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Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents

Pediatric Tuberculosis Collaborative Group

ABSTRACT. Comprehensive new guidelines for screening, targeted testing, and treating latent tuberculosis infection (LTBI) in children and adolescents are presented. The recent epidemiology of TB and data on risk factors for LTBI are reviewed. The evidence-based recommendations provided emphasize the paradigm that children and adolescents should be screened for risk factors by using a risk-factor questionnaire for TB and LTBI and tested with the tuberculin skin test only if ≥1 risk factor is present. The use of administrative or mandated tuberculin skin tests for entry to day care, school, or summer camp is strongly discouraged. Treatment regimens, suggestions to improve adherence, and methods to monitor toxicities are summarized. Children and adolescents with LTBI represent the future reservoir for cases of TB. Thus, detecting and treating LTBI in children and adolescents will contribute to the elimination of TB in the United States. ***Pediatrics*** **2004;114:1175–1201;** ***latent tuberculosis infection, tuberculin skin test, children, adolescents, pediatrics, tuberculosis.***

ABBREVIATIONS. TB, tuberculosis; LTBI, latent tuberculosis infection; USPHS, United States Public Health Service; CDC, Centers for Disease Control and Prevention; TST, tuberculin skin test; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; AAP, American Academy of Pediatrics; TU, tuberculin units; PPD, purified protein derivative; MPT, multiple-puncture test; INH, isoniazid; DOT, directly observed therapy; MDR, multidrug-resistant; BCG, bacillus Calmette-Guérin; TNF-α, tumor necrosis factor α; CT, computed tomography; DTH, delayed-type hypersensitivity; NTM, nontuberculous mycobacteria; ESAT-6, early secreted antigenic target 6 kDa; QFT, QuantiFERON-TB; IFN-γ, interferon γ; ELISPOT, enzyme-linked immunospot; OR, odds ratio; CI_{95}, 95% confidence interval.

EXECUTIVE SUMMARY

Targeted tuberculin skin testing and appropriate management of individuals with latent tuberculosis (TB) infection (LTBI) are critical components of the TB-elimination strategy promoted by the United States Public Health Service (USPHS) Advisory Council on the Elimination of Tuberculosis.[1] Updated recommendations to improve testing and treatment of LTBI were developed recently by experts convened by the American Thoracic Society and the Centers for Disease Control and Prevention (CDC).[2]

The recommendations in this article have been developed by the Pediatric Tuberculosis Collaborative Group to address the need for specific recommendations for children and adolescents for health care providers serving pediatric populations. The age used to define pediatric TB disease and LTBI varies; for example, the CDC defines pediatric TB as occurring in persons <15 years of age. However, this article addresses the needs of children and adolescents from birth to 18 years of age. In this article, LTBI is defined as a child or adolescent with a positive tuberculin skin test (TST) who has no evidence of TB disease. A glossary of terms used in this article is presented in Table 1.

There are numerous differences in the strategies for targeted tuberculin skin testing and management of LTBI in adults compared with children and adolescents. Targeted skin testing in adults is focused primarily on finding individuals at risk for progression to TB disease (eg, persons recently infected, persons with clinical conditions such as human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS], renal disease, or diabetes, which are associated with a high risk of progression from LTBI to TB disease). In contrast, targeted skin testing in children and adolescents focuses on pediatric populations at high risk for LTBI in addition to those patients at risk of progression to TB disease. Treatment is recommended for all children and adolescents diagnosed with LTBI because (1) the drugs used are safe in the pediatric population, (2) infection with *Mycobacterium tuberculosis* is more likely to have been recent, (3) young children are at a higher risk for progression to TB disease, and (4) the pediatric population has more years to potentially develop TB disease. Furthermore, targeted testing for LTBI in the general pediatric population is likely to be conducted by primary health care providers such as pediatricians, family practitioners, and nurse practitioners.

This consensus statement was developed by experts in the care of children and adolescents with TB disease and LTBI. This panel was convened by the co-chairs in consultation with the CDC, and this process was endorsed by the American Academy of Pediatrics (AAP). The multidisciplinary panel included health care professionals from health departments, the CDC, the National Tuberculosis Centers, and academic institutions. Relevant studies and unpublished data sets compiled by the participants

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were summarized. Evidence-based recommendations were developed to update and supplement the recommendations by the *2003 Report of the Committee on Infectious Diseases*.[3]

The data presented in this article support a paradigm shift and a change in guidelines for tuberculin skin testing. Children and adolescents should be screened for risk factors for TB and LTBI and tested with a TST only if ≥1 risk factors are present. "Routine" or "mandated" LTBI testing policies for pediatric patients without risk factors are strongly discouraged (eg, entry into day care, school, summer camp, or college).

Targeted Tuberculin Skin Testing

Targeted tuberculin skin testing is intended to identify children and adolescents at risk for LTBI who would benefit from treatment to prevent the progression to TB disease. Targeted testing discourages tuberculin skin testing of low-risk populations and focuses on testing children with risk factors. Several recent studies have delineated risk factors for LTBI in children (Table 2). These studies were conducted in different pediatric populations but found very similar risk factors including foreign birth, foreign travel, and a close association with persons having TB disease or LTBI. Based on these factors, a risk-factor questionnaire was developed by the consensus panel to facilitate screening by pediatric health care providers in a variety of clinical settings (Table 3). The use of the screening questionnaire and the precise questions asked will vary from population to population depending on local epidemiology.

Specific types of targeted testing include contact investigations, source-case investigations, associate investigations (Table 1), and school-based screening. Throughout this article a distinction is made between source-case investigations (ie, evaluating the contacts of a child with TB disease) versus associate investigations (ie, evaluating the contacts of a child with LTBI). The use of these investigations should be considered in the context of their yield in specific settings, their available resources, and the ability of the health care system to thoroughly evaluate and treat all those tested.

Administration, Reading, and Interpretation of TSTs

The only recommended TST method is the intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD) from *M tuberculosis* administered by the Mantoux technique. Multiple-puncture tests (MPTs) or the Tine test are not recommended for use. TSTs should be read 48 to 72 hours after placement by a trained health care provider. Results should be recorded as millimeters of induration (eg, 00 mm, 12 mm, etc).

The results of the TST are interpreted in the context of the patient's risk of *M tuberculosis* infection, ie, exposure to TB disease or risk of progression to TB disease. Three cutoff levels (≥5, ≥10, or ≥15 mm) are used to improve the sensitivity and specificity of the TST (Table 4).

Evaluation for a Positive TST

Children and adolescents with a positive TST should undergo the following evaluations. A history should be taken to determine the presence of symptoms of TB disease or coexisting medical conditions that could complicate medical therapy for LTBI or increase the risk of progression to TB disease (Table 5). A physical examination (Table 6) and a chest radiograph should be performed to exclude TB disease. Baseline liver-function tests are not recommended for children or adolescents before or during treatment with isoniazid (INH) for LTBI unless co-

TABLE 1. Definition of Terms Used

Term	Definition
Associate investigation	Associate investigations can be conducted by health departments or primary care providers for children with LTBI to identify the individual who may have infected the child. The household contacts (including other children, adolescents, and adults) of a child with LTBI are evaluated by history, physical exam, TST, and/or chest radiograph to detect TB disease or LTBI.[44]
Associate	Person who shares a residence, who frequently sleeps in the residence, or is in close contact with the index child with LTBI. Associates may be other children, parents, grandparents, a babysitter, friend, or other relatives.[44]
Contact investigation	Contact investigations are generally conducted by health departments to identify persons exposed to patients with infectious TB, promptly evaluate the exposed persons for LTBI or TB disease, and provide treatment, if indicated.[1]
LTBI	Infection with *M tuberculosis* is usually detected by a TST. Such persons have no signs or symptoms of pulmonary or extrapulmonary TB disease, have a chest radiograph that is not suggestive of TB disease, or has evidence of healed TB disease (eg, granulomas, calcification). Such persons are not infectious.[150]
Source-case investigation	Source-case investigations are generally conducted by health departments for children with active TB to identify the individual who may have infected the child. The close contacts (including other children, adolescents, and adults) of a child with TB disease are evaluated by history, physical exam, TST, and/or chest radiograph to detect TB disease or LTBI.
Targeted skin testing	Targeted skin testing uses a screening questionnaire to elicit risk factors for TB and LTBI and the selective use of the TST in children and adolescents with identified risk factors.
TB disease	Persons with TB disease (also referred to as active TB or TB) may have signs and/or symptoms of illness caused by *M tuberculosis*, although children with TB disease may be asymptomatic. Disease may be pulmonary, extrapulmonary, or both. Children and adolescents with TB disease of the lungs or larynx can be infectious to others.

