

Latent Tuberculosis Infection: A Guide for San Francisco Providers

Prepared by
Tuberculosis Control Section
San Francisco Department of Public Health

March 2003

This document was adapted (with permission) from *Latent Tuberculosis Infection: A Guide for Massachusetts Providers* prepared by the Medical Advisory Committee for the Elimination of Tuberculosis (MACET), November 2000.

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Introduction

These guidelines were developed for primary care physicians and staff associated with community clinics and managed care organizations in testing for and treating latent tuberculosis infection. In addition, a step-by-step quantitative approach to evaluating the effectiveness of a program for testing and treating latent tuberculosis infection is included.

The recommendations on testing for and treating latent tuberculosis infection in Section I are based on local epidemiology, program experience, current National, State and local guidelines developed by the Centers for Disease Prevention and Control (CDC), the American Thoracic Society, the California TB Controllers Association (CTCA), the California Department of Health Services (CDHS), and the San Francisco TB Control Section (SFDPH).

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Latent Tuberculosis Infection: A Guide for San Francisco Providers

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I. Testing for Latent TB Infection

Question 1: What is latent tuberculosis infection (LTBI)?

Latent tuberculosis infection is an asymptomatic state in persons who are infected with *Mycobacterium tuberculosis*. LTBI is detected as a result of skin testing or quantiFERON blood test among persons with risk factors for TB, such as public health investigations of contacts of infectious TB cases. For persons with untreated latent TB infection and intact immunity, the estimated risk of developing symptomatic tuberculosis disease is 5% to 10% over a lifetime, with about half of that risk occurring during the first year or two after infection. For persons who are immunocompromised by HIV co-infection, the estimated risk of developing disease increases to 5% to 10% per year.

Active TB disease is not often discovered in asymptomatic persons by tuberculin skin testing. However, finding LTBI provides an opportunity to treat and prevent progression to active disease (reactivation). Studies have shown that TB reactivation can be prevented with 60%-80% efficacy. Because of the high risk of TB prevalence in San Francisco, treatment of LTBI is considered an important public health strategy to prevent future cases in generations to come.

Question 2: What is the best test for LTBI, and how should test results be recorded?

Tuberculin skin testing with intermediate strength (5 TU) purified protein derivative (PPD), administered by the Mantoux intradermal technique (*not by multiple puncture devices, such as Tine® or Mono-Vacc®*), is the most readily available test for detecting LTBI. The test is administered by injecting 0.1 ml (5 TU) Tubersol® intradermally (not subcutaneously) into the ventral surface of the forearm. Forty-eight to 72 hours after the test is administered, the diameter of palpable or visible induration (raised swelling) should be measured transverse to the long axis of the arm and recorded in mm.¹ Note: *redness without induration should be ignored*.

The quantiFERON TB test is a whole blood assay for diagnosing TB infection. A minimum of 5cc of blood is required and must be processed within 12 hours after collection. The blood sample is mixed with 3 antigens (PPD, avian sensitin and a mitogen control). Interferon gamma responses are compared between antigens to determine a positive or negative result. Advantages of this test include, single patient visit, less subject to reader bias and interpretive error and automated lab results. Current CDC guidelines call for conservative use of this test until more research data is available.

Question 3: Who should be tested for LTBI in San Francisco?

¹ Two reading methods have been recommended. With one method, the arm is positioned so that a light shines tangentially over the skin reaction, highlighting any induration. The lateral edges of the visible induration are marked with a pen and measured with a millimeter (mm) ruler. With the second method, the lateral edges of the induration are determined by moving a ballpoint pen across the arm from each side until resistance is met. A mark is made and the diameter is measured with a mm ruler. With either method, only the measurement transverse to the long axis of the arm (not two dimensions) is recorded.

Tuberculin skin testing should be reserved for persons who meet some or all of the following criteria:

- Are at high risk of TB infection (see Question 4).
- If infected, are at high risk of developing active TB.
- If infected, would be a candidate for treatment to prevent active TB.
- If they developed active TB, would place vulnerable contacts at risk.

Question 4: Who is at high risk of TB in San Francisco today? (*Please also refer to Appendix 3 SF guideline on “Who Should Be Screened”*)

High-risk persons in San Francisco who should have a TB test include:

- Close contacts of known active pulmonary TB cases, or persons working or residing in congregate settings (shelters, jails, and some health care facilities) where known TB cases exist and others suspected or likely.
- Foreign-born persons from high-prevalence countries, especially if they are newcomers to the US (<5 yrs) and/or have additional medical or population risk factors.²
- Persons with fibrotic abnormalities on chest x-ray³ consistent with previous, untreated TB.
- Persons with clinical conditions associated with progression to active TB, such as HIV infection, silicosis, diabetes, chronic renal failure/hemodialysis, gastrectomy, jejunioileal bypass, solid organ transplantation (renal, cardiac), carcinoma of the head and neck, and being more than 15% underweight. Note: *Some of these are common conditions. Testing should be reserved for persons with these medical conditions who are also likely to have been exposed to TB infection.*
- Injection drug users.
- Homeless persons.
- Children who meet these criteria or who have been in regular contact with high-risk adults are also considered at risk.

Note: *A patient questionnaire and physician assessment form for use in clinical settings to help determine a patient’s risk of tuberculosis and the need for a tuberculosis skin test can be found in Appendix 1 and 2, respectively).*

² High-prevalence places from which San Francisco TB cases have come in recent years include, but are not limited to, China, Philippines, Southeast Asia, India, Mexico, Central America, and South America. TB case rates have doubled in the former Soviet Union in the past 10 years, and an increasing number of cases among recent arrivals is expected.

