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Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

ATS/CDC Statement Committee on Latent Tuberculosis Infection

The following article includes excerpts from the MMWR article with the above title (2000;49[RR-6]:1-54). This official statement of the American Thoracic Society (ATS) was adopted by the ATS Board of Directors, July 1999. It is a joint statement of the ATS and the Centers for Disease Control and Prevention (CDC) and was endorsed by the Council of the Infectious Diseases Society of America, September 1999. The sections of this statement that relate to infants and children were endorsed by the American Academy of Pediatrics, August 1999. The statement provides new recommendations for targeted tuberculin testing and treatment regimens for persons with latent Mycobacterium tuberculosis *infection (LTBI) and updates previously published guidelines.*

Introduction

Tuberculosis (TB) is a chronic bacterial infection of the lungs and other organs caused by the tubercle bacteria, *Mycobacterium tuberculosis* and *Mycobacterium bovis*. In the United States, disease caused by *M. bovis* is rare. Transmission of the organism is almost always airborne by droplet nuclei from a person with active respiratory disease. The initial infection is usually asymptomatic or produces nonspecific symptoms such as fever, cough, and malaise. Early lung lesions commonly heal and leave no residual changes except occasional pulmonary or tracheobronchial lymph node calcifications. Direct progression from initial infection to active pulmonary or extrapulmonary disease occurs in only about 5% of immunocompetent persons and in up to 50% of persons with advanced human immunodeficiency virus (HIV) infection. Approximately 90-95% of those initially infected enter a latent phase from which there is lifelong risk of reactivation. Persons with latent tuberculosis infection (LTBI) are asymptomatic and not infectious. They usually have a positive reaction to the tuberculin skin test. About 10% of persons with LTBI will develop TB disease at some time in life, but the risk is considerably higher for persons who are immunosuppressed.

For more than three decades, treatment of persons with LTBI to prevent the development of active disease has been an essential component of TB control in the United States. Until recently, isoniazid was the only drug proven effective and a regimen of 6-12 months of isoniazid therapy was the recommended treatment for LTBI. (The terms "preventive therapy" and "chemoprophylaxis" were used in the past to describe treatment of patients with LTBI).

In the early 1970s, the association between isoniazid and potentially fatal hepatitis was recognized, leading to the development of guidelines regarding pretreatment screening and monitoring to minimize the risk for severe complications. In 1974, following a study to quantify the risk for isoniazid-related hepatitis, guidelines for treatment of LTBI were updated. These revised guidelines recommended that persons older than 35 years who were at low-risk for developing TB disease not be treated for LTBI. Subsequent controversy over the appropriate age cut-off for these low-risk, tuberculin-positive persons ensued, and the resultant confusion led to a decrease in the use of LTBI treatment, even for persons at high risk for whom treatment was indicated.

During the past decade, a series of studies of treatment of LTBI in persons with HIV infection has been undertaken. The results of these studies have contributed substantially to the LTBI treatment guidelines presented in this report.

Identification and treatment of persons with latent infection who are at high risk for active TB have become essential components of the TB elimination strategy promoted by the Public Health Service Advisory Council on the Elimination of Tuberculosis. Because testing persons for infection and providing treatment are interrelated, these recommendations include sections on program activities aimed at identifying high-risk infected persons, as well as recommendations on the use of new, short-course treatment regimens. A summary of changes from prior recommendations is outlined in Table 1.