TABLE 2. Comparison of Studies Assessing Risk Factors for LTBI in Children and Adolescents by Multivariate Analysis

Study Location	Study Design (n = No. of Participants)	Risk Factors					
		Contact With TB disease	Foreign Birth	Foreign Travel	BCG Immunization	Family Member With LTBI	Additional Factors
California[17] (statewide)	Case (n = 72) Control (n = 881)	NA	NA	OR = 3.9 (CI_{95} = 1.9–7.9)	NS	NA	Household visitor from a high-prevalence country: OR = 2.4 (CI_{95} = 1.0–5.5) Female: OR = 1.8 (CI_{95} = 1.0–3.2)
New York, NY[18]	Case (n = 96) Control (n = 192)	RR = 61.6 (P = .0004)	RR = 9.2 (P < .0001)	RR = 7.5 (P = .0002)	NS	RR = 15.7 (P < .0001)	NS
San Diego, CA[19]	Case (n = 51) Control (n = 72)	NS	NS (collinear with BCG excluded from model)	NS	OR = 53 (CI_{95} = 13–224)	OR = 4.9 (CI_{95} = 1.4–16.5)	TST within 12 mo: OR = 24 (CI_{95} = 1.7–347)
Northern California[20]	Prospective observational (n = 31 926)	See "Family Member With LTBI"	OR = 8.6 (CI_{95} = 6.2–12.1)	OR = 2.1 (CI_{95} = 1.5–2.9)	OR = 2.3 (CI_{95} = 1.7–3.1)	Household member with history of positive TST or TB disease OR = 1.5 (CI_{95} = 1.1–2.0)	Asian or Latin American ethnicity: OR = 1.6 (CI_{95} = 1.1–2.3)
Bronx, NY[21]	Prospective standard criterion (n = 2920)	OR = 91.7 (CI_{95} = 32.3–260.7)	OR = 14.8 (CI_{95} = 6.7–32.7)*		NA	NA	Age >11 y old: OR = 4.9 (CI_{95} = 2.2–10.9) Contact with high-risk adult†: OR = 6.5 (CI_{95} = 2.4–17.5)

NA indicates not assessed; NS, not significant; RR, risk ratio.
* The foreign birth and foreign travel factors were assessed together in a single question.
† Those who are HIV-infected, homeless, incarcerated, and/or illicit drug users.

TABLE 3. Risk-Assessment Questionnaire*

Questions
1. Was your child born outside the United States?
   If yes, this question would be followed by: Where was your child born? If the child was born in Africa, Asia, Latin America, or Eastern Europe, a TST should be placed.
2. Has your child traveled outside the United States?
   If yes, this question would be followed by: Where did the child travel, with whom did the child stay, and how long did the child travel? If the child stayed with friends or family members in Africa, Asia, Latin America, or Eastern Europe for ≥1 week cumulatively, a TST should be placed.
3. Has your child been exposed to anyone with TB disease?
   If yes, this question should be followed by questions to determine if the person had TB disease or LTBI, when the exposure occurred, and what the nature of the contact was. If confirmed that the child has been exposed to someone with suspected or known TB disease, a TST should be placed.
   If it is determined that a child had contact with a person with TB disease, notify the local health department per local reporting guidelines.
4. Does your child have close contact with a person who has a positive TB skin test?
   If yes, see question 3 (above) for follow-up questions.

Risk-assessment questionnaires can include the following questions based on local epidemiology and priorities
1. Does your child spend time with anyone who has been in jail (or prison) or a shelter, uses illegal drugs, or has HIV?
2. Has your child drank raw milk or eaten unpasteurized cheese?
3. Does your child have a household member who was born outside the United States?
4. Does your child have a household member who has traveled outside the United States?

* Adolescents can be asked these questions directly.

TABLE 4. Definitions of Positive TST Results in Children and Adolescents Using 3 Cutoff levels

Induration ≥5 mm
- Children or adolescents in close contact with a known or suspected infectious case of TB
- Children or adolescents with suspected TB disease:
  - Finding on chest radiograph consistent with active or previously active TB
  - Clinical evidence of TB disease
- Children or adolescents who are immunosuppressed (eg, receiving immunosuppressive therapy or with immunosuppressive conditions [eg, HIV infection])

Induration ≥10 mm
- Children or adolescents at increased risk of disseminated disease:
  - Those <4 y old
  - Those with concomitant medical conditions (eg, Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition)
- Children or adolescents with increased risk of exposure to cases of TB disease:
  - Those born in a country with a high prevalence of TB cases
  - Those who travel to a country with a high prevalence of TB cases
  - Those with parents born in a country with a high prevalence of TB cases
  - Those frequently exposed to adults with risk factors for TB disease (eg, adults who are HIV-infected or homeless, users of illicit drugs, those who are incarcerated, or migrant farm workers)

Induration ≥15 mm
- Children ≥4 y old with no known risk factors

Modified from American Academy of Pediatrics. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 25th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:642–660.

existing medical conditions are present that increase the risk of hepatotoxicity.

Treatment Regimens for LTBI and Improving Adherence to Treatment

The treatment recommendations presented in this article are rated by using the USPHS rating scale that grades the strength of the recommendation[4] and the quality of the evidence[2] (Table 7). Treatment of LTBI with 9 months of daily INH remains the recommended regimen for children and adolescents without a known source case or with a source case whose *M tuberculosis* isolate is susceptible to INH. Intermittent (2- or 3-times-per-week) regimens are acceptable if these regimens are administered by using a directly observed therapy (DOT) program (Table 8). Daily rifampin for 6 months is a suitable alternative for patients with LTBI who have been exposed to a source case whose isolate is resistant to INH but susceptible to rifampin or for those who cannot tolerate INH. Shorter-course regimens with rifampin and pyrazinamide are not recommended because of hepatotoxicity observed in adults and the lack of clinical data in children.[5,6] The care and treatment of children and adolescents exposed to a source case with a multidrug-resistant (MDR) *M tuberculosis* strain should be in consultation with an expert in the management of children with MDR TB using DOT.

Before initiating therapy, it is critical to provide patients and families with verbal and written information regarding signs and symptoms of hepatotoxicity and other side effects. During treatment for LTBI, children should be evaluated monthly by a health care provider to reinforce adherence, to be evaluated for toxicities, and to assess possible progression to TB disease. At this time, completion rates of treatment for LTBI are suboptimal. Strategies to monitor and improve adherence to treatment are needed. Potential strategies to improve adherence include educational, organizational, and behavioral interventions (Table 9).

Summary

In conclusion, the following steps are required to appropriately screen, test, evaluate, and treat children and adolescents for LTBI:

- Assess an individual child or adolescent for risk factors for LTBI or TB disease by using a risk-factor questionnaire.
- If any risk factors are present, test for LTBI/TB with a TST.
- Determine the induration of the TST by measuring the transverse diameter of the reaction and record in millimeters.
- Decide if the millimeters of induration represent a positive TST based on the criteria for the 3 cutoff levels.
- If the TST is positive, decide if further evaluation is needed, including a complete history, targeted physical examination, and chest radiograph.
- After evaluation is complete, determine if treatment for LTBI is indicated.

TABLE 5. Medical History to be Obtained for a Child With a Positive TST

Evaluations	Comments
Signs and symptoms of TB disease	Cough; wheezing; fever; weight loss; failure to thrive; anorexia; decreased activity, playfulness, or energy; hemoptysis; musculoskeletal pain; lymph node swelling; personality changes
Past medical history	Previous history of LTBI or TB treatment
TB disease or LTBI	Previous TST history
Other	Concomitant medications With INH: alterations in phenytoin drug levels and carbamezipime increases risk of hepatotoxicity With rifampin: many drugs may interact, and potential interactions should be reviewed Past hospitalizations Underlying diseases (eg, hepatitis, HIV) Drug allergies Maternal HIV status (if known) Recent immigration from an area with a high incidence of TB-drug resistance
Potential source-case identification	Known contact with TB patient TB treatment history (erratic or previous treatment predicts drug resistance) of source case Susceptibilities of isolate of source case (if known)
Assessment of factors that can impact adherence	Living in temporary housing or shelter Family remaining in treatment area Travel plans while on treatment Availability of DOT program Understanding of TB disease and LTBI

TABLE 6. Elements of the Targeted Physical Exam for Children With a Positive TST

Elements of Targeted Physical Examination	Physical Findings of TB Disease
General appearance and growth	Poor weight gain, falling off growth curve
Conjunctiva	Scleral icterus
Neck flexion	Neck stiffness
Lymph node palpation	Lymphadenopathy (neck, axilla)
Ascultation of lung	Rales, wheezes, decreased breath sounds over affected lung field
Auscultation of heart	Tachycardia, friction rub
Abdomen and flanks	Hepatosplenomegaly, flank tenderness
Spine/bones	Bone tenderness/limping
Skin	Jaundice or preexisting rashes (nodules, ulcers, papules, erythema nodosum)

TABLE 7. Recommended Regimens for the Treatment of LTBI in Children and Adolescents

Drugs	Duration, mo	Interval	Rating* (Evidence)
INH	9	Daily	A(II)
INH	9	2 or 3 times per wk (DOT)	B(II)
Rifampin†	6	Daily	A(III)
Rifampin-pyrazinamide	2	—	D(II)

Strength of the recommendation: A indicates preferred; B, acceptable alternative; C, offer when preferred or alternative regimens cannot be given and should not generally be given; D, should never be offered. Quality of evidence supporting the recommendation: I indicates at least 1 randomized trial with clinical endpoints; II, data from clinical trials that are not randomized or were conducted in other populations; III, expert opinion.

* USPHS rating system.[2]

† Rifampin preferred for LTBI caused by INH-resistant, rifampin-susceptible source.

- Ensure appropriate treatment and follow-up to promote completion of LTBI therapy.