³ Prior tuberculosis disease can have a variety of nonspecific appearances. However, radiographically dense, upper lobe linear or nodular changes are characteristic. Hilar, lower lobe, and pleural densities are also seen, but are less specific for TB. For example, in the Ohio River Valley, hilar calcifications are more likely to represent previous histoplasmosis than TB. Apical pleural thickening without parenchymal scarring is specifically not associated with TB.

Question 5: Should persons who have been vaccinated with BCG (*bacille Calmette-Guerin*) be tested for LTBI, and if tested, how should the results be interpreted?

BCG is a vaccine administered to more than 80% of children in the world as part of the Extended Program on Immunization. The vaccine is given primarily in countries with rates of TB infection much higher than those found in the US or Western Europe, and many persons who have previously received BCG also may have TB infection because BCG does not prevent TB infection. Efficacy of the BCG vaccine is very poor and estimated at 50% (Colditz et al., JAMA 3/94), although the vaccine does decrease TB death and disease dissemination (such as meningitis) by 75% in children. A single BCG at birth should not result in a positive test unless the test was administered within the past year. Persons who have received BCG should be tested for LTBI as otherwise indicated. Induration considered positive (using appropriate criteria – see Question 7) should be assumed to be due to TB infection, not BCG, and treatment should be recommended, unless contraindicated. BCG is not a contraindication to TB testing by skin test or quantiFERON. Consult local TB experts at SF TB Control (206-3387) if interpretation is confusing.

Question 6: Which persons, if they develop active TB, pose an especially high risk to the community?

Persons with active TB who especially threaten public health include anyone working or living in a congregate setting with especially vulnerable persons, such as HIV/AIDS, cancer and dialysis patients, the elderly, homeless persons, newborn babies, and children 5 years of age and under.

Question 7: What tuberculin skin test (PPD) induration diameter is considered indicative of TB infection?

Two cut-offs for a positive PPD are used in California: ≥ 5 mm or ≥ 10 mm, depending on the risk of TB infection or disease in the individual or population being tested.

- **5 mm or greater PPD induration:** is considered positive *only* in persons at the highest risk for infection or active disease. In this group, detecting all TB infections is considered more important than the risk of including some false positive reactions. Four high-risk subgroups are included:
 - *Close contacts* of active pulmonary cases.
 - *HIV-immunocompromised persons* (the risk of progression to active TB, if TB infected, is 5% to 10% per year).
 - Persons with *fibrotic chest x-ray findings* consistent with old TB.
 - Other immunocompromised individuals such as those with hematological malignancies or immunosuppressive treatment.
- **10 mm or greater PPD induration:** Such tests are considered positive for all others. Included in this group are:
 - *Foreign-born persons* from high-prevalence countries (see footnote 2).

- *Disadvantaged low-income persons* (malnutrition, crowded housing, medically underserved).
- Persons *over age 70 and under age 4*.
- Persons residing or having resided for extended periods in *congregate settings* known to be associated with TB transmission, such as SROs, shelters, jails, prisons, and detoxification or drug-rehabilitation centers and renal dialysis units.
- Injection drug users.
- *Health care workers and other workers* in facilities serving populations at increased risk of unsuspected TB disease, or engaged in high-risk procedures such as bronchoscopy, sputum induction, autopsies, mycobacteriology laboratory work, or work in homeless shelters.
- Other high-risk professions, such as mortuary work.

Note: *Out of date local and State regulations require TB screening of food handlers, teachers, and school entrants of the San Francisco Unified School District. Many of these individuals are not at increased risk but are required by law to be screened for TB.*

Question 8: Who should be retested for LTBI in San Francisco and at what frequency?

Annual or regular testing should only be done if there is an ongoing risk of TB infection or exposure. Ideally, an annual TB symptom review and infection risk assessment should be done before deciding on repeating the PPD. However, from a practical standpoint it may be better to decide on the frequency of repeat testing by clinic and per clinic demographics, census tract and general TB risk factors of the population served. The clinic director and nurse manager should develop the best policy for their patient population. Risk factors for ongoing exposure include the following:

- Homelessness
- HIV infected persons with population risk factors for TB
- Congregate living or adult day care arrangement (long term care, jail, dialysis units, substance abuse treatment, HIV housing, mental health facilities and halfway homes, etc.)
- Health care workers and individuals working with the groups previously listed
- Individuals living and working in the Tenderloin/SoMkt and Chinatown areas

Question 9: Can repeat skin testing for TB cause a positive reaction in an uninfected person?

No, PPD contains too little TB antigen to cause hypersensitivity to future skin testing by itself. However, waning hypersensitivity due to past infection to TB, may cause a “false negative” when first tested. A repeat test can be *boosted* by a subsequent PPD test, resulting in induration indicative of true infection. The repeat PPD may appear to have *converted* from negative to positive. These reactions reflect true hypersensitivity, possibly due to TB infection, but not recent infection. In addition to avoiding repeat TB testing, unless indicated, using a *2-step baseline skin test* (see Question 10) and using a *change in induration of 10 mm as criteria for conversion*, are both recommendations intended to minimize false skin test conversions.

Question 10: What is 2-step PPD testing, and when is it indicated?

2-step testing should be done at the beginning of the series of repeat or regular ongoing testing to prevent the misinterpretation of boosted responses as PPD conversions (new TB infection). It should be done if the individual has not had a PPD in the past 1-2 years. The 2nd test should always be done between 1 and 4 weeks after the first test placed.

2-step testing may also be advised for individuals over 55 years of age who have medical and population risk factors for TB disease.

Note: *Using the quantiFERON blood test eliminates the need for 2-step testing and will not result in boosted reactions. SF TB Control recommends its use when serial testing is needed.*

Question 11: Can a PPD test be read after 72 hours? Can a PPD be placed on a Thursday and read on a Monday at 96 hours?