Targeted Tuberculin Testing

Testing for TB infection should be done for persons in groups at high risk for developing TB. These high risk groups can be divided into two main categories:

Persons at higher risk for recent TB exposure or infection including:

- Close contacts of persons known or suspected to have TB (i.e., those sharing the same household or other enclosed environments)
- Foreign-born persons recently (<5 years) arrived from areas that have a high TB incidence or prevalence (e.g., Asia, Africa, Latin America, Eastern Europe, Russia)
- Residents and employees of high-risk congregate settings (e.g., correctional institutions, nursing homes, mental institutions, other long-term residential facilities, and homeless shelters)
- Health care workers who serve high-risk clients
- Infants, children, and adolescents exposed to adults in high-risk categories
- Injection drug users

Persons at higher risk for TB disease once infected including:

- Immunosuppressed persons
- Persons who were recently infected with *M. tuberculosis* (within the past 2 years), particularly infants and very young children
- Persons with certain medical conditions such as diabetes mellitus, end stage renal disease, silicosis, head and neck cancer, and hematologic and reticuloendothelial diseases
- Injection drug users
- Persons with a history of inadequately treated TB

Targeted tuberculin testing programs should be designed for one purpose: to identify those high-risk persons who would benefit by treatment of LTBI. In other words a decision to do the tuberculin test is a decision to treat. Following that principle, targeted tuberculin testing programs should be conducted among groups at risk for recent infection with *M. tuberculosis* and those who, regardless of duration of infection or age, are at increased risk for progression to active TB.

Testing is discouraged unless a plan has been developed to complete a course of treatment in persons found to have LTBI. Such planning should include arrangements for medical evaluation (e.g., chest radiographs) of persons with positive skin tests and for the medical supervision of the course of treatment.

With the exception of initial testing of persons at low risk whose future activity will place them at increased risk of exposure (e.g., employment in a setting where TB transmission may occur), screening of low-risk persons is discouraged because it diverts resources from activities of higher priority. In addition, a substantial proportion of tuberculin-test-positive persons from low-risk populations may have false-positive skin tests. Screening of low-risk persons and testing for administrative purposes (e.g., certification of school teachers) should be replaced by targeted testing.

Table 1. Changes from Prior Recommendations on Tuberculin Testing and Treatment of Latent Tuberculosis Infection (LTBI)

Tuberculin testing

- Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for tuberculosis (TB), regardless of age; testing is discouraged among persons at lower risk
- For patients with organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of ≥15 mg/day prednisone for 1 month or more), 5 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity (see Table 2)
- A tuberculin skin test conversion is defined as an increase of ≥10 mm of induration within a 2-year period, regardless of age

Four options for treatment of latent tuberculosis infection

- For human immunodeficiency virus (HIV)-negative persons, isoniazid given for 9 months is preferred over 6-month regimens
- For HIV-positive persons and those with fibrotic lesions on chest x-ray consistent with previous TB, isoniazid should be given for 9 months instead of 12 months
- For HIV-negative and HIV-positive persons with isoniazid-resistant, rifampin-susceptible TB, rifampin and pyrazinamide should be given for 2 months
- For HIV-negative and HIV-positive persons with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide, rifampin should be given for 4 months

Clinical and laboratory monitoring

- Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI, except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly
- Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment, as indicated

Diagnosis of Latent Tuberculosis Infection

The tuberculin skin test is the only proven method for identifying infection with *M. tuberculosis* in persons who do not have TB disease. Although the available tuberculin skin-test antigens are <100% sensitive and specific for detection of infection with *M. tuberculosis*, no better diagnostic methods have yet been devised. Proper use of the tuberculin skin test requires knowledge of the antigen used (tuberculin), the immunologic basis for the reaction to this antigen, the technique(s) of administering and reading the test, and the results of epidemiologic and clinical experience with the test. Detailed information on these topics is provided in the ATS/CDC Statement, *Diagnostic Standards and Classification of Tuberculosis in Adults and Children.* (*Am J Respir Crit Care Med* 2000; 161:1376-1395.)

Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and ≥15 mm of induration (Table 2). For persons who are at highest risk for developing active TB,

Table 2. Criteria for Tuberculin Positivity, by Risk Group

Reaction ≥5 mm of Induration	Reaction ≥10 mm of Induration	Reaction ≥15 mm of Induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 years) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/day of prednisone for 1 month or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≤10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Any child <4 years of age Children and adolescents exposed to adults at high risk	

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

†For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE:Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No.RR-11):19-34.