INTRODUCTION

Trends in Pediatric TB

The CDC and state and local health departments continue to improve strategies to eliminate TB disease in the United States in partnership with pediatric health care providers. Rates of TB disease in children, especially among those from birth to <4 years of age, are important measures of the success of TB-control programs in interrupting and preventing TB transmission. In acknowledgment of the importance of pediatric TB disease and LTBI, the CDC has funded several recent studies and programs in pediatric populations including Zero Tolerance for Pediatric Tuberculosis and An Exploration of the Case Management of Pediatric Tuberculosis. After a recent resurgence of TB, there has been an overall decline in the TB case rate in the United States since 1992 (Fig

TABLE 8. Recommended Dosage for the Treatment of LTBI in Children and Adolescents

Dosage	INH
Daily dose	10–15 mg/kg
Maximum dose	300 mg
Daily dose by weight categories	
3–5 kg	50 mg
6–7.5 kg	75 mg
7.5–10 kg	100 mg
10–15 kg	150 mg
15–20 kg	200 mg
>20 kg	300 mg
Weekly dose	
2 times per wk	20–30 mg/kg
Maximum dose	900 mg
3 times per wk	20–30 mg/kg
Maximum dose	900 mg

Rifampin is occasionally used for LTBI treatment for children at 10 to 20 mg/kg per dose up to a maximum of 600 mg.

TABLE 9. Interventions to Promote Adherence to Treatment of LTBI

Educational	Disease-specific
	Language/culture-specific
	Content-appropriate cognitive level
	Parents/guardian
	Children
	Counseling
	Medical staff
	Peers
Organizational/support	DOT
	Clinic
	Home
	School
	Enablers
	Minimal waiting time in clinic
	Extended clinic hours
	Transportation assistance
	Dedicated staff
	Medication on site
	Medication reminders
	Appointment reminders
Behavioral	Reinforcement at each visit
	Incentives
	Monetary
	Entertainment coupons
	Refreshments
	Family therapy

1). In 1993, the case rate for children 0 to 4 years of age was 5.5 per 100 000, and the case rate for children 5 to 14 years of age was 1.7 per 100 000. In 2002, the case rates declined to 2.8 and 0.9 per 100 000, respectively. The decline in case rates from 1993 through 2002 was 49% for children 0 to 4 years of age and 47% for children 5 to 14 years of age.[7] Thus, pediatric TB disease remains a relatively rare disease with well-defined epidemiology in the United States.

Six states have two thirds of the cases of pediatric TB disease (Table 10).[7] Foreign-born children have higher case rates of TB disease than US-born children, although more cases occur in US-born children. Most of the burden of pediatric TB occurs in urban areas and among Hispanic and black, non-Hispanic children. The highest case rates in children continue to occur in those <5 years of age, with a second peak in rates during adolescence (Fig 1). Risk factors for TB disease in children have been well described,[8–11] as have missed opportunities to prevent pediatric TB disease in children <5 years of age.[12]

Partnership Between Health Departments and Other Pediatric Health Care Providers to Eliminate TB

Control of TB disease in children and adolescents must occur nationally as well as locally as health departments partner with pediatric health care providers. A hierarchy of TB-control activities is conducted by health departments to prevent TB disease and LTBI. The most important efforts are the timely identification and effective treatment of patients with TB disease to interrupt transmission. Other critical control measures to prevent TB disease are contact and source-case investigations generally conducted by health departments (Table 1). Although contact, source-case, and associate investigations are conducted primarily by health departments to detect undiagnosed cases of TB disease within the community, these activities lead to the identification of many persons, including children and adolescents, with LTBI.

The third level of TB control is the identification and treatment of individuals with LTBI. This effort, although conducted in part by health departments, is more likely to be conducted by other pediatric health care providers such as pediatricians, family practitioners, and nurse practitioners. Strategies to accomplish this third level of control include a variety of targeted tuberculin skin-testing programs including screening high-risk children and adolescents for LTBI risk factors during primary care visits or in school through school-based screening programs.

Increasing Importance of Targeted Tuberculin Skin Testing in the United States

As the rate of TB disease has declined in the United States, accurate identification and completed treatment of persons with LTBI are increasingly critical components of TB-elimination strategies.[13] Previous recommendations prioritized the identification of high-risk persons, including children and adolescents, at increased risk of progression to TB disease.[14] More recent studies have further delineated risk factors for LTBI in children and adolescents and allow further refinements for targeted tuberculin skin testing in general pediatric populations. Thus, the recommendations in this article will focus exclusively on children and adolescents both to identify those at the highest risk of progression to TB disease and those most likely to have LTBI who would benefit from treatment.

SCIENTIFIC RATIONALE FOR RECOMMENDATIONS

Strategies for Targeted Skin Testing

Several groups of children and adolescents should undergo tuberculin skin testing, including patients at high risk of recent infection such as contacts of persons with TB disease, those at high risk of progression because of underlying conditions such as those with HIV/AIDS, or those with signs or symptoms of

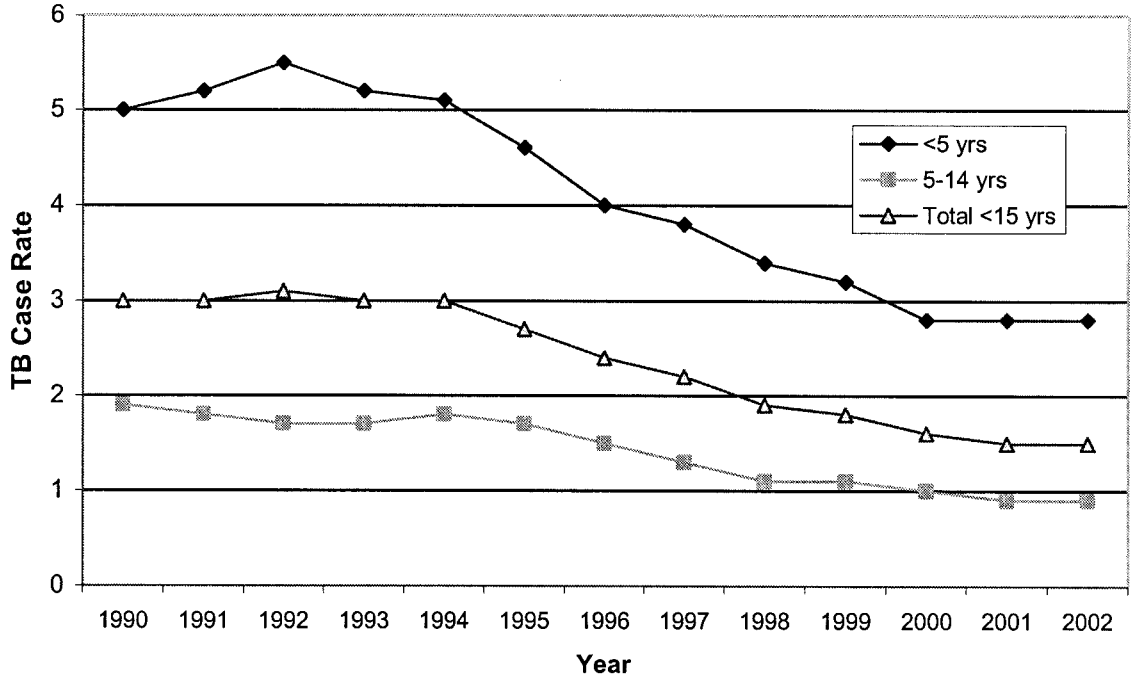

Fig 1. Shown are pediatric TB case rates in the United States per 100 000 population from 1990 to 2002 by age groups: <5 years of age, 5 to 14 years of age, and all children <15 years of age.7

TABLE 10. States With the Highest Number of Pediatric TB Cases as Reported to the CDC, 1990–2002

State	Cumulative Pediatric Cases[7]	
	n	%
California	4883	28
Texas	2064	12
New York	1686	10
Illinois	845	5
Florida	748	4
Georgia	690	4
All other states	6481	37
Total	17 397	100

TB disease. Pediatric patients who have signs or symptoms consistent with TB disease must undergo immediate tuberculin skin testing as part of the assessment process. It is important to note that a negative TST does not exclude TB disease. A detailed discussion of TB disease in pediatric patients is beyond the scope of this article, but several recent publications address this topic.[8–11]

In addition to testing the groups of children listed above, this article presents a paradigm shift in the recommendations for pediatric health care providers to promote the targeted tuberculin skin testing of children and adolescents. Targeted skin testing replaces the concept of a routine TST placed in primary health care settings. "Administrative" or mandated TSTs for entry to day care, school, summer camp, or college are strongly discouraged in the absence of risk factors. Instead, children and adolescents should be screened for risk factors for TB disease and LTBI by using a risk-assessment questionnaire as described below and tested with a TST only if ≥1 risk factors are present.

Contact and Source-Case Investigations

Pediatric patients who are contacts of a patient with known or suspected TB disease must be evaluated promptly for TB disease or LTBI and undergo immediate tuberculin skin testing as part of the assessment process, which would include testing the contacts of an infectious adult or adolescent (contact investigation) as well as testing the contacts of a child with TB disease (source-case investigation).

Studies continue to emphasize the value of contact investigations to identify children with TB disease or LTBI.[12,15,16] Marks et al[15] compared the outcomes of contact investigations with and without home visits that were conducted for 1080 infectious adult TB patients. Home visits identified 6.7 close contacts, whereas only 4.7 contacts were identified when home visits were not conducted. The additional contacts identified were likely to be children <6 years of age. In this study, 21% (132 of 618) of children <6 years of age had a positive TST (≥5 mm), and 5% (35 of 705) of such children had evidence of TB disease. Thus, identifying and evaluating young children during contact investigations of infectious adults are critical components of TB-control efforts.

