New Jersey
Department of Health and Senior Services

Standards of Care for Tuberculosis Disease and Latent TB Infection

Tuberculosis Medical Advisory Board
March 2007

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Assignment of Responsibility

The Centers for Disease Control and Prevention, American Thoracic Society and Infectious Disease Society of America published a joint statement titled, *Treatment of Tuberculosis* in the Morbidity and Mortality Weekly, June 20, 2003, 52(RR-11); 1-77.

This joint statement clearly outlines the goals for the treatment of tuberculosis as "1) to cure the individual patient, and 2) to minimize the transmission of *Mycobacterium tuberculosis* to other persons." The statement continues; "Thus, successful treatment of tuberculosis has benefits both for the individual patient and the community in which the patient resides. For this reason the prescribing physician, be he/she in the public or private sector, is carrying out a public health function with responsibility not only for prescribing an appropriate regimen, but also for successful completion of therapy." It goes on to state, "Prescribing physician responsibility for treatment completion is a fundamental principle in tuberculosis control. However, given a clear understanding of the roles and responsibilities, oversight of treatment may be shared between a public health program and a private physician."

The New Jersey Department of Health and Senior Services (NJDHSS) as advised by its Tuberculosis Medical Advisory Board,* supports the assignment of responsibility for appropriate treatment and the completion of therapy for patients with *Mycobacterium tuberculosis* to the prescribing physician as a fundamental principle of its TB prevention and control efforts statewide.

It is recognized that the use of directly observed therapy (DOT) and such procedures as sputum induction are not options that are readily available or even practical for a private physician to provide, but these and other services are available through collaboration with the public health department. Through such collaboration, responsibility for patient outcomes is shared between the public health department and private providers. Additional services such as nurse case management, anti-TB medications, field services and incentives and enablers to monitor and promote patient adherence are also accessible to private providers and their patients with TB in New Jersey. Such collaboration is essential to meeting the NJDHSS Standards of Care for Tuberculosis Disease and Latent TB Infection (LTBI) for privately managed patients. Collaboration will increase the likelihood of continuity of care until treatment completion, regardless of provider. Both individual patients and the community will benefit as a result.

* The members of the NJDHSS TB Medical Advisory Board are not NJDHSS employees and are not compensated by NJDHSS for the time they serve on this Board. These physicians are affiliated with either university or private hospitals and/or in private medical practice. Collectively, these physicians manage a substantial majority of all TB cases reported in New Jersey each year.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 1: Diagnosis of Latent TB Infection

Justification: Mantoux tuberculin skin testing remains the recommended methodology to identify latent TB infection (LTBI). Unfortunately, a reaction to this test is not necessarily an indication of infection by *Mycobacterium tuberculosis*. A delayed hypersensitivity reaction to tuberculin solution will also result from infection by other mycobacterial species of no public health concern but prominent in the environment (e.g., *M.avium*, *M.gordonae*). Such infections generally only present a danger of active disease to severely immune compromised individuals, are not transmissible person-to-person and are generally resistant to the drug(s) used to treat LTBI.

The lack of specificity inherent in the Mantoux tuberculin skin test necessitates the application of cut-points (5mm, 10mm or 15mm) to determine the significance of a reaction to the test. These cut-points take into consideration the likelihood of LTBI and the risk of progression to active disease if infected. These cut-points differ between individual patients, and appropriate application is essential to minimize the incidence of false positive reactions resulting in misdiagnosis of LTBI. Preventing misdiagnosis of LTBI will prevent the inappropriate prescription of drugs toxic to the liver.

To minimize the incidence of false positive reactions and improve the value of screening for LTBI, this standard strongly discourages the tuberculin skin testing of:

1. Adults that are **NOT** at increased risk of progression to active disease, if infected, and

2. Adults and children that are at low risk for LTBI (i.e., a 15mm induration in response to tuberculin skin testing is required for a diagnosis of LTBI).

Tuberculin skin testing is <u>NOT</u> generally recommended:

- For persons with a documented previous significant Mantoux tuberculin skin test;

- Less than four weeks after a live virus vaccination (the Advisory Committee on Immunization Practices recommends tuberculin skin testing be done on the same day or four to six weeks after vaccination);

- For children less than six months of age, unless active disease is suspected or the child is identified as a contact to a person with infectious or potentially infectious TB disease;

- For persons at low risk for latent TB infection without other specific indications (see Priorities and Indications for Tuberculin Skin Testing in NJ, page 3 of this Standard.

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Standard # 1: Diagnosis of Latent TB Infection

QuantiFERON-Gold (QFT-G) Test

The QFT-G test is a blood assay for *M.tb* which is now available as an alternative in vitro test for the identification of LTBI. The CDC states that QFT-G may be used in all circumstances in which the Mantoux tuberculin skin test is currently used (MMWR, Dec 16, 2005, Vol. 54).

While addressing the specificity issues surrounding Mantoux tuberculin skin testing, the QFT-G test presents logistical and cost barriers that make it impractical in most clinical testing environments in New Jersey. The result of a QFT-G test is a valid and acceptable method for identifying LTBI where it is practical.

Previous Bacille Calmette-Guerin (BCG) Vaccination

Prior vaccination with BCG is **NOT** a contraindication for tuberculin skin testing in persons from areas of the world where TB is endemic. The risk for LTBI in this population is sufficient to minimize the risk of a false positive reaction to a Mantoux tuberculin skin test.

Prior BCG is also **NOT** a contraindication for prescribing treatment for LTBI.

Tuberculin Skin Testing Philosophy in New Jersey

1. Knowledge of the result of a tuberculin skin test provides **NO** benefit to the public health **WITHOUT** treatment for LTBI, if identified. Therefore, a decision to administer a tuberculin skin test is a decision to treat LTBI, if identified and not medically contraindicated.

2. The medical provider identifying a positive tuberculin skin test is responsible for the additional evaluation (chest radiograph & physician assessment) required for diagnosing LTBI. This provider is also responsible for and for prescribing appropriate treatment and monitoring the patient for adverse reactions until therapy is completed.

3. The risk for false positive tuberculin skin test results increases proportionally to the decrease in the risk for LTBI in the population or individual being tested. Tuberculin skin testing must **NOT** be offered to populations or individuals at low risk for LTBI. The exceptions are individuals with symptoms consistent with active TB disease and those at a significantly increased risk for rapid progression from LTBI to active TB disease, if infected. In certain instances, these risks are sufficient to warrant tuberculin skin testing even with no identified increased risks for LTBI (i.e., persons with immune suppressive conditions or those subject to immune suppressive treatments.

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Priorities and Indications for Tuberculin Skin Testing in New Jersey

Priority 1: Contacts to confirmed or suspected active infectious or potentially infectious TB disease.

Contacts must be Mantoux tuberculin skin tested as soon as possible after exposure to an infectious or potentially infectious TB case or suspect. More urgency exists when sputum smears of the index case are positive for acid fast bacilli (AFB).

If the initial skin test is significant (≥ 5mm of induration), no further testing is required.

"Window" Period
If the initial skin test result is not significant (<5mm of induration) and exposure has ended, a second test must be administered at least eight (8) weeks after the end of exposure.

If the initial skin test result is not significant and exposure is on-going, a second tuberculin skin test is required at least eight (8) weeks after the TB suspect or case is no longer infectious.

If atypical mycobacterial cultures are identified and disease due to *M.tb* is ruled out during this "window" period, a second tuberculin skin test for contacts is not necessary.

See Standard #6: Treatment, page 15 of 19 for identification of contacts with an induration of <5mm or no reaction to the initial tuberculin skin test who require treatment during the eight (8) week "window" period prior to the second skin test.

Priority 2: Immigrants, refugees or other recent arrivals referred by the CDC for evaluation and classified by overseas physicians as:
Class A (active disease, currently infectious), OR
Class B1 (active disease, not currently infectious), OR
Class B2 (TB disease, not currently active).

Priority 3: HIV infection OR corticosteroid therapy (receiving the equivalent of ≥15 mg/day of prednisone for ≥ one month) OR treatment with TNF alpha blockers.

Priority 4: Individuals with symptoms consistent with active TB disease, regardless of identified risk or lack of risk (patient must be referred for a chest radiograph prior to knowing and regardless of tuberculin skin test result).

Priority 5: Infants, children and adolescents (aged 0-17 years) who do not meet the criteria of Priorities 1-4 above, but with risk factors in either column #1 **OR** column #2 of the table on page 4 of this Standard.

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Priority 6: Adults (aged 18 years or older) who do not meet the criteria of Priorities 1-4 on the previous page, but with risk factors in column #2 of the table below.

Column # 1	Column # 2
Increased Risk for Latent TB Infection	**Increased Risk for Disease Once Infected**
Foreign-born from high incidence country, regardless of time in the U.S.	Diabetes mellitus
US born minority, low income and medically underserved population member	Silicosis
	Cancer of the head and neck
Injection drug use	Hematologic and reticuloendothelial disease
	End-stage renal disease
	Intestinal bypass or gastrectomy
	Chronic malabsorption syndromes
	Low body weight (10% or more below the ideal)
	Persons on immunosuppressive therapy (other than corticosteroids or TNF alpha blockers)
	Injection drug use
	Foreign-born from high incidence countries and in the U.S. for ≤ 5 years

Mandated Tuberculin Skin Testing

Tuberculin skin testing is required for licensure in NJ, by state regulation or policy for specified occupational groups and associated population groups as a basis for an effective infection control program. With the exception of students specifically required to be skin tested prior to starting school by the Department of Education, the employer, potential employer or institution is responsible for providing or contracting for the tuberculin skin test **and** associated evaluation to consider appropriate treatment. Referrals to public health clinics for skin testing and/or evaluation to satisfy these licensure requirements, regulations or policies are inappropriate, unless provided by contractual agreement.

