Maryland TB Guidelines for Prevention and Treatment of Tuberculosis

2007

Maryland Department of Health and Mental Hygiene

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Table 1. International Classification of Tuberculosis [1]

Class	*Type*	*Descriptions*
0	No TB exposure Not Infected	No history of exposure Negative reaction to tuberculin skin test
I	TB exposure No evidence of infection	History of exposure Negative reaction to tuberculin skin test
II	TB infection No disease	Positive reaction to tuberculin skin test Negative bacteriological studies (if done) No clinical, bacteriological or radiographic evidence of active TB
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 test Negative bacteriologic studies (if done) ***AND*** No clinical or radiographic evidence of current TB disease
V	TB suspected	Diagnosis pending

Notes:
International Classifications of Tuberculosis are used by WHO, CDC, and other national and international programs to communicate a general status of TB patients, e.g. on an inter jurisdictional report form.

QuantiFERON® results are interpreted in the same manner as tuberculin skin test results when assigning a TB classification (Maryland TB Control 2007).

Guidelines for Prevention and Treatment of Tuberculosis

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I. INTRODUCTION

The following **Guidelines for Prevention and Treatment of Tuberculosis** are provided as a resource for Maryland health-care providers. They are largely based upon Centers for Disease Control Guidelines and have been approved by the Maryland TB Expert Panel. These are minimum standard recommendations, and a local health officer or the medical director of an institution may establish more stringent guidelines for defined sub-populations.

The standards for prevention and treatment of tuberculosis in Maryland are:

- **Report TB cases and suspects** to the local health department within 24 hours.
- **Co-manage all TB cases** with the local health department.
- **Initiate four-drug initial therapy** for TB cases/suspects.
  (isoniazid, rifampin, pyrazinamide, ethambutol)
- **Order drug susceptibility testing** on all initial isolates.
- **Provide directly observed therapy (DOT)** for all TB cases/suspects.
- **Never add a single drug** to a failing TB regimen.
- **Target tuberculin screening to high-risk** populations only.
- **Plan for evaluation and treatment of infected persons** prior to tuberculin skin testing.
- **Provide HIV counseling and testing** for individuals with latent TB infection, TB disease and who are high or medium-priority contacts to tuberculosis cases.

Significant changes from previous guidelines are summarized in Table 2. This document does not provide detailed answers to complex questions that may arise from either a clinical or a public health perspective. However, for most patients, strict adherence to the clinical standards and recommendations will result in improved patient care and control of tuberculosis in Maryland.

Expert consultation should be obtained when treating tuberculosis complicated by drug resistance, drug intolerance, HIV infection, tuberculosis meningitis, or when dealing with complex clinical situations that may not be fully discussed within this manual. Information on medications and possible adverse reactions are summary references only; consult pharmacy texts and manufacturers' literature as necessary. Consultation is available through local health departments and the Division of Tuberculosis Control, Maryland Department of Health and Mental Hygiene (Appendix F).

Comments or questions regarding these Guidelines should be directed to:

Maryland Department of Health and Mental Hygiene
Division of Tuberculosis Control, Refugee and Migrant Health
201 West Preston Street, Room 307-A
Baltimore, Maryland 21201 Telephone: (410) 767-6698 FAX: (410) 669-4215
WEB Site: *http://www.edcp.org/tb*

Table 2. Summary of Recent Changes to TB Guidelines

Health-Care Settings[2]

- The risk assessment process includes the assessment of additional aspects of infection control, such as undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medication).
- The term "tuberculin skin test" (TST) is used instead of "purified protein derivative" (PPD).
- The whole blood interferon gamma assay, QuantiFERON® -TB Gold test, is a Food and Drug Administration (FDA)-approved in vitro cytokine-based assay for cell-mediated immune reactivity to *M.tuberculosis*. This test may be used instead of TST in TB screening programs for health-care workers (HCWs).
- The frequency of TB screening for HCWs has been decreased in various settings, and the criteria for determination of screening frequency have been changed. This change will decrease the number of HCWs who will need serial TB screening.
- The scope of settings in which the guidelines apply has been broadened to include laboratories and additional outpatient and nontraditional facility-based settings (such as long-term care settings and medical settings in prisons, jails and homeless shelters).
- New terms, airborne infection isolation precautions (AII precautions) and airborne infection isolation room (AII room) are defined.
- The criteria for releasing patients from AII rooms include three acid-fast bacilli (AFB) negative sputum smears collected in 8-24 hour intervals, as long as one specimen is collected in the early morning. This may allow patients to be released from AII precautions in two days.
- Recommendations for a respiratory protection program are introduced that include selection of respirators, training and fit testing.

Reference: Guidelines For Preventing The Transmission of Mycobacterium tuberculosis In Health-Care Settings, 2005. MMWR 2005;54(No.RR- 17):1-141.
http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf

New Blood Assay Testing, such as QuantiFERON® -TB Gold (QFT-G)[3]

- FDA has approved the use of QuantiFERON®-TB Gold as a new in-vitro blood assay test for *Mycobacterium tuberculosis (BAMT)* test to aid in the diagnosis of LTBI and active TB disease.
- QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had recent BCG vaccination, and TB screening of health-care workers and others undergoing serial evaluation for *Mycobacterium tuberculosis* infection.
- Note: Because there is limited research on the use of the QuantiFERON®-TB Gold test in children and immune-compromised individuals, the MD Expert Panel does not recommend its use in these groups at the present time without expert consultation..

Reference: Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States. MMWR 2005;54(No. RR-15):49-55.
http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdr

Contact Investigations[4]

- Decisions to initiate a contact investigation are based on clinical factors: pulmonary, laryngeal or pleural TB disease with 1) pulmonary cavities, 2) respiratory specimens that have AFB on microscopy, or 3) both.
- Infectious period of the index patient is determined by clinical characteristics (e.g., if TB symptoms, AFB sputum smear-positive and cavitary chest radiograph, then the beginning period of infectiousness is 3 months before symptom onset or first positive finding consis-

tent with TB, whichever is longer.)

- For contacts, the recommended period between most recent exposure and final TST or QFT-G is 8-10 weeks.
- Data for high and medium- priority contacts should dictate the need for expanding contact investigations. These can best be determined by evaluating achievement of program objectives. Other criteria include an unexpectedly high rate of infection, evidence of second-generation transmission, or infection in any contacts aged ≤ 5 years.
- The index patient should be interviewed between 1 and 3 business days after notification of suspect or confirmed case. Evaluation of contacts including symptom review, TST or QFT-G should occur ≤ 7 days after identification for high-priority contacts; and ≤ 14 days for medium-priority contacts.

Reference: Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis. MMWR 2005;54(No.RR-15)1-47.
http://www.cdc.gov/mmwr/pdf/rr/rr5415.pdf

Correctional and Detention Facilities[37]

- Target audience broadened to include detention facilities.
- Risk assessment approach used to designate facilities as either *minimal risk* or *non-minimal risk.*
- Need for all facilities to conduct a review of symptoms of TB for all inmates and detainees at entry is discussed.
- Testing of inmates based on assessment of inmate risk and facility risk.
- Testing by TST or QFT-G.
- Importance of collaboration with public health for training, discharge planning and contact investigation is highlighted.
- Training of staff and program evaluation emphasized.
- Expanded content on environmental controls with an additional section on respiratory protection.
- Role of Immigration and Customs Enforcement (ICE) in screening for the foreign-born in the U.S. is included.

Reference: Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC. MMWR 2006;55(No.RR-9):1-44.
www.cdc.gov/mmwr/pdf/rr/rr5509.pdf

II. ROLE OF THE HEALTH DEPARTMENT IN TUBERCULOSIS CONTROL

The primary goal of the Maryland Tuberculosis Control Program is to decrease the incidence of new tuberculosis cases. This can be achieved by meeting the following general objectives:

1. Prompt identification of persons with clinically active tuberculosis.
2. Appropriate treatment of all tuberculosis cases.
3. Prompt identification and screening of TB contacts.
4. Appropriate provision of treatment of latent TB infection to high-risk reactors.
5. Targeted testing and treatment of latent TB infection to high-risk populations.

It is the responsibility of the local health department to ensure that all persons who are suspected of having tuberculosis are identified and evaluated promptly and that an appropriate course of treatment is prescribed and completed successfully.

Adequate treatment of pulmonary tuberculosis cases is the most important TB control strategy to achieve a decline in TB incidence. Treatment of infectious cases not only cures the individual of tuberculosis, but interrupts transmission of *Mycobacterium tuberculosis*, thus decreasing the pool of infected persons who contribute to future cases.

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."[5]

DOT is the only mechanism to assure that a person with active disease is completely treated. Studies of directly observed therapy (DOT) in Baltimore, New York City and elsewhere document that widespread use of DOT results in a significant reduction in TB rates compared to like jurisdictions not using DOT[6].

Limited public health resources should be allocated and prioritized to best serve the public health (Table 3). Complete treatment of tuberculosis cases utilizing DOT is the top priority for Maryland local health department tuberculosis control programs. Next is the prevention of disease in HIV-infected persons, in close contacts and other high-risk reactors. Last in order of priority is TB screening of high-risk populations. Testing of low-risk populations should be eliminated. Local health department TB control programs should regularly evaluate TB control activities by referring to the priority listing (Table 3) to determine if resources should be reallocated.

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.

The goal for treatment of latent TB infection (TLTBI) and treatment of active TB disease is completion of a recommended treatment regimen. In addition to a comprehensive treatment plan, it is the responsibility of the health-care provider to provide ongoing patient education (both written and verbal) at an appropriate literacy level and appropriate to the patient's age, language, culture and beliefs. A trained interpreter is necessary when the patient and health-care provider do not speak the same language.

Factors associated with incomplete treatment include diagnosis in and subsequent release from a correctional facility, drug and alcohol abuse and homelessness. Communication and coordination of services between different health-care providers, different states and even different countries may be required to assure treatment completion. The DHMH TB control program should be notified to assist with interjurisdictional or intrajurisdictional referrals and accessing appropriate referral programs for migrant patients.

Table 3. Maryland Department of Health and Mental Hygiene Priorities for Tuberculosis Control Resource Allocation

Priority 1: Tuberculosis Treatment

a. AFB smear-positive pulmonary TB cases
b. All other pulmonary TB cases
c. All other TB cases

Priority 2: Contact Investigations of High-Risk Reactors

a. Contact Investigations of smear-positive cases
b. Treatment of Latent TB Infection (TLTBI) for:
    1. HIV-infected contacts and known HIV / TB co-infected
    2. Contacts age < 5 exposed to smear-positive cases
c. Contact investigations of other pulmonary TB cases
d. TLTBI for other high-risk TST reactors
    (recent convertors, old-healed TB on CXR, injection drug users, immunosuppressed persons, etc.)

Priority 3: Targeted Testing and Treatment of Latent TB Infection*

a. HIV-infected
b. Injection drug users
c. Recent immigrants from high-risk countries
d. Other high-risk persons (see Table 4)

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

III. PATHOGENESIS

Tuberculosis is usually transmitted through an airborne route when an individual with active pulmonary or laryngeal tuberculosis coughs, sneezes, speaks or sings. Infection with tuberculosis usually requires prolonged contact with an infectious case in an enclosed space. The majority of persons who become infected never develop active disease. In Maryland (2006), 68% of TB cases were born in countries where TB is endemic.

Latent TB infection (LTBI) is diagnosed by a positive tuberculin skin test (TST) and a negative CXR. Approximately 5% of infected persons develop active TB disease in the first year or two after infection. Another 2-5% will develop disease later in their lives.

Certain medical conditions increase the risk that TB infection will progress to disease (Table 4). The risk may be approximately 3 times greater (e.g., diabetes) to more than 100 times greater (e.g., HIV infection) [4].

Figure 1. Pathogenesis of TB in immune-competent individuals exposed to TB

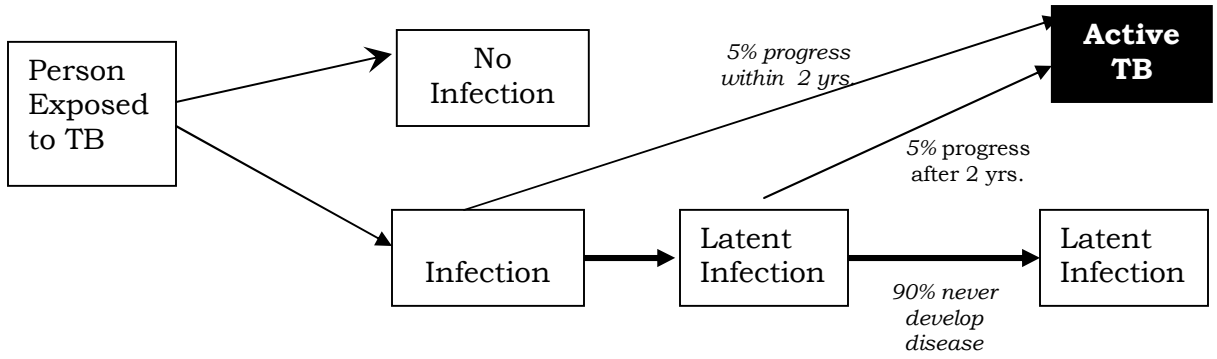


Table 4. Tuberculosis Risk Factors

- Close contact to infectious TB case
- Foreign born from high-incidence countries *(Appendix A)*
- 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)
- HIV-infected persons
- TST convertors / Recently infected
- Persons with fibrotic changes on chest radiograph consistent with old-healed TB or history of inadequately treated TB
- Persons with certain clinical conditions:
  - organ transplant
  - immunosuppressed patients (equivalent to > 15 mg/d prednisone for > 1 month)
  - persons on tumor necrosis-alpha (TNF-a) antagonists [for example; infliximab (Remicade), etanercept (Enbrel), adalimumab (Humira)]
  - silicosis
  - diabetes mellitus
  - chronic renal failure
  - certain hematologic disorders (leukemia / lymphomas)
  - carcinomas of the head and neck and lung
  - underweight (> 10% under ideal body weight)
  - gastrectomy / jejuno-ileal bypass

IV. TARGETED TUBERCULIN SKIN TESTING (TST)

National TB guidelines emphasize targeted testing of high-risk populations who would benefit from treatment of latent TB infection (TLTBI)[7]. Tables 5 and 6 outline priority risk groups for targeted testing and the recommended testing frequency for these groups.

Targeted tuberculin skin testing programs should be developed by utilizing available data to identify groups at high-risk for tuberculosis. Screening programs should be implemented only when the following criteria can be met: the group can be successfully screened, TST-positives medically evaluated, and completion of a full course of TLTBI is feasible. When it is unlikely that an individual can complete a full course of therapy, screening is generally not recommended.

In general, "A decision to test is a decision to treat". High-risk TST reactors are candidates for treatment (regardless of their age). The use of an age cut-point to determine eligibility for treatment is no longer recommended.

Testing of low-risk populations is generally *not* recommended. A substantial proportion of TST-positive persons from low-risk populations will have false-positive skin tests. The estimated general population prevalence in the U.S. is 5 to 10%. The yearly incidence of new tuberculosis infection in the general U.S. population without known exposure to tuberculosis is estimated to be 0.1 to 0.01 %[8]. Therefore, screening of groups without a known or likely exposure to *M. tuberculosis* is not recommended. The primary reason a low-risk person should be tested is to establish a baseline prior to employment in a high-risk setting (e.g., corrections, health-care). Testing is also discouraged unless a plan has been developed for medical evaluation of TST-positive persons identified and for TLTBI.