Similarly, Lobato et al[16] assessed the yield of source-case investigations conducted for children <5 years of age with active TB for detecting cases of undiagnosed TB and LTBI in children and adolescents in California.[16] In all, 111 source-case investigations were performed, and 31% (254 of 815) of persons with whom the index cases had frequent exposures were <15 years of age. In all, 6% (7 of 141) of children <5 years of age were found to have undiagnosed TB disease. The rates of LTBI were 24% (34 of 141) and 32% (36 of 113) among children <5 and 5 to 14 years of age, respectively. This study

confirms the importance of assessing other children for TB and LTBI during a source-case investigation.

Screening Children and Adolescents for Risk Factors for LTBI Using a Questionnaire

Several recent studies have assessed risk factors for LTBI in pediatric populations and provided additional justification for targeted tuberculin skin testing. Rather than the use of a TST as a screening tool, these studies promoted the use of a questionnaire as a screening tool. Although these studies assessed different populations, there were marked similarities in their findings (Table 2). Lobato and Hopewell[17] conducted a case-control study in 953 children <6 years of age who had a TST read at health clinics in California. Risk factors for a positive (≥10-mm) TST included foreign travel within the previous 12 months (defined as a trip of >1 week to a country with a high prevalence of TB disease) or a household visitor from such a country.

In a similar study, Saiman et al[18] performed a matched case-control study among children 1 to 5 years of age in northern Manhattan and Harlem (New York) whose TSTs were placed by their health care provider as part of routine primary care. Contact with an adult with TB disease, foreign birth, foreign travel, or a relative with a positive TST were identified as risk factors for LTBI. Besser et al[19] performed a similar analysis of risk factors for LTBI among children <6 years of age in San Diego, California. In this population, bacillus Calmette-Guérin (BCG) immunization, a TST within 12 months, and a relative with a positive TST were risk factors for a positive TST (≥10 mm). Froehlich et al[20] performed a study to determine if a risk-assessment questionnaire could predict a positive TST in children in northern California and found that foreign birth, BCG immunization, living outside the United States, Asian or Hispanic ethnicity, or contact with a household member with TB disease or LTBI were independent predictors of LTBI.

Finally, Ozuah et al[21] sought to determine the sensitivity, specificity, and predictive validity of a New York City Department of Health questionnaire[22] in 2920 children. In all, 14% (413 of 2920) of children had at least 1 risk factor (Table 2), and of these, 6% (23 of 413) had a positive TST (≥10 mm). In contrast, 0.16% (4 of 2507) of children without risk factors identified had a positive TST. The sensitivity of the questionnaire was 85% and the specificity was 86%; the negative predictive value was 99.9%, but the positive predictive value was only 5%. Notably, the questionnaire failed to detect risk factors in 4 children with positive TSTs, of whom 3 were >11 years of age. This suggested that the questionnaire may not have addressed all risk factors in adolescents such as exposure to individuals outside of the immediate household.

Delineation of High-Risk Adults

Past recommendations have suggested that exposure to adults at high risk of TB disease places a child at increased risk for LTBI and TB disease. However, few studies have characterized the magnitude of risk. The studies detailed above attempted to clarify which populations of adults were "high risk."

In the population studied by Saiman et al,[18] contact with adults with illicit drug use or HIV/AIDS or adults who were homeless or incarcerated were not risk factors for LTBI in children, nor were foreign-born parents, visitors from abroad, or foreign travel by parents. In contrast, Lobato et al[17] found that a visitor from abroad was a risk factor for LTBI in children in California. Ozuah et al[21] found that contact with an adult with HIV or illicit drug use or who was homeless or incarcerated was a risk factor for LTBI in children in the Bronx. Thus, the definition of a high-risk adult varied from population to population.

International Adoption of Children

For over a decade, the unique medical needs of internationally adopted children have been recognized, because these children are at risk for infectious diseases acquired in their countries of origin.[23] Several investigators have evaluated international adoptees for LTBI and TB disease. Saiman et al[24] performed TSTs on 404 internationally adopted children; 19% (75 of 404) had positive TSTs (TST ≥ 10 mm) and normal chest radiographs. In contrast, previous rates of LTBI among international adoptees ranged from 0.6% to 5%.[23,25–29]

The marked differences in the prevalence of LTBI noted in different studies may reflect changes in the epidemiology of internationally adopted children. As the primary countries of origin have changed, the prevalence of prior BCG immunization and possible exposure to TB disease (eg, in orphanages) have both increased. In addition, during the 1990s, the rates of TB disease rose worldwide. In earlier studies, most international adoptees were born in Korea and Romania,[25,30] whereas the children evaluated by Saiman et al[24] were primarily born in China and Russia. Among 873 Korean adoptees, none had received BCG immunization, and 90% had lived with foster families.[25] In contrast, 60% of the children adopted from 1997 to 1998 had received BCG immunization, and 88% had lived in orphanages.[24]

TB disease is far less common than LTBI among internationally adopted children, but a recent report described extensive transmission of TB disease to close contacts of a child adopted from the Marshall Islands.[31] Evaluation with a TST on US arrival and treatment for LTBI may have prevented the development of TB disease in this child who was clinically well at the time of adoption.

In summary, several studies have identified risk factors for LTBI in children, such as contact with an adult with active TB, foreign birth (including internationally adopted children), travel to a country with a high prevalence of TB, and a household member with LTBI. Additional risk factors such as contact with high-risk adults or household visitors from a country with a high prevalence of TB disease may be risk factors in some populations. However, few of these studies addressed risk factors for adolescents. Risk factors should be assessed on an individual basis to determine the need for placement of a TST.

School-Based Screening for LTBI

Routine placement of TSTs at school entry has been used as an opportunity to screen children and adolescents for TB disease and LTBI. A recent study of universal school-based screening throughout the United States has demonstrated low rates of TB disease (<0.02%) and LTBI (<2%).[32] However, the prevalence of TST positivity among foreign-born students was 6 to 24 times higher than among US-born students. Thus, it has been recommended that only foreign-born students from countries with high case rates of TB be targeted for assessment for LTBI by tuberculin skin testing.[33]

As additional support of a targeted approach for school-based screening for LTBI, Mohle-Boetani et al[34] evaluated the cost-effectiveness of screening strategies to prevent TB disease. These authors compared a screen-all strategy (ie, testing all kindergarten and high-school entrants) with targeted screening (ie, testing only high-risk students in these age groups, defined as birth in a country with a high prevalence of TB disease). Targeted screening was more cost-effective because it was estimated to prevent 85 cases of TB disease per 1000 persons tested, compared with the screen-all strategy, which only prevented 15 cases per 1000 persons tested. In this analysis, the screen-all strategy would be cost-effective only if the prevalence of LTBI was ≥20%.

Additional studies have suggested that school-based targeted testing should be focused primarily on foreign-born adolescents. Scholten et al[35] reported the prevalence and risk factors associated with positive TSTs among school children in New York City, New York, from 1991 to 1993. Overall, 2.1% (6326 of 298 506) of new school entrants had a positive TST (≥10 mm). However, 0.5% (931 of 199 728) of US-born children had a positive TST compared with 9% (3794 of 41 346) of foreign-born students. Older children had the highest prevalence of LTBI; 11% (1548 of 14 067) of adolescents in grades 7 to 12 had a positive TST. Similar findings were observed in Los Angeles County, California, among students in grades kindergarten to 12; 1.4% of US-born students versus 18.3% of foreign-born students had a positive TST.[36]

Gounder et al[37] expanded these previous observations and described the experience in New York City from 1991 to 1998 (Table 11; Fig 2). In 1990, a TST was mandated for all new school entrants, but in 1996 the health code was amended, and a TST was mandated only for new entrants to secondary schools. In this study, 788 283 children and adolescents were evaluated for LTBI. The proportion of students with positive TSTs varied by age, race, and birth place; US-born Asian students and foreign-born students were most likely to have a positive TST. Among US-born students, 0.5% (2553 of 515 005) had a positive TST, whereas among foreign-born students, 9.3% (10 413 of 112 081) had a positive TST. Older age, defined as 12 to 16 years of age, was associated with an increased prevalence of positive TSTs in both US- and foreign-born students (Table 11). Unfortunately, changes in the health code did not substantially alter tuberculin skin-testing practices. Moreover, the majority of children tested by this semitargeted strategy were at low risk for LTBI. The authors concluded that improving targeted testing and educating and garnering the support of pediatric health care providers and school personnel were needed to alter tuberculin skin-testing practices.[37]

School-based screening for LTBI is allowed under the state health and safety code in California.[38] Pong et al[39] demonstrated high rates of TST positivity among 1504 high school students in San Diego. Two high schools were studied, and positive TSTs were found in 13% (95 of 744) and 24% (207 of 860) of students. Non–US-born students were significantly more likely to have positive skin tests than US-born students in all ethnic groups except Latinos (at 1 school). Overall, excluding Latinos, non–US-born students had positivity rates of 40%, whereas US-born students had positivity rates of 2%. Among foreign-born versus US-born Latinos, the TST positivity rate was 41% vs 13%, respectively, which suggests that local epidemiology must be considered when designing targeted testing programs for schools.

