent with TB	Medium
CXR abnormal not consistent with TB	Low
Non-pulmonary (pulmonary disease ruled out)	Not usually indicated
Children < age 5	Source case investigation only

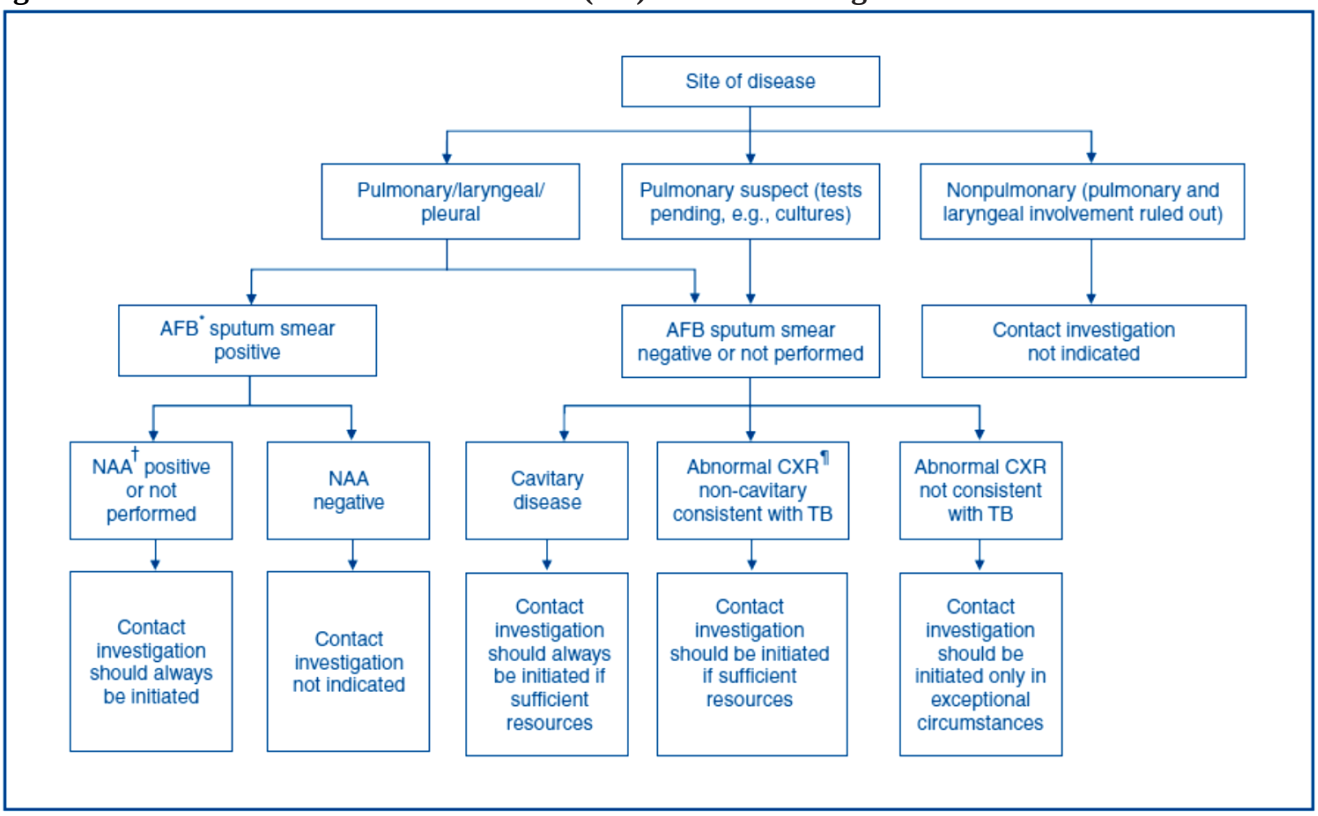
.

Table 16. Priorities for Evaluation of Contacts		
High-Medium Priority Contacts		
Contact Characteristics	AFB-sputum smear +, GeneXpert/culture +	AFB sputum smear ─, culture +
	Household or Other Congregate living Age ≤ 4 years Age 5 to 15years Exposed during bronchoscopy, sputum induction, or autopsy	Age ≤ 4 years Risk factor(s) for TB Exposed during bronchoscopy, sputum induction, or autopsy Congregate setting
Medical risk factor(s) for TB		
HIV Steroids Diabetes TNF alpha inhibitors	Lung Disease Other immunosuppressants Current smoker Head/neck cancer	Excessive alcohol Underweight (<10% ideal bod weight) Kidney disease
Environmental Characteristics*	Consider the ventilation and air flow, size of space, duration of exposure, for example. • ≥ 4 cumulative hours in small space • ≥ 8 cumulative hours in classroom size space • ≥ 50 cumulative hours in large open space Exposure limits should be established by LHD depending on settings involved.	
Low Priority contacts		
Contacts do not meet requirements for high-medium priority. Low priority should only be counted for testing that has been done for good will or administrative purposes and should be minimal (e.g. workplace or school contacts that have no direct contact with the index case).		

***There are no published data that definitively link exposure time to likelihood of infection.**

Table 17. Guidelines for Estimating the Beginning of the Period of Infectiousness of Patients with Tuberculosis by Index Case Characteristics			
Patient Characteristic			
Tb Symptoms	**AFB Smear + Sputum**	**Cavitary CXR**	Recommended minimum beginning of likely period of infectiousness
Yes	Yes/No	Yes/No	3 months before symptom onset or first positive finding consistent with TB (e.g., abnormal CXR), whichever is longer.
No	Yes	Yes	3 months before first positive finding consistent with TB.
No	No	No	1 month before date of suspected diagnosis.
Infectious period ends when patient is admitted to AII or is considered no longer infectious.			

Figure 2. Decision to initiate a tuberculosis (TB) contact investigation



* Acid-fast bacilli.
† Nucleic acid assay.
§ According to CDC guidelines.
¶ Chest radiograph.

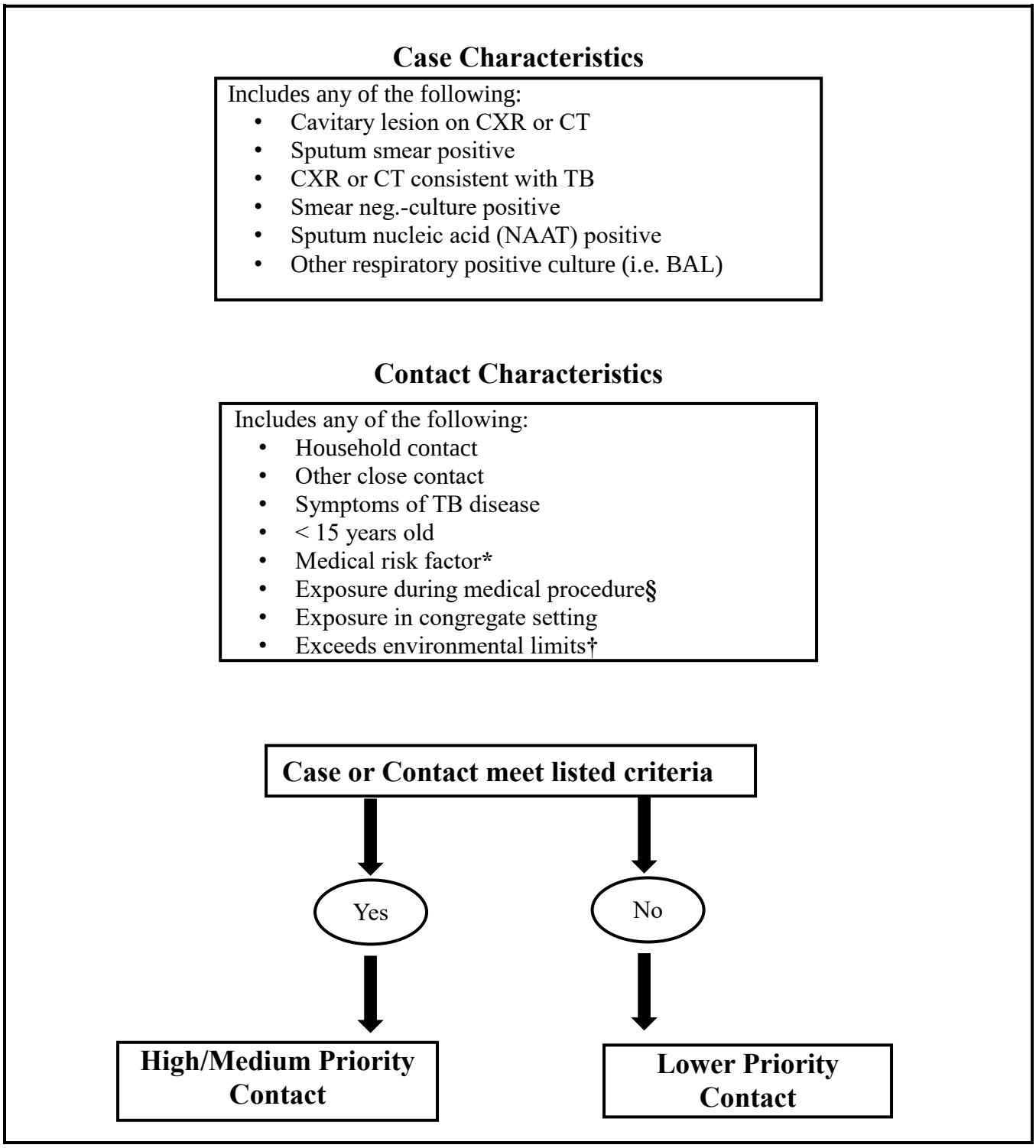
CDC Descriptions of Types of Contacts

Smear positive: Patient has pulmonary or laryngeal or pleural TB with cavitary lesion on chest radiograph or is AFB sputum smear positive
High/Med Priority Contact
Household
< 15 years old
Medical risk factor
Exposure during medical procedure (bronchoscopy, sputum induction, autopsy, intubation)
Exposure in congregate setting
Exceeds environmental time limits

Smear negative/culture positive: Suspect or confirmed pulmonary/pleural TB AFB sputum smear negative, abnormal chest radiograph consistent with TB disease, might be NAAT positive and/or AFB culture positive. This includes other respiratory culture positive cases (i.e. BAL)
High/Med Priority Contact
Child less than 5 years old.

Other respiratory: Patient has suspected pulmonary TB, is AFB sputum smear negative, NAA T negative/culture negative and/or abnormal chest radiograph not consistent with TB disease
Contact s could include some of the same categories i.e., a child < 5 years old, presence of a significant medical risk factor, the exposure occurred during a medical procedure, or contact resides in household. (*See Figure 3, page 66*).

Figure 3. Flow Chart for Assessing Priority Status of Contacts



*Medical risk factors: HIV, diabetes, immunosuppressive medication, other medical risk factors
§Bronchoscopy, sputum induction, intubation, autopsy
†Exposure exceeds duration/environment limits per unit time established by the health department for high- and medium-priority contacts.

Use of Social Media

Social media is used widely, and can be a helpful tool for enhancing contact, outbreak, and genotype cluster investigations. Privacy and confidentiality issues must be addressed when developing local protocols on how to use social media and what is permitted within each LHD. Points to consider when developing local protocols for using social media for public health work include, but are not limited to the following:

- Review LHD and MDH policies and protocols regarding use of social media, including confidentiality and privacy protection.
- Consider creating a LHD generic and private profile or account for use by LHD staff that restricts use of social media for approved purposes only.
- Notify CTBCP if you plan to use social media for TB contact investigations.
- The following references provide more detailed information about social media applications in public health,

Curry International Tuberculosis Center: http://www.currytbcenter.ucsf.edu/sites/default/files/course-material/%5Bnid%5D/2._henry_leslie-using_social_media_to_augment_traditional_tb_ci_methods.pdf

CDC tool kit on using social media: https://www.cdc.gov/socialmedia/tools/guidelines/pdf/socialmediatoolkit_bm.pdf

Article on using social networking, and genotyping in contact investigation: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382754/

X. INFECTION CONTROL

General infection control protocols and procedures should be based on the 2005 CDC. Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health Care Settings, 2005. MMWR December 30, 2005/Vol. 54/No.RR-17. www.cdc.gov/mmwr/pdf/rr/rr5417.pdf These guidelines remain in effect as published with the exception of a recent change in recommendations specific to health care personnel as noted below.

Airborne infection isolation (AII) should be initiated on all hospitalized individuals suspected of having tuberculosis (TB). Healthcare personnel (HCP) caring for TB cases or clinically suspected cases in the hospital or in other settings, including the home, should follow appropriate infection control recommendations, including the use of N-95 respirators.

Respirator use for TB is regulated by the Occupational Safety and Health Administration (OSHA) under the general industry standard for respiratory protection. Specific respirators are certified for use in protection against airborne *M. tuberculosis*. In health care settings, either N95 respirators or powered air-purifying respirators may be used. When any type of respirator is used, the facility must have a respiratory protection plan in place that includes training and fit-testing.

Discontinuation of Airborne Infection Isolation Precautions (AII) within Hospital

Pulmonary TB patients can be transferred from an AII bed to a non-isolation hospital bed when another diagnosis has been assigned ***OR*** the patient continues to be suspected of having TB ***AND*** all the following criteria are met:

- Has received at least 2 weeks of treatment with an appropriate TB treatment regimen to which the strain is known or likely to be susceptible, *and*
- Demonstrates clinical and/or radiographic improvement, *and*

- Has three (3) negative acid-fast bacillus (AFB) smears from sputum specimens collected at 8-24-hour intervals (one early morning) **OR**

Meets criteria for discharge from AII based on GeneXpert testing.[42] **(**Appendix I**).** http://www.tbcontrollers.org/resources/airborne-infection-isolation/#.XLdPa-hKiM8

Multi-drug Resistant TB (MDR-TB) and Extensively-drug Resistant TB (XDR-TB)

Patients with MDR/XDR-TB should remain in an AII room until culture conversion or until discharged to home (see criteria below). Consult with the local health department (LHD) and Center for TB Control and Prevention (CTBCP) prior to discontinuing isolation of an MDR/XDR- TB patient.