TST requirements vary from state to state and between local jurisdictions. Local School Boards, in collaboration with local health departments, determine any TST-screening requirements for the local school district. These requirements vary depending on local TB epidemiology and may change over time. Universal testing of school children is not recommended. Available data in Maryland reveal very low (0.8%) prevalence among a largely U.S. born Baltimore inner city population[9]. In contrast, foreign-born students screened upon school entry into the Montgomery County school system have significantly higher rates[10].

Administering and Reading Tuberculin Skin Tests

The Mantoux tuberculin skin test (TST), previously called the purified protein derivative (PPD) test, is used to diagnose TB infection. The use of multiple puncture tests (such as the tine test) is not recommended.

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 check http://www.edcp.org/tb.

Mantoux TSTs are administered by injecting 0.1ml of five tuberculin units (TU) of PPD solution intradermally into the dorsal or volar aspect of the forearm. A tense white wheal ≥ 5 mm in diameter should appear. If not, the test should be repeated immediately at least two 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 and lot number of tuberculin used.

In general, once a person has had a positive tuberculin skin test, the test is not repeated. However, when verification of a prior positive TST is needed and no records are available, the test can be repeated (except when the person has a history of a vesiculating reaction to a TST) .

Table 5. Adult Risk Groups for Targeted Testing and Treatment of LTBI with TST Cut-Points and Recommended Testing Frequency

TST Positive	*Risk Group*	*Testing Frequency*
≥ 5 mm	**HIV infection** (human immunodeficiency virus)	At diagnosis, annually (only if person has other risk factors for tuberculosis), and with immune reconstitution (CD4 > 200 cells/µl)
	Recent contacts of TB case patients	Baseline, and if negative, 8-10 weeks after exposure ended
	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/d of prednisone for 1 month or more)	Prior to transplant or immunosuppressive therapy, perform two-step testing
	Persons taking anti-TNF-alpha drugs	Prior to starting treatment, perform two-step testing
≥ 10 mm	**Recent immigrants (** within the last 5 years) from high-incidence countries (Appendix A).	Upon arrival. Immigrants here < 5 years are the highest priority.
	Injection drug users	Annually
	Residents of long term care facilities and assisted living facilities	Two-step baseline upon admission only. No TST for re-admissions unless recently exposed.
	Prison and jail inmates	At intake and annually
	Homeless persons / Migrant farm workers	Only test if it is likely that the person can complete a full course of TLTBI
	Employees of: • prisons and jails • long-term care facilities for the elderly • hospitals and other health-care facilities • residential facilities for AIDS patients • homeless shelters	Two-step baseline initially; then periodically (usually annually) according to facility risk assessment. For pre-employment testing of employees, previously at low risk, use a ≥ 15 mm cut-point.
	Mycobacteriology laboratory personnel	Two-step baseline; then annually
	Persons with the following clinical conditions: • silicosis • diabetes mellitus • chronic renal failure • some malignancies (e.g., leukemias, lymphomas, carcinoma of the head, neck, lung) • underweight (≥ 10% under ideal body weight) • gastrectomy and jejuno-ilieal bypass	At diagnosis
≥ 10 mm increase	**Skin test converters** (TST converts from negative to positive within two years)	Not applicable
≥ 15 mm	**Low-risk adults; includes pre-employment screening if no other risk factors apply**	Not recommended

Table 6. Pediatric Risk Groups for Targeted Testing and Treatment of LTBI with TST Cut-Points and Recommended Testing Frequency

TST Positive	*Risk Goup*	*Testing Frequency*
≥ 5 mm	**HIV-infected children**	At diagnosis, annually (only if other TB risk factors), and with immune reconstitution (CD4 > 200 cells/µl)
	Contacts of persons with confirmed or suspected TB	Baseline, and if negative, 8-10 weeks after exposure ended
	Radiographic or clinical findings suggesting TB	Immediately
	Age < 1 with no risk factors	Not recommended
≥ 10 mm	**Children** ≥ 6 months who have immigrated **from** or lived ≥ 12 months in **high incidence countries** (MD defines as ≥ 15 smear pos/100,000)	Immediately
	Foreign-born children from high incidence countries who do not have prior TST results in the U.S.	Upon school entry
	Children with the following medical conditions (e.g., diabetes mellitus, lymphoma, chronic renal failure, ≥ 10% below ideal body weight, leukemias and other malignancies)	At diagnosis
	Children ≥ 6 months of age **upon entry into the foster care system**	Prior to foster placement only
	Children 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	Upon incarceration and annually
	Age 1—4 with no risk factors	Not recommended
≥ 15 mm	**Age ≥ 5 with no risk factors**	Not recommended

Tests are read within two to three days after administration, recording *the transverse diameter of induration*. If greater than 3 days have elapsed the test should be repeated. (Exception: if the individual has a positive reaction measurable up to 7 days after the test was administered, the test does not need to be repeated.)

Record all tests in millimeters of induration (not erythema); record the absence of a reaction as "0 mm".

Interpreting Skin-Test Reactions

Three cut-points for TST reactions size (≥ 5 mm, ≥ 10 mm and ≥ 15 mm) have been recommended for defining a positive tuberculin reaction based upon risk factors for both TB infection and for TB disease if infected. Tables 5, 6 and 7 delineate TST cut-points based upon risk factors and age. Except for young children, the cut-point for low-risk persons (for whom screening is generally not recommended) is 15 mm .

Inaccurate results can occur because of inappropriate placement or reading of the test or clinical characteristics of the person being tested. False-negative results can occur by injecting the PPD solution too deep, with 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 tuberculosis and prior Bacille Calmette-Guerin (BCG) vaccination (see page 12).

TST "Convertors" vs. "Reactors"

A TST reactor is anyone who has a positive TST . A TST reactor is a high-priority for treatment of LTBI only if they have TB risk factors.

For persons with negative TST reactions who undergo repeat skin testing (e.g., health-care workers), an increase in reaction of ≥ 10 mm within a period of two years should be considered a skin test conversion indicative of recent infection with *M. tuberculosis.* When evaluating TST conversions, risk factors for TB infection should be considered. TST convertors are high-priority candidates for treatment of latent TB infection, regardless of age.[2]

Booster Phenomenon and Two-Step Skin testing

Some individuals infected with *M. tuberculosis* may have an initial negative TST, when tested many years after first being infected. This skin test, however, may stimulate or "boost" the immune system's ability to react to tuberculin, causing a positive reaction to subsequent tests. 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 subject to repeat tuberculin skin tests (e.g., health-care workers, correctional workers) and as a baseline test for residents of 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 TST within the last year do not need a two-step test.[2].

Table 7. Tuberculin Skin Test Cut-Points By Age Low-risk Persons

Adults		15mm
Children	Age $\geq$ 5	15 mm
	Ages 1 - 4	10 mm
	Age < 1	5 mm

Two-Step Procedure

If the initial TST reaction is negative, a second test should be placed 1 to 3 weeks later. If the second test is also negative, the person is considered uninfected. Any subsequent positive test would be considered new infection (skin test conversion). If, however, the second test is positive, the person should be classified as infected (but not a convertor) and treated accordingly.

Special Situations

Children

Routine testing of low-risk children is NOT recommended[7, 11]. Guidelines for targeted testing of children are summarized in Table 6. A "yes" answer to any of the following questions may be an indication for a TST[12]:

1. *Has your child had any contact with a case of TB?*
2. *Was your child or any household member born in or visited for more than a year in areas where TB is common (e.g., Africa, Asia, Latin America, Eastern Europe, and the Caribbean)?*
3. *Does your child have regular (e.g., daily) contact with adults at high-risk for TB (e.g., those who are HIV-infected, homeless, incarcerated, and/or illicit drug users)?*
4. *Does your child have HIV infection?*
5. *Has your child ever had raw milk or unpasteurized cheese?*

If children are deemed to be at low-risk, "Not indicated" can be recorded on health forms which include a blank space for TST results.

Live-virus Vaccinations

Live-virus vaccinations (e.g., MMR, Flu-Mist, Varicella) can be administered simultaneously with a TST; however, a TST should not be placed until at least four weeks after a live-virus vaccine has been administered[13, 14]. Until further research is performed, use the same guidelines when using a blood assay test for *M. tuberculosis* such as Quantiferon®-TB Gold.

Pregnancy

Pregnancy is not a contraindication for a TST because no adverse effects on the fetus have been demonstrated. Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for TB[7].

HIV Infection

When HIV infection is first identified, the patient should receive a TST. Anergy testing for HIV-infected persons with negative skin tests is not recommended[15]. Annual testing is only recommended for those HIV-positive individuals who have ongoing risk of TB exposure (e.g., injection drug use, working or residing in a prison or long-term care facility). Repeat TSTs are recommended for HIV-infected persons whose initial TST is negative and whose immune function has improved in response to highly active antiretroviral therapy, i.e., CD4+ cells/µl has increased to > 200[16].

Foreign-born from High Incidence Countries

Individuals with latent TB infection, who have immigrated from countries with high TB incidence, are at the highest risk of developing active tuberculosis during the first 5 years after arrival in the U.S. Screening and treatment for latent TB infection (TLTBI) for new arrivals from high incidence countries is recommended. Foreign-born students should be screened upon arrival and offered TLTBI. Screening and TLTBI for those who have been here longer than 5 years is a lower priority[7]. The general TST cut-point for foreign-born individuals from the high incidence countries (See Appendix A) where incidence of TB is ≥ 15 cases per 100,000 population is ≥ 10 mm (regardless of BCG history). The "low-risk" cut-point of ≥ 15 mm should be used for individuals from countries with < 15 cases per 100,000 population. If the foreign-born 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 radiograph) then the associated lower cut-point (≥ 5 mm) should be used.

Class A/B TB Notifications

Immigrants applying for permanent U.S. residency are required to have a chest radiograph screening for TB prior to departure. Those with chest radiograph abnormalities receive a "Notice of Arrival of Alien with Tuberculosis" which is sent from the quarantine station at point of entry to the state health department in the state where the person is moving. The notification classification system is as follows:

Class A: "Tuberculosis, infectious, non-communicable for travel purposes": Abnormal CXR or series of CXRs suggestive of active TB, history of one or more sputum smears positive for acid-fast bacilli, currently on recommended treatment, and sputum smears negative for acid-fast bacilli on 3 consecutive days. Immigrants with Class A notifications must have a health provider in the U.S. who has agreed to provide care for their tuberculosis.

Class B-1: "Tuberculosis, clinically active, not infectious": Abnormal CXR suggestive of active TB and sputum smears negative for AFB on 3 consecutive days. About 12 to 14% of Class B-1's are ultimately diagnosed with active TB in the U.S. and therefore are a high-priority for evaluation.

Class B-2: "Tuberculosis, not considered active": Abnormal CXR considered suggestive of tuberculosis, not clinically active. Sputum smear examinations are not required.

Local health departments are responsible for screening and follow-up of immigrants with TB notifications and sending documentation of screening to DHMH TB Control. A new arrival with a Class B notification should have a TST placed and if positive, a new chest radiograph. Obtain sputums if the person has a productive cough. Those with a positive TST and a negative chest x-ray are high-priority candidates for TLTBI[17, 18].

BCG Vaccination

BCG (Bacille Calmette-Guerin) 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. BCG vaccination complicates the interpretation of TST results because it can produce a false-positive reaction to the TST. There is no way to distinguish a positive reaction due to BCG vaccination from one due to TB infection. Sensitivity to tuberculin in BCG-vaccinated persons 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 A) is a high-priority for testing.

A positive TST (≥ 10 mm) in a BCG-vaccinated person originating from a high incidence country is considered indication of tuberculosis infection. After active TB has been ruled out, the person should be evaluated for treatment of latent TB infection.

For BCG-vaccinated individuals from *high incidence countries* with no other risk factors, a 10 mm cut-point should be utilized. For BCG-vaccinated individuals from *low incidence countries* (e.g., Canada, England), without other risk factors, a 15 mm cut-point should be used.[19]

*QuantiFERON®-TB Gold Test**

The Food and Drug Administration (FDA) has approved the use of QuantiFERON®-TB Gold (QFT-G) as a new in-vitro test to aid in the diagnosis of LTBI and active TB disease. QFT-G can be used in all circumstances in which the TST is used, including contact investigations, evaluation of recent immigrants who have had BCG vaccination, and TB screening of health-care workers and others undergoing serial evaluation for *M. tuberculosis* infection. The test is currently not recommended for young children (≤ 5 years), and persons with impaired immune systems (i.e. HIV infection, those who are being treated with TNF-α antagonists) [3].

**As of the date of publication, the DHMH Laboratory does not offer QFT-G. Check our website or your local health department for availability.*

Tumor Necrosis Factor-Alpha (TNF-α) Antagonists

The FDA has determined that TB disease is a potential adverse reaction from treatment with the tumor necrosis factor-alpha (TNF-**α**) antagonists infliximab (Remicade), etanercept (Enbrel), and adalimumab (Humira). These products work by blocking TNF-**α**, an inflammatory cytokine, and are approved for treating rheumatoid arthritis and other selected autoimmune diseases (such as Crohn's disease, ankylosing spondlitis and plaque psoriasis). Screen patients for risk factors for *M. tuberculosis* and test them for infection before initiating immunosuppressive therapies, including TNF-**α** antagonists. Two-step baseline testing is recommended with a 5mm induration cut-point for TST positivity.[20]

Screening, diagnosis and treatment of LTBI and TB disease in patients receiving TNF-α antagonists

- Screen patients for risk factors for *Mycobacterium tuberculosis* and test them for infection before initiating immunosuppressive therapies, including TNF-**α** antagonists.
- Two-step TST is recommended.
- Exclude TB disease before starting treatment for LTBI.
- Start treatment for LTBI before commencing TNF-**α** blocking agents, preferably with 9 months of daily isoniazid.
- Consider treating for LTBI in patients who have negative TST results but whose epidemiologic and clinical circumstances suggest a probability of LTBI.
- Pursue TB disease as a potential cause of febrile or respiratory illness in immunocompromised patients, including those receiving TNF-**α** blocking agents.
- Consider postponing TNF-**α** antagonist therapy until the conclusion of treatment for LTBI or TB disease.

V. TREATMENT OF LATENT TB INFECTION (TLTBI)

Treatment of Latent TB Infection (TLTBI) is used to decrease the likelihood that an individual with latent TB infection progresses to active TB disease. TLTBI should be targeted to individuals in high-risk groups regardless of the patient's age. Tables 5 and 6 outline the risk groups which should be targeted. The highest risk group for progression to TB disease is HIV/TB co-infected persons. Those patients taking anti-TNF-alpha drugs are also considered a high-risk group as are high-priority contacts to sputum smear-positive cases, TST-positive immigrants in the US < 5 years, and children less than 5 years of age[20, 21].

TLTBI for low-risk individuals is generally not recommended. When an individual at low-risk for tuberculosis infection or disease presents with a positive tuberculin skin test (≥ 15 mm), the person should be advised that because they are at low-risk for TB, there is a chance that their TST is falsely positive. The person should be given the option for treatment of latent TB infection and be advised of the risks and benefits associated with the treatment.