Moser presented additional experience with targeted testing of adolescents in San Diego (K. Moser, MD, MPH, written communication, 2003). To facili-

TABLE 11. Demographic Factors Associated With a Positive TST Among 788 283 New School Entrants in New York City, 1991–1998

Characteristic	Tested, *n* (%)	Positive TST, *n* (%)	US-Born, OR_{ad} (CI_{95}) (*n* = 515 005)*	Foreign-Born, OR_{ad} (CI_{95}) (*n* = 112 081)
Age, y				
3–5	539 121 (68)	4675 (0.9)	1.0	1.0
6–11	178 688 (23)	6224 (3.5)	1.6 (1.4–1.7)	1.5 (1.5–1.6)
12–16	70 474 (9)	6801 (9.7)	3.7 (3.3–4.2)	3.0 (2.8–3.2)
Race/ethnicity				
White	120 160 (15)	1968 (1.6)	1.0	
Black	152 686 (19)	2959 (1.9)	1.8 (1.5–2.1)	—
Asian	59 039 (8)	3139 (5.3)	2.8 (2.4–3.4)	—
Hispanic	188 282 (24)	4018 (2.1)	1.9 (1.7–2.2)	—
TB incidence in birthplace				
Low	552 468 (70.1)	5470 (1.0)	NA	1.0
High†	72 895 (9.3)	7297 (10.0)	NA	1.6 (1.5–1.6)

NA indicates not assessed; OR_{ad} = adjusted OR; —, not assessed. Modified from Gounder CR, Driver CR, Scholten JN, Shen H, Munsiff SS. *Pediatrics*. 2003;111:e309.

* Birthplace was unknown for 20% of tested children.

† Defined as countries estimated as having ≥20 acid-fast–bacilli sputum smear-positive cases per 100 000 people.[151]

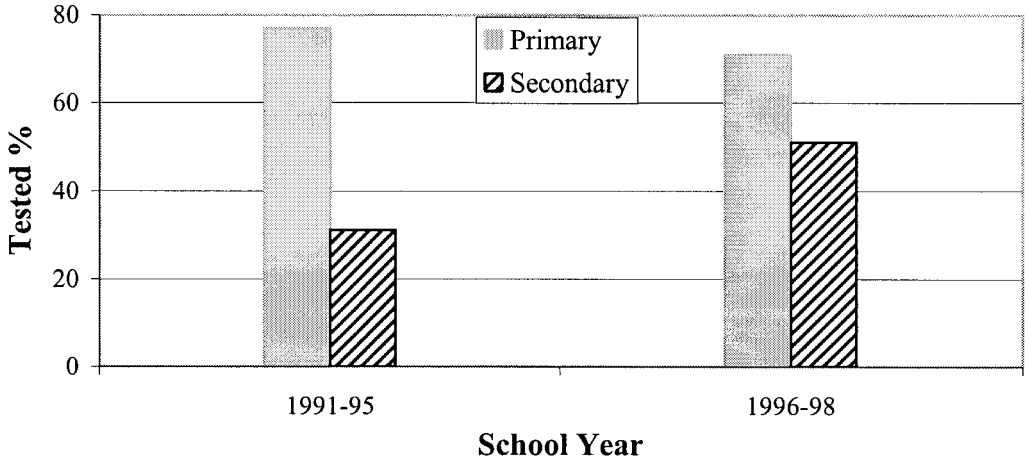

Fig 2. Shown are TB testing rates of first-time entrants to New York City schools from 1991 to 1998 by school level and year. In 1996, the health code was amended to test only new entrants to secondary schools. Modified from Gounder CR, Driver CR, Scholten JN, Shen H, Munsiff SS. *Pediatrics*. 2003;111:e309.

tate such screening, a school coordinator was hired in 2001, and several models were developed in high schools and middle schools based on their populations and capacities. One district tested foreign-born high school students and had a 32% (154 of 489) TST positivity rate. One district tested middle and high school students in English-learners' classes, and another tested high school migrant-education–supported students, yielding a 25% (16 of 64) and 43% (23 of 54) TST positivity rate, respectively. A 3-question risk-assessment questionnaire was used in 2 high schools: (1) Were you born in or have you lived in Asia, Africa, Eastern Europe, and/or Latin America (including Mexico)? (2) Have you visited Asia, Africa, Eastern Europe, and/or Latin America (including Mexico) for >2 weeks? (3) Have you spent time close to someone sick with TB? Among students who answered "yes" to any of the 3 questions, the TST positivity rates were 19% in 1 school and 32% in the other. Combined data from 1073 students tested through targeted efforts in San Diego high schools and middle schools in the 2001 and 2002 academic years demonstrated that foreign-born students, US-born Hispanics, and US-born non-Hispanics had TST positivity rates of 35% (237 of 684), 24% (82 of 335), and 5% (1 of 21), respectively.

Hsu et al[40] examined the correlation with self-reported risk factors and recent TSTs to determine if at-risk adolescents were being screened for LTBI in Boston public schools. Although the majority of 9th-grade students surveyed (75% [436 of 578]) did report at least 1 risk factor, only 40% (231 of 578) had been tested for LTBI. Notably, 81% reported that they had an annual checkup. The authors concluded that screening and testing for LTBI was not occurring appropriately among adolescents in Boston attending public schools and that school-based programs were needed.

Thus, data suggest that, in some communities, middle school and high school may be ideal settings to screen and test adolescents for LTBI because of the higher prevalence of infection. To be effective, a risk-factor questionnaire should consider local TB epidemiology. The increased risk of developing reactivation and infectious TB among adolescents also makes school-based screening, targeted testing, and treatment desirable.[41]

Associate Investigations as a Targeted Tuberculin Skin-Testing Strategy

Associate investigations traditionally are performed by health departments whereby the close contacts of children with LTBI (ie, their associates) are tested to detect undiagnosed cases of infectious TB. However, associate investigations may detect greater numbers of associates with LTBI and thus may be considered a form of targeted testing for LTBI. The AAP currently recommends that the associates of children with a positive TST undergo tuberculin skin testing.[3] In general, most health departments perform associate investigations for children <4 years of age with LTBI because young children are likely to have been infected recently and have a limited number of associates, which theoretically makes the likelihood of finding an active case of TB among their associates high.

The yield of associate investigations has been evaluated in several studies. Sullam et al[42] conducted associate investigations for 297 children with LTBI <8 years of age. The associates were largely foreign-born, primarily Asian, and resided in San Francisco, California. Associate investigations detected undiagnosed cases of TB disease in 0.36% (3 of 831) of associates, but more striking is that 40% (330 of 831) of associates had positive TSTs and were considered candidates for LTBI treatment.

Soren et al[43] studied 659 associates of 187 children and adolescents ≤21 years of age with LTBI in northern Manhattan. This study population was largely Hispanic immigrants, primarily from the Dominican Republic. No cases of TB disease were detected among the associates, but 32% (210 of 659) had positive TSTs (≥10 mm).

Driver et al[44] examined the yield of associate investigations conducted in New York City by the Department of Health. In all, 980 associates of 207

children ≤3 years of age were evaluated, and 26% (255 of 980) had a positive TST. However, the yield was higher among household associates: 30% (198 of 668) had a positive TST, compared with 18% (57 of 312) of nonhousehold associates ($P < .01$). This associate-testing effort detected TB disease in 0.3% (3 of 980) of those assessed.

The Health Department in San Diego performed associate investigations among 234 children ≤5 years of age reported from January 2001 to March 2002 (K. Moser, MD, MPH, written communication, 2003). In all, 910 associates of these primarily Hispanic children were identified, and 78% (713 of 910) were evaluated. No cases of TB disease were detected, but 41% (292 of 713) of associates had a positive TST.

The Tarrant County (Texas) Health Department conducted targeted associate investigations from January 1999 to December 2001.[45] Associate investigations in Tarrant County are targeted to associates of non–BCG-immunized children <6 years of age because such children are hypothesized to be more likely to have a positive TST from community transmission of *M tuberculosis*. Overall, 16% (38 of 232) of children with LTBI met these criteria, and 259 of their associates were tested (median: 7.8 associates per investigation). Undiagnosed, culture-confirmed TB disease was detected in 3% ($n = 8$) of associates, all of whom were foreign-born, yielding a rate of 21 new cases of TB disease per 100 investigations performed. In addition, 43% (110 of 259) of associates had LTBI, of whom 72% ($n = 79$) were foreign-born.

In summary, among high-risk populations (eg, foreign-born persons), associate investigations can identify associates with a high prevalence of LTBI. Some health districts have further refined associate investigations by targeting efforts to non–BCG-immunized children. These strategies also may enhance efforts to detect new cases of TB disease. The cost-effectiveness of associate investigations compared with other methods of targeted testing has not been studied.

Underlying Medical Conditions and Concomitant Medications

Several medical conditions and concomitant medications increase the risk of progression to TB disease in persons infected with *M tuberculosis*. Thus, children and adolescents with such conditions or receiving such medications are candidates for LTBI screening. These medical conditions include HIV infection, diabetes, organ transplantation, chronic renal failure, and malignancies. The use of high-dose steroids, chemotherapy,[8–11] or agents with activity against tumor necrosis factor α (TNF-α) (eg, infliximab [Remicade]) has also been associated with progression to TB disease. Although the published reports linking TNF-α antagonists with active TB have been in adults,[46] these agents are being increasingly used for the treatment of joint, skin, and gastrointestinal diseases in pediatric patients. The manufacturers of these agents recommend assessing patients for LTBI before use. A review of the risks associated with these agents, proposed mechanism of action, and clinical management has been published.[47]

There are few published reports evaluating the risk of progression to TB disease in children and adolescents with LTBI who are receiving inhaled corticosteroids. Bahceciler et al[48] studied the effect of inhaled budesonide in 32 asthmatic children with positive TSTs (≥10 mm) and normal chest radiographs. The children were treated for a mean of 10 months with budesonide (mean cumulative dose: 275 mg) but did not receive INH. All 32 children had high-resolution computed tomography (CT) of the chest, and 22% (7 of 32) were thought to have detectable mediastinal lymph nodes that were unchanged on high-resolution CTs performed 9 months later. The authors concluded that inhaled steroids did not effect the progression to TB disease in patients untreated for LTBI. However, this report described a limited number of children followed for a relatively short period of time. Thus, larger studies with longer follow-up are needed.