Tuberculin Skin Testing Method for Identifying Infection by *M.tb* in New Jersey
Mantoux tuberculin skin test

Administration of a Mantoux Tuberculin Skin Test
The proper administration of this test requires an intradermal injection of 0.1 ml of purified protein derivative (PPD) tuberculin containing five tuberculin units (TU) into the inner surface

of the forearm. The injection should be made just beneath the surface of the skin using a disposable tuberculin syringe with the needle bevel facing upward. This should produce a discreet, pale elevation of the skin (a wheal) six to ten millimeters in diameter. Record the forearm (right or left) on which the Mantoux tuberculin skin test was administered.

Reading the Mantoux Tuberculin Skin Test

- Appropriate Personnel to Read the Skin Test: An adequately trained health care worker. Tuberculin skin tests must **NEVER** be read by family members or other untrained persons. No one should be allowed to read and report their own tuberculin skin test reactions, **EVEN** an adequately trained health care worker. This includes non-reactive or negative tuberculin skin tests.

- Timeline: The reaction to a Mantoux tuberculin skin test should be read 48 to 72 hours after administration. If a patient fails to appear for a scheduled reading, a significantly measurable reaction (see "Classification of Mantoux Tuberculin Skin Test Reaction" below) may be considered reliable up to seven days after the test was administered. An insignificant tuberculin reaction or no observable reaction must be repeated unless read within 72 hours of administration.

- Method: The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. The diameter of the indurated area must be measured across the forearm (perpendicular to the long axis). Erythema (redness) must **not** be measured to determine the significance of the reaction.

Recording the Measured Reaction to a Mantoux Tuberculin Skin Test
All tuberculin skin test reactions must be recorded in millimeters of induration. If no induration is found, "0 mm" must be recorded.

Classification of Mantoux Tuberculin Skin Test Reactions
A significant or positive reaction to tuberculin is considered evidence of latent TB infection.

An induration of greater than or equal to 5 mm is considered significant or positive for:

1. HIV-infected

2. Contacts to confirmed or suspected infectious or potentially infectious TB disease

3. Persons with fibrotic changes on chest radiograph consistent with old healed TB

4. Organ transplant recipients

5. Patients taking corticosteroid therapy (receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ one month), those on TNF alpha antagonists or severely immune suppressed for other reasons.

An induration of greater than or equal to 10 mm is considered significant or positive for:

1. Foreign-born from high-prevalence countries (without consideration of previous BCG vaccination)

2. Injection drug users

3. Residents and employees of high-risk congregate settings (prisons and jails, nursing homes and other long-term care facilities for the elderly, hospitals and other health care facilities, residential facilities for AIDS patients and homeless shelters)

4. Mycobacteriology laboratory personnel

5. Persons with the following clinical conditions:
    - Diabetes mellitus
    - Silicosis
    - Cancer of the head and neck
    - Hematologic and reticuloendothelial diseases
    - End-stage renal disease
    - Intestinal bypass or gastrectomy
    - Chronic malabsorption syndromes
    - Low body weight (10% or more below the ideal)
    - Persons on immunosuppressive therapy (other than those listed in #5 above)

6. Children less than 5 years of age

Two-Step Tuberculin Skin Testing

Rationale

Serial skin testing is done in populations at increased risk for LTBI to assess for TB transmission in the period between tests. It would be suspected that transmission had occurred if an individual with an insignificant reaction to a previous test(s) converted to a significant reaction upon subsequent testing. Evidence of transmission within a facility warrants investigation to determine the source of infection. This is an essential but difficult and laborious task.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 1: Diagnosis of latent TB Infection

The purpose of initial two-step tuberculin skin testing is to rule out the effect of "boosting" on the outcome of subsequent skin tests. If LTBI occurred years ago, individuals may not react to a single tuberculin skin test. However, this first test may "boost" or stimulate their ability to react to a subsequent test, even though infection has **NOT** occurred in the time between the two tests. Two-step testing ensures an accurate baseline skin test result, so "boosting" is not confused with evidence of transmission or new infection upon subsequent testing.

Criteria for Two-Step Tuberculin Skin Testing

1. Two-step testing is only applicable to:

    - Groups for whom serial skin testing is required as part of an infection control policy, such as health care workers and correctional officers, and

    - Residents of long term care and other facilities where having a "true" baseline LTBI status is essential for determining the level of transmission after exposure to infectious TB disease.

Consult your facility's licensure requirements, PEOSH regulations applicable to your facility or the New Jersey Department of Health and Senior Services' TB Program at (609) 588-7522 to determine if initial two-step or serial skin testing is required.

2. Two-step testing is only required on the initial assessment of individuals participating in a serial tuberculin skin testing program.

3. If documentation of a previous insignificant or negative tuberculin skin test result within 12 months is provided, two-step testing is **NOT** required. For these individuals, the result of a single skin test is sufficient to establish a valid baseline.

4. Two-step testing is **ONLY** required if the individual is non-reactive or reacts insignificantly to the first tuberculin skin test. A significant or positive reaction to the first skin test is sufficient evidence of pre-existing LTBI.

5. If initial two-step tuberculin skin testing is required (individual does not meet either criteria #3 or #4 on page 7 of this Standard), the second test must be administered within one to three weeks of the first test. If the results of the second test are non-reactive or insignificant, the individual is not infected and annual testing is required. If the results of this second test are significant or positive, this is evidence of pre-existing LTBI and no further testing is required.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 2: Frequency of Physician Evaluation

Justification: Physician visits are essential to ensure the quality of care provided for patients with active TB disease and latent TB infection (LTBI) but are often demanding and costly to the patient population (e.g., lost wages, sick leave). Physician visits are also demanding on limited physician time. This standard establishes minimal frequencies for physician evaluations for the effective medical management of most individuals with active TB disease and LTBI. It is acknowledged that patients with complications during treatment (i.e., the advent of adverse reactions) will require more frequent physician evaluation to promote continuity of therapy and ensure patient safety.

Frequency of Physician Evaluation for Individuals with Confirmed or Suspected Disease:

All TB cases and suspects require (1) an initial clinical visit, (2) a physician evaluation or case review after two months of treatment (at the end of the initial phase), and (3) a medical visit to discharge the patient from treatment. The physician will order additional clinical visits as needed to appropriately medically manage the patient. In the interim, TB cases or suspects will be assessed monthly by a licensed nurse to monitor for drug toxicity, response to therapy and adherence. The nurse will refer any complications to the physician.

Special Considerations for Multi-Drug Resistant (MDR) TB:

MDR-TB is defined as resistance to both isoniazid and rifampin. All TB cases diagnosed with MDR-TB require monthly clinical visits with a physician for medical evaluation while being treated. The physician may order additional clinical sessions as needed to appropriately manage the patient. In addition, a physician evaluation is required at six month intervals for up to two years after the completion of treatment for MDR-TB.

Standard Requirement for Frequency of MD Evaluations for LTBI:

All patients with a significant or positive tuberculin skin test require an initial physician evaluation to rule-out active TB disease, diagnose LTBI and consider a prescription for appropriate treatment**.** Evaluation should include chest radiograph and may require acid fast bacilli (AFB) smear and culture identification if the patient is symptomatic or the chest x-ray suggests possible active TB disease. If active disease is suspected, see above for appropriate frequency of follow-up physician evaluation.

Patients with LTBI will subsequently be assessed monthly by a licensed registered nurse to monitor for drug toxicity and adherence. The nurse will refer any complications to the physician. Additional clinical sessions with the physician will be ordered as needed to appropriately medically manage the patient.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 2: Frequency of Physician Evaluation

Special Considerations for LTBI associated with MDR-TB:

All persons with LTBI suspected as a result of exposure to an active case with MDR-TB disease must be followed for at least two years, irrespective of treatment.

If Treatment is Prescribed

Patients do not require follow-up physician visits unless drug toxicity or adherence issues are identified by monthly nursing assessments while on treatment. Nursing staff assigned this responsibility must refer any complications to the physician for evaluation.

If Treatment is NOT Prescribed

Nursing assessments to review for the emergence of symptoms consistent with active TB disease must be conducted periodically as directed by a physician for two years post-infection. If symptoms consistent with active TB disease are identified, the patient must be immediately referred to the physician for evaluation.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 3: Baseline and Follow-Up Chest Radiographs

Justification: The chest radiograph is essential to detect and describe chest abnormalities suggestive of active pulmonary TB disease or inactive TB. This standard defines the minimum frequency of chest radiographs required to diagnose active TB disease, inactive TB and latent TB infection (LTBI) and medically manage uncomplicated TB disease.

Baseline Radiographs Essential to Evaluate Significant Mantoux Tuberculin Skin Test Reactors

A baseline chest radiograph must be done for all significant reactors to a Mantoux tuberculin skin test, except those who can provide a chest x-ray performed within a month of the tuberculin skin test that can be maintained in the chest clinic. A written or oral report alone is not acceptable.

All chest x-rays should be read by the physician at the time of the patient's visit and findings documented in the patient's medical record.

A licensed radiologist's reading and written report should be obtained and incorporated into the patient's medical record.