Medical Evaluation for a Positive TST

Individuals found to have a positive TST reaction should be examined by a provider to rule-out TB disease and be evaluated for treatment of latent TB infection. The evaluation consists of a TB symptom review, chest radiograph, HIV counseling and testing and evaluation of other medical conditions. An assessment should be made to determine the need for laboratory testing prior to or throughout TLTBI (see Table 8).

Chest Radiographs

Chest radiographs (CXR) should be performed to rule out active 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.

Pregnant women: A CXR should be done immediately during the first trimester, for pregnant women who:

- Have symptoms suggestive of TB disease
- Are HIV-positive (either TST-positive or negative) and have had close contact to a TB case
- Are TST-positive and are a close contact to a smear-positive or cavitary case.

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

Repeat chest radiographs (e.g. annual) are not needed after an initial negative CXR unless symptoms develop that could be attributed to TB[2]. In an asymptomatic person being evaluated for TLTBI, a negative chest radiograph is "good" (for the purposes of ruling out active TB disease) for 3 to 6 months in HIV-negative persons and up to one month in HIV-positive persons.

HIV Counseling and Testing

HIV testing is the standard of care for all tuberculosis cases and suspects and is recommended for all contacts to cases.[7] Because HIV/TB-coinfected persons have a high risk of developing active tuberculosis, HIV testing should also be considered for all others with LTBI. HIV/TB-coinfected persons are a very high priority for TLTBI.

Table 8. Regimens for Treatment of Latent TB Infection And Recommended Monitoring

<table>
<tr><th>Drugs</th><th>Interval</th><th>Dose</th><th>Medical Monitoring</th></tr>
<tr><td colspan="3">Adults Recommended</td><td rowspan="3">Adults - INH (9 months) and RIF (4 months)

Clinical Monitoring
Pretreatment: ask about previous TB drugs, oral contraceptives (if using rifampin) and other medications, history of liver disease, alcoholism and allergies. When using rifampin, use barrier method of contraception, increase methadone, etc. (See Appendix C).

Monthly (in person): check for anorexia, nausea, vomiting, abdominal pain, dark urine, jaundice, scleral icterus, rash, fatigue, fever or paresthesias.

Laboratory (AST, ALT & bilirubin)
Pretreatment: only necessary for persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who have a history of past or current alcohol abuse or injection drug abuse, HIV infection or women who are pregnant or < 3 months post-partum.

During treatment: Monthly LFTs are recommended if baseline tests elevated, history of or risks for liver disease, the patient is pregnant/postpartum, or there are adverse reactions to treatment.</td></tr>
<tr><td>Isoniazid (INH)
9 months
Provide only one month supply at a time</td><td>Daily</td><td>INH 5 mg/kg (Max: 300 mg)</td></tr>
<tr><td>Twice Weekly DOT</td><td>INH 15 mg/kg (Max: 900 mg)</td></tr>
<tr><td colspan="3">HIV-Negative Adults - Alternative</td></tr>
<tr><td>Rifampin (RIF)
4 months
Provide only one month supply at a time</td><td>Daily</td><td>RIF 10 mg/kg (Max: 600 mg)</td></tr>
<tr><td colspan="3">Children* (ages 0-18)</td><td rowspan="3">Children - INH (9 months)

Clinical Monitoring
Pretreatment: ask about other medications and medical conditions, allergies.

Monthly (in person): check for anorexia, nausea vomiting, abdominal pain, dark urine, jaundice, scleral icterus, rash, fatigue, fever or paresthesias.

Laboratory - no routine studies needed.</td></tr>
<tr><td>Isoniazid (INH)
9 months
Provide only one month supply at a time</td><td>Daily</td><td>INH 10-20 mg/kg (Max 300 mg)</td></tr>
<tr><td>Twice Weekly DOT</td><td>INH 20-40 mg/kg (Max: 900 mg)</td></tr>
</table>

* Rifampin six months daily is an alternative regimen for children (10-20 mg/kg, maximum 600 mg), particularly those exposed to INH resistant disease.

Treatment Completion: nine months daily = 270 doses within 12 months. Six months daily = 180 doses within nine months. Nine months twice weekly DOT= 76 doses within 12 months. Six months twice weekly DOT = 52 doses within nine months. Four months daily rifampin (or rifabutin) = 120 doses within six months.

Regimens for Treatment of Latent TB Infection (TLTBI)

There are currently two primary options for TLTBI. Decisions about which regimen should be used should be based upon the clinical characteristics of the individual and the likelihood that they will comply with a particular regimen.

Isoniazid (INH) - 9 months (either daily self administered or twice weekly DOT) is the preferred treatment for latent TB infection. It is the only regimen routinely recommended for children under age 18[11].

Rifampin (RIF) - 4 months (daily) is an acceptable alternative for HIV-negative adults. Rifampin six months is an alternative regimen for children who are exposed to an INH-resistant case.

A previous regimen for latent TB infection based on 2 months of rifampin and pyrazinamide is no longer recommended by the CDC due to a number of severe hepatotoxic reactions.[22, 23].

Table 8 outlines the treatment regimens and recommended medical monitoring.

Intermittent regimens (e.g., twice weekly) **must be directly observed.**

Special Situations

Children

The only regimen routinely recommended for children is a nine-month regimen of INH. (Exception: Rifampin 6 months is recommended for children who are contacts to INH resistant patients)[11]. Directly observed treatment of latent TB infection is recommended for children who are close contacts to infectious cases. School health programs are often able to assist with DOT for their students.

Pregnancy / Post-Partum

In most pregnant women, preventive treatment should be delayed until 2 to 3 months after delivery, even though no harmful effects of INH on the fetus have been documented[7].

Exceptions:

First trimester for TST-positive (≥ 5mm) women who are HIV positive, have behavioral risk factors for HIV and refuse HIV testing, or who were close contacts to smear-positive, pulmonary TB cases (at physician discretion).
After the first trimester if documented TST conversion in past 2 years.
Two to three months after delivery for all other pregnant women at high-risk for TB.
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 conversion within 2 years).

Breast Feeding

Breast feeding should not be discouraged for HIV sero-negative women placed on INH. Furthermore, the low concentration of anti-TB medications in breast milk should not be considered effective treatment for disease or as preventive treatment for a nursing infant. Supplementary pyridoxine (8mg pyridoxine/100mg INH) is recommended by CDC for breast feeding infants on INH or whose mothers are on INH[7,19]. A regular vitamin supplement appropriate for the infant's age provides adequate pyridoxine (vitamin B_6) and is preferred over 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

HIV infection is the single most important risk factor for development of tuberculosis if the person is TB infected. Directly observed treatment of latent TB infection is recommended for HIV co-infected persons. The generally recommended regimen for treatment of latent TB infection in an HIV-infected person is a 9 month regimen of INH (daily or twice weekly). Rifampin is generally contraindicated or should be used with caution in persons who are taking some antiretroviral medications[7]. Always seek consultation with a TB expert for HIV-infected patients who are also being treated with antiretroviral therapy.

Renal Insufficiency and End-Stage Renal Disease

TST-positive persons with renal insufficiency or on renal dialysis are a very high priority for treatment. INH can be administered daily (5 mg/kg, maximum 300 mg) or thrice (3x) weekly after dialysis (15 mg/kg, maximum 900 mg). Often arrangements can be made with the dialysis center to administer the medication[5].

Contacts

Contacts of patients with drug susceptible tuberculosis and who have positive tuberculin skin test reactions (≥ 5mm TST reaction) should be treated regardless of age. In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptibility to severe disease, children younger than age 5 with negative skin tests should have treatment initiated and have another skin test performed at least 8-10 weeks after contact has ended. If the repeat skin test is positive, treatment should continue for the recommended duration. If the repeat test is negative, treatment can be discontinued. This period of TLTBI between the first and second TST test is sometimes referred to as "window prophylaxis". HIV-infected contacts should receive a full course of treatment regardless of TST results.

Contacts to patients with drug resistant tuberculosis are treated on a case by case basis. Contacts to INH-resistant tuberculosis are generally treated with rifampin. Those who are contacts to multiple drug-resistant tuberculosis are evaluated individually and a determination made about the need for treatment and which drugs to utilize. Always consult an expert prior to treating a contact to a MDR-TB case.

Persons with Fibrotic Lesions

For patients who have a chest radiograph demonstrating old fibrotic lesions thought to represent previous infection with TB, a positive TST (≥ 5mm) without evidence of active disease, and no history of treatment for TB, two acceptable regimens can be used for treatment. These regimens include:

- nine months of isoniazid or
- four months of rifampin (with or without isoniazid), providing that infection with drug-resistant organisms is judged to be unlikely and patient is HIV-negative.

Suspected TB Disease Ruled Out

Patients who begin multidrug therapy (i.e rifampin, isoniazid, pyrazinamide, ethambutol) for suspected pulmonary TB but are subsequently determined not to have active disease (i.e. AFB cultures are negative and chest radiographs are stable) should complete treatment with at least 2 months of a regimen containing rifampin and pyrazinamide if the tuberculin skin test is positive and other causes of the radiograph abnormalities have been excluded[7]. A two-month regimen using rifampin and pyrazinamide exclusively is no longer recommended for treatment of latent TB infection[22].

Pyridoxine (Vitamin B6) Supplementation While on INH

Persons with the following conditions should take pyridoxine when taking INH: conditions where neuropathy is common (diabetes, malnourishment [≥ 10% below ideal body weight], alcoholism, cancer, chronic liver disease, HIV infection) and pregnancy. 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 paresthesias while taking INH. The dose should be 25 mg for each 300 mg of INH daily or 50 mg for twice or thrice weekly therapy, depending on the dosing schedule being utilized. For breast feeding infants the dose should be 8mg pyridoxine/100mg INH. A regular vitamin supplement appropriate for the infant's age provides adequate pyridoxine (vitamin B_6) and is preferred over use of pyridoxine alone. Supplemental pyridoxine should not be given to infants in addition to a regular vitamin supplement without consulting a TB expert. Pregnant women should take 50 mg daily[7,19].

Monitoring Treatment

Monthly in-person clinical evaluations (including monthly weight checks) should be conducted with all patients on TLTBI. This involves ongoing education of patients about the symptoms and signs that can be associated with adverse effects of the drugs being prescribed and the need for prompt cessation of treatment and clinical evaluation should they occur. Patients should be educated monthly regarding occurrence of the following symptoms and reminded to stop the medications and report them if they occur: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness in the right upper quadrant, easy bruising or bleeding, malaise and arthralgias [(4)].

The most important measure to prevent severe hepatitis is to instruct the patient to STOP taking medications immediately if hepatitis symptoms occur.

Baseline Laboratory Monitoring

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 are present. Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurement of serum AST (SGOT) or ALT (SGPT) and bilirubin. Baseline testing is also indicated for patients infected with HIV, pregnant women and those in the immediate post-partum period (i.e., within 3months of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who have history of alcohol abuse, injection drug use, use alcohol regularly, and 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 relative contraindications for TLTBI.

Routine Laboratory Monitoring

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

Withhold TLTBI treatment if transaminase levels exceed 3 times normal in symptomatic persons or 5 times normal in asymptomatic persons with no risk factors for hepatic disease. Serious adverse events associated with TLTBI (hospitalization, permanent disability, or death) should be promptly reported to DHMH Division of Tuberculosis Control and to US FDA's MedWatch program by phone, 1-800-FDA-1088, fax 1-800-FDA-0178 or internet www.fda.gov/medwatch.

Managing Interruptions in Treatment

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

VI. DIAGNOSIS OF TUBERCULOSIS

The symptoms of pulmonary TB include cough, chest pain and hemoptysis; the specific symptoms of extrapulmonary TB depend on the site of disease. Systemic symptoms of active TB include fever, chills, night sweats, fatigue, loss of appetite and weight loss. Approximately 30% of Maryland TB cases are extrapulmonary (with or without pulmonary involvement), with symptoms specific to the particular site affected. Extrapulmonary TB should be considered in the differential diagnosis of persons with systemic symptoms of TB and who are at high-risk for TB. HIV-infected persons often have atypical symptomatic and radiographic presentations of TB.

Components of a tuberculosis diagnostic work-up include a medical history, physical exam, tuberculin skin test (unless there is a history of a prior positive TST or TB is culture confirmed at time of diagnosis), chest radiograph and bacteriology. Components of the diagnostic work-up are reviewed in Table 9.

HIV testing is the standard of care for all tuberculosis cases and suspects, and is recommended for all contacts to cases[7]. Knowledge of HIV status is critical both because the presentation of tuberculosis in HIV-infected persons can differ from that in immunocompetent persons and the TB treatment regimen is adjusted based upon the CD4+ cells/µl count.

A recent Maryland study indicated that 27% of pulmonary TB patients had a delay in diagnosis of greater than 2 months after reporting TB symptoms to a physician[24]. These delays were associated with presumptive antibiotic use. In a patient with pulmonary disease, including community acquired pneumonia, whose chest radiograph and/or clinical course is consistent with pulmonary tuberculosis, an appropriate diagnostic work-up (including submitting specimens for AFB) should be done promptly, preferably before initiating antibiotics.

Chest Radiograph Manifestations of TB

Below are listed typical radiographic features of pulmonary tuberculosis:

- **Location:** apical and/or posterior segment of right upper lobe (RUL), apicoposterior segment of left upper lobe (LUL) or superior segment of either lower lobe
- **Infiltrate:** fibronodular, 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 HIV-infected persons and young children

HIV-infected persons often have atypical chest radiograph presentations and can have infectious, pulmonary TB with a negative film[25].

Extrapulmonary Tuberculosis

The diagnostic work-up for extrapulmonary tuberculosis is dependent on the disease site. At any site, evidence of necrotizing or caseating granuloma on the pathology report is presumed to be indicative of tuberculosis unless proven otherwise. Co-existent pulmonary disease should be ruled out in all cases of extrapulmonary disease. Diagnosis of the more common forms of extrapulmonary TB are discussed briefly below.

TB Meningitis. The key diagnostic procedure is examination of the cerebrospinal fluid.

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

TB lymphadenitis. The diagnosis is established by culture of *M. tuberculosis* from lymph node biopsy or aspirate. Presumptive diagnosis is often made with demonstration of AFB in tissue or pathologic evidence of caseating granuloma.

Table 9. Components of a Tuberculosis Diagnostic Work-up

Medical History	**TB history:** history of TB exposure, prior TST 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 4) or may affect ability to tolerate TB treatment. **TB symptom history:** fever, weight loss, cough > 3 weeks duration, hemoptysis, chest pain.
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.
Tuberculin Skin Test	Tests can be negative in the presence of active disease or HIV infection. Not needed if disease already confirmed with a positive culture.
Chest Radigraph	Posterior/anterior (P/A) view initially; others as appropriate. Children should routinely have a lateral in addition to a P/A.
HIV	Because of implications of HIV infection for TB treatment, **HIV counseling and testing is the standard of care for the initial work-up of all TB Suspects.** If HIV positive, obtain CD4+ count and viral load.
AFB Smears, Cultures & Sensitivities	A positive smear indicates mycobacterial infection which may or may not be *M. tuberculosis*. Bacteriologic culture for *M. tuberculosis* confirms the diagnosis of TB; however, clinicians should not wait for culture results before initiating therapy if they suspect active disease. *
Histology	Pathology reports indicating caseating or necrotizing granuloma are presumed to be TB unless proven otherwise.