Yes, a PPD can be read up to a week after placement if the reaction is positive. However, a negative result should not be read after 72 – 96 hours. Although the practice of placing PPDs on a Thursday and reading it on Monday (96 hours) strays from the State and CDC guidelines, local SF experience and data show that reading the PPD at 96 hours will miss less than 3% of PPD positives. Therefore, SF TB Control will not frown upon this practice since it is a practical approach for clinics that are closed on the weekend. This will allow placement of PPDs 5 rather than 4 days a week.

II. Treatment of Latent TB Infection

Question 12: Who should be treated for latent TB infection?

(Please also refer to Appendix 4: SF LTBI Treatment Guidelines)

Anyone at high risk for TB who has a positive test for latent infection is a candidate for treatment, if they also fulfill the following criteria:

- No symptoms, signs, or radiographic evidence of active TB.⁴ ACTIVE DISEASE MUST BE RULED OUT prior to treatment by chest x-ray and medical evaluation. In addition, asymptomatic patients with fibrotic abnormalities on chest x-rays need 3 negative sputum cultures to rule out TB.
- Willing to complete a full course of therapy (treatment of LTBI is always optional for the patient, even if strongly recommended).
- Available to be clinically monitored during the full course of treatment (that is, not about to leave the country).

⁴ In the absence of symptoms suggesting pulmonary or extrapulmonary TB, only the chest x-ray should be part of a clinical work-up for LTBI. Other tests, such as sputum or urine culture, have an extremely small yield, and are subject to false-positive results if done routinely. The erythrocyte sedimentation rate (ESR) is neither sensitive nor specific for active TB.

- No medical contraindications to treatment, such as severe liver disease, drug hypersensitivity, or medical conditions that make adherence unlikely, such as mental illness or alcoholism (Where available, directly observed treatment can increase adherence for high-risk persons).

Question 13: What are the currently recommended treatments for LTBI in San Francisco?

INH daily or twice-weekly for 6 months in adults and children ≥ 15 yrs of age

- Considered the optimal treatment in terms of program efficacy and treatment completion.
- Short duration encourages initial acceptance and adherence to complete treatment.
- The twice-weekly regimen must be supervised by SF TB Control or by a provider using directly observed therapy.

INH daily or twice-weekly for 9 months

- Recommended for children⁵ <15 years and adults, with HIV co-infection and fibrotic chest x-ray abnormalities suggesting old TB.
- The twice-weekly regimen must be done using directly observed therapy.

INH/Rifampin (RIF) daily for 4 months

- Considered the treatment of choice for individuals with fibrotic chest x-ray abnormalities suggesting old TB.

RIF/PZA for 2 months

- May be prescribed to HIV-infected individuals (see note below).
- Rifabutin may be substituted for Rifampin if the HIV patient is on protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Note: SF TB Control does not advocate the use of the 2-month RIF/PZA treatment regimen in any group other than HIV infected individuals. SF TB Control treatment guidelines differ from CDC guidelines and were developed by expert consensus based on the local epidemiology, treatment outcomes and program experience particular to the city and county of San Francisco.

Question 14: How do I decide which treatment to choose for my patient?

Choosing a treatment is based on several considerations, such as

- **Efficacy:** All 4 treatments are considered efficacious, although the 9-month INH and 2-month RMP/PZA regimens are considered more efficacious than the 6-month INH treatment or the 4-month RMP regimen alone.

⁵ Due to the absence of children in clinical trials of shorter, Rifampin-based regimens, only INH for 9 months is recommended for children with LTBI.

- **Medical considerations:**
 - Active liver disease: postpone therapy or consider RIF alone.
 - Essential medications that interact with RIF (including HIV therapy) – avoid RIF or reconsider treatment.
 - Birth control pills and implants – avoid rifampin or find alternative birth control.
 - Pregnancy – INH and rifampin are considered relatively safe (category C) during pregnancy, when necessary, but are generally reserved for close contacts and HIV-infected persons; B6 is recommended with INH. PZA is contraindicated.
 - Breast feeding – not a contraindication to therapy, but some patients prefer to wait until completion of breastfeeding.
 - Daily alcohol use.
- **Logistical considerations:** Persons who will be moving from the area or who are in a supervised setting for a limited duration (e.g., detox, rehabilitation, prison) may complete a shorter regimen. Persons who can be supervised over a longer period (e.g., in prisons) may be given the 9-month INH treatment without fear of non-adherence.
- **Age:** Risk of INH-induced hepatitis increases with age. Previous ATS/CDC recommendations limited INH to persons under age 35 years, over 35 years only with other risk factors such as recent conversion, HIV co-infection, or x-ray abnormalities suggesting old TB. The current ATS/CDC recommendations assume that because only high-risk persons are tested, INH is warranted at any age.
- **Cost:** INH is much less expensive than RIF/PZA or RIF alone. Drug intolerance, drug interactions, and laboratory tests are among the other costs to be considered – if cost is an issue. In San Francisco, treatment for LTBI is available free of charge through the DPH TB Clinic located on the San Francisco General Hospital campus.
- **Patient choice:** In the absence of factors dictating one regimen or another, patients often have strong opinions about taking one INH pill daily for 6 or 9 months, 2 RIF capsules plus one INH pill daily or 2 rifamate capsules (contains both INH and rifampin) daily for 4 months.

Question 15: What are the appropriate dosages for the 4 LTBI treatment options, and how should they be prescribed?