Adults
The Posterior-Anterior (PA) view of the chest is the standard radiograph needed for detection and description of chest abnormalities for individuals eighteen years of age or older. In some cases, lateral and/or lordotic views may be necessary in this age group.

Children and Adolescents
In order to detect TB in children and adolescents, two radiographic views are essential.

- Children five years of age and younger suspected of having active TB disease must have an Anterior-Posterior (AP) and lateral view of the chest.

- Children six to seventeen years of age must have a Posterior-Anterior (PA) and lateral view of the chest.

Pregnancy
Pregnant women who are being evaluated for active TB must undergo a chest radiograph without delay, even during the first trimester. A lead shield must be used for all chest x-rays of pregnant women and those of child-bearing age.

Extra-pulmonary TB
Although the majority of TB cases are pulmonary, an individual may have both pulmonary and extra-pulmonary disease. Individuals suspected of having extra-pulmonary TB must have a

baseline chest radiograph to rule out coexisting pulmonary disease.

Follow-up Radiographs for TB Cases and Suspects

Pulmonary TB Disease Confirmed by Positive Culture of *M.tuberculosis*
The frequency of follow-up chest x-rays for culture confirmed TB cases is dependent upon the patient's clinical improvement and assessment by the physician. A repeat chest x-ray must be done at two months after the initiation of treatment, absent documentation of improving smears and cultures.

Pulmonary TB Disease Confirmed by the Clinical Case Definition
If sputum/other pulmonary cultures are negative or if no specimen could be obtained for culture identification/confirmation, a presumptive diagnosis of TB must meet the clinical case definition for pulmonary TB to be confirmed. The clinical case definition requires that the following three conditions are met:

1. Tuberculin skin test reading was significant or positive, indicating LTBI
2. Effective anti-tuberculosis therapy was prescribed and taken
3. Radiographic change (improvement or worsening) occurred

Therefore, patients who are initially culture negative or for whom a culture identification is not available must have a repeat chest x-ray after two months of treatment (to determine if pulmonary TB can be confirmed or should be ruled out), and again when treatment is completed.

Use of CT Scans

CT scans are often utilized unnecessarily in the diagnosis of pulmonary TB. These scans are of most value when used to confirm or rule out cavitary disease if the sputum cultures remain positive after two months of treatment. In this context, CT scans assist in the determination of an adequate treatment regimen (six months total duration for non-cavitary disease versus nine months for cavitary disease).

Tuberculin Skin Test Reactors

Asymptomatic individuals with significant or positive tuberculin skin test reactions (not suspected to have active TB) must have a chest radiograph to rule out active TB or chest abnormalities prior to initiating treatment for LTBI (see page 1 of this Standard). Some of these reactors may be determined to have inactive, but untreated or Class IV TB. These individuals are at increased risk for relapse to active TB and cannot be diagnosed without a chest radiograph. Repeat chest radiographs for any asymptomatic tuberculin reactor is not indicated.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 3: Baseline and Follow-Up Chest Radiographs

The following radiographic views must be obtained based on the age of the individual:

- Patients aged six years or older must receive a Posterior-Anterior (PA) chest radiograph.

- Children five years of age and younger must receive Anterior-Posterior (AP) and lateral chest views.

Contacts to Active TB Disease

- Children less than five years of age that are contacts to active TB disease must receive Anterior-Posterior (AP) and lateral chest views, regardless of initial tuberculin skin test result. For treatment recommendations see Standard #6: Treatment, pages 15 and 16 of 19.

- Patients five years of age or older that are contacts to active TB disease with an initial tuberculin skin test induration < 5mm do not require a chest radiograph unless they:

    1. Have TB-like symptoms (see below), or

    2. Are HIV-infected and under consideration for treatment of LTBI during the eight (8) week "window" period. See Standard #1: Diagnosis of Latent TB Infection, page 3 of 7 for an explanation of the "window" period applicable to contacts. See Standard #6: Treatment, pages 15 and 16 of 19 for treatment recommendations for HIV-infected contacts during the "window" period.

- Except for contacts aged less than 5 years and those with co-existing HIV infection, initiation of treatment is generally delayed until the results of the final skin test (after the eight (8) week "window" period) and started only if LTBI is detected by an induration of 5mm or more. See Standard #6: Treatment, page 15 of 19 for treatment recommendations for the exceptions above during the "window" period.

Symptomatic Individuals Regardless of Tuberculin Skin Test Results

ALL individuals with symptoms compatible with active pulmonary TB disease must be suspected to have active TB disease and receive a chest radiograph immediately, regardless of tuberculin skin test result. If active TB is suspected, see page 2 of this Standard under "Follow-up Radiographs for TB Cases and Suspects" for frequency of follow-up chest radiographs. If active TB is ruled out, no further chest radiographs are indicated.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 3: Baseline and Follow-Up Chest Radiographs

Class A, B1 or B2 Immigrants and Refugees

For newly arrived immigrants and refugees reported to the New Jersey Department of Health and Senior Services by the Division of Global Migration and Quarantine of the Federal Centers for Disease Control and Prevention, a repeat tuberculin skin test and chest radiograph is required to adequately evaluate current status. This is necessary even if the patient reports to the provider with a chest x-ray taken overseas.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 4: Collection and Evaluation of Sputum or other Specimens

Justification: Sputum and other bacteriology specimens are important in the diagnosis and treatment of tuberculosis. Initial and subsequent sputum specimens for AFB smear are essential to the diagnosis of pulmonary TB, the determination of infectiousness, the duration of treatment required, the efficacy of treatment and the appropriate time for initiation of intermittent treatment for patients on directly observed therapy. The identification of *M.tb* on culture from a specimen of any source will confirm the diagnosis of TB. In the case of extra-pulmonary TB, culture identification from specimens collected from the site of disease (e.g., pleural fluid, lymph node biopsy, CSF) may be the only method to confirm the diagnosis of TB. Drug susceptibility test results identify the appropriate drug regimen and duration of treatment. Important medical decisions regarding the treatment regimen in the continuation phase are based on the microbiological status at the end of the initial phase of treatment. In addition, these laboratory findings (consecutive sputum smears negative for AFB) will determine eligibility for housing of homeless pulmonary TB cases and suspects.

Sputum Collection

An attempt must be made to collect sputum from **ALL** adult pulmonary TB suspects, regardless of other specimens collected during a bronchoscopy or biopsy. This is essential as the results of bacteriological tests on sputum have value beyond confirmation of active TB disease.

Sputum may be collected spontaneously or induced for those individuals who do not have a cough or have difficulty submitting a specimen. However, in some patients more invasive techniques such as bronchoscopy or bronchoalveolar lavage are needed.

Early morning gastric aspirates on three consecutive days are recommended for children who are hospitalized and unable to produce sputum (if induction is impractical or unsuccessful), unless the likely source of transmission has been identified and culture and drug susceptibility test results for this source case are known.

Sputum Collection Schedule

All persons with suspected pulmonary and/or laryngeal TB should have three sputum specimens collected on consecutive days. Preferably, all three of these specimens would be collected prior to the initiation of therapy, but at least one of these specimens must be collected prior to the initiation of therapy. Early morning sputum specimens are preferable.

Patients who have positive AFB sputum smears at the time of diagnosis must have sputum collected every one to two weeks until a smear negative for AFB is reported. Once the first smear negative for AFB is reported, sputum should be collected on the following two consecutive days to confirm non-infectiousness.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 4: Collection and Evaluation of Sputum or other Specimens

During the course of treatment, a sputum specimen for AFB smear and culture should be obtained at monthly intervals until two consecutive specimens collected at least one month apart are negative for *M.tb* on culture. For patients with MDR-TB the collection of sputum must continue monthly until treatment is completed.

The re-emergence of TB-like symptoms, worsening of chest radiograph and/or documented non-adherence to prescribed treatment after the above conditions are met would require resumption of the collection of additional sputum specimens.

Evaluation of Bacteriological Specimens other than Sputum

Suspicion of Extra-pulmonary TB
Individuals who are suspected of having extra-pulmonary TB may have specimens collected from the site of disease such as, but not limited to, spinal fluid, pleural fluid, lymph nodes, urine, stool or abscesses. If TB is suspected, the specimen should be sent to the laboratory for AFB smear, culture identification and drug susceptibility testing.

Biopsy, Granulomatous Tissue Found
Frequently, TB is not suspected and a biopsy is done to determine the cause of illness. If the histology reveals granulomatous tissue (suggestive of TB), a specimen must be sent to the laboratory for AFB smear, culture identification and drug susceptibility testing, in addition to the specimen for histology.

Initial and Follow-up Drug Susceptibility Testing

Drug susceptibility test results for *M. tuberculosis* are critical to appropriate treatment and must be performed on the initial isolate from **ALL** patients from whom *M. tuberculosis* is recovered.

Drug susceptibility testing must be repeated if the patient:

- Remains culture positive after **four** months of continuous therapy, AND/OR
- Develops positive cultures after a period of negative cultures, AND/OR
- Has documented adherence issues with an appropriate regimen, AND/OR
- Has received an inadequate treatment regimen.

Assumptions Based on the Results of First-Line Drug Susceptibility Test Results

Resistance to rifampin is associated in nearly all instances with cross-resistance to rifabutin and rifapentine. Rare strains with rifampin resistance retain susceptibility to rifabutin, associated with uncommon mutations of the RNA-polymerase locus in the bacillus. However, unless in vitro susceptibility to rifabutin is demonstrated, this agent should not be employed in cases with

rifampin resistance. Cross-resistance between rifampin and rifapentine appears almost universal.