≥5 mm of induration is considered positive. These include persons who are immunosuppressed because of disease (e.g., HIV infection) or drugs (e.g., systemic corticosteroids), persons who have had recent contact with an infectious TB patient, and persons with abnormal chest radiographs consistent with prior TB (Table 2).

A reaction of ≥10 mm of induration is considered positive for those persons with an increased probability of recent infection or with other clinical conditions that increase the risk for TB (e.g., recent immigrants from high prevalence countries and injection drug users) (Table 2).

Routine tuberculin testing is not recommended for populations at low risk for TB. However, if those persons are tested, ≥15 mm of induration is considered positive.

Treatment of Latent Tuberculosis Infection

In this report, treatment recommendations use an adaptation of the rating system from recent U.S. Public Health Service documents that grades the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendation (I, II, or III). Four regimens are recommended for the treatment of adults with LTBI. (See Tables 3 and 4 for detailed recommendations, dosages, and contraindications.)

Isoniazid for Nine Months

The isoniazid daily regimen for 9 months is recommended because prospective, randomized trials in HIV-negative persons indicate that 12 months of treatment is more effective than 6 months of treatment; however, in subgroup analyses of several trials, the maximal beneficial effect of isoniazid is likely achieved by 9 months. Minimal additional benefit is gained by extending therapy to 12 months. When compared with placebo, both 6-month and 12-month regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials.

Isoniazid for Six Months

Although a 9-month regimen of isoniazid is the preferred regimen for the treatment of LTBI, a 6-month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 months may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local conditions, health departments or providers may conclude that a 6-month rather than a 9-month course of isoniazid is preferred.

Both the 9-month and 6-month isoniazid regimens may be given intermittently (i.e., twice weekly). When isoniazid is given intermittently, it should be administered only as directly observed therapy (DOT).

Rifampin and Pyrazinamide for Two Months

The 2-month daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons that showed the 2-month regimen to be similar in safety and efficacy to a 12-month regimen of isoniazid. Twice-weekly treatment with rifampin and pyrazinamide for 2 or 3 months may be considered when alternative regimens cannot be given. This intermittent regimen should always be administered as DOT. Some experts recommend that the 2-month regimen of daily rifampin and pyrazinamide also be given by DOT, which can consist of five observed and two self-administered doses each week. In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

Rifampin for Four Months

Rifampin given daily for 4 months is recommended on the basis of the efficacy of a similar regimen in a) a prospective randomized trial of tuberculin-positive persons with silicosis and b) a nonrandomized trial in per-

Table 3. Medications to Treat Latent Tuberculosis Infection: doses, toxicities, and monitoring requirements