The dosages are listed below. (Please also refer to Appendix 4: SF LTBI Treatment Guidelines)

- **INH: (50, 100, 300 mg pills)**
 - Adults: 300 mg daily, or 900 mg twice-weekly.
 - Children: 10-20 mg/kg up to 300 mg daily, or 20-40 mg/kg twice-weekly up to 900 mg twice-weekly.
- **Rifampin: (150, 300 mg pills)** 600 mg daily, 600 mg twice-weekly (unlike twice-weekly INH, dose is not increased).
- **Rifabutin:**¹³ **(150 mg pills)** 300 mg daily, 300 mg twice-weekly (rifabutin daily or 2/wk with dose adjustments according to the type of PI or NNRTI).
- **Pyrazinamide: (500 mg pills)** 15-20 mg/kg daily, up to 2 gm

¹³ Rifabutin should be substituted for rifampin in HIV/AIDS patients who are being treated with anti-retroviral therapy (see Question 16).

Question 16: How should I monitor safety and adherence during LTBI treatment? (Please also refer to Appendix 2: SF LTBI Treatment Guidelines. A summary table is provided on the last page)

Monitoring treatment for LTBI serves 2 purposes – to encourage and monitor adherence, and the early detection of side effects. Recommended monitoring varies with the 4 regimens. No more than a month supply should be dispensed at a time and monthly visits are recommended for mono-INH and INH/RIF regimens.

- **INH:** Possible complications of INH therapy include the following.
Hepatitis. INH induced hepatitis occurs with increasing frequency with age. However in over 11,000 patients receiving INH in a public health clinic, Nolan reported a very low hepatitis rate of only 0.1% (JAMA 1999 281; 1014-18). Only clinical monitoring for symptoms (fatigue, malaise, and nausea) was used on a monthly basis. All confirmed cases of hepatitis recovered with prompt cessation of the drug.
 - Most patients can be followed without baseline or routine follow-up liver function tests *if* they can be closely followed clinically and questioned at least monthly about symptoms.
 - Indications for baseline and periodic biochemical monitoring include patients with known abnormal liver function or known liver disease, the concurrent use of other hepatotoxic agents and chronic alcohol use.
 - PATIENTS MUST BE *instructed to stop INH and call their provider IMMEDIATELY for further instructions if symptoms of anorexia, nausea and fatigue develop.* (The rare fatalities associated with INH hepatitis have all been associated with continued INH ingestion despite hepatitis symptoms.) The provider should discontinue INH if transaminase elevations exceed 3 – 5 times normal in the absence of symptoms (the higher threshold should be used for HIV patients).

Peripheral neuritis. Uncommon, even among patients not receiving pyridoxine (vitamin B6). However, B6, 10-50 mg daily is recommended for the elderly, diabetics, HIV+ patients, individuals with neurologic disease, poor nutrition (e.g., alcoholics) or with increased nutritional needs (e.g., pregnant or breastfeeding women).

- **Rifampin (RIF):** Although rifamycins have been associated with a wide range of side effects, including hepatocellular or cholestatic hepatitis, neutropenia, and a flu-like syndrome, complications are not common. Compared to INH, RIF (when used alone) causes much less hepatitis and has the best safety profile of the major anti-tuberculous agents. However, deaths and severe hepatitis have been reported in patients using the 2-month RIF/PZA regimen and therefore more frequent clinical and biochemical monitoring is recommended when using this regimen. Other side effects of RIF and rifabutin include:
 - Discoloration of the urine, sweat and tears (orange-red color)

- Drug-drug interaction caused by the induction of hepatic microsomal enzymes (RIF effect >> rifabutin). Accelerated metabolism is seen with other important drugs, including methadone, birth control pills and implants, coumadin, some antihypertensives, protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and many others.
- Baseline CBC, liver function tests and uric acid (if on PZA concurrently) is recommended for persons on RIF or rifabutin when other TB drugs are used concurrently (e.g. INH or PZA). Monthly clinical monitoring is recommended for patients on the 4-month RIF/INH regimen, whereas clinical and biochemical monitoring (AST and bilirubin) at 2, 4, 6 and 8 weeks is recommended for patients on the 2-month RIF/PZA regimen.

Question 17: How much treatment of LTBI can be missed before the patient must start over?

This question applies to all 4 regimens, but is of greatest concern with the 2-month regimen. Ideally, patients should take the equivalent of the entire treatment course even if additional time is needed due to interruptions. Some clinical judgment is needed, since clinical trial data is not available to support the efficacy of the countless possible patterns of drug ingestion. For the 2-month regimen, it is especially important for the patient to take at least 60 doses within a period of 3 months, which is to say that a total of 30 doses could be missed without restarting the regimen. For the 9-month INH regimen, at least 270 doses should be ingested within 12 months. For the 6-month INH regimen, at least 180 doses should be ingested within 9 months. Finally, for the INH/rifampin regimen, at least 120 doses should be administered within 6 months. With any regimen, clinical re-evaluation is indicated for interruptions of greater than 2 months.

Question 18: If a patient will not or cannot take treatment for LTBI, what is appropriate follow-up?

Patients without medical risk factors who cannot or will not take treatment for LTBI should have an annual symptom review and TB risk factor assessment as part of routine health maintenance. Neither periodic clinical exams nor periodic chest x-rays have been shown to be effective in detecting TB reactivation before symptoms develop. However, patients with medical risk factors for TB progression or reactivation should be followed per guidelines in Appendix 5. Patients should keep a record of their positive PPD and understand its significance. Patients should be instructed to seek medical care if they develop an unexplained cough that lasts more than 2 weeks, and to remind their provider of their positive PPD status. Patients who complete a course of treatment for LTBI require no further follow-up.

(Please also refer to Appendix 5: Follow-up Protocols for Patients with a Positive PPD)

Question 19: When should I seek consultation with a specialist?