Discharge from Hospital

There is no minimum number of days of anti-tuberculosis medication that are required before a patient may be discharged from the hospital to home as long as the patient is able and willing to follow LHD instructions regarding home isolation, and there are no individuals in the household that a) are high-risk for becoming infected, or b) for developing active TB if infected already (e.g., immune compromised), or c) are at risk for severe manifestations of TB if they develop active disease (e.g., infants). It is important to remember that all identified *close* contacts (household and non-household) may have already had significant exposure to the index case by the time the diagnosis is made.

Hospitalized, AFB sputum smear-positive TB patients who are not suspected of having drug resistant TB can be discharged to home if they meet *all* the following criteria *and* a discharge plan is in place that has been developed in conjunction with the LHD:

- Patient is in stable clinical condition,
- Patient is prescribed and is tolerating treatment with an appropriate antituberculosis regimen to which the strain is known or likely to be susceptible,
- Residence is stable, and address has been verified,
- Patient will be living alone OR returning to an environment where others have already been exposed to the patient and no significant contact with infants, young children, or immunosuppressed persons will occur,
- No service in which a provider (e.g., home attendant) will be routinely visiting the patient for several hours per day is required,
- Patient is willing to stay home (except for LHD approved medical appointments) until sputum smear negative, and
- Patient agrees to no visitors at home until LHD gives approval.

Patients suspected or confirmed MDR -XDR-TB disease should be kept in AII during the entire hospitalization or until culture conversion is documented, regardless of sputum AFB smear or GeneXpert results.

In consultation with the LHD and CTBCP, a MDR/XDR-TB patient may be discharged to home when an appropriate treatment regimen has been initiated, suitable arrangements have been made so that treatment can be continued and properly monitored on an outpatient basis, and the patient will not put any additional people at risk for exposure.

Admission to Long Term Care (LTC), Rehabilitation or Hospice Facilities

Patients must meet the criteria for discontinuation of airborne infection isolation (AII) unless AII can be provided in the facility.

Readmission to Long Term Care (LTC) Facilities

TST or IGRA testing for readmission to LTC facilities is not recommended for individuals who have completed an initial admission screening within the previous 12 months if there has been no exposure to a documented TB case, as verified by the LHD. Upon readmission, the resident should receive a TB "signs and symptoms" screening. If previous exposure has occurred, a TST or IGRA should be done upon readmission and the resident should be medically evaluated for TB.

Return to work or school

It is the responsibility of the LHD to determine when a patient with pulmonary/laryngeal TB

can return to school/work based upon the following general criteria:

Drug-susceptible (pan-sensitive) TB

- Completion of at least two weeks of treatment with a recommended TB treatment regimen, AND
- Clinical or radiographic improvement AND
- Three negative AFB smears from sputum specimens collected at 8-24- hour intervals. One of the 3specimens must be obtained in the early morning.

Patients working in high-risk settings (work sites with clients living with HIV, neonatal intensive care units, nursing homes, and congregate settings such as prisons, hospitals and shelters) may need to have three negative cultures to return to work, at the discretion of the LHD. Consultation with CTBCP is strongly recommended.

MDR/XDR-TB (culture confirmed)

- The resolution of fever and the resolution or near resolution of cough, AND
- At least two weeks of treatment with an antituberculosis regimen approved by CTBCP AND
- Three negative AFB **cultures** from sputum specimens collected 8-24 hours apart with at least one specimen collected in the early morning.

Infection Control Plans Local Health Departments (LHD)

Each LHD must have an up-to-date TB Infection Control Plan. The plan should be based on the risk assessment of the facility and address administrative controls, environmental controls, and respiratory protection.

Administrative controls consist of policies aimed to reduce the risk of exposure to individuals who might have TB disease, including TB testing and education of employees. *Environmental controls* include the use of measures such as local exhaust ventilation and AII rooms to prevent the spread and reduce the concentration of infectious TB droplet nuclei in the air. *Respiratory protection controls* include the training in and use of respiratory protection equipment and respiratory hygiene.

LHD TB infection control plans should be re-evaluated and updated as needed, but at least annually. Overall responsibility for the plan should be assigned to a specific staff position. A template is available from CTBCP which is based on the latest Centers for Disease Control (CDC) and OSHA recommendations regarding TB prevention and control for health care facilities. [(2)].

Long Term Care Facilities

All LTC facilities should have a written TB control plan based on the TB risk of the facility. Plans should include policies for testing of employees and residents, and procedures for evaluation of residents who develop TB symptoms. Guidance and a template for completing a risk assessment is available at https://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

All facilities should assess facility risk and update TB control plans annually. Risk assessments and TB Control Plans should be kept on file for reference.

Addictions Treatment Facilities

In Maryland, no active TB cases have been directly associated with any addiction treatment facilities in many years, indicating that the facilities themselves are low risk sites for TB transmission, according to the CDC "Guidelines for Preventing the Transmission of *Mycobacterium tuberculosis* in Health-Care Settings. 2005."

Clients of Maryland addictions facilities and programs should be assessed for TB risk and referred for TB testing only if one or more risk factors (in addition to drug use) are identified.

Hospitals

Hospital infection control and occupational health programs should utilize the CDC recommendations in the 2005 and 2019 documents to determine facility risk and employee testing requirements.[(2,64)]

Other Types of Residential Facilities

The need for a formal infection control plan for residential facilities such as group homes or assisted living facilities varies with local

epidemiology, clients served and ownership. LHD programs should consider reaching out to such facilities to a) determine if a plan exists or is needed and b) if any TB or LTBI education or training would be helpful.

Recommendations for Screening, Testing and Treatment of Health Care Personnel

Revised recommendations for TB screening, testing and treatment of health care personnel developed in collaboration with the National Tuberculosis Controllers Association and CDC, and vetted through both the Advisory Council on the Elimination of Tuberculosis (ACET) and the Healthcare Infection Control Practices Advisory Council (HICPAC) were published by CDC in May 2019.[52] These recommendations should substantially decrease the amount of serial testing done in health care settings. Please also refer to the ACOEM's for clarification and strategies for implementing these revisions.[53]

The changes in recommendations for health care personnel (formerly considered at higher risk for TB secondary to occupational exposure) are based on a substantial decline in TB cases overall in the U.S. since 2005, and a review of the literature which indicated TB incidence among health care personnel is now similar to that of the general population (~ 5%).

It is important to note the new recommendations do not eliminate the need for periodic facility risk assessments. These should continue to be done annually as noted previously.

Recommendations for health care personnel (HCP) engaged in any health care occupation or setting (either paid or volunteer) include the following;

a) Baseline (preplacement) risk assessment screening and testing.

Screen individual employees for TB risk and baseline TB testing using an IGRA or 2-step TST for those with no documentation of prior LTBI or TB disease, *plus* TB symptom review prior to starting work (preplacement). The IGRA or TST results provide comparison data in the event of a later potential or known TB exposure and help detect LTBI or TB disease before job placement.

The risk assessment assists in interpretation of testing results and symptom review. For example, in those who have an initial preplacement positive IGRA or TST but are asymptomatic and are assessed to be low risk for TB upon screening, a repeat test should be done which must also be positive for the diagnosis of LTBI to be made. [52]

The new recommendations suggest using the simple risk assessment screening described below. [64]

Indicators of risk* for tuberculosis (TB) at baseline health care personnel assessment†

Health care personnel should be considered to be at increased risk for TB if they answer "yes" to any of the following statements.

1. Temporary or permanent residence (for ≥1 month) in a country with a high TB rate (i.e., any country other than Australia, Canada, New Zealand, the United States, and those in western or northern Europe).

OR

2. Current or planned immunosuppression, including human immunodeficiency virus infection, receipt of an organ transplant, treatment with a TNF-alpha antagonist (e.g., infliximab, etanercept, or other), chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month), or other immunosuppressive medication.

OR

3. Close contact with someone who has had infectious TB disease since the last TB test.

* Individual risk assessment information can be useful in interpreting TB test results. (Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infec Dis 2017;64:111–5). https://academic.oup.com/cid/article/64/2/111/2811357external icon

† Adapted from a tuberculosis risk assessment form developed by the California Department of Public Health. https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-CA-TB-Risk-Assessment-and-Fact-Sheet.pdf

b) Postexposure screening and testing.
After a suspected or known exposure to a person with potentially infectious TB disease without use of adequate personal protection, health care personnel should have a timely symptom evaluation and additional testing, if indicated. Personnel without documented evidence of prior LTBI or TB disease should have an IGRA or a TST performed. Those with documentation of a prior diagnosis of LTBI or TB disease do not need additional testing as a result of an exposure.

If testing does take place, those with an initial negative test should be retested 8–10 weeks after the last exposure, preferably by using the same test type as was used for the prior negative test.

c) Serial screening and testing for health care personnel without LTBI.
In the absence of a known TB exposure or evidence of ongoing TB transmission within the facility, U.S. health care personnel (as identified in the 2005 guidelines) without LTBI should not undergo routine serial TB screening or testing at any interval after baseline (e.g., annually).

Health care facilities may consider serial TB risk assessment screening of certain groups who might be at increased occupational risk for TB exposure (e.g., pulmonologists or respiratory therapists) or for employees working in certain settings where transmission has occurred in the past (e.g., emergency departments).

These determinations should be individualized on the basis of factors that might include the number of patients with infectious pulmonary TB who are examined in these areas, whether delays in initiating airborne isolation occurred, or whether prior annual testing has revealed ongoing transmission. Consultation with the local or state health department is encouraged to assist in making these decisions.

*Routine serial **testing** of health care personnel in any setting is no longer recommended. This includes, TST testing, IGRA testing and CXRs.*

d) Evaluation and treatment of personnel diagnosed with LTBI
Health care personnel who are diagnosed with LTBI should be educated about TB infection, risks (both occupational and non-occupational) that can be associated with progression to active disease and provided with opportunities to initiate and complete treatment.

Treatment for latent TB infection (TLTBI) may be coordinated through the LHD or private provider/physician, as appropriate. Employees should be provided with documentation of their baseline testing, any medical follow-up including CXR results, and any subsequent tests for TB (including date, type of test and results) for future reference.

e) Education
Annual education of health care personnel on TB disease and LTBI, TB risk factors, signs and symptoms of TB and where to report any concerns is recommended. Annual education should be documented according to facility/company protocols and should include an emphasis on the treatment of any person with diagnosed LTBI. Employees should be told they can be treated for LTBI at any time, regardless of when the diagnosis was made, how risks for someone with LTBI to develop active TB can change over time, and that shorter, highly effective treatment regimens for LTBI now exist.

The updated recommendations can be found at: https://www.cdc.gov/mmwr/volumes/68/wr/mm6819a3.htm?s_cid=mm6819a3_w

XI. TB CONTOL IN CORRECTION AND DETENTION FACILITIES

Importance

Although overall incidence of new tuberculosis (TB) cases among the U.S population has remained at <10 cases per 100,000 persons since 1993, substantially higher case rates have been reported in correctional populations. Many incarcerated individuals are at high risk for TB secondary to pre-existing comorbidities such as HIV infection and the impact of other social determinants such as poverty, homelessness and substance abuse.

The physical structure of the facilities contributes to disease transmission, as facilities provide close living quarters, might have inadequate ventilation, and can be overcrowded. Movement of inmates into and out of overcrowded and inadequately ventilated facilities, coupled with pre-existing TB-related risk factors of the inmates, combine to make correctional and detention facilities high-risk environments for the transmission of *M. tuberculosis* and make implementation of TB control measures particularly difficult.

All correctional facilities should have a written TB control plan. The plan, developed in collaboration with the local health department (LHD), should be reviewed and updated annually. Plans are based on the TB risk assessment for the facility and should cover all aspects of TB control at the facility. Any agreements with the LHD for testing and treatment of inmates or staff, and continuation of treatment for inmates after release should also be included in the plan.

Facility Risk Assessment for TB

Facilities are designated as either minimal risk or non-minimal risk. Recommendations are from the TB Expert Panel, state of Maryland, November 2013.

Minimal TB Risk Facilities (defined as facilities with no cases for ≥ one year).

- Use full TB risk screening tool for everyone Test anyone for TB who answers "yes" to ANY screening question.

Non-minimal TB Risk Facilities (defined as facilities with ≥ one case within the past year).

- Follow CDC guidelines: *Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC*; MMWR 2006; 55 (No. RR-9). https://www.cdc.gov/mmwr/pdf/rr/rr5509.pdf

TB Testing and Facility Risk

Employee testing does not differ between minimal risk and non-minimal risk facilities. Testing of inmates is determined by the facility risk assessment.

Minimal Risk Facility

Employees: All employees should receive a single IGRA test or 2-step TST on hire, with evaluation of all positives. Employees who are TST/IGRA negative on hire should be tested annually. Employees who have a history of positive TST/IGRA should receive an annual risk assessment and TB symptom review.

Inmates: All inmates should be screened at entry for TB symptoms (such as cough, fever, night sweats) and referred to an airborne infection isolation (AII) room for further evaluation as necessary. Inmates with a personal TB risk should be tested within 7 days of incarceration. TB testing in minimal risk facilities may be considered for inmates with no identified personal risk and no TB symptoms. Consultation with the LHD and/or CTBCP is recommended.

Non-Minimal Risk Facility

Employees: All employees should receive a single IGRA test or 2-step TST on hire, with evaluation of all positives. Employees who are TST/IGRA negative on hire should be tested

annually. Employees who have a history of positive TST/IGRA should receive an annual risk assessment and symptom review.