*Between 10% and 20% of Maryland TB cases are culture negative, pulmonary TB (abacillary). A negative culture for *M. tuberculosis* does not rule out a diagnosis of pulmonary TB. Patients with abnormal chest readiographs and symptom histories compatible with TB should be treated presumptively. Individuals on antituberculosis treatment with CXR improvement and negative cultures are considered to have culture-negative TB.

Skeletal TB. Skeletal TB (bones and joints) most commonly occurs in the spine (Pott's Disease) and in the weight-bearing joints. It is diagnosed by x-ray films of the involved joint, followed by specimen collection and culture.

Pleural TB. With thoracentesis, acid-fast bacilli stains are seldom positive and cultures only positive in 25% to 30% of cases. A transthoracic needle pleural biopsy supports a diagnosis of pleural TB based upon demonstration of caseating granuloma on tissue stains[19].

Abdominal TB. Diagnosis occurs after other causes of severe pain are ruled out. *M. bovis* should be considered in children presenting from households where unpasturized milk products are common.

Diagnostic Microbiology

Specimen Collection Persons with suspected pulmonary TB should have at least 3 sputum specimens examined for AFB (acid-fast bacilli) smear and culture. Specimens should be obtained in 8-24 hour intervals, as long as one specimen is collected in the early morning[2]. Sputum specimens should be clearly labeled with patient identifying information and the date collected. Sputum specimens may be refrigerated overnight, but should be shipped as soon as possible (goal 24 hours).

- TB patients often do not have purulent sputum. Watery specimens after a few deep coughs are acceptable.
- Sputum induction with hypertonic saline or bronchoscopy may be done to obtain specimens in an individual who cannot produce sputum when there is reasonable suspicion of TB disease. Nebulized sputums should be clearly labeled "induced sputums". Nebulized sputums should be obtained in a sputum induction booth or airborne infection isolation room with staff utilizing appropriate respiratory protection.
- Tissue specimens for the culture of *M. tuberculosis* should be placed in sterile saline, delivered promptly to the laboratory and should NOT be placed in formalin.
- Gastric aspiration is occasionally used in young children to obtain specimens of swallowed bacilli when the susceptibility results of the source case are unknown. However, 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.

Laboratory Examination

AFB Smear

Smear examination permits only the presumptive diagnosis of TB because the AFB on the smear may be mycobacteria other than *M. tuberculosis*. Many patients with active TB disease have negative AFB smears. (Do not delay treatment if TB is suspected and smears are negative.)

AFB Culture

Cultures should be obtained for all specimens, regardless of AFB smear results. Solid media and conventional biochemical tests yield results within 8 to 12 weeks. Liquid media radio metric methods (e.g. BACTEC ®) may yield AFB culture results in 8 to 21 days.

AFB Culture Identification

Once an acid-fast culture grows it is necessary to identify which acid-fast organism it is. This is generally done using either nucleic acid probes or high performance liquid chromatography (HPLC) (2-8 hours) or NAP inhibition tests (5 days). Note: Anytime a laboratory report indicates "Positive AFB Culture", further testing is necessary to identify which acid fast organism is growing.

- A positive culture for *M. tuberculosis* confirms a diagnosis of TB; however, treatment for tuberculosis should be initiated on the basis of clinical signs and symptoms while awaiting culture results.
- A report of *"M. tuberculosis complex"* indicates the presence of one of several organisms *(M. tuberculosis, M. bovis, M. microti, M. canetti* and *M. africanum).* Over 98% of organisms in the complex ultimately are identified as *M. tuberculosis*. 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 is performed on all initial *M. tuberculosis complex* isolates to determine speciation and final identification. A final report will identify the isolate as *M. tuberculosis* or another organism.

Drug Susceptibility Testing

Obtain susceptibilities on all initial *M. tuberculosis* culture-positive isolates. The DHMH State laboratory automatically tests 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 on a patient from a private laboratory, contact the laboratory to assure that susceptibility testing is being done. If payment is an issue, have cultures sent to the DHMH TB laboratory for testing. It is crucial 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 2 months of treatment. 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 MDR-TB is found or upon physician request.

Nucleic Acid Amplification (NAA) Tests
(e.g., Amplicor® and MTD®)

This is a relatively new category of tests that can detect the presence of *M. tuberculosis* DNA or RNA in sputum. The test should only be performed prior to institution 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. The big advantage of this test is that results can be obtained in 24 hours. Sensitivity for AFB smear-positive specimens is > 95% and as low as 50% for smear-negative specimens. Specificity for both is 98%[26]. While the test is not licensed for use on extrapulmonary specimens, it is sometimes done upon physician request[27].

At DHMH TB laboratory, an NAA test is routinely done on all initial pulmonary AFB smear-positive specimens. Because of the low sensitivity on smear-negative AFB specimens, do not routinely request that these be performed. At the discretion of the treating physician, the NAA test should be requested only on pulmonary AFB smear-negative patients with a high suspicion of TB and whose contact investigation would involve patients at high-risk of developing TB disease if infected (such as schools, correctional facilities, nursing homes and homeless shelters). When requesting an NAA on a smear-negative test, indicate why the test is warranted on the laboratory request form. This helps the laboratory prioritize their workload.

DNA Fingerprinting

DNA fingerprinting of *M. tuberculosis* isolates from culture-positive patients has been used in Maryland since 1996. Tests include restriction fragment length polymorphism (RFLP) and spoligotyping.

The purpose of DNA fingerprinting is to identify or confirm 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. To determine whether transmission has occurred, the DNA fingerprint results must be supported by local epidemiology (e.g., the cases must know each other or have been in the same place at the same time).

When a culture-positive patient's disease is inconsistent with TB, DNA fingerprinting is also useful to confirm that laboratory contamination has occurred. Laboratory contamination 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[28]. If laboratory contamination is suspected, requests for testing should be made to the State TB Control office.

VII. TREATMENT OF TUBERCULOSIS DISEASE

General Principles

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

Four drugs must be included in the initial treatment regimen.

Standard initial treatment consists of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB). The only routine exceptions to this standard are very young children who cannot do visual acuity testing (exclude EMB) and pregnant women (exclude PZA). The purpose of a four-drug regimen is to prevent acquisition of drug resistance.

Directly observed therapy (DOT) is the standard of care for treatment of active TB.

DOT is the direct observation by a trained health-care worker of every antituberculosis medication dose administered. DOT should be used with both pulmonary and extrapulmonary TB patients.

Never add a single drug to a failing regimen.

Doing so can lead to acquired drug resistance.

Manage TB patients 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 utilizing various strategies including comprehensive case management, identification of barriers to treatment, working with the patient to eliminate barriers, provision of directly observed therapy and the use of incentives and enablers. Ultimately, responsibility for assuring completion of treatment rests with the local health department.

At the beginning of treatment, patients should be advised via the "TB Patient / Provider Agreement" of their legal responsibility to take medications. Failure to comply can result in legal action (see section on "Managing Nonadherence").

Nurse Case Management

This is an essential component of Maryland local health department TB control services. Nurses, in conjunction with the physician, and other appropriate individuals, work with the patient and family to develop a treatment plan, identify barriers to treatment and attempt to overcome them. Patient-centered case management is often key to assuring adherence to treatment.

Directly Observed Therapy

It has been observed in the literature on patient compliance that roughly a third of patients 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 [(29)]. DOT has been demonstrated to significantly increase TB completion rates and reduce acquired drug resistance. It is now the standard for TB treatment throughout the world. Given that compliance cannot be predicted, universal DOT is a nondiscriminatory way to assure TB treatment completion

Table 10. Examples of Incentives and Enablers

Enablers	*Incentives*
• Transportation vouchers • Convenient clinic location / hours • Bilingual staff (in appropriate languages) • Social service assistance • Housing • Groceries	• Small toy or book (for a child) • Money • Pre-paid phone card • Drug store vouchers • Gift cards

DOT is the standard of TB care in Maryland. All Maryland local health departments can provide DOT to TB cases and suspect cases through co-management with the private physician. **All intermittent TB treatment MUST be administered DOT.**

Incentives and Enablers.

It has been demonstrated that the use of incentives and enablers (Table 10) can improve adherence to TB treatment and improve TB treatment completion rates. Enablers are anything that helps the patient complete therapy. Incentives are defined as anything that motivates the patient, generally tailored to individual patient wishes and needs and thus, valued and meaningful to the patient. The Maryland Division of Tuberculosis Control has limited funds to supplement local health department efforts to provide incentives and enablers. Requests for funds should be submitted by the LHD to the State office. Requests will be considered on a case-by-case basis.

Tuberculosis Treatment Regimens

The standard treatment regimen for Maryland consists of two phases (see Table 11).

Initiation Phase:

INH, RIF, PZA and EMB for a total of 8 weeks. Daily therapy is provided initially followed by twice weekly treatment for the remainder of therapy. The first weeks of therapy can be handled by giving every dose directly observed for either 7 days per week for 2 weeks, or 5 days per week for 3 weeks. Providing medication in weekend and holiday packets is not recommended for the first 2 weeks of therapy.

After completion of the daily therapy portion of the Initiation Phase, the preferred drug regimen for pan-sensitive tuberculosis is twice-weekly, directly observed therapy for the remainder of treatment. For those rare patients unable to tolerate the higher doses used for twice weekly therapy, daily therapy can be utilized.*

Continuation Phase:

After completing the Initiation Phase, the regimen should be changed to:

INH and RIF administered twice weekly DOT for 18 weeks ***or***
INH and RPT (rifapentine) administered once weekly DOT for 18 weeks (eligible patients only).

Treatment should be extended in specific circumstances (see Table 12).

The standard treatment regimen for Maryland should be utilized routinely. There are several additional dosing options which can be utilized when clinically indicated (see Appendix B).

* The Centers for Disease Control concluded via expert opinion that "based upon substantial clinical experience, five-day a week DOT is equivalent to seven-day administration; either can be considered daily". However, five-day per week therapy has not been studied in clinical trials. If daily therapy must be utilized after the first two weeks, the Maryland TB Expert Panel indicated that the preferred mode of administration is to administer DOT five-days per week and to utilize weekend and holiday packets. This should be counted as 100% directly observed. Count only observed doses.

Table 11. Standard Tuberculosis Treatment Regimen - Maryland

Initial Phase (8 —9 wks)		Continuation Phase[d] (18 wks)	
Drugs	***Interval[c]/Weeks (Doses)***	***Drugs***	***Interval[c]/Weeks (Doses)***
INH **RIF[a]** **PZA** **EMB[b]**	**5 days/wk x 3 wks** then **twice weekly x 6 wks** (15doses) plus (12 doses) **———OR———** **7 days/wk x 2 wks** then **twice weekly x 6 wks** (14 doses) plus (12 doses)	**INH** **RIF**	**Twice weekly x 18 wks** (36 doses) **———OR———**
		INH **RPT[e]**	**Once weekly x 18 wks** (18 doses) *(eligible patients only)*

INH = isoniazid, RIF = rifampin, PZA = pyrazinamide, EMB = ethambutol, RPT = rifapentine

[a] **HIV-infected patients** on certain antiretroviral drugs may need medication adjustment because of drug interactions with rifampin. HIV infected persons with <100 CD4+ cells/µl should be given daily therapy for the first 8 weeks and daily or thrice weekly for the remaining 18 weeks. Consult a HIV/TB expert.

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

[c] **All regimens** (once, twice (2x) or thrice (3x) weekly and 5 days/wk) **must be DOT.**

[d] **Treatment should be extended in certain circumstances** (see Table 12).

[e] **Use Rifapentine (RPT)** only in **HIV-negative adults** with non-cavitary, pulmonary TB with negative cultures within 2 months

Table 12. Minimum TB Treatment Duration by Case Characteristics

TB Diagnosis	**Months of Treatment** (minimum)
Standard drug sensitive TB disease	**6**
Culture negative (abacillary) pulmonary TB	**4**
Drug resistance / Intolerance	
Without INH	**6**
Without PZA (pregnancy and *M. bovis)*	**9**
Without RIF	**9 to 12**
Without INH / RIF ± other drugs	**18 to 24**
Cavitary chest x-ray / culture positive @ 2 months	**9**
Extrapulmonary	
Central nervous system	**9**
Bone Joint	**9**
Miliary	**9**
Other extrapulmonary	**6**

Table 13. First-Line TB Drugs Dose in mg/kg (Maximum Dose)

Drugs	Daily		Weekly					
			1X		2X		3X	
	Child	Adult	Child	Adult	Child	Adult	Child	Adult
INH	10-15 (300 mg)	5 (300 mg)	XXX	15 (900 mg)	20-30 (900 mg)	15 (900 mg)	XXX	15 (900 mg)
RIF	10-20 (600 mg)	10 (600 mg)	XXX	XXX	10-20 (600 mg)	10 (600 mg)	XXX	10 (600 mg)
PZA[a]	15-30 (2 g)	15-30 (2 g)	XXX	XXX	50 (4 g)	50-70 (4 g)	XXX	50-70 (3 g)
EMB[a]	15-20 (1 g)	15-25 (1600 mg)	XXX	XXX	50 (4 g)	50 (4 g)	XXX	25-30 (2400 mg)
RBT	XXX	5 (300 mg)	XXX	XXX	XXX	5 (300 mg)	XXX	5 (300 mg)
RPT[b]	XXX	XXX	XXX	600 mg 10 mg/kg if > 60kg	XXX	XXX	XXX	XXX

Note: 1x weekly and 3x weekly <u>not</u> recommended for children

INH = isoniazid, RIF = rifampin, PZA = pyrazinamide, EMB = ethambutol, RBT = rifabutin
RPT = rifapentine XXX = not recommended

[a]CDC recently recommended dosing based on weight ranges for PZA and EMB[(5)]. After reviewing available data, the Maryland TB Expert panel recommended that the former dosage recommendations be utilized, advising that the lowest possible dose in the dose range be used[(1)].

[b]Data indicates that 900 mg of RPT is well-tolerated and some experts are utilizing this higher dose[(30)].

Medication Dosing

All medication doses should be calculated based upon weight for both children and adults (see Table 13). In general, utilize the lowest possible dose for weight. Adjust doses as the individual's weight changes. For obese patients, dosing should be based on ideal body weight to avoid toxicity.

Count only observed doses. Weekend and holiday packets for patients on daily therapy should not be counted. During the initiation phase of treatment, it is strongly recommended that a minimum of 14 or 15 doses be directly observed.

All regimens must be given DOT. If doses are missed they should be added on to the end of therapy. Once weekly doses should have at least 5 days between doses; twice (2x) weekly doses should have at least 72 hours between doses; thrice (3x) weekly doses should have at least 48 hours between doses. In general, doses should not be split over the course of a day.

In the rare event that medication is self-administered (with explicit approval by the local health department and DHMH), combination drugs (Rifater® and Rifamate®) should be utilized to prevent acquisition of drug resistance (see Appendix D).

Completion of therapy should be determined based upon the total number of doses ingested.