Primary care providers are encouraged to request consultation from San Francisco TB Control Clinic MDs (415-206-8524), for the following reasons:

- TB drug complications and interactions.
- Treatment of LTBI in pregnancy.
- Treatment of LTBI in patients on complex therapy for HIV.
- Treatment of LTBI or active TB when drug resistance is likely (contact of a known drug-resistant case).
- Diagnosis and management of active TB, including interpretation of mycobacteriology laboratory data.

III. Public Health Aspects

Question 20: Is LTBI reportable to the health department?

LTBI is *not reportable* to the health department. However, active TB and patients suspected of active TB are reportable by law, pending final diagnosis. Cases and suspect cases can be reported to the San Francisco TB Control Surveillance Unit by calling (415) 206-8524.

Question 21: What public health resources are available to me and to my patients?

The San Francisco TB Control Program provides comprehensive TB services for persons with both active and latent TB infection in San Francisco. The San Francisco TB Clinic located on the SFGH campus offers medical expertise, radiography, mycobacteriology, and free TB therapy for both latent TB infection and disease. Contact investigations of infectious cases and directly observed therapy are essential public health services. For active TB cases, case management is the shared responsibility of the treating physician and the local TB Control program staff with the support of culturally diverse outreach workers. For LTBI, initial evaluation, medications, and essential biochemical monitoring are provided. Consultation for private physicians treating cases of active TB and LTBI is another service of the San Francisco TB Control Program.

The main SF TB Clinic is a referral/evaluation site and does not offer TB skin testing for the public (with the exception of contact investigation). However, our satellite outreach sites in Chinatown (CHOPS) and the Tenderloin (TOPS) can provide TB testing for high-risk community members.

Chinatown Outreach Prevention Services (CHOPS): 1490 Mason Street, Suite #236. San Francisco, CA 94133. (415) 705-8549.

Tuberculosis Outreach Prevention Services (TOPS): 973 Market Street, Suite #205. San Francisco, CA 94103. (415) 597-7950.

Question 22: How do I refer a patient to the San Francisco TB Clinic for medical evaluation and/or LTBI treatment?

If you work at one of the CHN community clinics, a TB 47 triplicate referral form should be filled out with the pink copy given to the patient and other copies sent to the TB Clinic. For other providers, a letter of referral will suffice with documented TB test, chest x-ray (if available) symptom review and services requested.

San Francisco TB Clinic: 1001 Potrero Avenue, San Francisco General Hospital Campus, Bldg. 90, Ward 94. San Francisco, CA 94110. (415) 206-8524.

Question 23: What guidelines are available and how can I get them?

San Francisco TB Control guidelines and most recent epidemiologic bulletin are available on the San Francisco DPH website at the following address: <http://www.dph.sf.ca.us/PHP/TB/TB.htm>

Section II

Evaluation of Program Performance

The primary purpose of tuberculosis skin testing of healthy children and adults is to identify those with latent infection whose future risk of active disease can be reduced by preventive treatment. Preventing active tuberculosis also decreases the risk of the spread of tuberculosis to others. The prospect of tuberculosis elimination will be enhanced.

In order to be effective, a program of testing and treatment of latent tuberculosis infection (LTBI) requires completion of a number of steps, and the success of each step can be defined by a quantitative performance measure. Each office, health center, and clinic should maintain its own statistics that can serve as the basis for monitoring and continually improving performance. Statistics should be calculated every three months and annually. These statistics should be available for review by the San Francisco TB Control Program.

At some future time, a tuberculosis performance measure might be added to current Health Plan Employer Data and Information Set (HEDIS) parameters used to assess the quality of preventive health care, such as childhood immunization, Pap smear, and mammogram rates.

Step 1: Identify People at High Risk for Tuberculosis Infection

Risk of exposure to tuberculosis should be determined for every patient on entry into the health care system and at regular intervals thereafter. Depending on circumstances, a health care provider may decide to determine risk of tuberculosis exposure through individual clinical history taken or by administering a formal tuberculosis risk questionnaire (Section I, Appendix 1). Definition of risk categories should be according to the recommendations of the Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the San Francisco TB Control Program.

Performance Measure

$$\text{Proportion Screened} = \frac{\text{Number of People Screened for Tuberculosis Risk}}{\text{Number of People Seen}}$$

Step 2: Test People at High Risk for Tuberculosis Infection

The Mantoux test (intermediate PPD), (5 TU), not multiple puncture tests (such as Tine and Mono-Vacc), must be used.

Performance Measure

$$\text{Proportion Tested} = \frac{\text{Number of High Risk People Tested}}{\text{Number of High Risk People Identified}}$$

Step 3: Read Skin Test Results

All tests results, positive or negative, must be read by qualified health care personnel. Tests should be read between 48 and 72 hours after administration. The diameter of induration, not redness, is the basis of the reading. Test results should be measured in millimeters and interpreted as “positive” or “negative” according to the criteria recommended by the Centers for Disease Prevention and Control, the American Academy of Pediatrics, and the San Francisco TB Control Program.

Performance Measure

$$\text{Proportion of Tests Read} = \frac{\text{Number of Tests Read}}{\text{Number of People Tested}}$$

Steps 4: Obtain Chest Film for People with Positive Tuberculosis Skin Tests

People with a positive tuberculosis skin test should have a medical evaluation and chest film. A chest film is needed to distinguish latent tuberculosis infection from active disease.

Performance Measure

$$\text{Proportion of People with Positive Tuberculosis Skin Test} = \frac{\text{Number of Positive People Who have Chest Films}}{\text{Number of People with Positive Tests}}$$

Step 5: Initiate and Complete Preventive Treatment

Current recommendations of the CTCA/CDHS and the San Francisco TB Control Program on choice and duration of preventive treatment regimen, frequency of visits, and appropriate laboratory monitoring should be followed. In evaluating program success, use one year as the interval within which preventive treatment should be completed.