Thus, children receiving medical treatments or recently diagnosed with conditions known to predispose adults to progression to TB disease should have a TST and begin treatment immediately if LTBI is diagnosed.

Diagnosis of LTBI

TSTs

Currently, a TST is the recommended method of identifying latent infection with *M tuberculosis* in children and adolescents. The principle underlying the TST is the delayed-type hypersensitivity (DTH) reaction, induced by the antigenic components of *M tuberculosis*. However, it is important to recognize the limitations of the TST to maximize its usefulness in clinical practice.

Mantoux Skin Test

History of PPD Preparations. Koch prepared the first tuberculin from concentrated filtrates of heat-sterilized tubercule bacilli, but the heterogeneity of the filtrate caused unreliable and nonspecific reactions.[49] Thus, Seibert developed PPD tuberculin in 1934 by using a protein precipitation of culture filtrates that reduced the amount of polysaccharides and nucleic acids in the preparation.[49] In 1939, PPD-S was prepared and continues to serve as the international reference to ensure equal biological potency among various lots of PPD.[2,50]

Administration of the TST by the Mantoux Method. The recommended TST is administration of the standardized PPD by the Mantoux method in which 0.1 mL of 5 TU of PPD tuberculin is injected intradermally to form a wheal ~6 to 10 mm in diameter.[51,52] Other concentrations (1 or 250 TU per dose) are not well standardized, less sensitive and specific, and not recommended.[53] Two tuberculin PPD preparations, Aplisol and Tubersol, are available in the United States.[2]

DTH Reaction. DTH reaction to a TST manifests as an indurated area at the site of the intradermal injection and usually begins within 5 to 6 hours of administration of the PPD as previously sensitized lymphocytes, monocytes, and macrophages infiltrate the site. The DTH reaches a maximum size by 48 to 72 hours and subsides over the subsequent few

days.[51,54] Proper reading of the TST includes measuring and recording the diameter of the area of induration in millimeters 48 to 72 hours after TST placement.[51] An immediate wheal-and-flare reaction may occur but usually disappears by 24 hours and should not be interpreted as a positive reaction to a TST.[49] Rarely, the immediate reaction may be severe, and experts suggest that it may be prudent not to retest such individuals.[52] Although the area is frequently erythematous at 48 to 72 hours, only the area of induration should be measured. A negative TST should be recorded in millimeters (eg, 00 mm) and not as "negative." TSTs read after 72 hours of placement can underestimate the size of the initial DTH response, and if the TST is <10 mm, it should be repeated immediately. However, if a TST is read after 72 hours and is ≥10 mm, it can be considered positive if risk factors for LTBI are present. Duboczy and Brown[55] followed TST reactions for 7 days in adults with TB disease and found that 4.5% (14 of 239) of those with a TST >5 mm at 48 hours had no induration when read at 5 days. Thus, a TST must be read within 72 hours after placement to accurately determine the diameter of the area of induration.

There are several Web sites and educational materials that describe proper administration and reading of TSTs, including ones from the CDC Division of Tuberculosis Elimination (www.cdc.gov/nchstp/tb/pubs/slidesets/core/Chapter4/test8.htm and https://www2.cdc.gov/nchstp_od/piweb/tborderform.asp) and the New Jersey Medical School National Tuberculosis Center (www.umdnj.edu/ntbcweb/pr_frame.html).

MPTs

MPTs (eg, Tine, Aplitest, Mono-Vacc test, and the Heaf test) introduce tuberculin antigen into the skin through prongs coated with dried tuberculin or puncture the skin through a liquid film of tuberculin. There are several limitations associated with MPTs including: (1) the amount of antigen introduced is not precise, and reaction sizes are not standardized[51]; (2) all potentially positive reactions must be followed by a Mantoux test, which increases the cost and complexity of follow-up and prolongs the time until diagnosis and treatment; (3) MPTs may increase the potential for boosting; (4) MPTs have greater variability of sensitivity and specificity than the Mantoux method; and (5) the practice of allowing parents to interpret MPTs in non-health care settings further diminishes the accuracy of the test.[56]

Sensitivity and Specificity of TSTs

Unfortunately, there is no "gold standard" to diagnose LTBI. Thus, the sensitivity and specificity of the TST is difficult to calculate. The estimated sensitivity of currently available TSTs is based on the use of these tests in patients with TB disease and ranges from 80% to 96%.[51] Approximately 10% of immunocompetent children with TB disease have a negative TST.[56] False-negative and false-positive TSTS may be caused by several factors (Table 12).

Factors Associated With False-Negative TSTs

Active Infections. TB disease,[57,58] measles,[59] and varicella[60] may temporarily suppress the DTH response to a TST. Steiner et al[57] found that 14% (28 of 200) of children (1 month to 14 years of age) with culture-confirmed TB who were initially TST-negative (<5 mm) later became TST-positive. These children had meningitis, miliary TB, congenital TB, Pott's disease, or extensive pulmonary disease. In addition, 4.5% (9 of 200) of children with no apparent immunodeficiency and culture-proven pulmonary TB had persistently negative TSTs (<5 mm). Starr and Berkovich[59] studied 22 children with TB disease and positive TSTs who developed measles. In these children, the millimeters of induration were subse-

TABLE 12. Factors Associated With False-Negative or False-Positive TST Reactions

Factors	False-Negative Reactions	False-Positive Reactions
Infections	Viral illnesses (HIV, measles, varicella) Bacterial (typhoid fever, brucellosis, typhus, leprosy) Early TB infection (<12 wk) TB disease (meningitis, miliary, pleural) Fungal (*Blastomycosis*)	Exposure to NTM (eg, *M marinum*, *M kansasii*)
Live virus vaccines	Measles Polio Smallpox	BCG vaccine
Concomitant medical conditions	Metabolic abnormalities (chronic renal failure) Malignancies (Hodgkin's disease, lymphoma, leukemia) Sarcoidosis Poor nutrition	Transfusion with whole blood from donors with known positive TST[152]
Drugs and technical factors	Corticosteroids, chemotherapy Newborns and <2 y of age Material: poor quality; inadequate dose (1 TU); improper storage (exposure to heat/light); expired Administration: not injected intradermally; too long in syringe Reading: inexperienced or biased reader; recording error; read too early/late	Inexperienced or biased reader
Interpretative	Decreasing mm of induration	Increasing mm induration

quently decreased (some to 00 mm) during the measles incubation period and first 4 days of rash and remained decreased for an average of 18 days (range: 8–42 days). Similarly, a decrease in the millimeters of induration was noted during the incubation period of varicella through the first 6 days of rash in 41% (7 of 17) of children with TB disease who developed chickenpox. Upper respiratory infections are not known to influence the DTH response to a TST.

Live, Attenuated Vaccines. Live, attenuated vaccines such as measles, mumps, rubella, varicella,[61] oral polio,[62] BCG, and oral typhoid (TY21a) may temporarily suppress the DTH response to a TST.[2] Kupers et al[63] found a ≥50% decrease in the millimeters of induration in 13 of 17 TST-positive children 1 to 4 weeks after mumps immunization. Similarly, Berkovich et al[64] noted a decrease in millimeters of induration in 22% (4 of 18) of children with TB disease after mumps immunization. In another study of 24 children with TB disease conducted by Berkovich et al[65] to assess the impact of rubella immunization, 56% (10 of 18) of rubella-immunized children and 33% (2 of 6) of unimmunized children had a reduction in the size of their TST. A decrease in the size of a TST has been described 4 to 6 weeks after polio vaccine[62] and 1 month after smallpox vaccine.[66]

Brickman et al[67] sought to examine the impact of live viral vaccines administered at the same time as a TST. These authors administered measles, mumps, and/or rubella vaccines with TSTs to 100 children with previously positive TSTs. A control group consisted of 29 unimmunized children with previously positive TSTs. Overall, 3% (3 of 100) of immunized children and 3.6% (1 of 29) of unimmunized children had negative TSTs, supporting the recommendation that live vaccines and TSTs can be administrated at the same time. If the TST is indicated after a live, attenuated vaccine, it will likely be most accurate if 6 weeks have passed since vaccine administration.

Use of Corticosteroids. Corticosteroids may affect both the size of a TST and the progression of LTBI to TB disease. In adults, ≥15 mg of daily prednisone may cause suppression of previously positive TSTs, but the exact risk is unknown.[2] Bovornkitti et al[68] placed serial TSTs on adults with TB disease ($n = 58$) or adults with positive TSTs (≥5 mm) who had other illnesses requiring steroid treatment (40 mg/day of prednisone). The vast majority (97% [68 of 70]) reverted their TSTs to negative (00 mm) a mean of 14 days after starting steroids (treatment duration: 1–4 weeks). These adults reconverted to a positive TST a mean of 6 days after cessation of steroid treatment. In contrast, MacGregor et al[69] found no evidence of TST suppression in 12 adults with inflammatory diseases treated with alternate-day prednisone (average: 62 mg/day). Schatz et al[70] sought to examine the prevalence of positive TSTs among 132 patients with asthma (range: 9–76 years of age; mean: 47 years of age) receiving long-term steroids (mean duration of treatment: 4.7 years). The investigators placed TSTs on these study subjects and 28% (37 of 132) self-reported positive TSTs (≥10 mm). Those with negative TSTs received a significantly higher mean daily dose of corticosteroids than those with positive TSTs: 18 vs 11.6 mg/day, respectively ($P < .001$). However, the dose, dosing frequency, and length of treatment with corticosteroids that confer risk for a false-negative TST have not been defined for children and adolescents.