	Oral dose (mg/kg) (maximum dose)						
	Daily		Twice weekly*				
Drug	**Adults**	**Children**	**Adults**	**Children**	**Adverse Reactions**	**Monitoring**	**Comments**
Isoniazid	5 (300 mg)	10-20 (300 mg)	15 (900 mg)	20-40 (900 mg)	- Rash - Hepatic enzyme elevation - Hepatitis - Peripheral neuropathy - Mild central nervous system effects - Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	- Clinical monitoring monthly - Liver function tests† at baseline in selected cases‡ and repeat measurements if: -- Baseline results are abnormal or -- Patient is pregnant or in the immediate postpartum period or -- Patient is at high risk for adverse drug reactions or has symptoms of adverse reactions	-Hepatitis risk increases with age and alcohol consumption -Pyridoxine (vitamin B_6, 10-25 mg/day) might prevent peripheral neuropathy and central nervous system effects
Rifampin	10 (600 mg)	10-20 (600 mg)	10 (600 mg)	--	- Rash - Hepatitis - Fever - Thrombocytopenia - Flu-like symptoms - Orange-colored body fluids (secretions, urine, tears)	- Clinical monitoring at weeks 2,4 and 8, when pyrazinamide given - Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if: -- Baseline results are abnormal or -- Patient has symptoms of adverse reactions	- Rifampin is contraindicated or should be used with caution in HIV-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) - Decreases levels of many drugs (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin) - Might permanently discolor soft contact lenses
Rifabutin	5 (300 mg)§	--	5 (300 mg)§	--	- Rash - Hepatitis - Fever - Thrombocytopenia - Orange-colored body fluids (secretions, urine, tears) - With increased levels of rifabutin -- Severe arthralgias -- Uveitis -- Leukopenia	- Clinical monitoring at weeks 2,4 and 8, when pyrazinamide given - Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if: -- Baseline results are abnormal or -- Patient has symptoms of adverse reactions - Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs§	- Rifabutin is contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if rifabutin is administered with soft-gel saquinavir - Reduces levels of many drugs (e.g., PIs, NNTRIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptives, digitalis, sulfonylureas, diazepam, β–blockers, anticonvulsants, and theophylline) - Might permanently discolor contact lenses
Pyrazinamide	15-20 (2.0 gm)	--	50 (4.0 gm)	--	- Gastrointestinal upset - Hepatitis - Rash - Arthralgias - Gout (rare)	- Clinical monitoring at weeks 2,4 and 8 - Liver function tests† at baseline in selected cases‡ and repeat measurements if: -- Baseline results are abnormal or -- Patient has symptoms of adverse reactions	- Treat hyperuricemia only if patient has symptoms - Might make glucose control more difficult in persons with diabetes - Should be avoided in pregnancy, but can be given after first trimester

**All intermittent dosing should be administered by directly observed therapy.*
†AST or ALT and serum bilirubin.
‡HIV infection, history of liver disease, alcoholism, and pregnancy.
§If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg/day when used with nelfinavir, indinavir, or amprenavir; and to 150 mg (two or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg or 600 mg. Pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

Table 4. Recommended Drug Regimens for Treatment of Latent Tuberculosis Infection in Adults

			Rating* (Evidence)†	
Drug	**Interval and Duration**	**Comments**	**HIV-**	**HIV+**
Isoniazid	Daily for 9 months‡,§	In HIV-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), or non-nucleoside reverse transcriptase inhibitors (NNTRIs)	A (II)	A (II)
	Twice weekly for 9 months‡,§	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 months§	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 months§	DOT must be used with twice-weekly dosing	B (II)	C (I)
Rifampin plus pyrazinamide	Daily for 2 months	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB In HIV-infected patients, PIs or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenivir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir§§	B (II)	A (I)
	Twice weekly for 2-3 months	DOT must be used with twice-weekly dosing	C (II)	C (I)
Rifampin	Daily for 4 months	For persons who cannot tolerate pyrazinamide For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide	B (II)	B (III)

**Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given.*
†Quality of evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.
‡Recommended regimens for children younger than 18 years of age.
§Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.
§§Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other PIs or NNRTIs, dose adjustment of rifabutin may be required (see Table 3).

sons exposed to individuals with isoniazid-resistant TB. This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Before beginning treatment of LTBI, active TB should be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies.

Special considerations for treatment of LTBI apply to the following populations:

- When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior TB, 9 months rather that 6 months is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is recommended. For women at risk for progression of LTBI to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active TB is lower, some experts recommend waiting until after delivery to start treatment.
- For children and adolescents, isoniazid given either daily or twice weekly for 9 months is the recommended regimen.
- For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, rifampin and pyrazinamide given daily for 2 months is recommended, and for patients with intolerance to pyrazinamide, rifampin given daily for 4 months is recommended.
- For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) TB and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin or ofloxacin) for 6-12 months are recommended. Immunocompetent contacts may be observed without treatment or treated for at least 6 months, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 months.