Inmates: All inmates should be screened at entry for TB symptoms and referred to an AII room as described above. Inmates residing in non-minimal risk facilities should be tested within 7 days of incarceration. Consultation with the LHD and/or CTBCP is recommended.

HIV Testing

Because correctional facilities are considered settings in which the population is at increased risk for acquiring or transmitting HIV, routine HIV counseling, testing and referral is recommended for inmates.

Reporting

All entities, including federal facilities, must report suspected and confirmed TB cases to local and state health departments. ***Notify CTBCP as soon as a suspected TB case is identified, even if diagnostic test results are still pending***.

Airborne Infection Isolation (AII)

Inmates with symptoms of pulmonary TB should be isolated immediately. If an AII room is not available, the inmate should be placed in an area that reduces the possibility of exposure to staff and other inmates until transportation to a facility with AII can be arranged.
If AII is available at the facility, a respiratory protection program must be included in the TB control plan. Key elements of a respiratory protection program include 1) assignment of responsibility, 2) training, and 3) fit testing.

All confirmed and clinically suspected TB cases should be transported by ambulance. If an ambulance is not available, the inmate should wear a surgical mask (not a respirator) and staff should wear N-95 respirators during transport. If possible, the vehicle cab should be physically separate from the area where the inmate is located, and the ventilation system for the vehicle set to bring in as much outdoor air as possible, non-recirculating.

Release of Inmates with TB

Prior to release, plans for care of inmates with TB disease must be coordinated with the LHD. It is imperative that arrangements for directly observed therapy are in place before the inmate is released. Because treatment of latent infection may not be feasible in the correctional facility, collaboration with the LHD is important to identify those inmates with the highest risk and to coordinate plans for treatment after release.

Undocumented Individuals

Immigration and Customs Enforcement (ICE) is a division of the U.S., Department of Health and Human Services and detains approximately 200,000 people annually while enforcing immigration law. Local detention centers may contract with U.S. Marshalls or ICE (Immigration and Customs Enforcement) to detain and hold undocumented people who may come from high-risk nations.

LHDs should check with the local detention centers annually regarding federal contracts. Presently, ICE does not deport detainees with known infectious TB, but such persons might be deported when no longer infectious, even if treatment has not been completed or culture and susceptibility results are pending. If an ICE detainee is diagnosed with clinically suspected TB or TB disease, immediately contact the CTBCP to coordinate with ICE personnel for care of the detainee.

ICE may enroll confirmed and clinically suspected TB cases in programs (e.g., Cure TB, TB Net, and the U.S. Mexico Binational Tuberculosis Referral and Case Management Project) to facilitate TB referrals and follow-up for patients who move between the United States and other countries.

Unaccompanied minor children are often detained at the pint of entry and transported to facilities many miles from their point of entry to the U.S. pending review of their status. These children are also considered high-risk for TB.

Program evaluation

Program evaluation is an integral part of the overall correctional quality improvement/ assurance program. Evaluation should include routine assessment of facility TB risk, and collection and analysis of data on staff and inmate TSTs/IGRAs.

Contact Investigations

Contact investigations must be coordinated with local health departments. [41] Local TB program staff will provide guidance on determining the infectious period of the index case, assist in determining the extent of potentially exposed individuals and the logistics of screening and testing of those potentially exposed.
It is important that local TB programs receive aggregate data on the number of people identified, evaluated, infected, and treated. On rare occasions LHD or CTBCP staff might request to participate in a medical record review of the index case; particularly in instances where delayed diagnosis (either in the community or in the correctional setting), a diagnosis of MDR or XDR-TB or other issues might have contributed to exposure. These reviews are usually coordinated through the institution's infection control medical staff and are done as part of the larger public health investigation.

XII. NATIONAL TUBERCULOSIS INDICATORS PROJECT

The National Tuberculosis Indicators Project (NTIP) is a system developed by the Centers for Disease Control (CDC) to monitor progress of tuberculosis (TB) control programs in the U.S. toward national goals and objectives. These indicators reflect the national priorities for TB control activities, and all programs receiving federal funds are expected to monitor their programs using this system.

In 2010 the Maryland Center for TB Control and Prevention (CTBCP) began using NTIP data to assess the success of state TB control activities and to report progress toward achieving national objectives to the CDC in annual and interim reports. NTIP reports are provided by the CDC for state and big city level programs, and for some county level programs with higher rates of TB.

There are 15 categories of objectives, most pertaining to treatment of TB cases and contact investigations. NTIP data comes from several sources. TB case data are reported by the counties to CTBCP via the National Electronic Disease Surveillance System (NEDSS) Report of Verified Case of Tuberculosis (RVCT), which is then forwarded to the CDC.

Information on contact investigations for respiratory/pleural site of disease is reported to CTBCP on the Contact Investigation Summary report which is sent to CDC as a statewide Aggregate Report for Program Evaluation (ARPE). Information on the evaluation of immigrants and refugees with abnormal CXRs read overseas as consistent with TB is reported to CTBCP and entered into the Electronic Disease Notification (EDN) system by the CTBCP staff. State level data for all of the NTIP indicators are included in reports to the CDC, but not all are applicable to LHD TB control program goals and objectives.

NTIP National TB Program Objectives

(*indicates county level objectives)

- Completion of treatment (cases)*
- TB case rates
  - U.S.-born individuals
  - Foreign-born individuals
  - U.S.-born non-Hispanic blacks
  - Children younger than 5 years of age
- Contact investigations*

  - Elicitation of contacts
  - Evaluation of contacts
  - Initiation of TLTBI in contacts
  - Completion of TLTBI in contacts
- Laboratory reporting
  - Time from receipt of pleural/respiratory specimen to report of NAA test result
  - Initial drug susceptibility testing of positive cultures
- Initiation of treatment (cases)*
- Sputum culture conversion*
- Data reporting*
  - Completeness of RVCT data
  - Completeness of ARPE data
  - Completeness of EDN data
- 4-drug initial therapy (cases)*
- Universal genotyping
- Known HIV status (cases)*
- Evaluation of immigrants and refugees*
- Sputum culture result for respiratory/pleural TB cases*
- Program evaluation
- Human resources development
- TB training focal point

TB Program Evaluation

TB program evaluation is an essential component of TB prevention and control and is a core requirement of all programs receiving federal funds for TB control activities. The Maryland TB Program Evaluation Team utilizes NTIP and cohort review data to focus evaluation efforts. For more information on NTIP or TB Program Evaluation, contact CTBCP.

XIII. IMMIGRANT AND REFUGEE SCREENING FOR TUBERCULOSIS

The Centers for Disease Control (CDC), United States Public Health Service (PHS), is responsible for ensuring that anyone who is not a United States citizen (immigrants, refugees, asylees, and parolees) entering the U.S. do not pose a threat to the public health of the U.S. Immigrants and refugees entering the U.S. or applying for adjustment of status to permanent resident must have a physical and mental health examination as part of the visa application process. This examination includes an evaluation for tuberculosis (TB). Applicants with findings suggestive of inactive TB or with test results indicating latent infection are designated as Class B TB and are instructed to follow up with the local health department at their destination.

The majority of immigrants and refugees with Class B TB designations arrive in Maryland from high TB incidence countries. Given that individuals who recently immigrated are at higher risk for developing TB disease, the evaluation of these individuals is an important aspect of TB prevention in Maryland.

Overseas TB Screening

The CDC Division of Global Migration and Quarantine (DGMQ) has published revised Technical Instructions for Panel Physicians to implement stronger and more consistent standards for TB screening of refugees and immigrants applying for entry into the U.S. These instructions can be found on at www.cdc.gov/immigrantrefugeehealth.

These standards help to ensure that overseas screening for TB is conducted according to the highest clinical standards and screenings are consistent from one country to another, thereby reducing the diagnosis of TB disease among non-U.S.-born individuals after arrival in the U.S. Applicants with overseas evaluation for TB are assigned a TB classification (*Table 19*).

Patients with active pulmonary or laryngeal TB (Class A, TB) must complete directly observed TB treatment prior to U.S. immigration. In exceptional medical situations, this requirement can be waived. Waivers may be granted to young children with TB disease or to others who have a complicated clinical course that would benefit from receiving TB treatment in the U.S.

Table 18. Overseas TB Classifications by Panel Physicians	
TB Classification	Criteria
No TB Classification	Normal TB screening examination.
Class A TB with Waiver	Applicants who have pulmonary or laryngeal TB disease and have been granted a waiver to enter U.S. prior to treatment completion.
Class B0 TB, Pulmonary	Applicants who were diagnosed with pulmonary TB by the panel physician or presented to the panel physician while on tuberculosis treatment and successfully completed directly observed therapy under the supervision of a panel physician prior to immigration.
Class B1 TB, Pulmonary	Applicants have findings suggestive of pulmonary TB but have negative AFB sputum smears and cultures and are not diagnosed with TB or can wait to have TB treatment started after immigration.
Class B1 TB, Extrapulmonary	Applicants with evidence of extrapulmonary TB.
Class B2 TB, LTBI Evaluation	TST ≥ 10mm (TST ≥ 5mm for contacts) or positive IGRA, otherwise negative evaluation for TB.
Class B3 TB, Contact Evaluation	Recent contact of a known TB case without evidence of active TB disease. TST/IGRA results and information about source case should be documented. .

United States TB Screening

Upon arrival in the U.S., TB evaluation information for refugees and immigrants is collected by the U.S. Citizenship and Immigration Services (USCIS) of the Department of Homeland Security (DHS) and forwarded to the CDC Quarantine Station that has jurisdiction over the port of arrival.

The information is entered by DGMQ into the Electronic Disease Notification (EDN) system and forwarded to the state health department of final destination of the applicant. For refugees and immigrants arriving in Maryland, EDN notifications are received by the Center for TB Control and Prevention (CTBCP) and forwarded to the appropriate local jurisdiction.
Local health department (LHD) physicians provide a follow-up evaluation of all refugees and immigrants with TB classifications *(see Table 19 for Overseas TB Classifications; refer to Table 21 for U.S. Civil Surgeon Evaluation Guidelines for Class B TB).* After this evaluation is complete, a post-arrival TB diagnosis is assigned *(see Table 20,page 79).*

The evaluation, diagnosis, and treatment (if indicated) are documented on the TB Follow-Up Worksheet by the LHD and sent to CTBCP by courier or mail.

Technical Instructions for Tuberculosis Screening and Treatment for Civil Surgeons can be found on the CDC website. https://www.cdc.gov/immigrantrefugeehealth/exams/ti/civil/tuberculosis-civil-technical-instructions.html

National goals set by CDC for this population include:

- Initiation of evaluation within 30 days of arrival in the U.S.
- Completion of evaluation within 90 days of notification of arrival in the U.S.
- Initiation of treatment for latent infection.
- Completion of treatment for latent infection.

Percentages of evaluations performed within designated time frames and TLTBI outcomes are included in CTBCP reports to CDC.

Adjustment of Status

Other individuals may present to LHDs or be referred by local civil surgeons for medical evaluation, including immigrants and refugees applying for adjustment of status to permanent resident and other individuals required by USCIS to have a medical examination.

As part of this examination, civil surgeons perform a TB evaluation and ***must*** refer all individuals with abnormal CXR suggestive of active or inactive TB disease or with signs or symptoms of TB (regardless of the TST result or CXR findings) to the LHD for further evaluation *(see Table 20).* For these applicants, the civil surgeon does not classify, issue medical clearance for TB, or sign the clearance form until the applicant returns from the LHD with documentation of the results of his or her TB evaluation.

Applicants diagnosed with active pulmonary TB disease must complete a recommended course of treatment before the civil surgeon can medically clear them. Civil surgeons are required to report applicants diagnosed with LTBI to health departments including applicant's name, contact information, IGRA results, and chest x-ray results.

The 2018 TB Technical Instructions do not require health departments to contact these applicants or provide treatment for LTBI. However, if LHD resources permit TLTBI, this is a high-risk group for preventing active disease later. VDOT and use of short-course TLTBI may be appropriate for this population.

Maryland has one of the highest asylee populations in the nation. Please note that Refugee Medical Assistance (RMA) funds which are used to support and/or reimburse the cost of the initial health screens for new refugees and asylees cannot be used to pay for the health examinations required of asylees or other immigrants seeking change of status documentation.

Asylees and other immigrants who present for evaluation at LHDs may be charged for services, either through their health insurance plans or by self-pay with application of sliding scale fees if indicated. This is both legal and appropriate. Asylees who are truly indigent should be referred to local social services for evaluation and assistance.