Performance Measure

$$\text{Proportion Treated} = \frac{\text{Number of Infected People Who Complete Treatment}}{\text{Number of People with Latent Tuberculosis Infection}}$$

Thus, program success can be evaluated through a sequence of performance measures. Ideally, every person seen would be asked about tuberculosis risk factors, every high risk person would be skin tested, every skin test would be read, every person with a positive skin test would have a chest film, and every person with latent tuberculosis infection would start and complete a recommended course of preventive treatment within one year.

Appendix 1: Patient Tuberculosis Risk Questionnaire

The Tuberculosis Risk Questionnaire appears on the following page. It can be reproduced for distribution as needed.

Tuberculosis Risk Questionnaire

A person who has been infected with Tuberculosis (TB) may show no outward symptoms. However, infection can later lead to severe illness. To detect the problem before a person becomes ill, we perform a tuberculosis skin test. Instead of testing all people, we recommend that only some people should get a TB test. If a test is warranted, a person will be tested with the intermediate strength PPD (Mantoux) skin test or quantiFERON blood test. The less accurate multiple puncture skin tests, such as the Tine or Mono-Vacc, is not recommended.

 To help your health care provider determine whether you need to be skin tested, please answer the following questions.

| | YES | NO |
|---|--------------------------|--------------------------|
| Have you lived with or spent time with anyone who possibly or definitely had tuberculosis? | <input type="checkbox"/> | <input type="checkbox"/> |
| Does anyone living in your household have a positive skin test for tuberculosis? | <input type="checkbox"/> | <input type="checkbox"/> |
| Did you or anyone living in your household come to the United States from another country? | <input type="checkbox"/> | <input type="checkbox"/> |
| Are you homeless, living either on the street, SRO hotel or in a shelter, or do you work or spend time with homeless people? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you or does anyone in your household have AIDS or HIV infection? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you or does anyone in your household use intravenous drugs or other street drugs? | <input type="checkbox"/> | <input type="checkbox"/> |
| Have you lived or worked in a hospital, correctional facility, substance abuse facility, nursing home, or mental institution in the past 12 months? | <input type="checkbox"/> | <input type="checkbox"/> |
| Do you live or work in the Tenderloin/SoMkt or Chinatown districts | <input type="checkbox"/> | <input type="checkbox"/> |

If you have had a “positive” skin test for tuberculosis in the past, inform your health care provider. You will not need another test.

IF YOU HAVE ANY QUESTIONS ABOUT YOUR NEED FOR A TUBERCULOSIS SKIN TEST, PLEASE ASK YOUR HEALTH CARE PROVIDER!

Appendix 2: MD Risk Assessment Form

The Tuberculosis Risk Assessment and PPD Form appears on the following page. It can be reproduced for distribution as needed

Appendix 3: San Francisco Screening Guide for Community Providers

The SF TB Control screening guidelines appear on the following page. It can be reproduced for distribution as needed.



TB SCREENING IN SAN FRANCISCO

Community Clinics are important partners in TB control because of the high rates of tuberculosis in San Francisco. In assessing who should be screened, population and medical risk factors for TB (listed below) should be asked and/or determined as part of your patient's routine medical evaluation. The following information outlines who should be screened, the interval of screening and who should be referred to the TB Clinic at SFGH.

WHO SHOULD BE SCREENED FOR TB WITH A SYMPTOM REVIEW AND SKIN TEST or QUANTIFERON TB BLOOD TEST:

- Newcomers to the US (<5 yrs) from Asia and other endemic TB countries (SCREEN REGARDLESS OF AGE)
- Foreign born under the age of 35 from TB endemic areas
- Individuals with medical risk factors for TB reactivation (diabetes, renal failure, cancer, silicosis, malnutrition, HIV or on immunosuppressive drugs)
- Patients found to have an abnormal chest x-ray consistent with old or active TB without prior evaluation or treatment (e.g., CXR=upper lobe fibrotic infiltrates. Exclude: those with isolated granulomas or pleural lesions. Include: those with parenchymal infiltrates even if stable over time)
- Patients with unexplained chronic cough or weight loss
- Renal dialysis patients
- Residents and employees of high-risk congregate sites (e.g., nursing homes, jails, prison, shelters, substance abuse treatment facilities and hospitals)
- Homeless individuals
- Injection drug users
- Patients with planned or are post organ transplant
- Contacts to active TB cases
- Children who have the above risk factors or live with adults with the TB risk factors or travel to TB endemic countries for >2weeks

FREQUENCY OF TB TESTING: Individuals should be retested on a regular basis if there is an ongoing risk of TB exposure or infection. The frequency of testing should depend on the degree of risk of TB exposure. (e.g., TB Clinic and SFGH ER staff is tested every 6 months while primary care clinic staff is tested annually)

WHO SHOULD BE REFERRED TO TB CLINIC, WARD 94, SFGH

- ALL individuals listed above with a positive quantiFERON TB blood test or tuberculin skin test reading of **10 millimeters** or more, unless HIV+ or immunocompromised (**5 mm** considered positive)
- ALL individuals with an abnormal chest x-ray (described above) consistent with old or active TB regardless of skin test results
- ALL individuals with TB symptoms regardless of skin test results

Appendix 4: SF LTBI Treatment Guidelines and Table

The SF TB Control LTBI Treatment Guidelines and LTBI Drug Treatment Table appear on the following pages. They can be reproduced for distribution as needed.