Clinical and Laboratory Monitoring

Once patients have been tested and then identified with LTBI, they should receive an initial clinical evaluation. They should also receive follow-up evaluations at least monthly (if receiving isoniazid alone or rifampin alone) and at 2, 4, and 8 weeks (if receiving rifampin and pyrazinamide). This evaluation should include questioning about side effects and a brief physical assessment checking for signs of hepatitis. Patients should be educated about the side effects associated with treatment of LTBI and advised to stop treatment and promptly seek medical evaluation when they occur.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (see Table 3). Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) and bilirubin. Baseline testing is also indicated for persons with HIV infection, pregnant women, women in the immediate postpartum period (i.e., within 3 months of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and persons at risk for chronic liver disease. Baseline testing is not

routinely indicated in older persons. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.

Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver function tests are abnormal and other persons at risk for hepatic disease. Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during the course of treatment (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate complaints of joint pain). Some experts recommend that isoniazid should be withheld if transaminase levels exceed three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic.

Reporting of Serious Adverse Effects

Practitioners and other health professionals should report serious adverse events associated with the treatment of LTBI to the U.S. Food and Drug Administration's MedWatch Program. Serious adverse events include those associated with hospitalization, permanent disability, or death. Reporting may be by telephone [1(800)FDA-1088], FAX [1(800)FDA-0178], or the internet site [www.fda.gov/medwatch].

Nucleic Acid Amplification Tests for Tuberculosis

[The following article includes excerpts from the MMWR article with the above title (2000;49(26):593-4).] On September 30, 1999, the Food and Drug Administration approved a reformulated Amplified Mycobacterium Tuberculosis Direct Test (MTD) (Gen-Probe®, San Diego, California) for detection of *Mycobacterium tuberculosis* in acid-fast bacilli (AFB) smear-positive and smear-negative respiratory specimens from patients suspected of having tuberculosis (TB). MTD and one other nucleic acid amplification (NAA) test, the Amplicor® Mycobacterium Tuberculosis Test (Amplicor) (Roche® Diagnostic Systems, Inc., Branchburg, New Jersey), previously had been approved for the direct detection of *M. tuberculosis* in respiratory specimens that have positive AFB smears. This notice updates the original summary published in 1996 and provides suggestions for using and interpreting NAA test results for managing patients suspected of having TB.

Based on available information, the following algorithm is a reasonable approach to NAA testing of respiratory specimens from patients with signs or symptoms of active pulmonary TB for whom a presumed diagnosis has not been established.

Special Concerns in Virginia

The state laboratory, the Division of Consolidated Laboratory Services (DCLS), does not currently offer NAA tests, instead relying on established tests for identification of mycobacterial species. Clinical samples submitted to the DCLS are routinely first tested for the presence of mycobacterial organisms visible by smear. Results of this test are available within 24 hours. Samples are then cultured using modern, liquid (BACTEC) media as well as conventional (solid) media. Cultures that become positive are then identified using nucleic acid hybridization (probe) techniques. This method allows an organism to be identified with confidence within hours of the detection of growth in culture, shortening the time for identification by several weeks. Drug susceptibility results are obtained with a short turnaround time using the BACTEC system.

Diagnosis and management of tuberculosis requires results of all four laboratory procedures: smear, culture, identification, and drug susceptibility testing. Although public health laboratories perform all tests automatically as appropriate, private laboratories are required by law to have a physician's order for each test performed. ***Therefore, it is critical when a mycobacterial culture is ordered using a private laboratory, that a specific request is made for identification and drug susceptibility testing if* M. tuberculosis *is found.***