For more information and/or clarification on the CDC Technical Instructions for Panel Physicians and/or Civil Surgeons please refer to the MDH Center for TB Control and Prevention https://phpa.health.maryland.gov/OIDPCS/CTBCP/pages/Home.aspx
or the MDH Office of Global Migration and Immigrant Health https://phpa.health.maryland.gov/OIDPCS/OIH/pages/Home.aspx

Additional information and updates may be found on the CDC website at https://www.cdc.gov/immigrantrefugeehealth/exams/ti/civil/technical-instructions-civil-surgeons.html

Table 19. TB Classifications and Actions for Civil Surgeons [e]		
Classification	Criteria	Refer to LHD for Further Work-Up
Class A - Pulmonary TB Disease, Active, Infectious	• Abnormal chest radiograph(s) suggestive of active TB disease • Either one or more sputum smears positive for AFB, or one or more cultures positive for *Tuberculosis complex*	Required [a)]
Class B1 - Pulmonary TB, Active, Non-infectious	• Abnormal chest radiograph(s) suggestive of active TB disease • Three sputum smears negative for AFB and three cultures negative for *M. tuberculosis complex*	Required [a)]
Class B1 - Extrapulmonary TB, Active, Non-infectious	• Radiographic or other evidence of extrapulmonary TB disease • No pulmonary TB	Required [b)]
Class B2 - Pulmonary TB, Inactive	• Abnormal chest radiograph(s) suggestive of inactive TB disease • No sputum smears or cultures required[3]	Required [c)]
Class B–Latent TB Infection Needing Evaluation for Treatment	• TST reaction ≥ 10 mm or positive IGRA in recent U.S. arrivals • TST reaction ≥ 5 mm or positive IGRA in specific groups • No evidence of active TB disease	Recommended [d)]
Class B– Other Chest Condition (non-TB)	• Abnormal chest radiograph, not suggestive of TB disease, needing follow-up	N/A
If the applicant has TB signs or symptoms, he or she should be referred to the health department TB Control Program for further evaluation regardless of TST result or chest radiograph appearance.		

a) Refer to health department TB Control Program for work-up of suspicious chest radiograph

b) Make required referral to health department TB Control Program for further evaluation and, if needed, initiation of CDC/ATS/IDSA-recommended drug regimen for extrapulmonary TB

c) If health department TB Control Program decides to perform sputum smears and cultures, categorize as Class A or B1 depending on results

d) After discussing resources with health department TB Control Program

e) New technical instructions for overseas panel physicians allow for the classification of a person as a B0 waiver which indicates the person has completed an approved treatment regimen for TB under DOT and requires no additional follow-up upon arrival to the U.S.

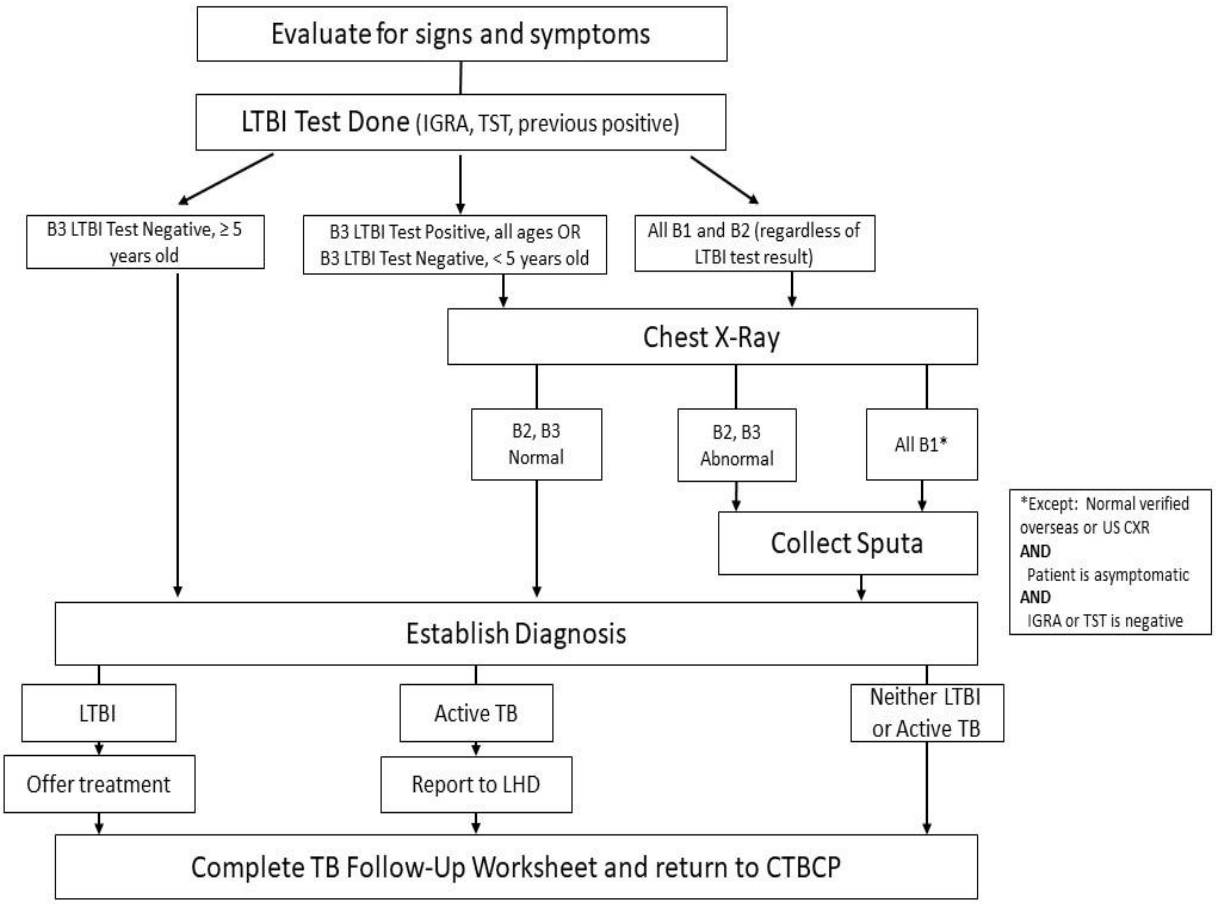
B-Waivers

Individuals coming to reside in the United States (regardless of reason) are required to undergo tuberculosis screening under guidelines and standards established by CDC. These various classifications also require specific follow-up once the individual arrives in the U.S. with required documentation reportable to state TB programs. Individuals with B1-waiver status are considered a very high-risk population in Maryland. Data from 2012-2015 indicates a case rate of 1,398 per 100,000, and 45% of B waivers were diagnosed with LTBI (2008-2012). Details on the overseas examinations can be found at https://www.cdc.gov/immigrantrefugeehealth/exams/ti/panel/tuberculosis-panel-technical-instructions.html . Recommendations for diagnostic follow-up of those arriving with B-waiver status are summarized in Table 21. below and (*See Figure 4, page 80*). B0 waiver classifications indicate the person has successfully completed treatment with DOT.

Table 20. Maryland CTBCP B Waiver Evaluation Recommendations

Class Status	Maryland CTBCP B Waiver Evaluation Recommendations
Class B1 TB: **Panel physician found evidence of extrapulmonary or sputum AFB smear negative pulmonary TB disease. Includes old healed TB, and previously treated TB.**	**1.** Evaluate for signs and symptoms of TB disease that may have developed since pre-departure exam. **2.** Administer a TST or IGRA (i.e., QFT® or T-SPOT®) regardless of BCG history, unless the person has a reliable history of previous treatment for TB or reliable documentation of a previous positive test. **3.** Obtain a CXR, regardless of TST/IGRA result. **4.** Verify any previous treatment for TB via pre-departure exam or by patient report. **5.** Do additional diagnostic tests (e.g., sputa for AFB, other imaging), as indicated, to determine diagnosis. **6.** Establish a diagnosis (i.e., LTBI, active TB disease, or neither). **7.** If active TB is suspected or diagnosed, report to CTBCP within one working day. **8.** If LTBI is diagnosed, prescribe treatment for LTBI.
Class B2 TB: **LTBI (TST > 10 mm) Panel physician diagnosed this patient with LTBI, and treatment was not initiated or completed prior to arrival.**	**1**. Evaluate for signs and symptoms of TB disease that may have developed since pre-departure exam. **2**. If previous results are unreliable, repeat TST or IGRA to confirm or rule-out LTBI diagnosis. **3.** Do a CXR unless the patient had repeated CXRs overseas showing improvement or stability, AND the most recent CXR was done less than 3 months ago. **4.** Do a CXR for those who are HIV (+), or who have signs and symptoms compatible with active TB disease, regardless of previous results. **5. – 8.** same as above
Class B3 TB: **TB Contact – Pre-departure exposure to a confirmed TB case and pre-departure screening test (TST or IGRA) was negative.**	**1.** Evaluate for signs and symptoms of TB disease that may have developed since pre-departure exam. **2.** Administer a TST or IGRA regardless of BCG history. **3.** Do a CXR for patients with a positive TST or IGRA, or with symptoms compatible with TB disease, regardless of the TST or IGRA result. **4.** If more information about the source case is needed (e.g. drug resistance), call CTBCP. **5. – 8.** same as above
Class B0 TB: Diagnosed pulmonary TB and successfully completed DOT under supervision of panel physician	**1.** Evaluate for signs and symptoms of TB disease that may have developed since pre-departure exam **2.** Do CXR if overseas CXR not available for review OR most recent CXR more than 1 year old **3.** Review overseas treatment and consult with CTBCP as needed for inadequate treatment
Return completed TB Class Follow-up Worksheet to: Center for TB Control and Prevention 201 W. Preston St, 3rd Floor Baltimore, Maryland 21201 Phone: 410-767-6698 Secure fax: 410-767-5972	

Figure 4. Diagnostic Evaluation Steps for All TB B-waiver individuals[†]



[†]Except B0 waivers

Questions regarding B-waiver evaluations should be directed to the Maryland Center for TB Control and Prevention at Phone: 410-767-6698 or Secure fax: 410-767-5972

Questions regarding treatment of TB infected individual evaluated as part of the B-waiver program may directed to the local health department (see *Appendix A* for contact information) or to the Maryland Center for TB Control and Prevention.

REFERENCES

1. CDC. Core curriculum on tuberculosis: what the clinician should know. 6th ed. Atlanta, GA; US Department of Health and Human Services, CDC, 2013. Available at: www.cdc.gov/tb.
2. CDC. Guidelines for Preventing the Transmission of Mycobacterium tuberculosis in Health Care Settings, 2005. MMWR December 30, 2005/Vol. 54/No.RR-17. Available at: www.cdc.gov/mmwr/pdf/rr/rr5417.pdf.
3. Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection - United States, 2010, MMWR 2010;59(No. RR-5).
4. CDC. Guidelines for Using the QuantiFERON-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. MMWR December 15, 2005/Vol. 54/No. RR-15. Available at: www.cdc.gov/mmwr/pdf/rr/rr5415.pdf.
5. CDC. Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis. MMWR December 15, 2005/Vol.54/No. RR-15. Available at: www.cdc.gov/mmwr/pdf/rr/rr5415.pdf.
6. U.S. Preventive Service Task Force Latent Tuberculosis Infection: Screening Recommendations . September 2016 http://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/latent-tuberculosis-infection-screening.
7. American Thoracic Society, Centers for Disease Control and Prevention and Infectious Disease Society of America Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603-662.
8. Chaulk P, Moore-Rice K, Rizzo T, et al. Eleven years of community-based directly observed therapy for tuberculosis. JAMA 1995;27:945-51.
9. MDH Health Officer Memorandum 16002 *Maryland DHNH TB Laboratory Recommendations for Interpretation of QFT-GIT Tests*, December 2015.
10. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR 2020;69 (RR-1):1-11.
11. Diagnosis of TB in Adults and Children , Clinical Infectious Disease 2017:64 (15 January) https://www.thoracic.org/statements/resources/tb-opi/diagnosis-of-tuberculosis-in-adults-and-children.PDF.
12. Miramontes R, et al. (2015) Tuberculosis Infection in the United States: Prevalence Estimates from the National Health and Nutrition Examination Survey, 2011-2012. PLoS ONE 10(11).
13. Serwint JR, Hall BS, Baldwin RM, Virden JM. Outcomes of annual tuberculosis screening by Mantoux test in children considered to be high risk: results from one urban clinic. Pediatrics 1999;99:529-533.
14. Montgomery County. Immunization and Screening Statistics. Montgomery County School Health Services, Maryland 2002.
15. American Academy of Pediatrics. 2018 Red Book: Report of the Committee on Infectious Disease. 25th ed., Elk Grove Village, IL: American Academy of Pediatrics; 2018.
16. Ozuah PO, Ozuah TP, Stein REK, Burton W, Mulvihill M. Evaluation of risk assessment questionnaire used to target tuberculin skin testing in children. JAMA 2001;285:451-453.
17. CDC. Recommendations for using smallpox vaccine in a pre-event vaccination program: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR 2003;52 (RR-7):13.
18. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). MMWR 2002; 51(RR-2):6-17.
19. CDC. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Accessed (June 2020)
20. CDC. Implementation of New TB Screening Requirements for U.S.-Bound Immigrants and Refugees, 2007–2014. MMWR 2014;63 (11):234-236.
21. New York City Department of Health, Bureau of Tuberculosis Control. Clinical policies and protocols (third edition). New York: New York City Department of Public Health: 1999.
22. CDC. Tuberculosis Associated with Blocking Agents Against Tumor Necrosis Factor-Alpha-California, 2002-2003. MMWR August 5, 2004/53 (30); 683-686.
23. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098-104.
24. CDC. Update: Adverse event data and revised American Thoracic Society/ CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection - United States, 2003. MMWR 2003;52:735-9.
25. CDC. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC Recommendations - United States, 2001. MMWR 2001;50:733-735.
26. Golub JE. Patient and health care delays in TB diagnosis in a low incidence state. Doctoral dissertation, Johns Hopkins University, 2002.
27. Iseman, MD. A Clinician's Guide to Tuberculosis. Baltimore: Lippincott Williams & Wilkens; 2000.
28. Carroll KC, Pfaller MA, ML Landry et al., Manual of clinical microbiology, 12th ed. American Society for Microbiology,