TREATMENT OF LATENT TB INFECTION – 2002

Treatment of latent TB infection (LTBI) is advised for the following:

A. Regardless of age: HIGHEST PRIORITY

1. All household or other close contacts of persons with current pulmonary tuberculosis:

a) High-risk contacts including children under 5 years and immunocompromised individuals (HIV infection, chronic corticosteroids, chemotherapy, etc) should receive treatment for LTBI regardless of tuberculin skin test (PPD) reaction if the index case is smear or culture (+) for *M. tuberculosis*:

b) Refer to Contact Investigation Guidelines for other groups

At 3 months, contacts with a negative PPD (<5mm) will be retested. If the non-immunocompromised contact is still negative (includes children) and the index case is on TB chemotherapy, treatment of LTBI may be discontinued. Immunocompromised close contacts should complete a full course of treatment regardless of repeat PPD results since test results may be unreliable.

2. Tuberculin converters:

Definition of conversion: Increase in the size of the tuberculin reaction by at least 10 mm from less than 10 mm to 10 mm or more within a 2 year period.

3. PPD reactors (5mm or greater) with abnormal chest films consistent with dormant tuberculosis that have not had adequate prior therapy.

It is important to exclude current disease by bacteriologic evaluation and/or a review of serial x-rays.

4. All PPD reactors (5mm or greater) with HIV infection or at high risk of HIV infection.

Homosexual/bisexual men and injection drug users are at high risk of HIV infection. Unless the HIV test is known to be negative and the patient does not belong to other high-risk groups, they should be encouraged to take INH.

5. PPD reactors (10mm or greater) who are newcomers to the U.S. (less than 5 years in U.S.), from areas of the world with a high TB incidence (includes Central and South America, Asia, Philippines, the former Soviet Union, and Africa).

6. PPD reactors (10mm or greater) who are injection drug users (HIV testing should be strongly encouraged for all individuals in this group).

7. All PPD reactors (10mm or greater) who are homeless or have a transient living arrangement (Note: Because of increased TB disease susceptibility and probability of TB exposure in group settings, HIV testing should be strongly encouraged for all homeless tuberculin reactors).

8. PPD reactors with special medical situations of increased risk. These include prolonged corticosteroid therapy (>15mg daily of prednisone or equivalent for 2-4 weeks), immunosuppressive therapy, leukemia or lymphoma, insulin-dependent diabetes, silicosis, post-gastrectomy (especially with weight loss) and renal failure with uremia.

Note: a 5 mm cut point is considered positive for persons who are on immunosuppressive therapy, corticosteroids, or have leukemia or lymphoma. A 10mm cut point should be used for other medical risk groups.

9. All PPD reactors (10mm) under 21 years of age.

B. Less than 35 years of age:

1. Foreign-born PPD reactors (10mm or greater) living in the U.S. greater than 5 years who come from areas of the world with a high TB incidence (includes Central and South America, Asia, Philippines, the former Soviet Union, and Africa).

2. Post-partum women with significant PPD reactions (10mm or greater)

INH is not contraindicated during pregnancy but in general should be delayed until after delivery unless additional risk factors such as HIV infection, being a close contact or recent skin test conversion exists. Nursing is not a contraindication to INH.

3. PPD reactors (10mm or greater) for whom the public health consequences of developing tuberculosis disease would be of special importance; i.e. persons who work with small children, such as day care providers, health care providers, teachers, school bus drivers, etc.
4. PPD reactors (10mm or greater) who are 21 - 35 years old. As a public health policy, we are not administering INH to this age group without other risk factors. However, if an individual wishes to take INH after reviewing risks and benefits, we will offer the therapy.

C. Contraindications:

1. Known previous adverse reactions INH, rifampin, or pyrazinamide (PZA). Unstable liver disease, with AST greater than 3 times normal. (for INH or PZA only)
3. History of gout when using PZA

D. Recommended Treatment Regimens:

For Dosages, see attached chart on page 4.

1. INH is prescribed for 9 months for:
 - Children under age 15,
 - Immunocompromised reactors (especially HIV seropositive persons)
2. The 2 month regimen of daily rifampin/PZA may be prescribed to:
 - HIV infected individuals [*rifabutin may be substituted for rifampin if the HIV patient is on protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs)*]

At the TB Clinic physician's discretion: (must be under TB Control DOT program)

- Homeless (prioritize PPD converters and contacts)
 - Incarcerated patients
3. Persons with abnormal chest films consistent with dormant tuberculosis may be treated with 4 months of the multi-drug regimen of rifampin /INH or 9 months of INH alone
 4. Other groups will receive 6 months of INH

E. Vitamin B6:

The routine use of B6 is recommended only for persons at high risk of developing peripheral neuropathy: persons with diabetes, uremia, chronic alcoholism, severe malnutrition, HIV infection, pregnant women and the aged.

F. BCG:

In most situations prior BCG history will be ignored when considering INH recommendations. Reactions over 10 mm are unusual several years after vaccination. If BCG has been given within 1 year of the tuberculin skin test, the PPD can be repeated after 1 year has passed before deciding on treatment.

G. Monitoring:

1. Baseline liver function tests (AST, Alkaline phosphatase and total bilirubin) are required only for individuals with:
 - Known liver disease
 - Alcoholism
 - Injection drug use
 - HIV infection
 - Those placed on any multi-drug regimen (INH/RIF for 4 months, RIF/PZA for 2 months)
2. Complete blood count, creatinine, and uric acid at baseline and monthly are required for those placed on the 2-month rifampin/PZA regimen.
3. If baseline results are abnormal, repeat measurements should be obtained monthly until documented stable or if the patient has symptoms of adverse reactions.
4. For individuals on the 2-month rifampin/PZA regimen, serum aminotransferase and bilirubin should be repeated at 2, 4 and 6 weeks of treatment.