There is no cross-resistance between streptomycin and the other injectable agents, amikacin, kanamycin and capreomycin (although resistance to all may occur as independent events). However, cross-resistance between amikacin and kanamycin is universal. Simultaneous use of two injectable agents is NOT recommended due to the absence of proof of efficacy and potential amplification of drug toxicity.

Resistance to PZA is uncommon in the absence of resistance to other first-line drugs. If mono-resistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is *M. bovis*, not *M. tuberculosis. M. bovis* is genotypically resistant to PZA and is not distinguished from *M. tuberculosis* by nucleic acid hybridization (probe assays that are commonly used for identification of mycobacteria).

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 5: Laboratory Testing and Patient Monitoring

Justification: Adverse reactions to TB medications may occur with varying degrees of severity. Laboratory tests are important in detecting any abnormality that may complicate the treatment regimen or necessitate its modification. Baseline laboratory tests enable comparison with later measurements if adverse reactions occur. Routine monitoring for adverse reactions is important during TB treatment.

TB Cases and Suspects

All adults treated with the first-line TB medications must have baseline measurements for the following:

- Complete blood cell count (CBC), including platelets
- Chemistry panel including AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin and creatinine

As a routine, it is not necessary to obtain subsequent laboratory tests unless there are abnormalities found in the baseline tests **AND** for patients who:

- Chronically consume alcohol,
- Take other potentially hepatotoxic medications,
- Have viral hepatitis or history of liver disease,
- Have HIV-infection, **OR**
- Have prior TB drug induced liver injury

Follow-up laboratory monitoring must also be done if the patient is:

- Suspected of experiencing an adverse reaction or intolerance to anti-TB medications,
- A poor historian, **OR**
- Impossible to monitor clinically (special situations, such as mental illness, etc).

Liver function tests and CBC, including platelets, must be done biweekly to monthly for all patients with symptomatic liver disease. Otherwise, these tests should be obtained only when clinically indicated.

New Jersey Department of Health and Senior Services
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Standard # 5: Laboratory Testing and Patient Monitoring

Monitoring for adverse reactions to TB medications must be individualized and depend upon the drugs given and the patient's risk for adverse reactions. TB medications should be stopped if the serum AST and/or ALT are greater than:

1. Three times the upper limit of normal for patients with pre-existing liver disease or current symptoms of liver disease **OR**

2. Five times the upper limit of normal for patients currently asymptomatic for liver disease or with previously normal liver function values and no risk for liver disease.

Consultation must be sought for an adjustment of the TB treatment regimen if serum AST and/or ALT levels are elevated to the degree indicated above (see Standard 7: Consultation, page 1 of 2).

Baseline laboratory tests are indicated in children seventeen (17) years of age or younger if they have one or more of the following:

- History of liver disease
- Treatment for seizure disorders
- Disseminated TB
- Treatment with second-line anti-TB medications
- Co-existing HIV disease
- Co-existing diagnosis adversely affecting the liver or treated with medications that may be hepatotoxic.

Other Baseline and Monthly Tests

Optic neuritis is the most frequent and serious adverse effect of ethambutol. Baseline and monthly visual acuity and color discrimination should be obtained for all patients treated with ethambutol, including children who are able to understand the instructions for the test. Ethambutol should be discontinued and the patient referred to an ophthalmologist if:

- Two or more errors (above the number of errors found at the baseline assessment) are documented on the Ishihara color plates, or

- The results of a follow-up visual acuity test are two or more deviations from the baseline assessment (e.g., baseline 20/20, follow-up 20/60).

HIV Counseling and Testing

TB cases and suspects who are co-infected with HIV disease have the potential for drug interactions, especially between the rifamycins and antiretroviral agents. Additionally, paradoxical reactions that may be interpreted as clinical worsening and the development of acquired resistance to rifamycins when treated with intermittent therapy may also occur. Therefore, it is important to know and document the individual's HIV status at the beginning of treatment. All TB cases and suspects, both adults and children, must receive HIV counseling and be offered testing as part of the routine initial medical evaluation or during the first two months of treatment.

If the individual had an HIV test done within the last six months, the results should be obtained and included in the medical record.

If the HIV status is unknown, the patient must be provided education regarding the importance of HIV and TB, and offered HIV counseling and testing. If the patient refuses testing, the risk factors for HIV disease should be discussed with the patient and the refusal documented in the medical record.

Laboratory Tests for Treatment of Latent TB Infection (LTBI)

Neither baseline nor routine laboratory testing is indicated for healthy individuals aged less than 35 years prior to the start or during treatment for LTBI (for guidance regarding patients aged 35 years or older, see page 4 of this Standard). However, baseline and follow-up serum AST, ALT and total bilirubin are recommended for patients meeting any of the following criteria:

- A history of chronic liver disease (e.g., chronic hepatitis B and C, alcoholic hepatitis and cirrhosis),
- Chronic use of alcohol,
- HIV infection treated with HAART,
- Concomitant hepatotoxic medication(s),
- Pregnant women or women up to three months postpartum.

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Baseline and follow-up monitoring of serum ALT should be considered for patients aged 35 years or older.

The frequency of routine monitoring may be monthly, every other month or at 1, 3 and 6 months for patients prescribed a 9-month treatment regimen depending on the perceived hepatotoxicity risk and the stability of ALT.

The decision to treat or defer treatment for LTBI should be carefully made on a case-by-case basis, weighing the risk of progression to active TB disease against the risk of isoniazid or rifampin related drug induced liver injury. Factors influencing the latter include:

- Degree of baseline ALT elevation,
- Alcohol consumption,
- Age, and
- Evidence of active replication of hepatitis virus.

If treatment for LTBI is started for these patients, measuring serum transaminases and bilirubin concentrations every 2 to 4 weeks for the first 2 to 3 months and as necessary is recommended.

HIV Counseling and Testing

Persons with HIV infection have a higher risk of progression to active TB disease once infected. Therefore, those diagnosed with LTBI must be offered HIV counseling and testing.

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Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 6: Treatment

Justification: To ensure adequate treatment for all cases of active tuberculosis disease and latent TB infection (LTBI) in the state of New Jersey, while optimizing the duration of treatment and minimizing the transmission of tuberculosis to others.

Directly Observed Therapy (DOT) versus Self-Administered Therapy

Directly observed therapy (DOT) is utilized nationwide and worldwide as a standard TB treatment strategy to monitor adherence to prescribed treatment. DOT is the ONLY treatment strategy available to document that medications were or were not taken as prescribed. Such documentation is essential when the number of doses taken within a prescribed time frame determines completion of adequate treatment. DOT is often essential to protect the public health against transmission of disease and the individual against treatment failure and/or the emergence of secondary drug resistance. The use of DOT will reduce the time required to adequately treat TB as well as facilitate the most rapid transition possible from daily to intermittent (twice weekly) treatment in eligible patients. Standardizing the use of DOT in specific classifications of patients is superior to the unnecessary transmission of infection in the community or sometimes debilitating consequences for the patient of the failure of self-administered therapy. DOT provides the opportunity to identify previously unknown contacts to infectious TB cases and to identify undisclosed substance abuse or other barriers to treatment adherence in the patient population. In addition, DOT allows a health care worker to build rapport with the patient to a degree not possible with self-administered therapy. While documenting and promoting adherence in the patient population, DOT also documents non-adherence, allowing legal interventions as necessary to protect the health of the individual and the public.

Self-administered therapy requires less effort on the part of the provider but relies entirely on the patient to take his or her medications as prescribed. While most patients remain conscientious while symptoms persist, the reliability of self-medicating can wane once symptoms have subsided. This is particularly true if the patient perceives that they are cured during the continuation phase of treatment or experiences any side effects from the medications, real or perceived. No significant correlation between an increased likelihood of adherence during the continuation phase of treatment and cultural, employment or socioeconomic factors has ever been documented. In short, adherence is not reliably predictable in any patient population with TB.

Definitions

Directly Observed Therapy: DOT is defined as the direct observation by a health care worker of a patient's ingestion of anti-TB medications at a frequency prescribed by the treating physician. For DOT to achieve its intended purpose, the health care provider must retain possession of the prescribed medication to prevent reports of self medication prior to the health care worker's arrival.

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Daily DOT: For the purpose of this Standard of Care, daily DOT is defined as 5 days per week. Medications for self-administration may be left with the patient on weekends or holidays but are not essential for completion of a therapeutic regimen.

Intermittent DOT: For the purpose of this Standard of Care, intermittent DOT is defined as twice weekly for patients with uncomplicated TB or three times weekly for HIV-infected patients (see exceptions to the use of intermittent DOT, pages 8 and 9 of this Standard).

DOT is the standard of care in New Jersey from the initiation through the completion of therapy for the following patients with confirmed or suspected TB disease:

1. Children and adolescents (up to 17 years of age), regardless of site of disease

2. Pulmonary TB with cavitary lesions or sputum smears positive for AFB

3. Patients with active TB disease receiving housing assistance

4. Patients with the following conditions and/or circumstances, regardless of site of disease:

    - History of previous treatment for active TB disease or latent TB infection (LTBI)
    - Resistance to isoniazid and/or rifampin
    - Co-existing HIV infection or AIDS
    - Homelessness/Unstable housing arrangement
    - Current or prior substance abuse
    - Current or prior psychiatric illness
    - Diagnosis of Alzheimer's Disease or memory impairment (diagnosed or admitted)
    - Underlying proclivity to hepatotoxicity
    - TB meningitis or TB of the central nervous system
    - Disseminated TB disease

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Appropriate Dosages

Self-Administered Therapy:
See Tables 1 and 2 on page 17 of this Standard for the appropriate dosing. For self-administered therapy, only the daily dosage in these tables should be utilized to treat either children/adolescents or adults.