Algorithm

1. Collect sputum specimens on 3 different days for AFB smear and mycobacterial culture.
2. Perform NAA test on the first sputum specimen collected, the first smear-positive sputum specimen, and additional sputum specimens as indicated below.
   a. If the first sputum specimen is smear-positive and NAA-positive, the patient can be presumed to have TB without additional NAA testing. However, unless concern exists about the presence non-tuberculosis mycobacteria (NTM), the NAA test adds little to the diagnostic work-up.
   b. If the first sputum is smear-positive and NAA-negative, a test for inhibitors should be done. The inhibitor test can be done as an option with Amplicor. To test for inhibitors of MTD, spike an aliquot of the lysated sputum sample with lysed *M. tuberculosis* (approximately 10 organisms per reaction, or an equivalent amount of *M. tuberculosis* rRNA) and repeat the test starting with amplification.
      1) If inhibitors are not detected, additional specimens (not to exceed a total of 3) should be tested. The patient can be presumed to have NTM if a second sputum specimen is smear-positive, NAA-negative, and has no inhibitors detected.
      2) If inhibitors are detected, the NAA test is of no diagnostic help. Additional specimens (not to exceed a total of 3) can be tested with NAA.
   c. If sputum is smear-negative and MTD-positive†, additional specimens (not to exceed three) should be tested with MTD. The patient can be presumed to have TB if a subsequent specimen is MTD-positive.
   d. If sputum is smear-negative and MTD-negative†, an additional

†Amplicor is not approved for use with smear-negative samples.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, October 2000: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through October: This Year	Last Year	5 Yr Avg
AIDS	65	0	12	11	5	37	642	717	905
Campylobacteriosis	37	10	8	7	5	7	494	555	578
***E. coli* O157:H7**	5	0	2	1	2	0	61	65	57
Giardiasis	36	4	15	11	5	1	357	383	333
Gonorrhea	1044	56	84	125	316	463	8803	7884	7935
Hepatitis A	12	1	6	3	1	1	130	146	169
B, acute	14	2	2	1	8	1	138	75	97
C/NANB, acute	0	0	0	0	0	0	3	10	16
HIV Infection	70	0	18	9	23	20	617	729	822
Lead in Children†	82	5	7	15	33	22	670	373	582
Legionellosis	4	1	2	1	0	0	31	28	24
Lyme Disease	9	2	4	0	2	1	133	109	63
Measles	0	0	0	0	0	0	2	13	4
Meningococcal Infection	1	0	0	0	0	1	37	45	47
Mumps	1	0	0	0	0	1	9	10	13
Pertussis	26	20	1	0	0	5	97	29	39
Rabies in Animals	43	7	12	8	7	9	486	483	485
Rocky Mountain Spotted Fever	2	1	0	1	0	0	7	15	25
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	80	18	27	11	14	10	848	1118	990
Shigellosis	52	0	8	42	1	1	394	116	309
Syphilis, Early§	35	2	11	6	2	14	236	317	581
Tuberculosis	20	0	13	1	3	3	216	247	276

Localities Reporting Animal Rabies This Month: Accomack 1 skunk; Alexandria 1 bat, 1 skunk; Augusta 1 raccoon, 1 skunk; Bath 1 skunk; Botetourt 1 raccoon, 1 skunk; Buckingham 1 skunk; Caroline 1 raccoon; Chesapeake 1 raccoon; Charles City 1 cat; Clifton Forge 1 skunk; Fairfax 1 bat, 2 raccoons, 4 skunks; Fauquier 1 fox; Franklin County 1 raccoon; Gloucester 1 fox; Halifax 1 raccoon; Hanover 1 raccoon; Henrico 1 fox, 1 raccoon; Highland 1 skunk; Lee 1 dog; Lynchburg 1 skunk; Nelson 1 skunk; Northampton 1 raccoon; Prince George 1 raccoon; Prince William 2 raccoons, 1 skunk; Pulaski 1 dog, 1 raccoon; Virginia Beach 1 fox, 1 raccoon; York 4 raccoons.

Occupational Illnesses: Asbestosis 53; Cadmium Exposure 1; Lead Exposure 12; Mesothelioma 2; Pneumoconiosis 3.