Anergy Testing. "Control" skin-test antigens such as *Candida*, mumps vaccine, diphtheria, or tetanus toxoid have been used to assess a patient's ability to mount a DTH response. This strategy was used in an attempt to improve the detection of a false-negative TST reaction, particularly among HIV-infected individuals with low CD4 lymphocyte counts. However, the use of control skin-test antigens has several limitations and is not recommended by the CDC as routine practice[71]: (1) the antigens administered and the reproducibility of the DTH have not been standardized[72]; (2) the diagnosis of anergy has not been associated with a high risk of developing TB disease; and (3) no demonstrable benefit from empiric INH therapy to prevent TB disease has been noted for anergic HIV-infected persons.[73]

Factors Associated With False-Positive TSTs

Previous BCG Immunization. Children born in countries with high case rates of TB disease are likely to have received BCG immunization in infancy. The World Health Organization estimates that 79% of the world's population has received a BCG vaccine. Twenty-two countries account for 80% of the world's TB cases and include India, China, Indonesia, Bangladesh, Nigeria, Pakistan, South Africa, the Philippines, Russia, Ethiopia, Kenya, Democratic Republic of the Congo, Vietnam, United Republic of Tanzania, Brazil, Thailand, Zimbabwe, Cambodia, Myanmar, Uganda, Afghanistan, and Mozambique (www.who.int/gtb/Country_info/index.htm). These nations recommend vaccination of children with BCG at birth, and some countries (eg, Brazil and Russia) revaccinate children during the school years. Mexico requires all children to receive BCG once between birth and 14 years of age, and the majority of children receive BCG by 5 years of age.[74,75] Thus, the impact of previous BCG immunization on TSTs is of great interest to pediatric health care providers in the United States caring for foreign-born children.

Numerous studies have assessed the relationship between the size of the TST and BCG immunization to determine the extent of false-positive reactions associated with BCG vaccine (Tables 13 and 14). Multiple studies have assessed the size of a single TST after a single BCG immunization. No significant effect of BCG immunization as a risk factor for LTBI was noted among children in New York,[18] northern Brazil,[76] Uganda,[77] or Botswana,[78] but the number of children in these studies was modest; only a few hundred children per study were assessed. Larger surveys conducted in Malawi[79] and Tanzania[80] consisted of >50 000 children and found a higher prevalence of positive TSTs (≥10 mm) in children with a BCG scar when compared with children without a scar. It is somewhat difficult to compare these studies because (1) different methods were used to document BCG immunization, including immunization

TABLE 13. Factors That May Influence the Effect of BCG Immunization on the TST

Factors	Comment
Age at immunization	Least effect if vaccinated at birth
Time since immunization	Most effect soon after immunization
Exposure to NTM	More effect with increased exposure
Prevalence of TB infection	Positive predictive value of TST increases with increasing prevalence of LTBI
Type of BCG vaccine used	Increased effect with increased number of viable bacilli

records and the presence of scars, (2) different vaccine strains and doses were administered, and (3) different TST methods were used.

Studies have also examined the size of the TST after a single BCG immunization. Lockman et al[78] studied 783 children in Botswana (age: 3–60 months) of whom 96% (755 of 783) had documentation of BCG immunization. The majority (79% [617 of 755]) had nonreactive TSTs (00 mm). Six percent ($n = 49$) had a TST between 1 and 4 mm, 8% ($n = 59$) had a TST between 5 and 9 mm, 5% ($n = 43$) had a TST between 10 and 14 mm, and only 2% ($n = 15$) had a TST of ≥15 mm.

Other studies examined the impact of age on the prevalence of TST positivity after BCG immunization. Rates of positive TSTs (≥10 mm) varied by age: 12% to 31% of 3-month-olds, 3% to 13% of 4-month- to 1-year-olds, and 0% to 18% of children over 1 to 5 years of age had positive TSTs.[76–78,81–84] Among older children, 4% to 36% of those 6 to 12 years of age and 7.5% to 15.5% of those 13 to 18 years of age had positive TSTs.[81,85–88]

Finally, the size of the TST after BCG immunization has been shown to correlate with the risk of developing TB disease. In Singapore, 17% (45 727 of 266 005) of school children who were vaccinated at birth had a TST ≥10 mm at 12 years of age.[89] These children then were followed for 4 years and found to have a 5- to 48-fold increased risk of developing TB disease when compared with children whose TST had been <5 mm at 12 years of age.

In summary, BCG immunization has a variable affect on TSTs. A minority of vaccinated children have a TST ≥10 mm, and older children are more likely to have a positive TST, suggesting the cumulative effect of exposure to TB disease and the risk of acquiring LTBI. Children who receive BCG after infancy or those who receive >1 BCG immunization also have an increased rate of positive TSTs (Table 14).[81,82,84,87,88,90,91] BCG immunization, especially if >1 BCG vaccination is given, is associated with boosting of the DTH response to TST.[53,92] Unfortunately, reactivity from BCG cannot be distinguished from reactivity from true infection with *M tuberculosis*, but data support the conclusion that children from countries with high case rates of TB disease are more likely to have a positive TST from LTBI than from BCG immunization.

Nontuberculous Mycobacteria. More than 200 *M tuberculosis* antigens are found in the precipitates of PPD preparations. Many of these antigens are common to *Mycobacterium bovis*, BCG, and nontuberculous mycobacteria (NTM) (eg, *Mycobacterium avium*, *Mycobacterium intracellulare*, *Mycobacterium fortuitum*, *Mycobacterium abscessus*, and *Mycobacterium kansasii*), which can result in cross-reactivity and false-positive reactions to TSTs.[93–95] However, a true positive TST can result from disease caused by *M bovis*. Some of the better-studied mycobacterial antigens include the 65-kDa heat-shock protein, the 38-kDa species-specific protein of *M tuberculosis*, and the early secreted antigenic target 6 kDa (ESAT-6).[96] Some of these antigens form the basis of newly developed tests to improve the specificity of the diagnosis of LTBI, as will be described below.

Boosting Effect. Over time the DTH to mycobacterial antigens may wane, and thus a TST could be negative. However, with subsequent TSTs, the DTH response may be stimulated by PPD and result in a positive reaction. Such a reaction can be misinterpreted as a recent TST conversion. This phenomenon is known as boosting, ie, an increase in TST size caused by repetitive TSTs in an individual previously sensitized to mycobacterial antigens, particularly BCG and NTM. Boosting is minimized if TSTs are placed <1 week apart.[53] However, if a person has not been infected with mycobacterial antigens, boosting will not occur.

Positive Predictive Value of TSTs

The positive predictive value of the TST is influenced by the specificity of the test and the prevalence of true LTBI in the population being tested. The lower the prevalence of LTBI in a given population or the higher the prevalence of exposure to NTM or BCG vaccine, the more false-positive TSTs will occur, which results in lower specificity and lower positive predictive value. Conversely, the positive predictive value of a TST is high when the prevalence of LTBI is high, such as among contacts of a case of TB disease.[53]

The use of 3 cutoff levels (≥5, ≥10, and ≥15 mm) to define a positive TST in different populations improves the positive predictive value of a TST. Thus, the definition of a positive TST depends on risk factors present in the individual being tested.[3] The interpretation of a TST is stratified based on the millimeters of induration (Table 4). A smaller TST (≥5 mm) is interpreted as positive in children in whom the risk of LTBI (or TB disease) is higher. This lower cutoff level yields a higher sensitivity of the TST (ie, fewer false-negatives). Conversely, in children at lower risk for LTBI or TB disease, a larger cutoff level improves specificity by reducing the number of false-positive interpretations. Notably, testers in California only use 2 cutoff levels (≥5 or ≥10 mm) (California Tuberculosis Controllers Association [www.ctca.org/guidline/combined%20ltbl%

TABLE 14. Selected Studies Assessing the Effect of BCG Immunization on TST Reactivity in Children and Adolescents

Country*	Subjects, *n*	BCG Immunization, age	TST Placed	TST ≥ 10 mm, %	Comment
Sri Lanka[81]	112	<1 mo	3 mo	~12	Values approximated from figures
	106	<1 mo	18 mo	~18	
	285	<1 mo	5 to 7 y	~7	
	237	<1 mo	9 to 11 y	~6	
United States (Navajo Indian)[83]	250	Birth	3 mo	31	
		Birth	9 mo to 4 y	0	
		Birth	5 y	2	
		Birth	6 y	4	
Saudi Arabia[85]	1522	Birth	5 to 11 y	6–13	Comparable to age-matched unvaccinated controls
	224	Birth	12 y	20	4% (3 of 77) among unvaccinated controls† ($P < .001$)
	199	Birth	13 y	16	4% (3 of 73) among unvaccinated controls† ($P = .006$)
Israel[82]	512	Birth	7 to 24 mo	2.5	
Chile[86]	40	Birth	6 y	10	Repeat TST in 2 wk: 45% ≥ 10 mm
Uganda[77]	151	Birth	≤5 y	15	53% (75 of 142) known TB exposure‡
South Africa[84]	85	Birth	6 mo to 6 y	13	
Canada[87]	463	Birth	11 y	5	
	198	Birth	16 y	8	
Brazil[76]	60	Birth	0 to 5 y	0	45% (18 of 40) known TB exposure‡
Botswana[78]	781	Birth	3 mo to 5 y	6–8	
Israel[82]	135	13 y	14 y	36	
Denmark[90]	601	7 y	8 to 10 wk later	~38–99	Values approximated from figures; dependent on vaccine type
			12 y	~39–97	
Canada[87]	306	2–8 y	11 y	13	
			16 y	17	
			18 to 25 y	26	
United States (Alabama)[91]	63	> 5 y	18 to 21 y (8–15 y later)	16	
Brazil[76]	233	Birth and school age	5 to 9 y	2	44% (22 of 50) known TB exposure‡
			≥10 y	6	53% (27 of 51) known TB exposure‡
South Africa[84]	42	Birth and school age	6 to 14 y	33	
Israel[82]	96	Birth and age 13 y	14 y	62	
Sri Lanka[81]	61	Birth and age 10 y	3 mo after 2nd BCG	53	

* The children studied were generally born in the country cited.
† Unvaccinated children had a negative history of immunization and no BCG scar.
‡ Exposure was defined as: household contact of adult with smear-positive TB disease.