DOT:
See Tables 3, 4 and 5 on page 18 of this Standard for the appropriate dosing of TB medications depending upon whether used to treat children/adolescents or adults and whether DOT is prescribed daily or intermittently (twice weekly or three times weekly).

Note: Table 2 on page 17 and Tables 4 and 5 on page 18 of this Standard list acceptable daily dosages of PZA and EMB (using whole tablets) for adults of three different weight ranges from 40 to 90 kilograms. Also included is an acceptable range of mg/kg of these medications for each of these groups for reference if the decision is made to treat with partial tablets.

Dosage adjustments or alternate drugs may be needed:

1. To adequately treat mono-drug resistant disease or multi-drug resistant disease

2. To compensate for drug interactions in patients with TB disease and HIV infection or AIDS who are concurrently treated with protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

3. To adequately manage the issue of treatment failure

4. To successfully manage adverse reactions to first-line anti-TB medications

In each of these situations, consultation with an expert in the management of such patients is required (see Standard # 7: Consultation, page 1 of 2).

Fixed Combinations (Rifamate and Rifater)

In addition to uncertainties regarding adherence to self-administered treatment regimens the issue of selective treatment (e.g., taking isoniazid [INH], but not rifampin [RIF] and/or pyrazinamide [PZA], has resulted in the development of secondary drug resistance. To minimize the likelihood of secondary resistance and reduce the total number of pills or capsules to be taken each day, fixed combinations are available and should be utilized liberally in substitution for individual medications in patients appropriately on self-administered therapy.

Rifamate

Rifamate is a fixed combination of INH and RIF. Each capsule contains 300mg of RIF and 150mg of INH. Two capsules per day is the recommended daily dose, compared to two RIF and one INH tablet if taken separately. If a patient weighs enough (at least 30kg for children and adolescents and at least 60kg for adults) to be prescribed the maximum dosage of INH (300mg) and RIF (600mg), Rifamate is a very favorable alternative to individual drugs in both the initial and continuation phase of treatment. For twice weekly intermittent therapy, the standard dosage is 900mg INH and 600mg RIF, this can be achieved by prescribing two rifamate capsules and two 300mg INH tablets at each DOT visit.

Rifater

Rifater is a fixed combination of INH, RIF and PZA. Each tablet contains 120mg of RIF, 50mg of INH and 300mg of PZA. The daily dose is based on weight as follows:

- 44 kg or less – four tablets per day
- 45-54 kg – five tablets per day
- 55 kg or more – six tablets per day

To obtain an adequate dose of PZA in patients weighing 90 kg or more, additional PZA tablets must be given. If a patient is in excess of 90 kg in weight, rifater provides little advantage because of the requirement to add additional PZA tablets to reach an adequate dose. Rifater, however, could be favorable to individual drugs for a patient below that weight.

Monitoring Patient Adherence with Self-Administered Therapy

Any count of the number of doses taken for a patient on self-administered therapy is an estimate. The best that can be achieved is making an educated estimate. There are two recommended approaches. The first and most preferable is random pill counts. In this approach, the number of pills remaining is compared to the number that should be remaining at the time of the count if the patient is adherent. The second method requires knowing when refills of prescribed medications are obtained. The difference between the anticipated date of refill and the actual date of refill allows an estimate of the patient's adherence. Neither of these strategies is comparable to DOT for determining a patient's level of adherence, but one or the other are essential if DOT is not prescribed. These assessments must be done routinely to determine the duration of treatment interruptions (see pages 11 and 12 of this Standard). Treatment interruptions may require the confirmation of a patient's current status with respect to infectiousness and/or drug susceptibility. If of sufficient duration, interruptions may require changes in treatment recommendations and/or the need for DOT to increase the likelihood of continuity of care and treatment completion.

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Standard Treatment Regimen - Initial Phase

The standard treatment regimen for all adults with previously untreated tuberculosis must consist of an initial phase of INH, RIF, PZA and EMB unless any of these drugs are contraindicated. In this initial phase, INH, RIF and PZA must be taken seven days per week for a minimum total of **56 doses in a self-administered treatment regimen**. EMB may be dropped in the initial phase as soon as it is confirmed that the bacilli are susceptible to both INH and RIF. To improve the efficacy of treatment, all drugs should be taken together rather than in divided doses.

The minimum time required to ingest these 56 doses is eight weeks, but the duration may be longer depending upon the adherence of the patient to the prescribed regimen. This is difficult to assess reliably with self-administered therapy (see page 4 of this Standard for adherence monitoring strategies). However, **if DOT is utilized and 40 doses are directly observed (5 days per week for 8 weeks) the regimen will be therapeutic.** If daily DOT is prescribed, medication should be left with the patient for self-administration on the weekends and holidays. These self-administered doses are not to be counted in the 40 doses of daily DOT required to complete the initial phase of treatment even if no evidence exists that these doses were not taken.

Unless drug resistance is documented or intolerance to medications is observed, treatment regimens for tuberculosis that can provide adequate therapy within 26 weeks must include INH, RIF and PZA in the initial phase. **Only those patients that can be treated adequately and tolerate this short course treatment regimen are eligible for self-administered therapy,** so long as they do not meet the criteria listed in 1-4 on page 2 of this Standard.

For the value and duration of EMB in the initial phase of treatment see below on this page.

For definition and management of treatment interruptions during the initial phase, see pages 11 and 12 of this Standard.

<u>Ethambutol (EMB):</u>
EMB may be dropped from the initial treatment regimen upon the receipt of drug susceptibility test results as it provides no benefit once resistance to INH and RIF is ruled out. If resistance to either INH or RIF is detected, see Standard #7: Consultation, page 1 of 2.

If PZA cannot be included in the initial phase of treatment, INH, RIF and EMB must be given daily for a total of **56 doses (if self-administered) or 40 doses (if DOT)** in the initial phase, unless the isolate is already known to be susceptible to INH and RIF. See page 6 of this Standard for valid reasons to withhold PZA from the initial phase of treatment.

For children whose visual acuity cannot be monitored, EMB is usually not recommended, except when there is an increased likelihood of the disease being caused by INH and/or RIF-resistant organisms or when the child has "adult type" tuberculosis (upper lobe infiltration or cavity formation).

Pyrazinamide (PZA):
PZA in the initial phase of treatment serves to reduce the duration of therapy. It will be dropped from the treatment regimen upon completion of the initial phase of treatment **(56 doses if self-administered or 40 doses if DOT)** so long as the bacilli are susceptible to both INH and RIF. If resistance to either INH or RIF is detected, see Standard #7: Consultation, page 1 of 2.

Examples of circumstances in which PZA may be responsibly withheld from the initial phase of treatment include severe liver disease, gout and perhaps, pregnancy.

If PZA cannot be used in the initial phase, treatment with EMB must be extended to a total of 56 doses if self-administered or 40 doses if DOT (see page 5 of this Standard).

Resistance to PZA alone most often indicates disease due to *M. bovis*, rather than *M. tuberculosis*.

Standard Treatment Regimen - Continuation Phase

Intermittent DOT is the Standard of Care in the "continuation phase" of treatment for all patients except those listed as inappropriate for intermittent therapy on page 7 of this Standard. It can only be prescribed after the ingestion of 40 doses of INH, RIF and PZA by daily DOT in the initial phase of treatment.

Justification: Reduces the demand on limited field service capacity with no decrease in the efficacy of treatment.

Intermittent treatment regimens cannot be used to treat TB unless DOT is utilized.

Treatment Schedule: The ideal frequency of intermittent DOT separates treatment by two days (e.g., Monday and Thursday or Tuesday and Friday), although this schedule can be adjusted temporarily to compensate for missed doses due to patient adherence issues. For HIV-infected TB patients, three times weekly intermittent DOT is preferable to twice weekly. Doses should be separated by a day (e.g., Monday, Wednesday and Friday).

Missed Treatment Days: If a treatment day is missed while a patient is on intermittent DOT, the health care worker must seek the patient on the following and every subsequent day until found. Prescribed medications should be given whenever the patient is found and the treatment

schedule adjusted accordingly. **If the patient falls below 80% adherence on an intermittent DOT treatment regimen (twice or three times weekly), daily DOT must be considered.**

Intermittent therapy in the continuation phase will consist of INH and RIF **two days per week for a total of 36 doses or three times per week for a total of 54 doses for HIV-infected patients**. The minimum time required to complete these regimens is 18 weeks.

DO NOT Use Intermittent DOT if the patient has:

1. Resistance or intolerance to INH and/or RIF
   Consult with an expert in the management of drug resistant TB (see Standard # 7: Consultation). Appropriate treatment regimens and duration differ based on the resistance pattern identified.

2. HIV infection and/or AIDS and CD4 counts are unknown or less than 100/µl.

3. Cavitary pulmonary disease **AND** a positive sputum culture for *M.tb* two months or longer after the initiation of therapy.

4. Co-infection with HIV/AIDS **AND** a positive sputum culture for *M.tb* two months or longer after the initiation of therapy.

5. Delayed clinical improvement.

For the patients listed above, daily DOT must be continued until completion of the continuation phase.