*Data for 2000 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

specimen should be tested with MTD. The patient can be presumed not to be infectious if all smear and MTD results are negative. The clinician must rely on clinical judgement in decisions regarding the need for antituberculous therapy and further diagnostic work-up because negative NAA results do not exclude the possibility of active pulmonary TB.

3. If the indicated repeat NAA testing fails to verify initial NAA test results, the clinician must rely on clinical judgement in decisions regarding the need for antituberculous therapy, further diagnostic work-up, and isolation.
4. Ultimately, the patient's response to therapy and culture results are used to confirm or refute a diagnosis of TB.

Cautions

NAA tests can enhance diagnostic certainty, but they do not replace AFB smear or mycobacterial culture, and they do not replace clinical judgement. Clinicians should interpret these tests based on the clinical situation, and laboratories should perform NAA testing only at the request of the physician and only on selected specimens. Laboratorians should not reserve material from clinical specimens for NAA testing if this compromises the ability to perform the other established tests that have better-defined diagnostic utility and implications. Specificity of NAA tests varies between laboratories as a result of unrecognized procedural differences and differences in cross-contamination rates. Information is limited regarding NAA test performance for nonrespiratory specimens, or specimens from treated patients. NAA tests often remain positive after cultures become negative during therapy and can remain positive even after completion of therapy.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, November 2000: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through November: This Year	Last Year	5 Yr Avg
AIDS	99	3	60	3	17	16	741	768	1016
Campylobacteriosis	36	9	9	9	2	7	531	583	622
***E. coli* O157:H7**	10	3	4	1	1	1	71	71	62
Giardiasis	36	3	16	7	6	4	393	419	375
Gonorrhea	777	30	59	72	181	435	9565	8473	8691
Hepatitis A	16	2	5	5	1	3	146	165	188
B, acute	14	0	5	2	2	5	152	87	106
C/NANB, acute	0	0	0	0	0	0	3	10	16
HIV Infection	82	4	22	9	17	30	699	789	897
Lead in Children†	61	4	5	11	22	19	732	457	646
Legionellosis	1	0	0	0	0	1	32	32	27
Lyme Disease	7	2	3	0	0	2	140	114	68
Measles	0	0	0	0	0	0	2	18	5
Meningococcal Infection	1	0	0	0	1	0	38	50	53
Mumps	1	0	0	1	0	0	10	10	15
Pertussis	9	8	0	0	0	1	106	50	54
Rabies in Animals	45	8	10	9	8	10	531	533	534
Rocky Mountain Spotted Fever	0	0	0	0	0	0	7	17	27
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	79	14	21	15	15	14	927	1172	1082
Shigellosis	37	2	9	24	0	2	431	124	340
Syphilis, Early§	16	0	2	4	5	5	252	342	622
Tuberculosis	25	1	14	2	3	5	241	272	299

Localities Reporting Animal Rabies This Month: Accomack 1 fox, 1 raccoon; Albemarle 1 raccoon; Augusta 1 skunk; Bedford 1 raccoon, 1 skunk; Culpeper 1 skunk; Cumberland 1 skunk; Fairfax 4 raccoons, 5 skunks; Franklin County 1 skunk; Frederick 1 skunk; Giles 1 skunk; Gloucester 1 cat; Grayson 1 bat; Halifax 1 cat; Henrico 1 raccoon; Highland 2 skunks; Hopewell 1 raccoon; Loudoun 1 raccoon; Lunenburg 1 skunk; Montgomery 1 cat; Newport News 2 raccoons; Northampton 1 raqccoon; Nottoway 1 skunk; Pulaski 1 skunk; Rockbridge 1 raccoon; Russell 1 skunk; Southampton 1 skunk; Surry 1 raccoon; Sussex 1 fox; Virginia Beach 1 raccoon; Washington 1 fox; Waynesboro 1 raccoon; York 1 cat, 1 raccoon.

Occupational Illnesses: Asbestosis 39; Cadmium Exposure 1; Lead Exposure 6; Pneumoconiosis 1.

*Data for 2000 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

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