Washington, D.C., 2019.
29. Woods GL, Bergmann JS, Williams-Bouyer N. Clinical evaluation of the Gen-probe Mycobacterium direct test for rapid detection of Mycobacterium tuberculosis in select nonrespiratory specimens. J Clin Microbiol 2001;39:747-749.
30. Jasmer RM, Roemer M, Hamilton J, Bunter J, Braden CR, Shinnick TM, Desmond EP. A prospective, multicenter study of laboratory cross-contamination of Mycobacterium tuberculosis cultures. Emerg Infect Dis 2002;8:1260-3.
31. Sbarbaro J. The patient-physician relationship: compliance revisited. Ann Allergy 1990:64:325.
32. CDC. Notice to readers: Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. MMWR 2002;51:214-215.
33. World Health Organization. WHO Report 2002, Global tuberculosis control. Geneva: World Health Organization; 2002. WHO/CDC/TB/2002.295. Available at http://www.who.int/gtb/publications.
34. Prevention and control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC. MMWR July 7, 2006/55 (RR-09); 1-44. Available at https://www.cdc.gov/mmwr/PDF/rr/rr5509.pdf
35. CDC. National TB Program Objectives and Performance Targets for 2025.
36. Maryland Code Annotated, Health General §§18-324 and 325.
37. Maryland Code of Regulations (COMAR) 10.06.01.
38. CDC. Provisional CDC guidelines for the use and safety monitoring of bedaquiline for the treatment of multidrug-resistant Tuberculosis. MMWR 2013; 62(RR-09):1-12.
39. CDC. Latent Tuberculosis infection: a guide for primary health care providers. Treatment of latent TB infection: treatment regimens. Available at: www.cdc.gov/tb .
40. Curry International Tuberculosis Center. Medication fact sheets. In, *Drug-resistant Tuberculosis: A survival guide for clinicians,* (pg. 99). (2016). (3rd ed.). http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
41. CDC. Treatment of Tuberculosis. MMWR June 20, 2003/Vol.52/No. RR-11. Available at: http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf.
42. Consensus statement on the use of Cepheid Xpert MTB/RIF® assay in making decisions to discontinue airborne infection isolation in healthcare settings, NTCA/APHL, April 2016. http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf
43. Journal of Clinical Infectious Disease, *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis,* August 11, 2016, pages 1-49. https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf
44. Andrey S. Borisov, MD1; Sapna Bamrah Morris, MD1; Gibril J. Njie, MPH1; Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent *Mycobacterium tuberculosis,* MMWR Morb Mortal Wkly Rep 2018;67:[723-726]. https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w
45. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis [online]. 2013. Available from URL: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm
46. Schaaf HS, Garcia-Prats AJ, Donald PR. Antituberculosis drugs in children. Clin Pharmacol Ther 2015; 98:252–65.
47. Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med 2014; 371:1599–608.
48. Andrea T. Cruz,1,2,3 Amina Ahmed,5 Anna M. Mandalakas,1,4 and Jeffrey R. Starke, Treatment of Latent Tuberculosis Infection in Children, Journal of the Pediatric Infectious Diseases Society, Vol. 2, No. 3, pp. 248–58, 2013. DOI:10.1093/jpids/pit030 © The Author 2013. Pub. by Oxford University Press on behalf of the Peds Infect Diseas Society.
49. Nahid P, Mase S, Battista G, et al. Treatment of Drug Resistant Tuberculosis: an official ATS/CDC/IDSA Clinical Practice Guideline, Am Journal Resp Crit Care Med, Vol. 200, No. 10, pp. e93-e142.
50. National Library of Medicine HealthReach 2019 (health information in many languages) https://healthreach.nlm.nih.gov/searchresults?keywords=TB&btnsearch=Search&author=&language=&format=&user=&records=10&page=2
51. Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, 2nd edition, WHO, 2014 https://apps.who.int/iris/bitstream/handle/10665/112360/9789241548748_eng.pdf;jsessionid=5BCA31584FFA627CFF0ACEFE4DF579F5?sequence=1
52. Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis Screening, Testing, and Treatment of U.S. Health Care Personnel: Recommendations from the National Tuberculosis Controllers Association and CDC, 2019. MMWR Morb Mortal Wkly Rep 2019;68:439–443. DOI http://dx.doi.org/10.15585/mmwr.mm6819a
53. Thanassi W, Behrman A, Reves R et al. Tuberculosis screening testing and treatment of US health care personnel: ACOEM and NTCA Joint Task Force on Implementation of the 2019 MMWR Recommendations. JOEM 2020; Vol. 62, No. 7, pp. e355-e369.

Appendix A. Maryland LHD Tuberculosis Control Directory

Maryland Local Health Department Tuberculosis Control Directory

COUNTY	TELEPHONE NUMBER	FAX NUMBER
01 ALLEGANY	(301) 759-5000	(301) 777-5669
02 ANNE ARUNDEL	(410) 222-7256	(410) 222-7490
03 BALTIMORE	(410) 887-2243	(410) 887-8251
04 CALVERT	(410) 535-5400	(410) 535-1955
05 CAROLINE	(410) 479-8000	(410) 479-4864
06 CARROLL	(410) 876-2152	(410) 876-4959
07 CECIL	(410) 996-5500	(410) 996-1019
08 CHARLES	(301) 609-6900	(301) 934-7048
09 DORCHESTER	(410) 228-3223	(410) 228-9319
10 FREDERICK	(301) 600-1029	(301) 600-1403
11 GARRETT	(301) 334-7777	(301) 334-7771
12 HARFORD	(410) 838-1500	(410) 420-3448
13 HOWARD	(410) 313-6300	(410) 313-6108
14 KENT	(410) 778-1350	(410) 778-7913
15 MONTGOMERY	(240) 777-1800	(240) 777-4899
16 PRINCE GEORGES	(301) 583-7879	(301) 772-9897
17 QUEEN ANNES	(410) 758-0720	(410) 758-3092
18 ST. MARY'S	(301) 475-4330	(301) 475-4308
19 SOMERSET	(443) 523-1700	(410) 651-5699
20 TALBOT	(410) 819-5600	(410) 819-5693
21 WASHINGTON	(240) 313-3200	(240) 313-3334
22 WICOMICO	(410) 749-1244	(410) 548-5151
23 WORCESTER	(410) 632-1100	(410) 632-0906
24 BALTIMORE CITY	(410) 396-4444	(410) 545-6645
	(410) 396-9413	(410) 396-9403

MDH Center for TB Control and Prevention	(410) 767-6698
MDH Mycobacteriology Laboratory	(443) 681-3942

For urgent matters after business hours, call MDH on-call pager (410) 767-6700

Appendix B. Tuberculosis Estimated Incidence 2019
(Per 100 000 population per year)

Source: World Health Organization http://www.who.int/tb/publications/global_report/en/

"High Incidence" areas are defined by the Maryland MDH, Center for TB Control and Prevention as areas with reported or estimated incidence of ≥ 15 cases per 100,000 persons. The ≥ 15 cases per 100,000 persons marker was selected based on a review of state TB epidemiology and countries represented.

Afghanistan	189
Albania	16
Algeria	61
American Samoa	2.1
Andorra	7.5
Angola	351
Anguilla	22
Antigua and Barbuda	0
Argentina	29
Armenia	26
Aruba	2.2
Australia	6.9
Austria	6.2
Azerbaijan	60
Bahamas	15
Bahrain	12
Bangladesh	221
Barbados	0
Belarus	29
Belgium	8.9
Belize	27
Benin	55
Bermuda	3.7
Bhutan	165
Bolivia (Plurinational State of)	106
Bosnia and Herzegovina	27
Botswana	253
Brazil	46
British Virgin Islands	3.9
Brunei Darussalam	64
Bulgaria	21
Burkina Faso	47
Burundi	107
Cabo Verde	46
Cambodia	287
Cameroon	179
Canada	5.5
Cayman Islands	6
Central African Republic	540
Chad	142
Chile	18
China	58
China, Hong Kong SAR	63
China, Macao SAR	65

Columbia	35
Comoros	35
Congo	373
Cook Islands	13
Costa Rica	10
Cotte d'Ivoire	137
Croatia	8
Cuba	6.5
CuraÃ §ao	7.2
Cyprus	5.3
Czech Republic	4.9
Dem. People's Rep of [North] Korea	513
Democratic Republic of the Congo	320
Denmark	5
Djibouti	234
Dominica	16
Dominican Republic	42
Ecuador	46
Egypt	12
El Salvador	58
Equatorial Guinea	181
Eritrea	86
Estonia	13
Eswatini	363
Ethiopia	140
Fiji	66
Finland	4.7
France	8.7
French Polynesia	20
Gabon	521
Gambia	158
Georgia	74
Germany	5.8
Ghana	144
Greece	4.3
Greenland	128
Grenada	3.1
Guam	54
Guatemala	26
Guinea	176
Guinea-Bissau	361
Guyana	79
Haiti	170
Honduras	31

Hungary	6.3
Iceland	4.4
India	193
Indonesia	312
Iran (Islamic Republic of)	13
Iraq	41
Ireland	5.8
Israel	2.9
Italy	7.1
Jamaica	3.2
Japan	13
Jordan	5.5
Kazakhstan	68
Kenya	267
Kiribati	436
Kuwait	22
Kyrgyzstan	110
Lao People's Democratic Republic	155
Latvia	26
Lebanon	13
Lesotho	654
Liberia	308
Libya	59
Lithuania	42
Luxembourg	9
Madagascar	233
Malawi	146
Malaysia	92
Maldives	36
Mali	52
Malta	14
Marshall Islands	483
Mauritania	89
Mauritius	12
Mexico	23
Micronesia (Federated States of)	100
Monaco	0
Mongolia	428
Montenegro	15
Montserrat	0
Morocco	97
Mozambique	361
Myanmar	322
Namibia	486
Nauru	182
Nepal	238
Netherlands	5
New Caledonia	9.4
New Zealand	7.5
Nicaragua	43
Niger	84
Nigeria	219
Niue	0
North Macedonia	12

Northern Mariana Islands	103
Norway	3.3
Oman	8.5
Pakistan	263
Palau	38
Panama	37
Papua New Guinea	432
Paraguay	46
Peru	119
Philippines	554
Poland	15
Portugal	19
Puerto Rico	1.4
Qatar	35
Republic of Korea	59
Republic of Moldova	80
Romania	66
Russian Federation	50
Rwanda	57
Saint Kitts and Nevis	1.5
Saint Lucia	3.8
Saint Vincent and the Grenadines	4.2
Samoa	11
San Marino	0
Sao Tome and Principe	114
Saudi Arabia	9.9
Senegal	117
Serbia	14
Seychelles	16
Sierra Leone	295
Singapore	41
Sint Maarten (Dutch part)	14
Slovakia	4.5
Slovenia	5.4
Solomon Islands	66
Somalia	258
South Africa	615
South Sudan	227
Spain	9.3
Sri Lanka	64
Sudan	67
Suriname	29
Sweden	5.5
Switzerland	5.4
Syrian Arab Republic	19
Tajikistan	83
Thailand	150
Timor-Leste	498
Togo	37
Tokelau	30
Tonga	11
Trinidad and Tobago	18
Tunisia	35

Turkey	16
Turkmenistan	45
Turks and Caicos Islands	12
Tuvalu	296
Uganda	200
Ukraine	77
United Arab Emirates	1
United Kingdom of Great Britain and Northern Ireland	8
United Republic of Tanzania	237

United States of America	3
Uruguay	35
Uzbekistan	67
Vanuatu	41
Venezuela (Bolivarian Republic of)	45
Viet Nam	176
Wallis and Futuna Islands	10
Yemen	48
Zambia	333
Zimbabwe	199

Appendix C. First Line TB Medications Major Adverse Reactions/Monitoring

Isoniazid (PO or IM) INH [a]

Adverse Reactions:
Hepatic enzyme elevation, peripheral neuropathy, hepatitis, rash, CNS effects, increased phenytoin, (Dilantin®), and disulfiram (Antabuse®) levels.

Recommended Monitoring:
Baseline hepatic enzymes. Repeat monthly if baseline abnormal, risk factors for hepatitis, or symptoms of adverse reactions. Hepatitis risk increases with age and ETOH consumption. Overdose may be fatal. Aluminum-containing antacids reduce absorption. Pyridoxine (vitamin B_6) may decrease peripheral neuritis and CNS effects.

Rifampin (PO or IV/IM) RIF [a]

Adverse Reactions: Hepatitis, fever, thrombocytopenia, flu-like syndrome, rash, GI upset, renal failure. Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, theophylline, dapsone, ketoconazole, protease inhibitors (PIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses.

Recommended Monitoring:
CDC no longer recommends routine monitoring tests. However, many clinicians continue to order baseline CBC, platelets, hepatic enzymes. Repeat if baseline abnormal, risk factors for hepatitis or symptoms of adverse reactions.

Patients on methadone will need an increased dose of methadone (average 50%) to avoid opiate withdrawal. Interaction with many drugs leads to decreased levels of one or both. May make glucose control more difficult in diabetics. Contraindicated for patients taking PIs and most NNRTIs. Women on birth control pills need a barrier method while on rifampin

Pyrazinamide (PO) PZA [b]

Adverse Reactions:
GI upset, hepatotoxicity, hyperuricemia, arthralgia, rash, gout (rare).

Recommended Monitoring: Baseline uric acid and hepatic enzymes. Repeat measurements if baselines are abnormal, patient has risk factors for hepatitis or patient has symptoms of adverse reactions

May complicate management of diabetes mellitus. Treat increased uric acid only if symptomatic. Most common reason for TB patients experiencing GI upset.

Ethambutol [b] (PO) EMB [b]

Adverse Reactions: Decreased red-green color discrimination, decreased visual acuity (optic neuritis), skin rash.

Recommended Monitoring: Baseline tests of visual acuity and color vision. Monthly testing for patients taking >15-25mg/kg, taking EMB for >2 months, and for patients with renal insufficiency.

Optic neuritis may be unilateral; check each eye separately. Not recommended for children too young to monitor vision unless drug resistant. Use lowest possible dose in range (except for drug- resistant patients). EMB should be discontinued immediately and permanently for any signs of visual toxicity.

Appendix C. First Line TB Medications Major Adverse Reactions/Monitoring (*continued)*

Rifabutin (PO) RFB

Adverse Reactions: Hepatitis fever, thrombocytopenia, neutropenia, leucopenia, flu-like symptoms, hyperuricemia. Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses. Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, theophylline, dapsone, ketoconazole, protease inhibitors (PIs), and non-nucleoside reverse transcriptase inhibitors (NNRTIs). With increased rifabutin levels, severe arthralgia, uveitis, leucopenia.