If daily therapy must be utilized in the "continuation phase" of treatment, it will consist of INH and RIF seven days per week for a total of **126 doses** for patients on self-administered therapy. The minimum time required to complete this regimen is 18 weeks. However, **if DOT is utilized and 90 doses are directly observed (5 days per week for 18 weeks) the regimen will be therapeutic.** If daily DOT is prescribed, medication should be left with the patient for self-administration on the weekends and holidays. These self-administered doses are not to be counted in the 90 doses of daily DOT required to complete the continuation phase of treatment even if no evidence exists that these doses were not taken.

For management of treatment interruptions during the continuation phase, see pages 11 and 12 of this Standard.

For the maximum duration of time within which these 36 doses (if intermittent DOT), 126

doses (if self-administered) or 90 doses (if daily DOT) must be ingested to be therapeutic in the continuation phase of treatment, see Treatment Completion, page 9 of this Standard.

Extended Treatment Regimen – Continuation Phase

Extended treatment in the continuation phase is required for the following groups:

- Patients with cavitary pulmonary tuberculosis caused by drug susceptible organisms whose sputum culture is positive at the time of completion of the initial phase of treatment **(56 doses if self-administered or 40 doses if DOT)**.

- Patients whose initial phase of treatment did not include PZA.

- Patients with pulmonary TB (cavitary or non-cavitary) and co-existing HIV infection or AIDS with a positive sputum culture after the initial phase of treatment **(40 doses of daily DOT)** is completed. **Self-administered therapy is not acceptable for patients with co-existing HIV infection**.

- Patients with TB meningitis.

- Children with disseminated TB disease.

- Children with upper lobe infiltrates or cavitary lesions on radiographic exam.

Daily DOT is required to treat patients listed in 1-5 on page 7 of this Standard and most also require extended treatment in the continuation phase. In addition, daily DOT is recommended for any patient requiring extended treatment in the continuation phase and listed above.

For all patients requiring extended treatment in the continuation phase, self administered therapy is not in accord with the Standards of Care in New Jersey. The exception is a patient with pulmonary non-cavitary disease and no HIV co-infection or AIDS who did not receive PZA in the "initial phase" of treatment. If a patient meeting this description is prescribed self administered therapy in the "extended continuation phase" of treatment, 217 doses of INH and RIF are required to be therapeutic.

For the patients listed above on daily DOT, the extended continuation phase of treatment will be therapeutic if 155 doses are directly observed (5 days per week for 31 weeks). If daily DOT is prescribed, medication should be left with the patient for self-administration on the weekends and holidays. These self-administered doses are not to be counted in the 155 doses of daily DOT required to complete the extended continuation phase of treatment even if no evidence exists that these doses were not taken. The minimum time required to complete this regimen is 31 weeks.

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Treatment Completion for TB Cases with Pan-Sensitive Organisms

The total duration of therapy depends on the drugs used, the drug susceptibility test results and the patient's response and adherence to prescribed therapy.

Treatment completion is determined primarily by the minimum number of doses ingested within a specified time frame.

- Standard Initial Phase of Treatment

The initial phase of uncomplicated TB treatment is defined as completed successfully if **40 doses** (if daily DOT) **or 56 doses** (if self-administered) **of INH, RIF and PZA** are taken **within three months** of initiating therapy.

- Standard Continuation Phase of Treatment

The standard continuation phase of treatment can be considered complete if **36 doses** (if twice weekly intermittent DOT), **54 doses** (if three times weekly intermittent DOT), **90 doses** (if daily DOT) **or 126 doses** (if self-administered) **of INH and RIF** are taken **within six months** after the completion of the initial phase of treatment.

- Extended Continuation Phase of Treatment

Intermittent DOT should not be used to treat patients requiring an extended continuation phase of treatment (listed on page 8 of this Standard). For these patients, the continuation phase can be considered completed if **155 doses** (if daily DOT) **or 217 doses** (if self-administered) **of INH and RIF** are taken **within nine months** of the completion of the initial phase of treatment.

If doses are missed so that the required numbers of doses for either standard or extended continuation phase treatments are not taken within the prescribed timeframes, refer to Figure 1, page 19 of this Standard to determine the appropriate action.

Resistance to INH or RIF

In either case, **ONLY** treatment by a **daily DOT** regimen is acceptable.

Resistance or Intolerance to INH

- Initial Phase – **a minimum of 40 doses** of rifampin (RIF), pyrazinamide (PZA) and ethambutol (EMB) are taken under daily DOT **within three months**. The minimum time required to complete this phase of treatment is two months.

- For patients with extensive disease – **a minimum of 40 doses** of a fluoroquinolone (preferably levofloxacin) by daily DOT may be advantageous during the initial phase of treatment

- Continuation Phase – an additional **minimum of 90 doses** of RIF, PZA and EMB taken by daily DOT **within six months** of completion of the initial phase of treatment. The minimum time required to complete this phase of treatment is four months.

Resistance or Intolerance to RIF

- Initial Phase – **a minimum of 40 doses** of INH, PZA, EMB and a fluoroquinolone (preferably levofloxacin) taken under daily DOT **within three months**. The minimum time required to complete this phase of treatment is two months.

- For patients with extensive disease – **a minimum of 40 doses** of an injectable agent (streptomycin or amikacin if the organism is resistant to streptomycin) may be advantageous during the initial phase of treatment.

- Continuation Phase – **a minimum of 220 to 350 doses** of INH, EMB and a fluoroquinolone (preferably levofloxacin) **taken by daily DOT within 12 to 18 months**. The minimum time required to complete this phase of treatment is 10 to 16 months.

Transition from Self-Administered Regimen to Directly Observed Therapy (DOT)

Patients not meeting the criteria for initial DOT (see page 2 of this Standard for a listing of patients requiring DOT), must be transitioned to DOT if any of the following occur:

1. Patient is repeatedly delinquent in picking up refills of self-administered medications, as defined by being greater than 7 days delinquent for two consecutive months (less than 80% adherent).

2. Patient is found to meet any of the criteria requiring initial DOT or requires incentives or enablers after self-administered treatment is prescribed.

3. Patient is restarted on anti-TB treatment after treatment interruption (see pages 11 and 12 of this Standard).

4. Patient experiences adverse effects to anti-TB medications.

5. Patient remains sputum culture positive after four months of treatment (see Managing Treatment Failure, pages 12 and 13 of this Standard).

6. Patient reverts to sputum culture positive from sputum culture negative while on self-administered treatment (disease reactivation).

7. Patient has a poor response to treatment on self-administered therapy.

8. Patient is under consideration for involuntary commitment but is currently on self-administered treatment (less restrictive alternative).

Managing Treatment Interruptions

Interruptions in the treatment of TB are common due to the extended duration of treatment and the false perception of cure prior to completing a therapeutic regimen. Health care providers are responsible for deciding whether to restart a complete course of treatment or to continue until completion of the prescribed number of total doses.

These decisions should be based on when the interruption occurred and the duration of the interruption. See Figure 1, Management of Treatment Interruptions (Initial & Continuation Phase), page 19 of this Standard.

<u>If the interruption occurs during the initial phase</u>, and the

1. Lapse is greater than or equal to 14 consecutive days – restart treatment from the beginning.

2. Lapse is less than 14 consecutive days – continue treatment to complete planned total number of doses (as long as all doses can be completed within three months).

If the patient is on self-administered therapy, it must be assumed that the patient missed 14 or more consecutive days of treatment during the first 30 days if the patient is 14 or more days delinquent in picking up the first refill. This must be assumed in the interest of the public health because it cannot be known if the doses missed were consecutive, only that 14 or more doses were missed. Since the second refill is not required prior to the completion of the initial phase, it cannot be known if additional doses were missed during the last 26 doses required in the initial phase of treatment without a pill count or other intervention. Such an intervention must be undertaken for patients on a self-administered treatment regimen.

If the interruption occurs during the continuation phase and the patient received

1. Greater than or equal to 80% of total required continuation phase doses and sputum was AFB smear negative on initial testing – additional treatment may not be necessary.

2. Greater than or equal to 80% of total required continuation phase doses and sputum was AFB smear positive on initial testing - continue therapy to complete the total number of planned doses.

3. Less than 80% of total required continuation phase doses and lapse is 90 consecutive days or more in duration – restart treatment from the beginning (including initial phase).

4. Less than 80% of total required continuation phase doses and lapse is less than 90 consecutive days in duration – continue therapy until all doses are completed (full course).

If the patient is on self-administered therapy, it must be assumed during the continuation phase of treatment that the patient has missed 90 consecutive days of prescribed treatment if the patient is 90 days delinquent in picking up ANY subsequent refills or if the patient is lost to medical supervision for 90 or more days.

If therapy is interrupted for 90 or more consecutive days during the continuation phase of treatment, see Figure 1, page 19 of this Standard for guidance.

Involuntary commitment or other less restrictive measure (directly observed therapy) must be prescribed for any patient on self-administered treatment if he or she falls below 80% adherence with prescribed therapy during any 30 day period. The NJDHSS TB Program must be notified to assist in determining the necessity or appropriateness of seeking a commitment order from the Superior Court.

Managing Treatment Failure

Patients whose sputum cultures remain positive after four months of appropriate therapy are considered to have failed treatment and must be referred for expert consultation.

Treatment failure is defined as continued or recurrently positive cultures in a patient receiving appropriate chemotherapy. Among patients with drug-susceptible pulmonary tuberculosis, even with extensive lung cavitation, 90-95% will be culture-negative after three months of treatment with a regimen that contains INH and RIF. During this time the vast majority of patients show clinical improvement, including defervescence, reduced cough and weight gain. Thus, patients with persistently positive cultures after four months of chemotherapy, with or

without on-going symptoms, should be evaluated carefully to attempt to identify the cause of the delayed response.