Rifapentine

Rifapentine is a new drug option for the continuation phase of treatment of tuberculosis in adults[5,30,31]. It has the distinct advantage of being administered once weekly with INH. It can be used with patients who meet **ALL** of the following criteria:

- Pulmonary disease
- HIV-negative (documented)
- Non-cavitary chest radiograph
- Organism sensitive to INH, RIF and PZA
- Culture negative after 2 months of treatment (2 consecutive negative cultures)
- Not pregnant

The Maryland TB expert panel recommends that Rifapentine not be started until culture conversion within 2 months of initiation of treatment has been documented. At that point, once weekly INH/RPT can be substituted for INH/RIF.

Pyridoxine Supplementation with INH

Persons with the following conditions should take pyridoxine when taking INH: conditions where neuropathy is common (diabetes, malnourishment [≥ 10% below ideal body weight], alcoholism, cancer, chronic liver disease, HIV infection) and pregnancy[7,19]. Routine administration of pyridoxine in children is not recommended for children taking INH except for breast feeding infants, children and adolescents with diets likely to be deficient in pyridoxine, or children who experience paresthesia while taking INH. The dose should be 25 mg for each 300 mg of INH daily or 50 mg for twice or thrice weekly therapy, depending on the dosing schedule being utilized. For infants the dose should be 8mg pyridoxine/100mg INH. Pregnant women should take 50 mg daily.

Special Situations

Children

Because of the potential for rapid progression of TB disease, children suspected of having tuberculosis should be started on therapy as soon as possible. Children generally tolerate TB medications very well. No routine laboratory monitoring is necessary with children under age 18. Follow recommendations for standard therapy with dosing by the child's weight. EMB should generally be avoided in children too young to perform visual acuity testing. EMB 15 mg/kg can be utilized in consultation with an ophthalmologist when the source case is drug resistant or of unknown status with a high likelihood of drug resistance.

Pregnancy

In almost all situations, a pregnant woman who has a positive *M. tuberculosis* culture or is suspected of having TB disease should be treated without delay. Treatment regimens for pregnant women differ from standard treatment regimens because pyrazinamide should be avoided and streptomycin is contraindicated.

The standard initial treatment regimen for pregnancy consists of INH, RIF and EMB. The EMB should be discontinued as soon as sensitivity to INH and RIF has been demonstrated. Treat for a total of 9 months. Pregnant women on isoniazid should be given pyridoxine 50 mg per day (unless already taking the equivalent in a prenatal vitamin).

HIV Infection

Tuberculosis complicated by HIV infection can pose significant treatment challenges. Consultation with a HIV/TB expert is ESSENTIAL when treating any HIV/TB patient.

CD4+ cells/µl < 100 in HIV/TB patients has been associated with development of acquired rifampin resistance during treatment. Therefore, recommendations have changed for this group to provide more intensive therapy as follows:

- Initiation Phase (8 weeks): Daily (5 days per week) DOT
- Continuation Phase (18 weeks): Daily or thrice (3x) weekly DOT

Antiretroviral Therapy

Highly active antiretroviral therapy (HAART) is frequently recommended for treatment of many HIV-infected patients. These agents complicate TB treatment because nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) interact with rifamycins which may significantly reduce the serum levels of these HAART drugs. Rifabutin, which has less interaction with NNRTIs and PIs than rifampin, has been shown to be an effective substitute. Coinfected patients, taking antiretrovirals when diagnosed with TB, should continue them. Delaying the initiation of HAART for 4-8 weeks after starting antituberculosis therapy has the potential advantages of being better able to ascribe a specific cause for a drug side effect, decreasing the severity of paradoxical reactions, and decreasing the adherence challenges for the patient.

Recommendations on managing drug/drug interactions are changing rapidly. Always seek consultation with a TB expert for HIV-infected patients who are also being treated with antiretroviral therapy[5,32,33,34,35].

Paradoxical Reactions

HIV-infected patients may have temporary exacerbation of symptoms, signs or radiographic manifestations of tuberculosis (paradoxical reaction) after beginning antituberculosis treatment, or after beginning antiretroviral therapy. These reactions presumably develop as a consequence of reconstitution of immune responsiveness brought about by HAART or perhaps, by treatment of the tuberculosis itself. If signs of clinical worsening on treatment occur, such findings should be attributed to a paradoxical reaction 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). Paradoxical worsening occasionally occurs in HIV-negative persons. For up-to date information on TB complicated by HIV an expert should be consulted. Consultation is available through the TB Control Program at DHMH by calling 410-767-6698. Consultation is also available through the Northeastern Regional Training and Medical and Consultation Center at the New Jersey Medical School Global Tuberculosis Institute on the internet at www.umdnj.edu/globaltb or by calling 800-482-3627.

Cavitary TB with Positive *M. tuberculosis* Cultures at 2 Months

Patients who present with cavitary disease and whose sputum cultures remain positive after 2 months of treatment have been demonstrated to have very high rates of relapse (21%) and therefore it is recommended that the continuation phase in such patients be extended by 3 months for a total treatment of 9 months[5].

Renal Insufficiency and End-Stage Renal Disease

Renal insufficiency complicates the management of tuberculosis because some antituberculosis medications are cleared by the kidneys. Management may be further complicated by the removal of some antituberculosis agents via hemodialysis. For patients with a creatinine clearance of < 30 ml / minute or who are on renal dialysis the alterations in dosing and frequency outlined in Table 14 should be utilized. For patients on hemodialysis, medications should be given 3 times per week after dialysis. Often arrangements can be made with the dialysis center to directly observe administration of the medications[5].

Culture-Negative (Abacillary) Tuberculosis

Culture-negative, pulmonary tuberculosis is diagnosed when there are chest radiograph and clinical signs consistent with TB but negative sputum cultures for TB, and clinical and CXR improvement on TB treatment. Treatment for culture-negative TB can be discontinued after a total of 16 weeks. For patients with documented culture-negative tuberculosis (with non-cavitary chest radiographs), who meet the eligibility requirements for rifapentine, it is acceptable to utilize once-weekly rifapentine/ isoniazid in the final 8 weeks of treatment.

Table 14. Dosing Recommendations for Patients with Reduced Renal Function (Creatinine Clearance <30ml/ min) or for Patients on Hemodialysis

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	XXX	25-35 mg/kg
EMB	XXX	15-25 mg/kg

XXX = not recommended

Extrapulmonary Tuberculosis

Extrapulmonary tuberculosis is treated according to standard TB guidelines using directly observed therapy. For TB meningitis, miliary and bone/joint TB, treatment is extended to a minimum of 9 months. For any form of extrapulmonary TB, treatment should be extended based upon clinical response. Expert consultation should be sought if patients with extrapulmonary TB fail to respond to treatment.

Drug Resistance and Intolerance

Consultation from a tuberculosis expert should be sought when treating tuberculosis complicated by either drug resistance or drug intolerance. The policy of the Maryland Division of Tuberculosis Control is to regularly consult on drug-resistant TB patients.

General recommendations include:

- **Regimens lacking INH:** Treat for a total of 6 months with a regimen of RIF, PZA and EMB. When INH resistance is identified, EMB must be continued for the duration of the treatment.
- **Regimens lacking PZA**(e.g.,pregnancy and *Mycobacterium bovis):* Treat for a total of 9 months with a regimen of INH and RIF.
- **Regimens lacking RIF:** Treat for 12 months with INH, PZA, EMB and a flouroquinolone (levofloxacin or moxifloxacin). An injectable agent (e.g., streptomycin) for the first 2 months should be considered for more extensive disease or if a shorter duration of therapy is desired (9 months).
- **Regimens lacking INH/RIF** (multi-drug resistant [MDR] TB): must be closely managed in consultation with the local health department utilizing multiple drugs to which the organism is sensitive (Appendix D). Treatment duration is 18 to 24 months[5].

Drug Interactions

Drug-drug interactions can result in changes in the concentrations of one or both of the 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 the antituberculosis drugs cause clinically relevant changes in the concentrations of other drugs. Most interactions are associated with rifampin. Below are described some of the more significant interactions.

Methadone

Because of the drug interaction between rifampin and methadone, TB patients on methadone will require up to a 50% increase in methadone while on treatment. Increase the methadone dose (to control withdrawal symptoms) by 5 mg every other day to a maximum of a 50% increase over the original dose.

Oral Contraceptives

Rifampin reduces the contraceptive effect of oral contraceptives. When a TB patient is on oral contraceptives, they should be advised to use a barrier method while on TB treatment.

Antiretrovirals

There are numerous interactions between rifampin and protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Frequently rifabutin is substituted for rifampin. Always consult a HIV/TB expert.

Other Drug Interactions

The rifamycins interact with several other classes of drugs. Patients on the anticoagulant warfarin sodium (Coumadin) require closer monitoring of prothrombin time and may require a two to three-fold increased dose. The rifamycins also can reduce blood levels of anticonvulsants, cardiovascular agents, bronchodilators, oral hypoglycemics, immunosuppressants (such as cyclosporine), antifungals and some psychotropic drugs[7].

Monitoring Treatment

Monthly in-person clinical evaluations (including a monthly weight check) should be conducted with all patients being treated for tuberculosis. Patients should also receive a general assessment during DOT visits. Patients should be systematically queried regarding occurrence of the following symptoms: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, and arthralgias. Patients should be instructed at every visit to immediately report the occurrence of any of these symptoms. Table 15 outlines monitoring of TB treatment.

Laboratory Monitoring

Baseline liver function tests, uric acid and complete blood count (including platelets) should be done for all adult patients. Children under age 18 do not need baseline blood work unless risk factors for hepatitis are present. Monthly liver function tests should be done only for those with abnormal baseline LFTs, development of hepatitis symptoms, liver disease, chronic hepatitis, heavy alcohol use, injection drug users, documented hepatitis B or C infection, HIV infection, and pregnant and post-partum women.

Follow-up Sputum Examinations

Important decisions concerning the continuation phase regimen hinge on the *M. tuberculosis* culture status at the end of the initial phase of treatment (i.e., extension of therapy for cavitary disease with positive cultures at 2 months and use of rifapentine for the continuation phase). At a minimum, 3 sputum specimens should be obtained monthly until two consecutive specimens are negative on culture. **Thus, if sputum conversion has not already been documented, it is important that sputum specimens be obtained no later than 60 days after the start of treatment to document culture conversion.** For smear-positive patients for whom smear conversion is being evaluated (e.g., to return to work or to discontinue AFB isolation), generally obtain no more than 3 specimens every 2 weeks.

Managing Adverse Reactions

As is true with all medications, combination chemotherapy for tuberculosis is associated with a predictable incidence of adverse effects, some mild, some serious. Expert consultation should be sought with any significant adverse reactions.

Gastrointestinal Reactions

GI symptoms are common, particularly in the first few weeks of therapy. In the presence of GI symptoms, medications should be stopped and serum AST and bilirubin measured. If the AST is $\geq$ 3 times normal the symptoms may represent hepatic toxicity, and the patient should be evaluated as described below. If the AST is < 3 times normal, the symptoms are presumed not to be due to hepatotoxicity. The initial approach in that instance is to change the hour of drug administration and/or to administer the drugs with food.

Rash

Rash can be caused by all antituberculosis drugs. The response to a patient with rash depends on its severity. A minor rash, affecting a limited area or being predominantly manifested as itching can be treated with antihistamines

Table 15. Monitoring for Treatment Response and Adverse Reactions (Baseline / Monthly)

Treatment Response	
Vital Signs / Weight	Weight gain is often a critical measure of treatment response.
Signs and Symptoms of TB	Check for cough, hemoptysis, chest pain, fever, night sweats, fatigue, malaise.
Sputums	Obtain specimens monthly until sputum culture conversion (2 consecutive negative cultures at least 7 days after last positive culture). To document conversion of smear (for return to work/school), generally obtain 3 specimens every two weeks. At end of treatment obtain one specimen (only if patient able to produce sputum).
Adherence	Evaluate adherence to prescribed regimens and develop plans to address nonadherence problems.
Chest x-ray (CXR)	After initial CXR, only repeat if clinically indicated. With suspected culture-negative TB perform a CXR at 2 months to evaluate for CXR improvement. For pulmonary cases, a CXR should be obtained at treatment completion.
Adverse Reactions	
Signs & Symptoms of Adverse Reactions	Nausea, vomiting, abdominal pain, decreased appetite, jaundice, dark urine, rash / itching, joint pains, tingling extremities.
Vision	While on ethambutol, check visual acuity (Snellen) and color vision (Ishihara)
Bloodwork (Adults) ***Note:*** *Children < age 18 do not need baseline blood work unless risk factors for hepatitis present.*	Baseline liver function tests, uric acid, and complete blood count including platelets should be done for all adult patients. Monthly liver function tests should be done only for those with: • Abnormal baseline liver function tests • 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
Audiometry	Only for patients on aminoglycosides, e. g., streptomycin, capreomycin.

for symptomatic relief and all anti-tuberculosis medications continued. For generalized rash, especially associated with fever, all medications should be stopped immediately. Seek expert consultation and restart medications one at a time to attempt to identify the offending drug. Petechial rashes could be due to rifampin-related thrombocytopenia. Platelets should be checked and, if low, the rifampin stopped.

Hepatitis

Three of the first-line antituberculosis 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, hepatotoxic drugs should be stopped immediately and the patient evaluated carefully. Risk factors for viral hepatitis should be assessed, and if indicated, serologic testing for Hepatitis A, B and C should be performed. Once the liver enzymes return to normal, drugs should be restarted one at a time.

Drug re-challenges should be conducted in consultation with a TB expert. Do not count re-challenge doses towards completion of therapy.

Serious adverse events associated with TB treatment (hospitalization, permanent disability or death) should be promptly reported to DHMH Division of Tuberculosis Control.

Managing Interruptions in Therapy

When patients miss doses, either because of nonadherence or problems with adverse reactions, the following rule should apply:

- If < 50% of doses (which should have been taken in a given phase of treatment) have been missed, add missed doses on to the end of the treatment.

- If ≥ 50% of doses have been missed, restart therapy from the beginning. Consultation with a TB expert is recommended when problems leading to significant interruptions in treatment occur. If treatment is interrupted for more than 2 months, the patient should be re-evaluated to rule out active disease (such as chest x-ray, repeat specimen for culture and drug susceptibility testing if necessary).

Treatment Completion

To determine if a patient has completed therapy, count the total number of doses received and compare it to the total which are recommended for that frequency and phase of treatment. See Table 11 for specifics. The patient should undergo medical evaluation (including CXR for pulmonary TB cases) to assess for appropriate response to TB treatment.

VIII. MANAGING NONADHERENCE

The goal of the Maryland Tuberculosis Control Program is to treat tuberculosis patients in the least restrictive manner possible. Measures to promote adherence are outlined previously. Contact the DHMH Division of Tuberculosis Control as soon as possible when problems with nonadherence arise.

Maryland's authority for requiring tuberculosis treatment is outlined in the Maryland Code of Regulations (COMAR) 10.06.01 and in Health-General §§18-324,325. The law allows the health department to require a clinical examination for patients with suspected tuberculosis, to require medical treatment for tuberculosis, and if failure to comply with treatment, medical quarantine. The law applies both to currently infectious patients and those who are non-infectious but whose failure to take medication poses a potential threat.