Recommended Monitoring:
Baseline hepatic enzymes. Repeat if baseline abnormal, risk factors for hepatitis or symptoms of adverse reactions.
Patients on methadone may need an increased dose to avoid opiate withdrawal. Interaction with many drugs leads to decreased levels of one or both. May make glucose control more difficult in diabetics. Women on birth control pills need to use a barrier method while on rifabutin.

In combination with non-nucleoside reverse transcriptase inhibitors or protease inhibitors dosages change significantly. Consult a HIV/TB expert.

Rifapentine (PO) RPT

Adverse Reactions: Hepatitis, thrombocytopenia, neutropenia, leucopenia, hyperuricemia, flu-like syndrome. Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, antiepileptics, theophylline, dapsone, ketoconazole, PI's and NNRTI's. Orange discoloration of secretions (sputum, urine, sweat, tears) and may permanently stain soft contact lenses.

Recommended Monitoring:
Baseline hepatic enzymes, CBC, and platelets. Repeat if baseline abnormal, risk factors for hepatitis or symptoms of adverse reactions.

Recommended Monitoring LTBI:
Baseline lab monitoring is not routinely indicated unless conditions exist such as: liver disorders, regular alcohol use, IV drug use, or HIV infection. Routine monitoring is recommended for abnormal baseline results in these individuals or if there is any concern for hepatic disease or adverse reactions.
See drug interactions with Rifampin.

[a] Combination drugs are recommended in the rare instance in which a patient is placed on self-administered therapy:

IsonaRif ®/ **Rifamate**® contain INH 150 mg, RIF 300 mg
Rifater® contains INH 50 mg, RIF 120 mg and PZA 300 mg

[b.] In 2003, CDC recommended dosing based on weight ranges for PZA and EMB [(7)]. After reviewing available data, the Maryland TB Expert panel suggested that the previously recommended dosage ranges continue to be utilized, advising use of the lowest possible dose within the dosing range.

[C.] For additional adverse reactions see the Medication Fact Sheets section of *Drug-resistant Tuberculosis: A survival guide for clinicians.* Found on the Curry International Tuberculosis Center website http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-2nd-edition

Appendix D. Second -Line TB Medications Major Adverse Reactions/Monitoring [a]

Amikacin [Amakin] / **Kanamycin** (IM or IV)

Adverse Reactions: Ototoxicity (hearing loss or vestibular dysfunction), renal toxicity, hypokalemia, hypomagnesemia.

Recommended Monitoring:
Audiometry (monthly), renal function, and electrolytes.
Give as a single daily dose. Ultrasound and warm compresses to injection site may reduce pain and induration. Renal toxicity may be greater than with streptomycin. Contraindicated in pregnancy.

Bedaquiline [Sirturo] (PO)

Adverse Reactions: QT prolongation, headache, GI upset, hepatotoxicity, arthralgia, hemoptysis, chest pain.

Recommended Monitoring:
Baseline ECG, electrolytes, and hepatic enzymes. Repeat hepatic enzymes at least monthly. Repeat ECG at least at 2, 12, and 24 weeks.
Weekly ECGs are recommended if any of the following are present: low value electrolytes, any other QT prolonging drugs are being taken, history of Torsade de Pointes, uncompensated heart failure, congenital long QT syndrome, hypothyroidism, or bradyarrhythmias.
Caution should be used when treating those with HIV co-infection, pregnancy, and in individuals age ≥65

Capreomycin [Capastat] (IM or IV)

Adverse Reactions: See Amikacin (above).

Recommended Monitoring: Audiometry (monthly), renal function, and electrolytes at baseline and monthly. (See Amikacin (above).

Clofazimine[c] [Lamprene] (PO)

Adverse Reactions: GI disturbances, orange/brown skin discoloration, severe abdominal pain, visual disturbances (rare).
Not FDA approved for TB treatment. Efficacy unknown. Take with food.

Cycloserine[c] [Seromycin] (PO)

Adverse Reactions: Psychosis, seizures, headache, depression, other CNS effects, rash, increased phenytoin (Dilantin) levels.

Recommended Monitoring: Neuropsychiatric status should be assessed monthly. Monthly phenytoin serum concentration levels for those on phenytoin. Start with low dosage and increase as tolerated. Serum drug levels can be useful for determining optimal dose. Give Vitamin B_6 (100-200 mg/d) to decrease CNS side effects.

Ethionamide[c] [Trecator] (PO)

Adverse Reactions: GI upset, bloating, hepatotoxicity, allergic reactions, hypothyroidsm (especially with PAS), metallic taste. Can cause severe GI side effects.

Recommended Monitoring: Monitor hepatic enzymes (if baseline abnormal) and thyroid function.
Avoid in pregnancy. Antacids, antiemetics, taking with food or at bedtime, or lying flat for 20 minutes after doses may help GI intolerance.

Gatiloxacin [Tequin] (PO or IV)

Adverse Reactions: See Levofloxacin below

Rarely used in U.S. outside of research studies. Not approved for use in children.

Appendix D. Second -Line TB Medications Major Adverse Reactions/Monitoring [a] *(continued)*

Kanamycin - See Amikacin (above)

Levofloxacin [Levaquin] (PO or IV)

Adverse Reactions: GI disturbance, diarrhea, photosensitivity, allergic reaction.

Recommended monitoring: No specific monitoring recommended.
Avoid in children due to concerns about effects on bone and cartilage growth. Antacids may interfere with absorption.

Linezolid [Zyvox] (PO or IV)

Adverse Reactions: GI disturbance, optic neuritis, peripheral neuropathy, myelosuppression, anemia, thrombocytopenia

Recommended monitoring:
Monitor for peripheral neuropathy and optic neuritis. Weekly CBC during initial period, then monthly, then PRN. Avoid in pregnancy or breastfeeding. All patients should be given Pyridoxine (vitamin B_6).

Moxifloxacin [Avelox] (PO)

See Levofloxacin (above)

Para-Aminosalicylic Acid [PAS] (PO)

Adverse Reactions: GI disturbance, hypersensitivity, hepatotoxicity sodium load, hypothyroidism

Recommended monitoring:
Monitor hepatic enzymes and assess volume status. Monitor cardiac patients for sodium load. Thyroid function at baseline and every 3 months.
Start with low dosage and increase as tolerated. Packets may be mixed with food. May cause hypothyroid condition, especially if used with ethionamide.

Streptomycin [SM] (IM/IV)

Adverse Reactions: Ototoxicity (hearing loss or vestibular dysfunction), renal toxicity hypokalemia, hypomagnesemia.

Recommended monitoring:
Audiometry (monthly), renal function, and electrolytes.
Ultrasound and warm compresses to injection site may reduce pain and induration. Contraindicated in pregnancy.

Appendix E. Dosage Chart for TB Drugs (mg/kg)

Weight		Weight Adjusted Dosages (mg/kg)								
lb.	**kg**	**5** mg/kg	**10** mg/kg	**15** mg/kg	**20** mg/kg	**25** mg/kg	**30** mg/kg	**40** mg/kg	**50** mg/kg	**70** mg/kg
11	**5**	25	50	75	100	125	150	200	250	350
22	**10**	50	100	150	200	250	300	400	500	700
33	**15**	75	150	225	300	375	450	600	750	1050
44	**20**	100	200	300	400	500	600	800	1000	1400
55	**25**	125	250	375	500	625	750	1000	1250	1750
66	**30**	150	300	450	600	750	900	1200	1500	2100
77	**35**	175	350	525	700	875	1050	1400	1750	2450
88	**40**	200	400	600	800	1000	1200	1600	2000	2800
99	**45**	225	450	675	900	1125	1350	1800	2250	3150
110	**50**	250	500	750	1000	1250	1500	2000	2500	3500
121	**55**	275	550	825	1100	1375	1650	2200	2750	3850
132	**60**	300	600	900	1200	1500	1800	2400	3000	4200
143	**65**	325	650	975	1300	1625	1950	2600	3250	4550
154	**70**	350	700	1050	1400	1750	2100	2800	3500	4900
165	**75**	375	750	1125	1500	1875	2250	3000	3750	5250
176	**80**	400	800	1200	1600	2000	2400	3200	4000	5600
187	**85**	425	850	1275	1700	2125	2550	3400	4250	5950
198	**90**	450	900	1350	1800	2250	2700	3600	4500	6300
209	**95**	475	950	1425	1900	2375	2850	3800	4750	6650
220	**100**	500	1000	1500	2000	2500	3000	4000	5000	7000
231	**105**	525	1050	1575	2100	2625	3150	4200	5250	7350
242	**110**	550	1100	1650	2200	2750	3300	4400	5500	7700

Appendix F. Protocol for Submitting Specimens for Therapeutic Drug Monitoring

State of Maryland Department of Health & Mental Hygiene
Protocol for Submitting Specimens for Therapeutic Drug Monitoring

1. Therapeutic Drug Monitoring (TDM) is a blood assay which measures the metabolite of a particular medication in a blood specimen drawn at a specific interval(s) after administration of a particular medication(s). It is a very sensitive test and the results can often be critical to determining adjustments to a particular treatment regimen. A limited number of laboratories in the United States have expertise in performing and interpreting the results of TDM specific to tuberculosis (TB) medications. At this time these laboratories are located out of Maryland.

2. The Maryland Department of Health State Laboratory (Laboratory) is available to assist local health departments in shipping specimens for therapeutic drug monitoring on Tuesdays and Wednesdays of each week, unless closed for a scheduled State holiday. All patients requiring therapeutic drug monitoring (TDM) must be scheduled to have their blood drawn on a Tuesday or Wednesday on a day the Laboratory is open. The Laboratory will not accept specimens for TDM on any other days.

3. At least *one week prior to submitting blood specimens for testing*, a requisition form must be submitted to the Laboratory. The form must be filled out completely and faxed to the laboratory at (443) 681-4506. Blood specimens cannot be accepted by the laboratory if a requisition has not been received at least one week prior to receipt of specimens. The Laboratory will fax a confirmation of the date of submission within 24 hours. If a faxed confirmation is not received within 24 hours, contact the Laboratory at (443) 681-3942 to confirm the receipt of the request.

4. Blood collection and handling should be performed in accordance to the testing laboratory requirements instructions. This includes completing requisition forms in a thorough and legible manner (see the Maryland Center for TB Control and Prevention (CTBCP) website for forms and instructions). The submitting health department is responsible for any monetary charges from the testing laboratory and should indicate so on the requisition form. The Laboratory should NOT be listed as the responsible party unless authorized by the Laboratory Administration, following a request from the Maryland CTBCP.

5. Once collected, blood specimens must be kept on ice/freezer packs during storage and transport. All specimens should be transported to the Laboratory as soon as possible, as **these specimens are very sensitive to time and temperature**. If blood for testing is collected at two different time periods (such as 2 and 4 hours post medication administration) it is preferable to transport each set of specimens separately. If this is not feasible, the earlier specimen(s) must be kept on ice in a cooler or refrigerator until all specimens are available for transport. Given the sensitivity of the specimens, the cost of the TDM testing and the critical nature of obtaining accurate results TB program staff should discuss any possible delays in transport with CTBCP or Laboratory personnel before submitting a TDM request.

6. Specimens should be transported directly to the Laboratory by a health department employee or special courier to avoid delays in initial processing and subsequent shipping. Specimens should be brought to the loading dock (located off Rutland Avenue) of 1770 Ashland Avenue, Baltimore Maryland 21205. The person delivering the specimens should call the Laboratory at (443) 681-3942 (or, alternately, (443) 681-3944 or (443) 681-3950) upon their arrival at the loading dock. A laboratory employee will come to receive the specimens directly and hand carry to the laboratory to expedite processing. TDM specimens should NEVER be left in the general laboratory specimen receiving area, as this will lead to delays which could compromise the quality of test results or require discard of the specimen

7. All specimens for therapeutic drug monitoring must be delivered to the Laboratory no later than 3:30 PM to allow time to harvest and freeze serum the same working day. Specimens arriving after 3:30 PM and unable to be processed timely will be discarded.

8. To assure quality results from this highly sensitive assay, the Laboratory will only accept specimens handled according to the protocol described. Any further questions or concerns regarding scheduling or procedures for submitting TDM specimens to the Laboratory should be referred to the laboratory Supervisor or Lead at (443) 681-3942.

9. The following information can be found on Maryland's Department of Health Center for TB Control and Prevention website to assist with this process:
    - Instructions for Serum & Plasma Collection & Sample Shipping and Handling
    - TDM Maryland State Laboratory Assistance Request Form
    - Infectious Disease Lab Requisition

Additional information and required forms can be found at the MDH Laboratory Administration website:
https://health.maryland.gov/laboratories/Pages/Therapeutic-Drug-Monitoring.aspx

Appendix G. Video/ Electronic Directly Observed Therapy (VDOT)

Maryland Center for TB Control and Prevention Guidance for Developing Policies/Procedures for Video/Electronic Directly Observed Therapy for Tuberculosis

(revised February 2019)

Maryland Definition of Video Directly Observed Therapy VDOT:

Video DOT is defined as live "real-time" or recorded videophone camera confirmation by a trained health care professional of a patient's oral ingestion of tuberculosis (TB) medications, regardless of the specific device being used (e.g., smart phone, personal computer, iphone, etc.) using a method approved by the local health department (LHD) and the Maryland Department of Health Center for Tuberculosis Control and Prevention (MDH CTBCP).