Definition: Positive cultures for *M.tb* after four months of continuous treatment.

Intervention: Repeat drug susceptibility testing immediately. Laboratory testing to determine absorption levels for drugs in the blood may also be required. Adjust treatment regimen as necessary after consultation with an expert in the management of treatment failure (see Standard # 7: Consultation, page 1 of 2).

Rule of Thumb: Never add a single drug to a failing TB treatment regimen.

Managing Adverse Reactions

Detection: All patients on treatment with anti-TB medications must be monitored for the emergence of adverse reactions monthly while on treatment.

Intervention: A physician evaluation is required for patients experiencing adverse reactions. Stop treatment pending physician evaluation. Consult with an expert on the management of adverse reactions and the reintroduction of anti-TB medications if they must be discontinued due to adverse reactions (see Standard # 7: Consultation, page 1 of 2).

Rule of Thumb: If medications are discontinued, drugs should be reintroduced one at a time, after consultation with an expert in the management of adverse reactions.

Standard Use of DOT until Discharge and/or Release and/or Completion

Justification: Knowing effective treatment is taken as prescribed may reduce the duration of the infectious period for patients with pulmonary or laryngeal TB, therefore reducing the risk of transmission in institutions and other congregate settings. In addition, these environments make it practical to utilize DOT to treat patients with active TB disease at any anatomical site.

Facilities requiring utilization of DOT to treat inmates, patients or residents with active TB disease:

1. Local jails
2. State prisons
3. Hospitals
4. Nursing homes
5. Residential/inpatient substance abuse treatment facilities
6. Residential/inpatient mental health treatment facilities
7. Other congregate living facilities

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Treatment of Latent TB Infection (LTBI)

Justification: To prevent persons with LTBI from progressing to active TB disease. Special emphasis is placed on (1) infected contacts of verified smear positive or cavitary pulmonary TB cases known or suspected to have been recently infected, (2) Class IV TB (old, untreated TB disease, not currently active) and (3) persons with co-existing LTBI and HIV infection or AIDS. These groups are at greatest risk of progressing to active TB disease.

The use of INH to treat LTBI is **contraindicated** for individuals who have experienced adverse reactions to INH in the past or those with hepatitis and/or end-stage liver disease.

Use of DOT to Treat LTBI in Infants and Young Children

Infants and young children are extremely vulnerable to rapid progression to active disease if infected. DOT can relieve family members of the often trying task of medicating an infant or young child. Family members are notoriously poor at administering medications to infants and young children due to their emotional attachment and the child's excessive protest, refusal or inability to take medications as issued by the pharmacy. Family members are notorious for not reporting such difficulty to health officials, leaving these infants and children at risk. Health care workers are often more successful in this endeavor than family members because they are emotionally detached, less susceptible to manipulation and can work with the family to determine enticements and/or special preparations that will make the medications more palatable or acceptable to the children. Health care workers more reliably report failure in the ability to medicate so additional intervention can be planned and implemented. If, however, DOT is prescribed to treat LTBI and a family member is successful in providing the medication, the health care worker may simply observe the family member giving the medication to the infant or young child to meet the condition and intention of DOT.

Appropriate Dosing of INH or RIF for Treatment of LTBI

See Table 1 on page 17 of this Standard. All dosages listed in Table 1 are for medications prescribed to be taken daily.

Table 1 lists appropriate dosages in a range of mg/kg for children/adolescents and adults. Maximum daily dosages are listed for both INH and RIF for both groups and coincides with daily DOT dosing on Table 3 on page 18 of this Standard.

Standard Adult Treatment Regimen

Treatment for patients with LTBI must consist of a minimum **270 doses of INH** taken **within**

12 months. The minimum treatment time required to ingest this number of doses is nine (9) months.

See Table #1 on page 17 of this Standard for appropriate daily dosages of INH by weight (mg/kg) for all patients regardless of age.

Treatment During the Contact's "Window" Period

The "window" period refers to the eight week period between an initial negative tuberculin skin test result for a contact and the second test administered a minimum of eight weeks later (see Standard #1: Diagnosis of Latent TB Infection, page 3 of 7 for clarification).

In this eight week "window" period, only contacts who are children <5 years of age AND adult contacts with HIV infection are recommended for treatment. If the second test is negative, treatment must be stopped.

Standard Treatment Regimen for Contacts

For infants and children < 5 years of age who are contacts to pulmonary or laryngeal TB, DOT is required.

Contacts to pan-sensitive TB cases must be treated with a minimum **270 doses of INH** taken **within 12 months**. The minimum treatment time required to ingest this number of doses is nine (9) months.

If infection with an organism **resistant to only INH** is suspected, an acceptable regimen is **120 doses of RIF** taken **within six months** to ensure adequate treatment. The minimum time required to ingest the appropriate number of doses is four (4) months.

If infection with an organism **resistant to only RIF** is suspected, **270 doses of INH** must be taken **within 12 months** to ensure adequate treatment. The minimum time required to ingest the appropriate number of doses is nine (9) months.

If infection with an organism **resistant to both INH and RIF** is suspected, consult an expert in the management of contacts to multi-drug resistant (MDR) TB (see Standard # 7: Consultation, page 1 of 2).

Standard Treatment Regimen for HIV Co-infected LTBI

Treatment of LTBI in persons with HIV infection requires **270 doses of INH** taken **within 12 months** to ensure adequate treatment. The minimum treatment time required to ingest this

number of doses is nine (9) months. This treatment regimen is most appropriate for HIV co-infected contacts.

A RIF treatment regimen is not the first choice for HIV co-infected individuals and should be used with caution in persons who are taking either protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI) due to drug interactions. See MMWR June 9, 2000; Vol. 49, No. RR-6; pages 1-54 "Targeted Testing and Treatment of Latent Tuberculosis Infection" for further reference.

Standard Treatment Regimen for Children

For infants and children < 5 years of age who are contacts to pulmonary or laryngeal TB, DOT is required.

LTBI in children requires **270 doses of INH** ingested **within 12 months** to ensure adequate treatment. The minimum time required to ingest this number of doses is nine (9) months.

Standard Treatment Regimen for Pregnant Women

Treatment with INH for LTBI is **NOT** contraindicated for pregnant women.

Treatment of pregnant women with LTBI must consist of **270 doses of INH** taken **within 12 months**. The minimum time required to ingest this number of doses is nine (9) months.

LTBI Treatment Interruptions

A treatment interruption is defined as a **continuous lapse in therapy of at least 14 days**. In the interest of adequate treatment, it must be assumed that the doses missed were consecutive if the patient is delinquent by 14 days or more in picking up refill medication if on a self-administered treatment regimen.

When the interruption of treatment for LTBI is **within the first three months** of initiating therapy, treatment must be **restarted from the beginning**.

If the interruption occurs **after the third month of treatment**, therapy should **resume completing the originally prescribed number of doses**.

When therapy is restored after an interruption of **more than two months, a clinical assessment to rule out active TB disease is indicated**, such an assessment is essential if symptoms exist and are consistent with TB.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 6: Treatment

Table #1: Appropriate Daily Dosing for TB Cases and Suspects on Self-Administered Therapy		
	Dosages in mg/kg and maximum dosage (in parenthesis)	
Medication	**Child/Adolescent**	**Adults**
Isoniazid (INH)	10-15 mg/kg (300mg)	5 mg/kg (300mg)
**Rifampin (RIF)	10-20 mg/kg (600mg)	10 mg/kg (600 mg)
Pyrazinamide (PZA)	15-30 mg/kg (2.0g)	See Table #2
Ethambutol (EMB)	15-20 mg/kg (1.0g)	See Table #2

** Directly observed therapy is the Standard of Care for all TB cases and suspects with HIV-infection or AIDS. The rifampin dosage may need to be adjusted or rifabutin considered as an alternative to rifampin to minimize drug interactions for HIV seropositives on concurrent treatment with protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI).

Table #2: Adult Daily Dosage for Pyrazinamide & Ethambutol (Self-Administered Therapy)			
Medication	**Whole Tablet Dosage and Dosage Range (mg/kg) by Weight (kg)**		
	40-55 kg	**56-75 kg**	**76-90 kg**
Pyrazinamide	1,000 mg (18.2 - 25.0)	1,500 mg (20.0 - 26.8)	2,000 mg (22.2 - 26.3)
Ethambutol	800 mg (14.5 - 20.0)	1,200 mg (16.0 - 21.4)	1,600 mg (17.8 - 21.1)

Maximum dose in 76-90 kg column is maximum dose regardless of weight.

Table #3: Appropriate Dosing for TB Cases and Suspects on Directly Observed Therapy				
	Dosages in mg/kg and maximum dosage (in parenthesis)			
	Daily DOT		Two or Three* Times Weekly DOT	
Medications	Child/Adolescent	Adults	Child/Adolescent	Adults
Isoniazid (INH)	10-15 mg/kg (300mg)	5 mg/kg (300mg)	20-30 mg/kg (900mg)	15 mg/kg (900mg)
**Rifampin (RIF)	10-20 mg/kg (600mg)	10 mg/kg (600mg)	10-20 mg/kg (600mg)	10 mg/kg (600mg)
Pyrazinamide (PZA)	15-30 mg/kg (2g)	See Table #4	50 mg/kg (2g)	See Table #4
Ethambutol (EMB)	15-20 mg/kg (1.0g)	See Table #5	50 mg/kg (2.5g)	See Table #5

* Three times weekly DOT should not be used in children
** Rifampin dosage may need to be adjusted or rifabutin considered as an alternative to rifampin to minimize drug interactions for the HIV-infected treatment with protease inhibitors or non-nucleoside reverse transcriptase inhibitors (NNRTI).