At the beginning of treatment, the patient's legal responsibility to comply with treatment should be explained and documented by having the patient sign the "Tuberculosis Patient / Provider Agreement" (DHMH Form 4511). When problems with nonadherence develop, the reasons should be explored and attempts made to address the problem. At every step, health department personnel should document measures taken to promote adherence and specific instances of nonadherence.

The following progressive steps can be taken if non-compliance persists.

1. Health Officer or Secretary of DHMH: Order for Treatment documents the nonadherence and serves as legal notification that the patient is required to take their TB medication and that failure to comply will result in more restrictive measures, e.g., quarantine in a state facility.

2. Health Officer or Secretary of DHMH: Order for Quarantine is served after failure to comply with an Order for Treatment. This orders the patient to a placement (can include health care facility or patient's home).

3. Violation of Quarantine Order: If a patient violates the Order for Quarantine, the person has committed a misdemeanor which can result in criminal prosecution and incarceration until treatment completion. Prosecution must be done by the local state's attorney's office.

As soon as a serious pattern of non-compliance is identified, contact the DHMH Division of Tuberculosis Control (410-767-6698) to coordinate an appropriate management plan. Treatment and/or Quarantine Orders should not be issued without review by the DHMH Division of Tuberculosis Control. This allows for planning with other agencies (i.e., Deer's Head Center or Department of Corrections) should more restrictive measures be needed.

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 the 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 a 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 complies with the laws, rules and regulations that relate to sanitation for and quarantine of infectious, contagious, and communicable diseases. *[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 condition 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 the treatment, if the individual does not comply with the terms of the order. *[1982, ch. 568; 1994, ch. 64; 1997, ch. 8.]*

IX. CONTACT INVESTIGATIONS

The goal of a tuberculosis (TB) contact investigation is both to identify other active cases of TB (rare) and to identify *and completely treat* individuals with new latent TB infection, particularly those at high-risk for developing disease. TB contact investigations are required for all pulmonary TB cases in Maryland and are coordinated by the local health department. Notify the Division of TB Control (410-767-6698) when planning for any large institutional investigations.

Prioritization

Local health departments have limited resources to conduct contact investigations. To appropriately focus contact investigations and utilize resources wisely, it is critical to prioritize them. The following scheme for prioritizing contact investigation activities is recommended.

TB Cases - Priority for Investigation

When a report of a TB case is received, an evaluation should be done immediately to determine its priority for a TB contact investigation. Table 16 outlines the priority of a case for investigation based upon clinical characteristics of the case. The highest priority for investigation are pulmonary TB cases and suspects with positive AFB smears and/or cavitation on CXR. Contact investigations are not indicated for smear-positive TB suspects with negative nucleic acid assays. They also are not indicated for extrapulmonary TB for whom pulmonary TB has been ruled out.

TB Contacts Priority for Evaluation

TB contacts to smear-positive or cavitary cases should be assessed to determine their priority for evaluation. This assessment is based upon both the likelihood that a contact will be infected and the risk of TB if the contact is infected. Table 17 outlines contact characteristics by their priority for evaluation. **HIV-infected contacts and those age 4 and under are always the highest priority for investigation because of their high risk for rapid progression to TB disease.**

Table 16. Priorities for Initiation of Tuberculosis Contact Investigations [4]

Disease Site/Characteristics	*Priority for Investigation*
Pulmonary/Laryngeal Disease	
AFB Smear-positive	
Nucleic acid assay (+) or not done	High
Nucleic acid assay (-)	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 4	Source case investigation only

Table 17. Priorities for Evaluation of Contacts [4]

High-Priority Contacts *(to smear-positive and/or cavitary case)*	
Evaluated by Contact Characteristics	Household HIV-infected Congregate living situation Age ≤ 4 Medical risk factor(s) for TB Exposed during high risk medical procedure
Evaluated by Exposure Time/Place* During Infectious Period of Index Case Times are cumulative	8 or more hours in a small, poorly ventilated space 16 or more hours in a small, well ventilated space 24 or more hours in a classroom sized space 100 or more hours in a large open space
Medium-Priority Contacts *(to smear-positive and/or cavitary case)*	
Evaluated by Contact Characteristics	Age 5 to 15
Evaluated by Exposure Time/Place* During Infectious Period of Index Case Times are cumulative	4 or more hours in a small space 8 or more hours in a classroom sized space 50 or more hours in a large open space
Low-Priority Contacts	
Contacts to smear negative/non-cavitary cases Duration of exposure/environment below threshold for medium-priority	

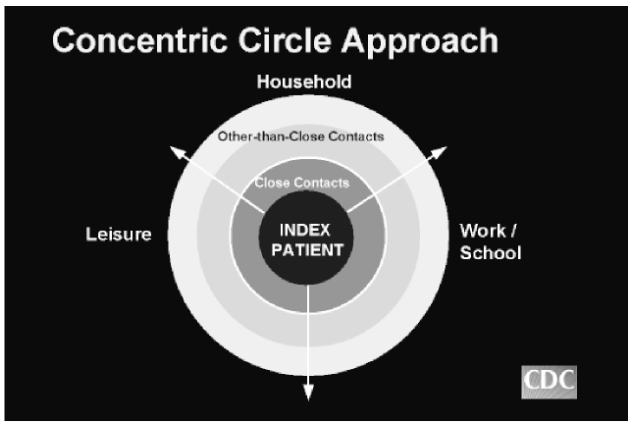
* Times listed are not based upon hard data. Each contact investigation should be evaluated and planned individually utilizing the concentric circle concept. All contact investigations should be conducted in conjunction with the local health department.

Concentric Circle Approach

Maryland local health departments conduct tuberculosis contact investigations on all cases of pulmonary tuberculosis utilizing the "concentric circle approach." In general, the closest contacts (those with the greatest duration and intensity of exposure) are tested first (household, social, work). It is possible that the initial investigation will exclude some of the "high-priority" contacts listed in Table 17 if there are a significant number of contacts with greater exposure than others. Only if there is evidence of tuberculosis transmission among close contacts, is the investigation expanded to contacts with less exposure to the index case.

Every effort should be made to *avoid* testing individuals who are at low risk of infection, i.e., because of public demand for testing.

Figure 2



Contact Investigation Procedures

1. Initiation: The index patient should be interviewed within 1-3 business days. Evaluation of contacts, including symptom review and TST or QFT-G, should occur within 7 days for high-priority contacts; and within 14 days for medium-priority contacts[4].

2. Data Collection: Data collection should consist of available medical and social history. Information obtained should include the TB disease site, AFB smear / culture results, chest radiograph results and nature and duration of TB symptoms.

3. Case interview: 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 ensure that his/her confidentiality is protected (see following page). Obtain information on the infectious period (duration of cough) and obtain information on individuals with close contact and locations and duration of potential exposures.

Obtain locating and demographic information on individuals who have been in contact with the case during the infectious period. Specifically ask if there are any contacts who are young children or who are HIV positive. When necessary, utilize an interpreter to communicate with the client.

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

5. Establish infectious period:
Start of infectious period: The start of the infectious period of the index patient is determined by clinical characteristics. If TB symptoms are present, then the period of infectiousness begins 3 months before symptom onset. If no symptoms are present, the period of infectiousness begins 3 months prior to first positive finding consistent with TB disease. See Table 18.

Table 18. Guidelines for Estimating the Beginning of the Period of Infectiousness of Persons with Tuberculosis (TB) by Index Case Characteristics[4]

Characteristic			*Period of Infectiousness*
TB Symptoms	*AFB* sputum Smear-positive*	*Cavitary CXR*	*Recommended minimum beginning of likely period of infectiousness*
Yes	No	No	Three months before symptom onset or first positive finding (e.g., abnormal chest radiograph) consistent with TB, whichever is longer.
Yes	Yes	Yes	Three months before symptom onset or first positive finding consistent with TB disease, whichever is longer.
No	No	No	Four weeks before date of suspected diagnosis.
No	No	Yes	Three months before first positive finding consistent with TB disease.

**Acid-Fast bacilli.*

Cases are usually considered to be no longer infectious after 2 weeks of treatment, diminished symptoms and mycobacterial response (decreasing number of acid-fast bacilli).

End of infectious period: The infectious period is closed when the following criteria are satisfied: appropriate antituberculosis treatment for ≥ 2 weeks, clinical improvement, and improving AFB smears.

6. Establish investigational priorities: Utilizing the prioritization scheme outlined in Table 17, determine how to proceed with the investigation.

7. Medical evaluation of high and medium-priority contacts (see below).

8. Determine infection rate: The infection rate should be calculated as follows:

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

Example: 23 contacts are identified in a given investigation. Twenty (20) are tuberculin skin tested and five are positive; one has a prior positive TST and 2 are never evaluated.

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

9. Determine need for expansion of investigation. Testing results for high and medium-priority contacts should determine the need for expanding contact investigations. Other criteria include an unexpectedly high rate of infection, evidence of second-generation transmission, or infection in any contacts aged <5 years[4].

Medical Evaluation of High And Medium Priority Contacts

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

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

- Symptom assessment and TST at the time contact is identified, and (if this test is negative and no symptoms present),
- Symptom assessment and TST 8-10 weeks after exposure ended.
- Those with symptoms consistent with active TB or those with a positive TST (≥ 5 mm) should receive a CXR .
- Once active disease is ruled out, evaluate for TLTBI.

Children age ≤ 4 who are close contacts of infectious cases should receive a TST and a CXR (PA and lateral) to rule out active TB disease. If the initial test is negative, the TST should be repeated 8-10 weeks after exposure ends. Regardless of the initial TST result, close contacts age 4 and under are provided window period prophylaxis. If the 8-10 week TST is negative, TLTBI is stopped[4,7]. If the TST is positive, a complete course of TLTBI should be given.

Infants under age 6 months who are close contacts to infectious cases should receive a TST and CXR and be started on window period prophylaxis. If the initial TST is negative, a repeat TST and CXR should be done at least 8-10 weeks after exposure ended *AND after the baby is at least 6 months old*. Window period prophylaxis should be continued until the baby is at least 6 months old AND has had a negative TST at least 8-10 weeks after the TB exposure ended[17]. If the TST is positive, a complete course of TLTBI should be given.

Documented prior positive TST or history of TB disease. In the absence of TB symptoms, there is generally no need for further evaluation. **Exception: HIV-positive contacts** should receive a chest radiograph and TLTBI regardless of prior history of infection or treatment.

HIV-infected and other immunocompromised persons who are close contacts to infectious cases should have a TST and CXR at the time of exposure and be given a complete course of treatment for presumptive latent TB infection regardless of the TST result. Those with a negative test should have it repeated in 8-10 weeks after exposure ends. A full course of TLTBI is recommended, even if the person has a prior history of TB treatment or TLTBI, because of the possibility of re-infection with TB.

Source Case Investigations

A search for a TB case who is the source of infection is performed for all cases of active TB age 4 and under. Source case investigations should also be done for TST-positive children age 2 and under (unless the child has known risk of TB infection, i.e., foreign adoptees). Close contacts are evaluated with a TST and symptom screen.

Confidentiality

A general principle for implementing tuberculosis contact investigations is to protect the confidentiality of the index case (unless the case chooses to inform contacts of their TB diagnosis). This means that when named contacts are approached, they are informed that they were named as a contact to an active tuberculosis case (without revealing the identity of the case). An exception to this rule occurs when there is a large institutional investigation and the only way to identify exposed contacts is to inform an appropriate administrator of the identity of the index case.

X. INFECTION CONTROL ISSUES

Airborne infection isolation (AII) should be initiated on all hospitalized TB suspect cases. Health care workers caring for suspect cases in the hospital or in other settings, including the home, should follow appropriate infection control recommendations, including the use of personal protective equipment, i.e., N-95 respirators[2].

Discontinuation of Airborne Infection Isolation Precautions (AII)

Pulmonary TB patients can be transferred from an AII bed to a non-isolation hospital bed when they meet the following criteria:

Another diagnosis has been assigned

OR

Patient remains a TB suspect *AND* has all 3 of the following:

- Clinical or radiographic improvement
- At least 2 weeks of treatment with an appropriate TB treatment regimen to which the strain is known or likely to be susceptible
- Three negative AFB smears from sputum specimens collected in 8-24 hour intervals. One of the 3 specimens must be collected in the early morning. This may allow patients to be released from AII precautions in 2 days

Multi-drug resistant TB (MDR-TB) patients should remain in AII room until culture conversion or until discharged to home (see criteria below). Consult with local health department (LHD) and DHMH TB Control prior to discontinuing isolation of an MDR-TB patient.

Discharge to Home

Discharge from the Hospital

There is no minimum number of days of antituberculosis treatment that is required before a patient may be discharged from the hospital. Hospitalized, AFB sputum-smear positive TB patients who are not suspected of having MDR-TB, can be discharged to home if they meet <u>all</u> of the following criteria:

- Patient is in stable clinical condition,
- Current treatment with an appropriate anti-TB regimen to which the strain is known or likely to be susceptible,
- Plan developed in conjunction with the LHD for patient follow-up,
- Stable residence at a verifiable address,
- Living alone or returning to a living environment where others are immunocompetent and have been previously exposed,
- No significant contact with infants, young children, or immunosuppressed persons,
- No services in which the provider (e.g., home attendant) will be routinely visiting the patient for several hours per day, and
- Patient willing to stay home (except for LHD approved medical appointment) until sputum smear-negative.

Persons with suspected or confirmed **MDR-TB** disease should be kept under AII during the entire hospitalization or until culture conversion is documented, regardless of sputum smear results. In consultation with DHMH, the patient may be discharged to home when an appropriate treatment regimen has been devised and initiated; and suitable arrangements have been made so that the regimen can be continued and properly monitored on an outpatient basis.

Discharge to Long Term Care

Patient must meet the criteria for discontinuation of airborne infection isolation (AII) unless AII can be provided in the long-term care facility.

Return to Work or School

It is the local health department's responsibility to determine when it is acceptable for a patient with pulmonary/laryngeal TB to return to school/work based upon the following general criteria:

Drug-susceptible TB

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

Persons working in **high-risk settings** (worksites with HIV-infected clients, 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 local health department. Consultation with a TB expert is strongly recommended

MDR-TB

- The resolution of fever and the resolution, or near resolution, of cough.
- At least two weeks of treatment with an antituberculosis regimen to which the strain is known to be susceptible.
- Three negative AFB **cultures** from sputum specimens collected 8-24 hours apart as long as one specimen is collected in the early morning.

Infection Control Plans

Long Term Care Facilities

The incidence of tuberculosis in Maryland long-term care facilities is very low. For the past 5 years (2002-2006) Maryland had 9 to 14 TB cases per year in long-term care facilities statewide (inclusive of Baltimore City). During this same time frame Maryland averaged 14 cases per year in health care workers statewide (all types of health care facilities).

Due to the low overall incidence of TB in both Maryland health-care workers and residents of long-term care facilities (facilities licensed as comprehensive or extended care facilities), the Division of TB Control, Refugee and Migrant Health recommends the following:

Long-term care facilities with < 200 beds and less than 3 cases of TB annually (patients, staff or combination of both) are considered low risk facilities regardless of the jurisdiction in which the facility is located.

Long-term care facilities with ≥ 200 beds and less than 6 cases of TB annually (patients, staff or combinations of both) are considered low risk facilities regardless of the jurisdiction in which the facility is located.

Long-term care facilities that do not fall within the two categories described above should be considered medium risk.