Video DOT should be used with carefully selected TB patients meeting established minimum criteria. TB program staff must be trained in appropriate patient selection, use of the VDOT equipment, procedures for observing treatment, and the standard criteria for utilizing VDOT with a patient as listed below. VDOT is an adjunct tool a local TB program may choose to use to enhance TB control and prevention efforts. It is to be used in conjunction with in-person DOT and monthly on-site monitoring. VDOT is not a substitution for case management activities that require personal contact with the patient. VDOT will only be used under approved circumstances and then, only if the patient meets all the DOT eligibility criteria listed below. Use of VDOT for treatment of latent TB infection and window prophylaxis for children may be considered. Consultation with MDH CTBCP is recommended.

Health Department General:

- Using a designated LHD computer or other identified equipment, a LHD provider will observe the patient self-administer TB medications via the patient's personal electronic device. The LHD will use secure computer systems for VDOT that follow LHD information technology (IT) policies and protocols.
- Patients who meet criteria to participate in VDOT must demonstrate to the LHD staff they are able to send and receive video images. *Use of personal phones by LHD staff to observe VDOT sessions is NOT recommended.*
- An order for VDOT by the TB Control provider is documented in the medical record.
- Patients sign a consent to receive medications by VDOT and a waiver approved by LHD administration stating that while every effort will be made to preserve the patient's privacy and confidentiality, neither MDH nor the LHD will be held responsible should any personal identifying information be inadvertently accessed or released (sample consent forms and checklists are available through the CTBCP nurse consultants).
- VDOT smart phone apps/programs utilized by local health department programs must be HIPAA compliant.
- Patient criteria for participating in VDOT may be altered at the discretion of the LHD provider, in consultation with the LHD TB Program Manager and MDH CTBCP.
- LHD TB Control programs may stop VDOT and resume in-person therapy any time it appears that treatment is being delayed, or for any reason the patient is demonstrating non-adherent behavior.
- V DOT will generally take place during the normal business hours of the LHD whenever possible. Some patients may not be able to take their medications during those hours due to work, school or travel situations or may be on treatment regimens requiring weekend DOT dosing. In

Appendix G. Video/ Electronic Directly Observed Therapy (VDOT) *(continued)*

these situations, medications may be taken earlier in the day or later in the evening and be observed as a live feed by the LHD staff member or recorded and reviewed within 24 hours or at a time determined by the LHD, as approved by the TB Control Program under the direction of the local TB Program Manager. Recorded or asynchronous VDOT options should be discussed with CTBCP consultant staff.

- VDOT utilization must be clearly documented in the medical record.
- VDOT is not to be used to "split" TB medication doses without consultation and approval from MDH CTBCP.

Health Department Patient Specific:

- Assess whether patient is eligible and interested in VDOT.
- Verify that the patient knows how to activate the video function on his/her phone and practice a VDOT session with patient. This practice session should be documented in the patient's medical record. *If the patient is going to be provided VDOT utilizing translation platforms both the patient and nurse case manager should practice until comfortable with how the programming works.*
- Document each patient VDOT encounter as directed by the local health department policy. This may include documentation in addition to the standard practice of medication administration documentation.
- Provide patient with written instructions on what to do in an emergency, if there is a technical failure, and/ or who to call with questions. In case of technical failures contact with the patient and a home visit to deliver DOT should be made as soon as possible.
- Provide medications in prepackaged medication doses.
- Verify that patient can open packets, identify, and name the medications, and demonstrate how they must be taken.
- Verify that patient understands side effects of each medication and what to do if he/she experiences any.
- Provide the patient with a plan as to how the VDOT visits will continue if the regular case manager is not available.

Patient Eligibility Criteria/Responsibilities:

- Patient is motivated to take medication via VDOT, has an internet enabled cell phone or computer with internet access that is suitable for webcam and has a microphone/speaker, plus any other local requirements as determined by the LHD IT/administrative staffs.
- Patient must be non-infectious, as determined by laboratory test results or documentation by a health care provider (if classified as a clinical case).
- Patient must have a pansensitive organism to first line drugs OR if not pansensitive a decision will be made in consultation with the MDH CTBCP to proceed with VDOT.

Appendix G. Video/ Electronic Directly Observed Therapy (VDOT) *(continued)*

- Patient must have demonstrated 100% cooperation with LHD requests for laboratory tests, etc. during initial diagnosis and treatment, including compliance with required clinic/provider visits.
- Patient must demonstrate understanding and need for TB treatment and the treatment plan.
- Patient must be able to accurately identify and name each medication.
- Patient must be able to state common side effects and have the ability to report any side effects either by a phone call to a case manager or during VDOT.
- Patient is able to demonstrate how to properly use the VDOT equipment.
- Patient must report to LHD TB clinic or health care provider on a monthly basis (at minimum) for evaluation of response to treatment, physical assessment, additional education as appropriate and review of ongoing treatment plan.
- Patients with the following conditions should be discussed with the MDH CTBCP prior to initiating. Criteria may be altered at the discretion of the LHD in consultation with the MDH-CTBCP. Examples include, but are not exclusive, to patients who are currently experiencing or have a history of :
    a. substance abuse
    b. prior TB treatment
    c. psychiatric illness
    d. memory impairment or inability to follow other treatment regimens
    e. language barriers that the VDOT platform in use cannot accommodate

Homelessness may or may not be an exclusionary criterion depending on the individual patient's situation. Some homeless patients may be excellent candidates for VDOT, depending on LHD assessment of each patient's situation.

Stopping VDOT once started may include, but are not limited to, the following situations:

- Patient has an adverse reaction to TB medications.
- Patient's physical health is not improving or showing signs of deterioration.
- Patient can no longer accommodate equipment in a confidential setting.
- Patient consistently misses VDOT calls and/or ingestion of less than 80% of scheduled VDOT medication doses within time frame established by LHD. This may vary depending on the patient's phase of treatment, sensitivity patterns, home/work situation, etc. The timeline should be clearly documented, and patient made aware of the consequences of non-compliance, both to their own personal health and to subsequent eligibility to remain on the VDOT program.
- Patient defaults on other aspects of adherence to treatment plan (e.g., missing medical appointments, refusing laboratory testing).

Update CTBCP nurse consultant staff, as appropriate, when initiating or stopping VDOT. Several Maryland local health departments have established protocols and policies for the use of VDOT, including check lists, consent forms, property management forms (if providing smart phones to patients) and others. Contact CTBCP nurse consultant staff at 410-767-6698 for more information regarding LHDs with established VDOT programs and/or sample forms for review.

Appendix H. International Classification of Tuberculosis

International Classifications of Tuberculosis are used by WHO (the World Health Organization), CDC (Centers for Disease Control and Prevention), and other national and international programs to communicate a general status of TB patients, e.g., on an interjurisdictional report form.

Table 21. International Classification of Tuberculosis

Class	Type	Description
0	No TB exposure Not infected	No history of exposure Negative reaction to tuberculin skin test or IGRA*
I	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test or IGRA
II	TB infection No disease	Positive reaction to tuberculin skin test or IGRA Negative bacteriological studies (if done) No clinical, bacteriological or radiographic evidence of TB disease
III	TB Clinically active	Positive culture for *M. tuberculosis* AND/OR Clinical, bacteriological or radiographic evidence of current TB disease
IV	TB Not clinically active	History of episode(s) of TB OR Abnormal but stable radiographic findings Positive reaction to tuberculin skin tests or IGRA Negative bacteriologic studies (if done) AND No clinical or radiographic evidence of current TB disease
V	TB suspected	Diagnosis pending

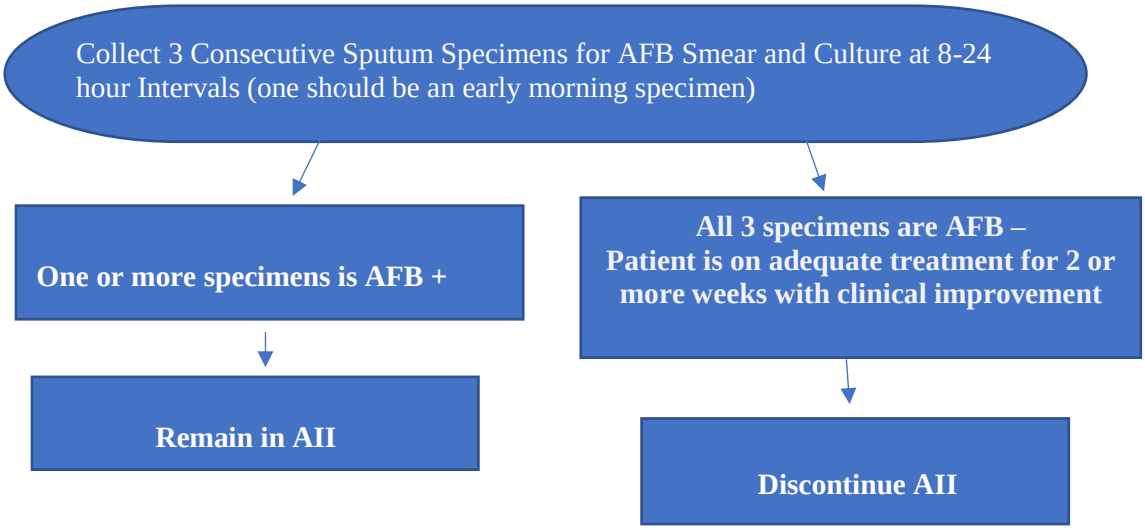
* IGRA (interferon gamma-release assay) results are interpreted in the same manner as tuberculin skin test results when assigning a TB classification (Maryland Center for TB Control and Prevention Expert Panel 2013).

Appendix I. Discontinuing Isolation

Discontinuation of TB Isolation must be based not only on the results of laboratory testing, but also on the clinical response of the patient to an appropriate treatment regimen and whether or not the patient will be returning to his/her home environment, to a congregate setting (e.g., a long-term care facility) or to an environment that houses others at high-risk for becoming infected with TB if exposed (e.g., transplant unit). Questions regarding TB isolation should be referred to the local health department TB program or to the Maryland Center for Tb Control and Prevention.

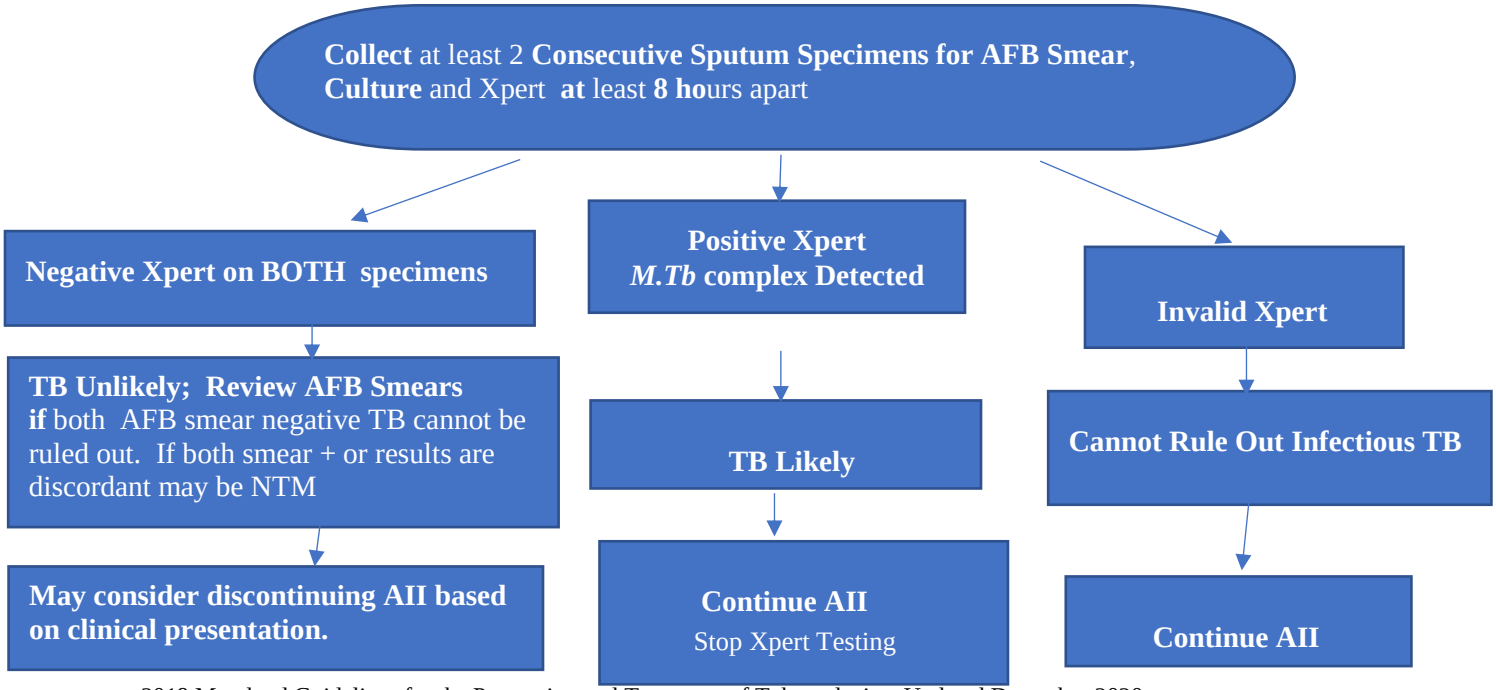
Use of Sputum AFB Smear

https://www.cdc.gov/tb/publications/factsheets/prevention/ichcs.htm



Use of GENEXPERT (Xpert)

http://www.tbcontrollers.org/docs/resources/NTCA_APHL_GeneXpert_Consensus_Statement_Final.pdf



Appendix J. Maryland TB Laws and Regulations*

Annotated Code of Maryland, Health-General §§ 18-324,325

18-324. Control of communicable tuberculosis.

(a) *Examination.* - The Secretary or a health officer may have an individual examined, if the Secretary or the health officer knows or is notified in writing by a physician that the individual is suspected of having tuberculosis.