DRUGS FOR LATENT TUBERCULOSIS INFECTION (LTBI)

| Drug | Supplied | Dose/frequency | Duration | Side Effects | Monitoring | Comments |
|----------------------------|---|---|---|--|---|--|
| Isoniazid (INH): | Tabs: 300mg 100mg Susp: 50mg/5ml Inj: 100mg/ml | <u>Adults:</u> 300mg daily or 900mg 2X weekly <u>Children:</u> 10 – 15mg/kg daily (>20kg = 300mg) or 20-30mg/kg 2 X weekly | <u>Adults:</u> 6 months (180 doses) <u>Children, HIV infected, immuno-compromised or has CXR consistent with old inactive TB:</u> 9 months (270 doses) | Hepatitis; peripheral neuropathy; mild CNS effects; skin rash; increased Dilantin levels. | LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently. | Give pyridoxine 25mg/day to prevent neuropathy in elderly, D.M., nutritionally deficient, renal disease, pregnancy, HIV, alcoholics. |
| Rifampin (RIF): | Caps: 300mg 150mg | <u>Adults:</u> 10mg/kg up to 600mg PO daily <u>Children:</u> 10 – 20mg/kg up to 600mg PO (use RIF only when INH cannot be used because of toxicity or INH drug resistance) | <u>Adults:</u> 4 months (120 doses) when used w/ INH <u>HIV+ adults only:</u> 2 months (60 doses) when used w/ PZA | Orange discoloration of secretions; cholestatic or hepatocellular hepatitis; febrile (flu-like) reaction; induces hepatic enzymes, drug interactions; thrombocytopenia; skin rash. | LFTs (not routine) unless known or suspected liver disease or other hepatotoxic drugs used concurrently. Baseline CBC. | Warn patient about orange discoloration of urine and other body secretions. Discoloration of contact lens. Induces hepatitis microsomal enzymes. |
| Rifabutin: | Caps: 150mg | <u>Adults only:</u> 5 mg/kg up to 300mg daily | As for rifampin | As for rifampin except hepatic enzyme induction less; risk of uveitis when used with macrolides, PI's and azole antifungal agents. | As for rifampin. | As for rifampin. |
| Pyrazinamide (PZA): | Tabs: 500mg scored | <u>Adults only:</u> 15 – 20mg/kg PO | HIV+ adults only: 2 months (60 doses) when used w/ RIF | Hepatitis; GI upset; hyperuricemia; arthralgias; photosensitive dermatitis. | LFTs and uric acid at start of therapy and LFTs every 2 weeks when used with rifampin. | Dose adjustment needed for renal disease. Safety not established in pregnancy. |

Appendix 5: Follow-up Protocols for Patients with a Positive PPD

The SF TB Control protocol for following-up on patients with a positive PPD appears on the following page. It can be reproduced for distribution as needed.



FOLLOW-UP PROTOCOLS FOR PATIENTS WITH A POSITIVE PPD

Patients with prior adequate treatment for latent TB infection (LTBI)

1. Adequate LTBI treatment decreases the lifetime risk of reactivation TB to less than 1.6 percent. Therefore, patients with prior treatment do not need rigorous follow-up unless they have TB symptoms or are re-exposed to individuals with contagious pulmonary TB.
2. Adequate treatment is defined as:
 - **Adults with normal CXR:** 6-9 months of INH
 - **Immune compromised adults or patients with abnormal CXRs consistent with old inactive TB:** 9 months of INH or 4 months of INH and rifampin
 - **Children:** 6-9 months of INH (current ATS and SF recommendation for LTBI Rx is 9 months of INH. SF recommendations before 2001 was 6 months)

Recommendation: *In general, patients with prior adequate LTBI treatment do not need medical follow up or CXRs unless they have symptoms of TB, are re-exposed to individuals with contagious pulmonary TB or a CXR is required by their work or school.*

Patients without prior adequate treatment or for LTBI

Risk of TB reactivation in these individuals will depend on medical risk factors for TB.

Recommendations:

If there are no medical risk factors present: An annual TB symptom review and risk assessment should be performed as part of routine health maintenance. A CXR should be done ONLY if symptoms are present or TB screening is required for entry into a congregate setting (such as a residential facility, nursing home, shelter, drug treatment program, school, etc.). If the patient is asymptomatic AND without new medical risk factors, a normal CXR done within the prior 6-12 months should be sufficient for required screening.

If medical risk factors are present: The frequency of TB screening and repeat CXRs should depend on the risk of disease. The listed groups below should be offered LTBI treatment because they represent TB Control's highest priority for prevention. However, if treatment is rejected, these patients should be educated on the signs and symptoms of TB and followed-up as described below:

- **HIV infection or other severe immune compromise (e.g. cancer chemotherapy, organ transplant, hematological malignancies, chronic**

prednisone 15mg/day > 2wks): Symptom review every 3 months and CXR every 6 months

- **PPD conversion to positive within the past 2 years:** CXR and symptom review every 6 months for a 2-year period
- **Arthritis or autoimmune disease being treated with immune modulating medication:** Symptom review every 3-6 months and CXR annually
- **End-stage renal disease, silicosis, jejunioleal bypass or carcinoma of the head or neck:** Symptom review every 6 months and CXR annually
- **Evidence of old inactive TB on CXR:** Annual symptom review at minimum. Would also have a low threshold for sputum collection and repeat CXR if any chronic pulmonary symptoms are present
- **Other medical risks: (diabetes, injection drug use, gastrectomy, under weight by >15%):** Annual symptom review at minimum and CXR if symptomatic without definite etiology

Any patient regardless of prior treatment should get a CXR and medical evaluation if TB symptoms of chronic cough and/or unexplained weight loss of more than 5 lbs are present.