All facilities should continue to assess facility risk annually and update as required. Annual updates should include assessment for any changes in local epidemiology and worker characteristics that might affect the risk assessment or other infection control practices. Risk assessments should be kept on file for reference.

Low and medium-risk categories require that new employees have a baseline two-step TB skin test (or a blood assay test for M. tuberculosis [BMAT] such as QuantiFERON®-TB Gold, if available) upon hire. If TST positive, a symptom assessment and chest radiograph should be done to rule out active disease. Treatment for latent TB infection should be coordinated through the local health department or private provider/ physician, as appropriate. Employees should be provided with documentation of their baseline testing, follow-up and any subsequent tests for TB (including date, type of test and results) for future reference.

Employees working in low risk facilities with positive TST results (obtained on site or documented from another facility) should be

evaluated for signs and symptoms of TB on an annual basis. There is no need to do annual skin testing or chest radiographs on these individuals. Persons moving from a low risk to medium risk facility with previous negative TB screening results should be screened annually for tuberculosis, by either TST or BMAT.

We recognize that some individual long-term care facilities may have policies and/or protocols that continue to require annual testing for TB regardless of the risk assessment of the individual facility. While serial testing is not going to harm employees, we do not encourage its routine use in low risk facilities.

The CDC Guidelines for Preventing the Transmission of Mycobecterium tuberculosis in Health Care Settings, 2005 should be referenced for other details on infection control in long-term care facilities. These guidelines can be found on the CDC website at *http://www.cdc.gov/mmwr/pdf/rr/rr5417.pdf.*

Questions specific to individual Maryland facilities may also be directed to DHMH Infection Control staff at 410-767-6704 or DHMH TB Control at 410-767-6698.

Hospital-Based Transitional Care Settings

All hospital-based transitional care settings should have the following TB protocol in place for assessment of patients admitted directly from the hospital for short-stay care: 1) symptom screen, and 2) documentation in the chart by a clinician that the patient is free from active TB. This recommendation applies to all hospital-associated rehabilitation centers that admit patients for less than 30 days. Any stay longer than 30 days is considered long-term care and will then fall under the guidelines established for long-term care settings.

In special situations, local health departments may deviate from these guidelines, in consultation with the DHMH Division of TB Control.

XI. CORRECTIONAL AND DETENTION FACILITIES

Importance

Although overall incidence of new 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.

Disparate numbers of incarcerated persons are at high risk for TB (e.g., users of illicit substances [e.g., injection drugs], persons of low socioeconomic status, and persons with human immunodeficiency virus [HIV] infection).

The physical structure of the facilities contributes to disease transmission, as facilities often 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 existing TB-related risk factors of the inmates, combine to make correctional and detention facilities a high-risk environment for the transmission of *M. tuberculosis* and make implementation of TB control measures particularly difficult.

Facility Risk Assessment

Facilities should be designated as either minimal risk or non-minimal risk.

Minimal TB risk

- No cases in the facility have occurred in the last year,
- The facility does not house substantial numbers of inmates with risk factors for TB (such as HIV and injection drug use),
- The facility does not house a substantial number of new immigrants from areas of the world with high rates of TB, and
- Employees of the facility are not otherwise at risk for TB.

Non-minimal TB risk

- TB cases have occurred in the facility in the past year**,**
- Many inmates have personal risk factors for TB (i.e., HIV infection, injection drug use),
- Large percentage of inmates are foreign born, or
- Employees have risk factors for TB other than working in the facility.

TB Screening

TB skin testing (TST) or blood assay testing (such as QFT-G) in **minimal risk** facilities is optional for inmates with no risk. **All inmates, regardless of facility risk or personal risk should be screened for TB symptoms (such as cough, fever or night sweats) and referred to an airborne infection isolation (AII) room for further evaluation as necessary.** Inmates residing in **non-minimal** risk facilities and/or have a personal TB risk should be tested with a TST or QFT-G within 7 days of incarceration. (For example, it is reasonable to wait until day 4 of incarceration to test an inmate with a TST if a large number of inmates typically get released within that time, such as in jails or detention centers).

Employees who are TST or QFT-G negative on hire should be tested annually regardless of the facility risk. See Table 19.

Recommendation Highlights

TB Control Plans. Each facility's risk for TB should be assessed annually. A TB Control plan, developed in collaboration with the LHD and correctional facility should be shared between the two entities and reviewed annually. Agreements about roles and responsibilities may be formal or informal, but they should be noted in writing. Formal agreements include memoranda of understanding and written policies or plans.

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, should report suspect and confirmed cases to local and state health departments.

Airborne Infection Isolation. TB suspects should be isolated immediately. Under rare circumstances, if an AII room is not available and the immediate transfer of the inmate with suspected infectious TB is not possible, the inmate should be housed temporarily in a room that has been modified to prevent the escape of infectious aerosols outside the TB holding area. Consult with the state TB program infection control staff.

The key elements of a respiratory protection program include 1) assignment of responsibility, 2) training, and 3) fit testing.

All TB suspects/cases should be transported by ambulance. If that is not possible, the inmates should be masked and staff should wear N-95 respirators.

Release of Inmates. Plans for discharge must be coordinated early with the local health department. Starting all inmates at high risk on LTBI therapy might not be feasible while they are in the correctional facility, and the policy determining which risk groups to start on treatment should be made in collaboration with public health personnel.

Undocumented Aliens. Immigration and Customs Enforcement (ICE) is a division of the Department of Health and Human Services and detains approximately 200,000 persons annually while enforcing immigration law. Local detention centers may contract with U.S. Marshalls or ICE to hold detained persons. Many of these persons come from high-risk nations. Local health departments 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 contagious, even if treatment has not been completed or the final culture and susceptibility results are pending.

ICE seeks to enroll TB cases/suspects 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.

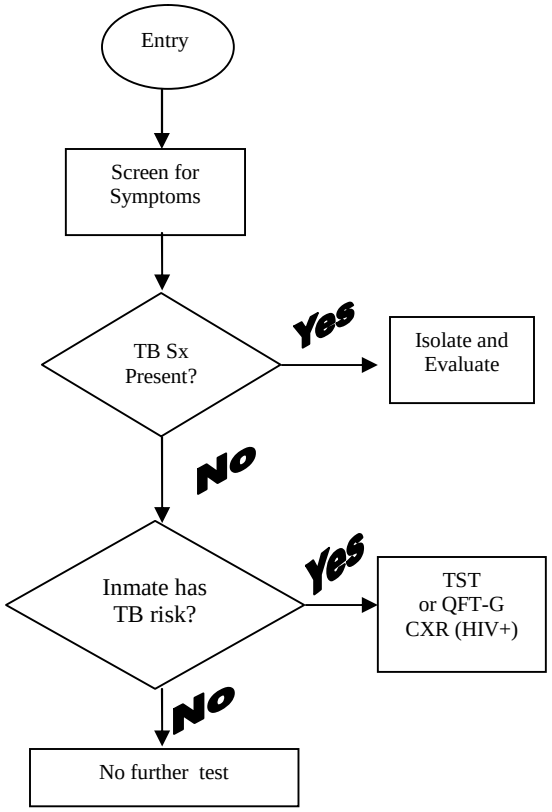
Program evaluation. Program evaluation should be incorporated into the overall correctional quality improvement/assurance program. Evaluation should include routine assessment of risks, and collection and analysis of data on staff and inmate skin testing. Improvements made should be based on findings.

Contact Investigations. All contact investigations should be coordinated with local health departments.

For additional information, see CDC Recommendations [37].

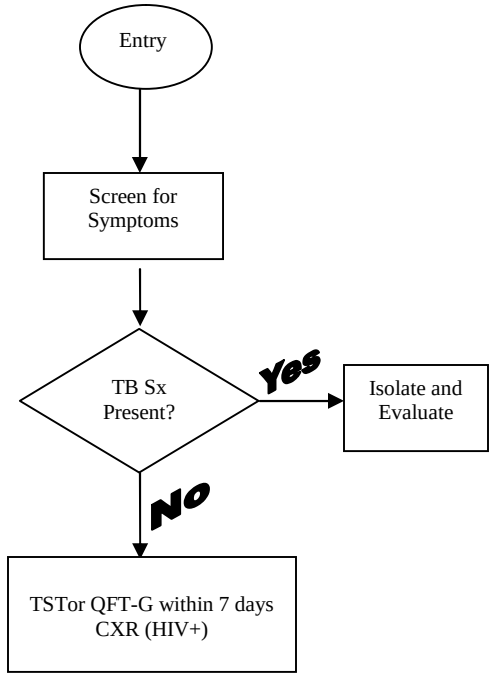
Table 19. TB Screening in Correctional and Detention Facilities

Minimal Risk Facility



Employees who are TST or QFT-G negative should be tested annually.

Non-Minimal Risk Facility



Long-term inmates and all employees who are TST or QFT-G negative should be tested annually

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APPENDICES

Appendix A. Countries/Area with and Estimated or Reported High Tuberculosis Incidence, 2005

Source: World Health Organization

"High Incidence" areas are defined by the Maryland DHMH, Division of TB Control as areas with reported or estimated incidence of ≥ 15 cases per 100,000 persons.

Communicable Diseases - Tuberculosis (as of 22 March 2007) - Estimated Incidence, All Forms (per 100 000 population per year) -> Total

(Periodicity: Year, Applied Time Period: from 2005 to 2005)

Afghanistan	168	**Bosnia and Herzegovina**	52
Albania	20	**Botswana**	654
Algeria	55	**Brazil**	60
American Samoa	9	**British Virgin Islands**	15
Andorra	18	**Brunei Darussalam**	54
Angola	269	**Bulgaria**	39
Anguilla	25	**Burkina Faso**	223
Antigua and Barbuda	7	**Burundi**	334
Argentina	41	**Cambodia**	506
Armenia	71	**Cameroon**	174
Australia	6	**Canada**	5
Austria	11	**Cape Verde**	174
Azerbaijan	76	**Cayman Islands**	4
Bahamas	38	**Central African Republic**	314
Bahrain	40	**Chad**	272
Bangladesh	227	**Chile**	15
Barbados	11	**China**	100
Belarus	62	**China, Hong Kong SAR**	75
Belgium	13	**China, Macao SAR**	81
Belize	49	**Colombia**	45
Benin	88	**Comoros**	45
Bermuda	4	**Congo**	367
Bhutuan	103	**Cook Islands**	16
Bolvia	211	**Costa Rica**	14

Croatia	41
Cuba	9
Cyprus	4
Czech Republic	10
Cõte d'lvoire	382
Democratic People's Republic of Korea	178
Democratic Republic of the Congo	356
Denmark	7
Djibouti	762
Dominica	16
Dominican Republic	91
Ecuador	131
Egypt	25
El Salvador	51
Equatorial Guinea	233
Eritrea	282
Estonia	43
Ethiopia	344
Fiji	23
Finland	6
France	13
French Polynesia	28
Gabon	308
Gambia	242
Georgia	83
Germany	7
Ghana	205
Greece	17
Grenada	5
Guam	38
Guatemala	78
Guinea	236
Guinea-Bissau	206
Guyana	149
Haiti	305
Honduras	78
Hungary	22
Iceland	3
India	168
Indonesia	239
Iran (Islamic Republic of)	23
Iraq	56
Ireland	12
Israel	8
Italy	7
Jamaica	7
Japan	28
Jordan	5
Kazakhstan	144
Kenya	641
Kiribati	380
Kuwait	24
Kyrgyzstan	121
Lao People's Democratic Republic	155
Latvia	63
Lebanon	11
Lesotho	696
Liberia	301
Libyan Arab Jamahiriya	18
Lithuania	63
Luxembourg	11
Madagascar	234
Malawi	409
Malaysia	102
Maldives	47
Mali	278
Malta	6
Mauritania	298
Mauritius	62
Mexico	23

Micronesia (Federated States of)	105
Monaco	2
Mongolia	191
Montserrat	9
Morocco	89
Mozambique	447
Myanmar	171
Namibia	697
Nauru	108
Nepal	180
Netherlands	7
Netherlands Antilles	9
New Caledonia	25
New Zealand	9
Nicaragua	58
Niger	164
Nigeria	283
Niue	44
Northern Mariana Islands	76
Norway	5
Oman	11
Pakistan	181
Palau	52
Panama	45
Papua New Guinia	250
Paraguay	68
Peru	172
Philippines	291
Poland	26
Portugal	33
Puerto Rico	5
Qatar	55
Republic of Korea	96
Republic of Moldova	138
Romania	134
Russian Federation	119
Rwanda	361
Saint Kitts and Nevis	11
Saint Lucia	17
Saint Vincent and the Grenadines	29
Samoa	20
San Marino	6
Sao Tome and Principe	105
Saudi Arabia	41
Senegal	255
Seychelles	34
Sierra Leone	475
Singapore	29
Slovakia	17
Slovenia	15
Solomon Islands	142
Somalia	224
South Africa	600
Spain	27
Sri Lanka	60
Sudan	228
Suriname	65
Swaziland	1,262
Sweden	6
Switzerland	7
Syrian Arab Republic	37
Tajikistan	198
Thailand	142
The former Yugoslav Republic of Macedonia	30
Timor-Leste	556
Togo	373
Tokelau	56
Tonga	25
Trinidad and Tobago	9
Tunisia	24

Turkey	29
Turkmenistan	70
Turks and Caicos Islands	20
Tuvalu	305
Uganda	369
Ukraine	99
United Arab Emirates	16
United Kingdom of Great Britain and Northern Ireland	14
United Republic of Tanzania	342
United States Virgin Islands	5
United States of America	5
Uruguay	28
Uzbekistan	113
Vanuatu	60
Venezuela	42
Viet Nam	175
Wallis and Futuna Islands	47
West Bank and Gaza Strip	21
Yemen	82
Zambia	600
Zimbabwe	601

Appendix B. Standard Drug Regimens for Treatment of Tuberculosis

Standard Maryland regimen highlighted

Initial Phase (8-9 weeks)			Continuation Phase[d] (18 Weeks)		
	Drug	**Interval[c] / Weeks (Doses)**		**Drug**	**Interval[c] /Wks (Doses)**
1	**INH** **RIF[a]** **PZA** **EMB[b]**	**5 days/wk x 3 wks** then **twice weekly x 6 wks** (15 doses) plus (12 doses) ----------**OR**---------- **7 days/wk x 2 wks** then **twice weekly x 6 wks** (14 doses) plus (12 doses)	**A** — **B**	**INH** **RIF[a]** —— **INH** **RPT[e]**	**Twice weekly x 18 wks** **(36 doses)** ---------**OR**--------- **Once weekly x 18 wks** **(18 doses)** [Eligible patients only]
2	**INH** **RIF[a]** **PZA** **EMB[b]**	**7 days/wk x 8 wks** (56 doses) ----------**OR**---------- **[f] 5 days/wk x 8 wks** (40 doses)	**C**	**INH** **RIF[a]**	**7 days / wk x 18 wks** (126 doses) ---------**OR**--------- **[f] 5 days / wk x 18 wks** (90 doses)
3	**INH** **RIF[a]** **PZA** **EMB[b]**	**Thrice (3x) weekly x 8 weeks** (24 doses)	**D**	**INH** **RIF[a]**	**Thrice weekly x 18 wks** (54 doses)

INH=isoniazid **RIF**=rifampin **PZA**=pyrazinamide **MB**=ethambutol **RPT** = rifapentine

[a] **HIV infected patients** on certain antiretroviral drugs may need medication adjustment because of drug interactions with rifampin. Consult an HIV/TB expert..