Table #4: Adult Dosage for Pyrazinamide by Frequency of Directly Observed Therapy			
	Whole Tablet Dosage and Dosage Range (mg/kg) by Weight (kg)		
Frequency	40-55 kg	56-75 kg	76-90 kg
Daily, max dose (mg/kg)	1,000 mg (18.2 - 25.0)	1,500 mg (20.0 - 26.8)	2,000 mg (22.2 - 26.3)
Twice weekly, max dose (mg/kg)	2,000 mg (36.4 - 50.0)	3,000 mg (40.0 - 53.6)	4,000 mg (44.4 - 52.6)
Three times weekly, max dose (mg/kg)	1,500 mg (27.3 – 37.5)	2,500 mg (33.3 – 44.6)	3,000 mg (33.3 – 39.5)

Maximum dose in 76-90 kg column is maximum dose regardless of weight.

Table #5: Adult Dosage for Ethambutol by Frequency of Directly Observed Therapy			
	Whole Tablet Dosage and Dosage Range (mg/kg) by Weight (kg)		
Frequency	40-55 kg	56-75 kg	76-90 kg
Daily, max dose (mg/kg)	800 mg (14.5 - 20.0)	1,200 (16.0 - 21.4)	1,600 (17.8 - 21.1)
Twice weely, max dose (mg/kg)	2,000 mg (36.4 - 50.0)	2,800 mg (37.3 - 50.0)	4,000 mg (44.4 - 52.6)
Three times weekly, max dose (mg/kg)	1,200 mg (21.8 – 30.0)	2,000 mg (26.7 – 35.7)	2,400 mg (26.7 – 31.6)

Maximum dose in 76-90 kg column is maximum dose regardless of weight.

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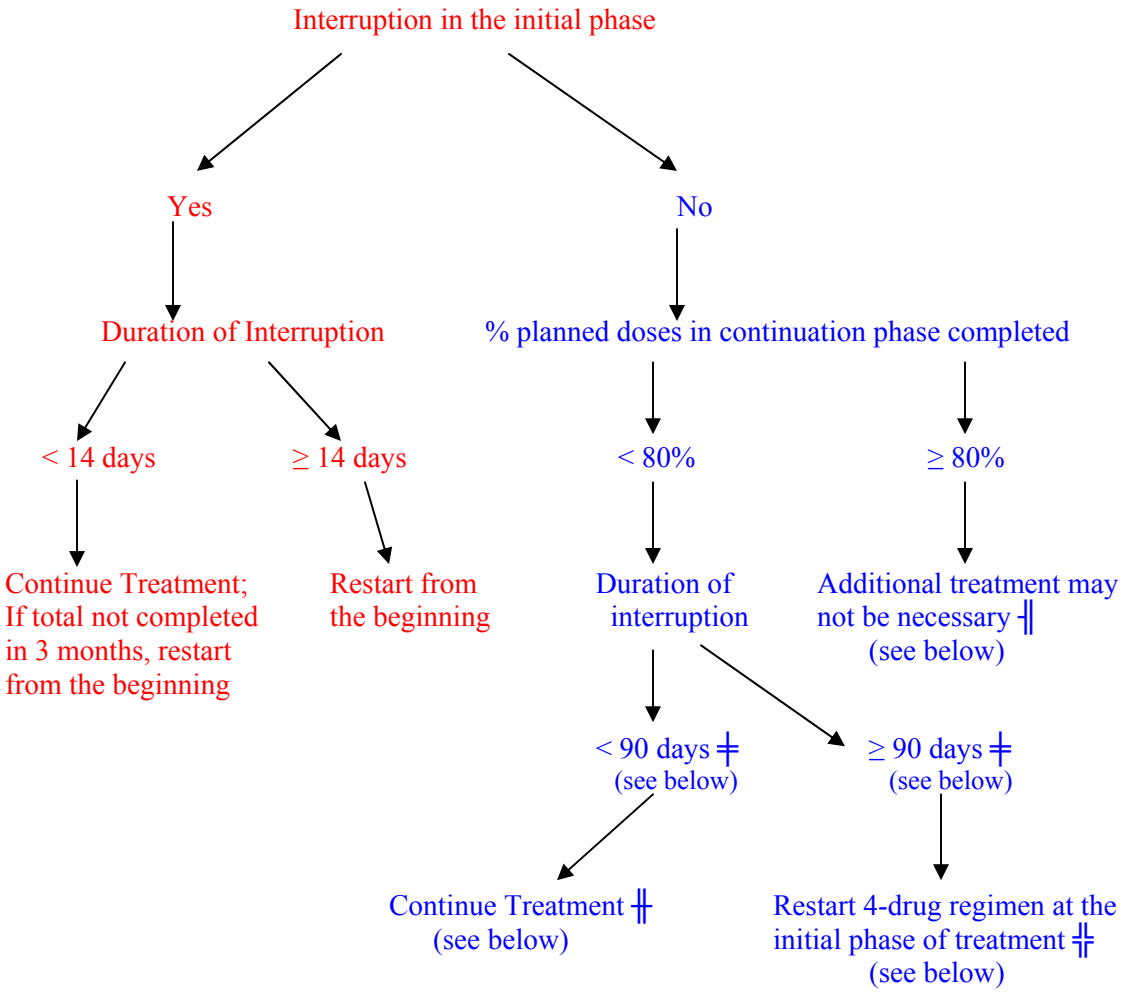
Figure 1: Management of Treatment Interruptions (Initial & Continuation Phase)



‖ Patients who were initially AFB smear-positive should receive additional therapy (see page 12 of this Standard)

╪ Repeat sputum smears & cultures (if positive, check drug susceptibility results). Start DOT if not already being used.

╫ If sputum smear and culture are negative, continue treatment to complete a total of nine (9) months. If smear is positive, restart initial 4-drug regimen. If culture is positive, treatment must be restarted from the beginning. If drug susceptibility results identify resistance, seek expert medical consultation for appropriate treatment.

╬ If sputum culture is negative, consider stopping therapy when or if patient has received a total of nine (9) months of treatment.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 7: Consultation

Justification: Although New Jersey ranks high in TB incidence among the fifty states, most areas of the state experience relatively low incidence annually. It is extremely difficult for physicians to encounter enough TB disease to become expert in its management. This issue is compounded when the treatment becomes complicated, requiring a deviation from standard treatment regimens and durations of treatment required to facilitate cure or when issues such as patient adherence, adverse reactions to anti-TB medications, treatment failure and/or disease reactivation arise. In these instances, those physicians and nurses that manage a significant burden of the TB in New Jersey are a valuable consultation resource to ensure that the highest quality of care is received, regardless of the provider.

Medical Consultation

Medical consultation with experienced physicians serving on the New Jersey Department of Health and Senior Services (NJDHSS) TB Medical Advisory Board is required in the following circumstances:

1. Multi-drug resistant (MDR) TB: documented resistance to both isoniazid (INH) and rifampin (RIF).

2. Co-existing HIV infection or AIDS and concurrently treated with protease inhibitors and/or non-nucleoside reverse transcriptase inhibitors (NNRTI).

3. Initial treatment or re-introduction of anti-TB treatment for individuals with AST and/or ALT:

    - Three times the upper limit of normal and symptomatic for liver disease.
    - Five times the upper limit of normal and asymptomatic for liver disease.

4. Anticipated prescription of any second-line anti-TB drugs.

5. Adverse effects of or intolerance to medications, requiring a change in the treatment regimen.

6. Persistently positive sputum cultures four months after initiation of treatment (treatment failure).

7. Reversion from negative sputum cultures to positive sputum cultures while on treatment or after previous treatment was completed (disease reactivation).

8. Poor response to treatment on a standard TB treatment regimen.

New Jersey Department of Health and Senior Services
Standards of Care for Tuberculosis Disease and Latent TB Infection
Standard # 7: Consultation

Referral Process

The NJDHSS TB Program staff will facilitate requests for medical consultation from providers throughout New Jersey. These services can be accessed by dialing the NJDHSS TB Program at (609) 588-7522.

Consultations may be verbal and informal or formal including a review of the medical records and/or chest radiographs of the patient in question.

If any of the situations requiring consultation are discovered in the course of investigation of a report of TB by the NJDHSS TB Program, the TB Nurse Consultant will contact the provider to discuss the case and arrange a consultation.

Consultants

Requests or referrals for consultation are forwarded to members of the NJDHSS TB Medical Advisory Board. These physicians routinely evaluate and treat more patients with TB than any other providers in New Jersey. They have proven their effectiveness in the medical management of complicated cases. Pulmonary physicians and infectious disease specialists staff this Board and specialists in both pediatric and geriatric medicine are also represented. These consultants include:

Dr. Reynard McDonald, UMDNJ University Hospital (Geriatric TB)
Dr. George McSherry, UMDNJ University Hospital (Pediatric TB)
Dr. Alfred Lardizabol, UMDNJ University Hospital
Dr. Henry Fraimow, Cooper University Hospital
Dr. Steven Williams, ID Care, Inc.
Dr. Lisa Pittarelli, ID Care, Inc.
Dr. Aman Vazir, St. Joseph's Hospital