(b) *Removal for treatment.*-

(1) If, after the examination, the Secretary or the health officer finds that the individual has tuberculosis and that the condition of the individual endangers, or may endanger, the public health of the community, the Secretary or the health officer may order the individual to receive appropriate medical care.

(2) If the individual fails to comply with the order, the Secretary or health officer may order the individual to be placed in any of the following types of medical quarantine in order to protect the public health:

(i) Medical isolation at home;

(ii) Domiciliary care, nursing home care, or hospital care; or

(iii) Other medically appropriate living arrangement.

(3) The order of the Secretary or the health officer may also contain such other conditions as the Secretary or the health officer believes are necessary to protect either the health of the infected individual or the public health.

(c) *Restrictions.* - The Secretary or a health officer may not require an individual to have a physical examination, other than a chest X ray and to render sputum samples. The Secretary or health officer may not restrict the right of the individual to select a treatment method, if the individual:

(1) In good faith relies on spiritual means through prayer for healing; and

(2) Complies with the laws, rules and regulations that relate to sanitation for and quarantine of infectious, contagious, and communicable disease.

[An. Code 1957, art. 43, 98; 1982, ch. 21, 2; ch. 568; 1994, ch. 64; 1996, ch. 104]

18-325. Prohibited acts; penalty.

(a) *Refusal to enter health facility.* - An individual may not refuse to comply with the placement ordered under 18-324 of this subtitle.

(b) *Disorderly behavior; leaving before proper discharge.* - While an individual is in any placement for tuberculosis treatment, the individual may not:

(1) Behave in a disorderly manner; or

(2) Leave the placement before being discharged properly.

(c) *Penalty.* - An individual who violates any provision of this section is guilty of a misdemeanor and on conviction shall be imprisoned in a penal institution with facilities for tuberculosis treatment until the Secretary or the Health Department of Baltimore City finds that the conditions of the individual no longer endangers the health of the community, or the Secretary obtains a court order that states that the individual:

(1) Is to be moved to a specified less restrictive setting for continuation of treatment;

(2) Must comply with the treatment until the Secretary determines the treatment has been completed.

(3) May not behave in a disorderly manner or leave the placement until the Secretary determines that the individual has completed the treatment; and

Following a hearing, will be imprisoned until the Secretary determines that the individual has completed treatment, if the individual does not comply with terms of the order.

[1982, ch. 568; 1994, ch. 64; 1997, ch. 8]

* Numerous state agencies, programs and other entities have their own regulations that may refer to TB screening and testing requirements for residents of state facilities or employees. This appendix does not include these other regulations. Readers are advised to access Maryland COMAR online.
https://mde.maryland.gov/programs/Permits/Pages/ComarOnline.aspx

Appendix J. Maryland TB Laws and Regulations (*continued)*

COMAR 10.06.01.20 Title 10 Department of Health and Mental Hygiene
Subtitle 06 Diseases
Chapter 01 Communicable Disease and Related Conditions of Public Health Importance
Regulation 20 Tuberculosis

A. Control of a Case.

(1) A health officer or health care provider shall isolate a patient who is in a communicable stage as long as the specific microorganism:
(a) Is excreted by the patient; or
(b) Can be isolated by culture in the case of multidrug resistant tuberculosis (MDR-TB) or extremely drug resistant tuberculosis (XDR-TB).
(2) A patient fulfills the requirements of isolation as long as the patient receives adequate chemotherapy, is under medical supervision, and observes instructions for isolation issued by a health officer.
(3) A health care provider shall place individuals with tuberculosis and suspected tuberculosis on a tuberculosis treatment regimen that is in accordance with current national and State standards of care, and that provide for direct observation by a trained health care worker of ingestion of each dose of medication.
(4) A health officer or health care provider treating an individual with tuberculosis or suspected tuberculosis shall provide human immunodeficiency virus testing and counseling.
(5) The health officer shall monitor the treatment of individuals with tuberculosis and suspected tuberculosis to determine if the treatment is appropriate.
(6) A health officer or health care provider treating an individual with tuberculosis or suspected tuberculosis may:
(a) Impose limitations on travel; and
(b) Place restrictions on hospital discharge.
(7) The health officer may remove the limitations and restrictions set forth in §A (6) of this regulation when appropriate and consistent with the individual's tuberculosis treatment plan.
(8) A health officer or the Secretary shall manage tuberculosis patients who are noncompliant with tuberculosis treatment in accordance with Health-General Article, §§18-324 and 18-325, Annotated Code of Maryland.
(9) A health officer may require an individual having tuberculosis in a non-communicable stage to be under medical supervision, which may include physical isolation from others, if the individual refuses to receive adequate chemotherapy.

B. Control of Contacts.

The health officer shall:
(1) Direct that testing for tuberculosis infection using Centers for Disease Control and Prevention approved method be performed on contacts of cases of tuberculosis in a communicable stage;
(2) Recommend appropriate treatment for latent tuberculosis infection; and
(3) Provide for the supervised presumptive treatment of latent tuberculosis infection for a child younger than 5 years old identified as a close contact to a confirmed case or suspected case of active pulmonary tuberculosis.

Appendix J. Maryland TB Laws and Regulations (*continued)*

COMAR 10.06.01.03
Title 10 Department of Health and Mental Hygiene
Subtitle 06 Diseases
Chapter 01 Communicable Disease and Related Conditions of Public Health Importance
Regulation o3 Reportable Diseases, Conditions, Outbreaks, and Unusual Manifestations; Submitting Clinical Materials

Authority: Health General Article, §§2-104(b), 18-102, 18-201, 18-202, and 18-205, Annotated Code of Maryland
10.06.01.03 (May 18, 2017).

A. A person, as set forth in Regulation .04 of this chapter, shall report the diseases or conditions listed in §C of this regulation, or any other condition as requested by the Secretary.

B. Within 1 working day of a positive laboratory finding for a disease or condition listed in §C of this regulation, or upon request of the Secretary, the director of a medical laboratory shall:

(1) Submit clinical material to the Department's public health laboratory; and

(2) Include information about the clinical material on a form provided by the Secretary.

C. List of Reportable Diseases and Conditions.

HEALTH CARE PROVIDERS, INSTITUTIONS, AND OTHERS[1]	LABORATORIES		TIMEFRAME FOR REPORTING[2]	
Diseases and Conditions	Laboratory Evidence of	Submit Clinical Materials to the Department[3]	Immediate	Within 1 Working Day
(77) Tuberculosis, active disease, and suspected active tuberculosis[6]	Mycobacterium tuberculosis complex	X	X	
(77-1) Tuberculosis, latent infection (LTBI)[7]	Mycobacterium tuberculosis complex, latent infection[7]			*X*

Tuberculosis confirmed by culture and suspected tuberculosis as indicated by:
(a) A laboratory confirmed acid-fast bacillus on smear;
(b) An abnormal chest radiograph suggestive of active tuberculosis;
(c) A laboratory confirmed biopsy report consistent with active tuberculosis; or
(d) Initiation of two or more anti-tuberculosis medications

Latent tuberculosis infection as indicated when:
(a) There is a positive result on an Interferon Gamma Release Assay, Tuberculin Skin Test, or any other test indicating tuberculosis infection; and
(b) Active or suspected tuberculosis has been ruled out.

Maryland TB Expert Panel – 2009

Akintoye Adelakun, M.D., M.S.
Prince George's County Health Department

Karla Alwood, C.R.N.P.
Johns Hopkins School of Medicine
Baltimore City Health Department

Elaine Balm, R.N.
Frederick County Health Department

Sharon Baucom, MD
Department of Public Safety and Correctional Services

Nancy Baruch, R.N., M.B.A.
Department of Health and Mental Hygiene

David Blythe, M.D.
Department of Health and Mental Hygiene

Richard Chaisson, M.D.
Johns Hopkins School of Medicine

Wendy Cronin, Ph.D.
Department of Health and Mental Hygiene

Maureen A. Donovan, R.N., M.A.
Department of Health and Mental Hygiene

Susan Dorman, M.D.
Johns Hopkins School of Medicine
Baltimore City Health Department

Jacquiline Dougé, M.D.
Frederick County Health Department

Bernard Farrell, M.D.
Anne Arundel County Health Department

Lynn Federline, R.N.
Prince George's County Health Department

Itala Fontana, R.N.
Montgomery County Health Department

Cathy Goldsborough, R.N.
Department of Health and Mental Hygiene

Jonathan Golub, Ph.D., MPH
Johns Hopkins School of Medicine

Loretta Gossett, R.N., M.A.
Anne Arundel County Health Department

Sherry Johnson-Ketemepi
Baltimore City Health Department

Walter Karney, M.D.
Prince George's County Health Department

John P. Krick, Ph.D.
Department of Health and Mental Hygiene

Sandra Matus
Department of Health and Mental Hygiene

Eric Nuermberger, M.D.
Johns Hopkins School of Medicine

Renee Powell, R.N.
Wicomico County Health Department

Sohail Qarni, M.D.
Anne Arundel County Health Department

William Randall, M.D.
Department of Health and Mental Hygiene

Elizabeth Ruff, M.D.
Carroll County Health Department

Kelly Russo, MD, MPH
Anne Arundel County Health Department

Judy Thomas, R.N.
Baltimore County Health Department

Thomas Walsh, M.D.
Montgomery County Health Department

Danielle Weber, R.N.
Somerset County Health Department

Lucy Wilson, M.D.
Department of Health and Mental Hygiene

Maryland TB Expert Panel – 2013

Akintoye Adelakun, M.D., M.S.
Prince George's County Health Department

Karla Alwood, C.R.N.P.
Johns Hopkins School of Medicine

Sharon Baucom, MD
Dept. of Public Safety & Correctional Services

Nancy Baruch, R.N., M.B.A.
Department of Health and Mental Hygiene

David Blythe, M.D.
Department of Health and Mental Hygiene

Sarah Bur, RN, MPH
Fed. Bureau of Prisons Infectious Disease

Richard Chaisson, M.D.
Johns Hopkins School of Medicine

Patrick Chaulk, M.D., MPH
Baltimore City Health Dept.

Wendy Cronin, Ph.D. MS
Department of Health and Mental Hygiene

Maureen A. Donovan, R.N., M.A.
Department of Health and Mental Hygiene

Kelly Dooley, MD, PhD,
Johns Hopkins School of Medicine

Susan Dorman, M.D.
Johns Hopkins School of Medicine
Baltimore City Health Department

Jacquiline Dougé, M.D.
Frederick County Health Department

Bernard Farrell, M.D.
Anne Arundel County Health Department

Itala Fontana, RN
Montgomery County Health Dept.

Cathy Goldsborough, R.N.
Department of Health and Mental Hygiene

Jonathan Golub, PhD, MPH
Johns Hopkins School of Medicine

Mark Hodge, RN, MS
Montgomery County Health Dept.

Eric Nuermberger, M.D.
Johns Hopkins School of Medicine

Richard Oatis, BS
MDH Laboratory Administration

Andrea Palmer, MPH
Department of Health and Mental Hygiene

Lisa Paulos, RN, MPH
Department of Health and Mental Hygiene

Sonia Qasba, MD, MPH
Montgomery County Health Dept.

Adapra Odunze, RN, MS, PhD
Dept. of Public Safety & Correctional Services

William Randall, M.D.
Department of Health and Mental Hygiene

Jafar Razeq, PhD
MDH Laboratory Administration

Sherry Roberts, FN
Baltimore County Health Dept.

Brenda Roup, RN, PhD, CIC Department of Health and Mental Hygiene

Kelly Russo, MD, MPH
Anne Arundel County Health Department

Maunank Shah, MD, PhD
Baltimore City Health Department

Thomas Walsh, M.D.
Montgomery County Health Department

Walter Karney, MD
Prince George's County Health Dept.

Danielle Weber, R.N.
Somerset County Health Department

Lucy Wilson, MD, ScM
Department of Health and Mental Hygiene

Maryland TB Expert Panel – 2017

Mohan Anlani, MD
Montgomery County Department of Health and Human Services

Karla Alwood, CRNP
Baltimore City Health Department

Nancy Baruch, R.N., M.B.A.
Maryland Department of Health

David Blythe, M.D., MPH
Maryland Department of Health

Richard Brooks, MD
Maryland Department of Health

Richard Chaisson, M.D.
Johns Hopkins School of Medicine

Panda Comfort, NP
Montgomery County Department of Health and Human Services

Wendy A. Cronin, PhD, MS
Maryland Department of Health

Patricia Cahaney, RN, BSN
Frederick County Health Department

Bernard Farrell, MD
Howard County Health Department

Itala Fontana, RN
Montgomery County Department of Health and Human Services

Dorothy Freeman, RN, MS
Maryland Department of Health

Melanie Gardiner, RN
Charles County Department of Health

Diana Gaviria, MD
Washington County Health Department

Cherie Helfrich, RN, MSN
Maryland Department of Health

Walter Karney, MD
Prince George's County Health Department

Jayne McGunigale, RN
Howard County Health Department

Richard Oatis, BS
Maryland Laboratory Administration

Frank Parrish, Metropolitan Transition Center
Dept. Public Safety and Correctional Services

Lisa Paulos, RN, MPH
Maryland Department of Health

Alexandra Pyan, MPH
Maryland Department of Health

William Randall, MD
Maryland Department of Health

Kelly Russo, MD, MPH
Anne Arundel County Health Department

Paul Saleeb, MD
Univ. of MD School of Medicine

Anna Schauer RN, BSN
Baltimore City Health Department

Maunank Shah, MD, PhD
Baltimore City Health Department

Kelly Shockley, RN
Wicomico County Health Department

Ruth Thompson
Maryland Department of Health

Kimberly Townsend BSN, RN
Montgomery County Department of Health and Human Services

Thomas Walsh, M.D.
Montgomery County Department of Health and Human Services

Margareth Weaver, RN
Prince George's County Health Department

Lucy Wilson, MD, ScM
Maryland Department of Health