[b] **EMB** can be discontinued (prior to 8 weeks) once susceptibility tests indicate sensitivity to INH, RIF & PZA.

[c] **All intermittent regimens** (once, twice weekly, thrice (3x) weekly and 5 days/wk) **must** be DOT.

[d] **Culture negative TB** - standard continuation phase is 8 weeks (16 wks total).
TB meningitis, bone/joint TB and miliary TB - standard continuation phase is 31 wks (39 wks total).
Cavitary TB with culture conversion after 2 mos. - standard continuation phase is 31 wks (39 wks total).

[e] **Rifapentine (RPT)** should only be used in HIV negative adults with non-cavitary, pulmonary TB with negative cultures within 2 months. Cases must be co-managed with the health department.

[f] The Centers for Disease Control concluded via expert opinion that "based upon substantial clinical experience, 5 day a week DOT is equivalent to 7 day administration; either can be considered daily"[(5)]. However, 5-day per week therapy has not been studied in clinical trials. If daily therapy must be utilized, the Maryland TB Expert Panel indicated that the preferred mode of administration is to administer DOT 5 days per week and to utilize weekend and holiday packets.

Appendix C. First Line Tuberculosis Medications

Drug Dose (maximum)	Major Adverse Reactions Recommended Monitoring	Dosage Forms / Comments
Isoniazid[a] (PO or IM) **INH**		
Daily **C:** 10-15mg/kg (300mg) **A:** 5 mg/kg (300mg) **Once weekly** **C:** Not recommended **A:** 15 mg/kg (900 mg) **Twice (2x) weekly** **C:** 20-30 mg/kg (900mg) **A:** 15 mg/kg (900mg) **Thrice (3x) weekly** **C:** Not recommended **A:** 15 mg/kg (900mg)	**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.	**Dosage Forms:** Scored tabs: 50 mg, 100 mg & 300 mg Syrup: 50 mg/ 5 ml Aqueous solution (IV/IM) scarce and may not be available **Comments:** 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[a] (PO or IV/IM) **RIF**		
Daily **C:** 10-20mg/kg (600mg) **A:** 10 mg/kg (600mg) **Once weekly** **C:** Not recommended **A:** Not recommended **Twice (2x) weekly** **C:** 10-20mg/kg (600mg) **A:** 10 mg/kg (600mg) **Thrice (3x) weekly** **C:** Not recommended **A:** 10 mg/kg (600mg)	**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.	**Dosage Forms:** Capsules: 150 mg and 300 mg Syrup: can be formulated from capsules by pharmacy Aqueous Solution (IV/IM) scarce and may not be available **Comments:** 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**		
Daily **C:** 15-30 mg/kg (2g) **A:** 15-30 mg/kg (2g) **Once Weekly** **C:** Not recommended **A:** Not recommended **Twice (2x) weekly** **C:** 50 mg/kg (2g) **A:** 50-70 mg/kg (4g) **Thrice (3x) weekly** **C:** Not recommended **A:** 50-70 mg/kg (3g)	**Adverse Reactions:** GI upset, hepatotoxicity, hyperuricemia, arthalgias, rash, gout (rare). **Recommended Monitoring:** Baseline uric acid and hepatic enzymes. Repeat measurements if baselines are abnormal, risk factors for hepatitis or patient has symptoms of adverse reactions.	**Dosage Forms:** Scored tablets: 500 mg **Comments:** May complicate management of diabetes mellitus. Treat increased uric acid only if symptomatic. Most common reason for TB patients experiencing GI upset.

[a]Combination drugs are recommended in the rare instance in which a patient is placed on self-administered therapy:
IsonaRif ® contains INH 150 mg, RIF 300 mg
Rifamate® contains 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[(5)]. After reviewing available data, the Maryland TB Expert panel recommended that the previously recommended dosage ranges be utilized[1], advising use of the lowest possible dose in the dose range.

Appendix C. First-Line Tuberculosis Medications *(Continued)*

Drug Dose (maximum)	Major Adverse Reactions Recommended Monitoring	Dosage Forms / Comments
Ethambutol [b] (PO) **EMB**		
Daily **C:** 15-20 mg/kg (1000mg) **A:** 15-25 mg/kg (1600mg) **Once weekly** **C:** Not recommended **A:** Not recommended **Twice (2x) weekly** **C:** 50 mg/kg (2.5g) **A:** 50 mg/kg (4g) **Thrice (3x) weekly** **C:** Not recommended **A:** 25-30mg/kg (2400mg)	**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.	**Dosage Forms:** Tablets: 100mg and 400 mg **Comments:** 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.
Rifabutin (PO) **RBT**		
Daily **C:** Not recommended **A:** 5 mg/kg (300 mg) **Once weekly** **C:** Not recommended **A:** Not recommended **Twice (2x) weekly** **C:** Not recommended **A:** 5 mg/kg (300 mg) **Thrice (3x) weekly** **C:** Not recommended **A:** 5 mg/kg (300mg)	**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 arthalgias, uveitis, leucopenia. **Recommended Monitoring:** Baseline hepatic enzymes. Repeat if baseline abnormal, risk factors for hepatitis or symptoms of adverse reactions.	**Dosage Forms:** Capsules: 150mg **Comments:** 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**		
Once weekly only **C.** Not approved for use in children **A.** 10 mg/kg (600mg) *(Data indicates that 900 mg of RPT is well-tolerated and some experts are utilizing this higher dose* [(31)]*)*	**Adverse Reactions:** Hepatitis, thrombocytopenia, neutropenia, leucopenia, hyperuricemia, flu-like syndrome. Reduces levels of many drugs, including methadone, warfarin (Coumadin), birth control pills, 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.	**Dosage Forms:** Tablets (film-coated): 150 mg **Indications:** Pulmonary TB patients who are HIV negative, non-cavitary, not pregnant, organisms pan-sensitive and culture negative at two months (two consecutive negative cultures). Administered once weekly with INH during the continuation phase of treatment. **Comments:** See drug interactions with Rifampin. Contraindicated for HIV infected patients.

Appendix D. Second-Line Tuberculosis Medications [a]

Drug Dose (maximum)	Major Adverse Reactions Recommended Monitoring	Dosage Forms/ Comments
Amikacin [Amakin] / **Kanamycin** (IM or IV)		
C: 15-30mg/kg/d (1g) **A:** See footnote b	**Adverse Reactions:** Ototoxicity (hearing loss or vestibular dysfunction), renal toxicity, hypokalemia, hypomagnesemia. **Recommended Monitoring:** Audiometry (monthly), renal function, and electrolytes.	**Dosage Forms:** Vials: 500 mg and 1 g vials **Comments:** 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.
Capreomycin [Capastat] (IM or IV)		
C: 15-30 mg/kg (1g) **Daily or twice weekly** **A:** See footnote b	**Adverse Reactions:** See Amikacin (above). **Recommended Monitoring**: Audiometry (monthly), renal function, and electrolytes at baseline and monthly.	**Dosage Forms:** 1 g vials **Comments:** See Amikacin (above).
Clofazimine[c] [Lamprene] (PO)		
A: 100-300 mg	**Adverse Reactions:** GI disturbances, orange/brown skin discoloration, severe abdominal pain, visual disturbances (rare).	**Dosage Form:** Capsules 50mg **Comments:** Not FDA approved for TB treatment. Efficacy unknown. Take with food.
Cycloserine[c] [Seromycin] (PO)		
C: 10-15 mg/kg/d (1g) **A:** 10-15 mg/kg/d (1g) (usually 500 to 750 mg per day in two divided doses)	**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.	**Dosage Forms:** Capsules 250 mg **Comments:** 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)		
C: 15-20 mg/kg/d (1g) **A:** 15-20 mg/kg/d (1g) (usually 500 to 750 mg per day in two divided doses)	**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.	**Dosage Forms**: Tablets 250 mg **Comments:** Avoid in pregnancy. Antacids, antiemetics, taking with food or at bedtime, or lying flat for 20 minutes after doses may help GI intolerance.

Appendix D. Second-Line Tuberculosis Medications *(Continued)*

Drug Dose (maximum)	Major Adverse Reactions Recommended monitoring	Dosage Forms/ Comments
Gatifloxacin[c] [Tequin] (PO or IV)		
C: Not approved **A:** 400 mg daily	**Adverse Reactions:** See Levofloxacin below	**Dosage Forms:** Tablets: 200 mg and 400 mg; Aqueous solution (200 mg/20ml) **Comments:** Not approved for use in children.
Kanamycin - See Amikacin (above)		
Levofloxacin[c] [Levaquin] (PO or IV)		
C: Not approved **A:** 500 - 1000 mg daily	**Adverse Reactions:** GI disturbance, diarrhea, photosensitivity, allergic reaction. **Recommended monitoring:** No specific monitoring recommended.	**Dosage Forms:** Tablets: 250mg, 500 mg, 750 mg; Aqueous solution: 500 mg vials **Comments:** Avoid in children due to concerns about effects on bone and cartilage growth. Antacids may interfere with absorption.
Moxifloxacin[c] [Avelox] (PO)		
C: Not approved **A:** 400 mg daily	See Levofloxacin (above)	**Dosage Forms:** Tablets (film coated): 400 mg **Comments:** See Levofloxacin (above).
Para-Aminosalicylic Acid[c] [PAS] (PO)		
C: 200-300 mg/kg/d in two to four divided doses **A:** 8-12 g/d in two to three divided doses	**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.	**Dosage Forms:** Granules: 4 g packets **Comments:** 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)		
C: 20-40 mg/kg (1g) **A**: See footnote b	**Adverse Reactions:** Ototoxicity (hearing loss or vestibular dysfunction), renal toxicity hypokalemia, hypomagnesemia. **Recommended monitoring:** Audiometry (monthly), renal function, and electrolytes.	**Dosage Forms:** Vials 1g/2.5 ml **Comments:** Ultrasound and warm compresses to injection site may reduce pain and induration. Contraindicated in pregnancy.

[a] **To be used only in consultation with a TB expert. This is a summary chart only – not inclusive of all available data on each drug.** Refer to current literature and PDR for more information. Dosages should be **adjusted based on changes in weight.**

[b] **Dose:** 15 mg/kg per day (max: 1 gm) and 10 mg/kg in persons age 60 and older (max: 750mg). Usual dose: 750-1000mg administered IM or IV given as a single dose 5-7 days per week and reduced to two to three times per week after the first 2 to 4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.

[c] There are no data to support intermittent administration.

Appendix E. Dosage Chart for TB Drugs (mg)

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. Maryland LHD Tuberculosis Control Directory

Maryland Tuberculosis Control Directory

COUNTY	TELEPHONE NUMBER	FAX NUMBER
01 ALLEGANY	(301) 759-5082	(301) 777-5669
02 ANNE ARUNDEL	(410) 222-7256	(410) 222-7490
03 BALTIMORE	(410) 887-2711	(410) 887-8251
04 CALVERT	(410) 535-5400	(410) 535-1955
05 CAROLINE	(410) 479-8021	(410) 479-4864
06 CARROLL	(410) 876-4926	(410) 876-4959
07 CECIL	(410) 996-5100	(410) 996-1019
08 CHARLES	(301) 609-6810	(301) 934-7048
09 DORCHESTER	(410) 228-3223	(410) 228-9319
10 FREDERICK	(301) 600-3349	(301) 600-1403
11 GARRETT	(301) 334-7770	(301) 334-7771
12 HARFORD	(410) 638-8454	(410) 420-3448
13 HOWARD	(410) 313-7568	(410) 313-6108
14 KENT	(410) 778-1350	(410) 778-7913
15 MONTGOMERY	(240) 777-1800	(240) 777-4899
16 PRINCE GEORGES	(301) 583-3110	(301) 772-9897
17 QUEEN ANNES	(410) 758-2838	(410) 758-3092
18 ST. MARY'S	(301) 475-78325	(301) 475-4308
19 SOMERSET	(443) 523-1746	(410) 651-5699
20 TALBOT	(410) 819-5692	(410) 819-5693
21 WASHINGTON	(240) 313-3455	(240) 313-3334
22 WICOMICO	(410) 543-6943	(410) 548-5151
23 WORCESTER	(410) 632-1100	(410) 632-0906
30 BALTIMORE CITY	(410) 396-4444	(410) 545-6645
	(410) 396-9413	(410) 396-9403

MARYLAND DIVISION OF TB CONTROL	(410) 767-6698
MYCOBACTERIOLOGY LABORATORY	(410) 767-6130

For After Hours, go to www.edcp.org

Appendix G . Common Terms and Abbreviations Used in TB Control

ACH	Air changes per hour
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
AII	Airborne infection isolation
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAMT	Blood assay for *Mycobacterium tuberculosis*
BCG	Bacille Calmette-Guérin
CDC	Centers for Disease Control & Prevention
CT	Computed tomography
CXR	Chest X-ray
DHHS	U.S. Dept. of Health and Human Services.
DHMH	Department of Health and Mental Hygiene
DNA	Deoxyribonucleic acid
DOT	Directly observed therapy
DTBE	Division of Tuberculosis Elimination
DTH	Delayed-type hypersensitivity
EMB	Ethambutol
FDA	U.S. Food and Drug Administration
HAART	Highly active antiretroviral therapy
HCW	Health-care worker
HEPA	High-efficiency particulate air
HIV	Human immunodeficiency virus
HPLC	High-pressure liquid chromatograph
HVAC	Heating, ventilation, air conditioning
ICE	Immigration and Customs Enforcement
IFN-g	Inteferon-gamma
IGRA	Interferon gamma release assay
INH	Isoniazid
LHD	Local Health Department
LTBI	Latent tuberculosis infection
LUL	Left Upper Lobe
MDR-TB	Multidrug-resistant tuberculosis
MOTT	Mycobacterium other than tuberculosis
MTD	Mycobacterium Tuberculosis Direct Test
NAA	Nucleic acid amplification
NIOSH	National Institute for Occupational Safety and Health
NNRTI	Nonnucleoside reverse transcriptase inhibitors
NTM	Nontuberculous mycobacteria
OSHA	Occupational Safety and Health Administration
PCR	Polymerase chain reaction
PI	Protease inhibitor
PPD	Purified protein derivative
PZA	Pyrazinamide
QFT	QuantiFERON®-TB test
QFT-G	QuantiFERON®- TB Gold test
RBT	Rifabutin
RFLP	Restriction fragment length polymorphism
RIF	Rifampin
RNA	Ribonucleic acid
RPT	Rifapentine
RUL	Right Upper Lobe
RZ	Rifampin and pyrazinamide
SARS	Severe acute respiratory syndrome
SGOT	Serum glutamic-oxalacetic transaminase (older term for AST)
SGPT	Serum glutamic-pyruvic transaminase (older term for ALT)
TB	Tuberculosis
TLTBI	Treatment of Latent TB Infection
TNF-α	Tumor necrosis factor alpha
TST	Tuberculin skin test
TU	Tuberculin unit
UV	Ultraviolet
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization

Maryland TB Expert Panel - 2007

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