20guide2002.pdf]). Targeted tuberculin skin testing should dramatically reduce testing of children at low risk for LTBI and TB and further improve the positive predictive value of TSTs.

Interpretation of the TST by Trained Health Care Workers

Several studies have emphasized that trained health care professionals must place, read, and interpret TSTs. Ozuah et al[97] showed that patients can reliably detect the presence or absence of induration but cannot reliably measure or interpret the TST reaction. Howard and Solomon[98] demonstrated that 63% (133 of 212) of patients with positive TSTs did not report induration, although 99% (520 of 525) of those with negative TSTs correctly interpreted their skin test as negative. Froehlich et al[20] compared TST readings by parents and health care professionals. Parents failed to detect 9.9% of positive TSTs when using the 10-mm cutoff level (1% of cohort) and 5.9% of positive TSTs when using the 15-mm cutoff level (0.5% of cohort). Similarly, Colp et al[99] found that only 6% (1 of 18) of patients correctly identified a TST with 10 to 20 mm of induration as ≥10 mm; 56% (10 of 18) considered the test negative, and 39% (7 of 18) were unable to make a judgment. Cheng et al[100] correlated parents' readings with those of a visiting nurse. In all, 6% (5 of 89) of parents did not note induration observed by the nurse, whereas 3% (3 of 89) reported induration for a negative TST.

These observations extend to untrained health care workers. Carter and Lee[101] studied pediatric providers with no specific training in interpreting TSTs to determine if they could interpret a 15-mm TST reaction correctly. Twenty-three percent (13 of 57) read the TST as <10 mm, and 18% (10 of 57) read it as <5 mm. In a similar study, Kendig et al asked 107 health care professionals to interpret a 15-mm TST.[102] Overall, 33% (17 of 52) of practicing pediatricians misinterpreted the 15 mm of induration as <10 mm, and only 7% (8 of 107) measured the induration correctly.

In summary, laypersons and untrained health care workers frequently misinterpret TSTs. Only trained health care workers should plant, read, and interpret a TST.

Newer Assays to Diagnose LTBI

In efforts to address the technical limitations of the TST and improve sensitivity, specificity, and convenience, newer assays have been developed that rely on cellular responses to specific antigens of *M tuberculosis*.

QuantiFERON-TB

QuantiFERON-TB (QFT) (Cellestis Limited, Carnegie, Victoria, Australia) is a Food and Drug Administration–approved diagnostic test for *M tuberculosis* that quantifies interferon γ (IFN-γ) released by sensitized lymphocytes. Whole blood containing lymphocytes is incubated with proteins from *M tuberculosis*, *M avium*, and control antigens. After exposure to *M tuberculosis* complex, lymphocytes that have been sensitized release IFN-γ that can be quantified. This assay is approved for use in adults.[103] Guidelines for using QFT for diagnosing LTBI in adults were published by the CDC in December 2002 and are summarized in Table 15.

Mazurek et al[104] compared the QFT assay with tuberculin skin testing and identified factors in adults associated with discordance between the 2 tests. The agreement between the TST and IFN-γ was 85% ($\kappa = 0.55$). Among persons being screened for LTBI who had ($n = 157$) and had not ($n = 770$) received BCG immunization, a positive TST and a negative QFT assay for *M tuberculosis* occurred in 22% (35 of 157) and 4% (33 of 770) of persons, respectively. Of the 33 unvaccinated subjects with a positive TST and negative QFT assay for *M tuberculosis*, 21% (7 of 33) had detectable IFN-γ for *M avium* complex. Factors found to be associated with a positive TST and negative QFT for *M tuberculosis* included a history of BCG immunization, Asian race, study site, and evidence of *M avium* complex by QFT assay.

Enzyme-Linked Immunospot

Enzyme-linked immunospot (ELISPOT) is an investigational immunoassay that detects IFN-γ molecules secreted by ESAT-6-specific T cells. ESAT-6 is a secreted antigen specifically expressed by the *M tuberculosis* complex but absent in strains of *M bovis*

TABLE 15. Recommendations for Using and Interpreting QuantiFERON to Assess Adults for LTBI

Population*	Initial Screening and Interpretation	Additional Evaluation
Increased risk for LTBI		
Recent immigrants from high incidence countries	TST induration ≥10 mm or QFT percentage of tuberculin response ≥15‡	Chest radiograph if either test is positive; confirmatory TST optional
Illegal drug users		
Residents and employees of high-risk congregate settings†		
Other reasons for possible testing among persons at low risk		
Military personnel	TST induration ≥15 mm or QFT percentage of tuberculin response ≥30	Chest radiograph if either test is positive; confirmatory TST recommended
Hospital staff at low risk of prior exposure to patients with TB disease		
US-born students at certain colleges and universities		

* QFT has not been adequately evaluated in children <17 years of age. Modified from Mazurek GH, Villarino ME, Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2003;52(RR-2):15–18.
† Defined as prisons, jails, homeless shelters, or health care facilities, where staff are at a higher risk of exposure to TB patients.
‡ Initial and serial testing of persons who are, by history, at low risk for LTBI but whose future activity might place them at increased risk for exposure.

BCG vaccine and most NTM.[94] Among patients with culture-confirmed TB disease, 96% (45 of 47) had ESAT-6-specific T cells.[93] Lalvani et al[93] compared ELISPOT with a multiple-puncture TST (Heaf test) in an effort to diagnose LTBI in contacts of newly diagnosed smear-positive cases of pulmonary TB. ELISPOT identified slightly more infected contacts (73% [16 of 22]) than the Heaf test (65% [13 of 20]). There was a strong positive association between ELISPOT results and increased exposure defined as proximity to the index case and duration of contact (odds ratio [OR]: 9.0 per unit increase in level of exposure; 95% confidence interval [CI_{95}]: 6.0–31.6; $P = .001$). None of the 19 contacts with BCG immunization and little or no exposure to case patients had a positive ELISPOT, whereas 31% (6 of 19) had a positive Heaf test.

In summary, these newer diagnostic assays show great promise and can differentiate T cell response to *M tuberculosis*, NTM, or BCG. Second-generation QFT tests are currently being evaluated and may prove more specific than the currently approved assays. There are no published studies in children to date.

Medical History

To diagnose and treat children and adolescents with LTBI correctly, a medical history must be obtained to elicit symptoms of TB disease and the presence of coexisting medical conditions that could complicate treatment of LTBI (Table 5). The most common symptoms of TB are cough, fever, wheezing, and failure to gain weight.[58] Infants and adolescents with pulmonary TB are generally more symptomatic than older children. Children with TB disease identified by contact investigations or targeted tuberculin skin testing are often asymptomatic.[58] Before initiating treatment for LTBI, other factors such as previous treatment for LTBI or TB, a possible infectious source case, concomitant medical conditions or medications, and maternal and child HIV status may guide treatment and monitoring.

Physical Examination

A directed physical examination in children and adolescents with a positive TST can identify signs of pulmonary or extrapulmonary TB disease (Table 6). Such an examination requires a short time to perform. Particular attention should be given to palpating the cervical lymph nodes, because this is a common site of TB disease in children.

Radiographic Studies

Chest Radiographs

Chest radiographs are considered essential to assess children and adolescents with positive TSTs for pulmonary TB. Chest radiographs in LTBI are usually normal, but findings may include dense nodules with calcifications (ie, a Ghon complex), calcified nonenlarged regional lymph nodes, or both, or pleural thickening (ie, scarring).[2,3] Patients with these lesions can be treated for LTBI, because these isolated findings are not associated with an increased risk of progression to active TB compared with radiographs with no abnormalities.[2] In contrast, findings consistent with TB disease include enlargement of hilar, mediastinal, or subcarinal lymph nodes and parenchymal changes such as segmental hyperinflation, atelectasis, alveolar consolidation, interstitial infiltrates, pleural effusion, or a focal mass.[52] Cavities are rare in young children but may occur in adolescents with reactivation disease. Patients with noncalcified nodular lesions and fibrotic scars may be at higher risk of progression to TB disease and may require additional evaluation for active TB.

Younger children are more likely to have intrathoracic lymphadenopathy than adolescents. Of 4607 children with TB disease studied in California from 1985 to 1995, 6% (157 of 2778) of children 0 to 4 years, 8% (150 of 1829) of children 5 to 14 years, and 0.5% (8 of 1615) of adolescents were reported to have intrathoracic adenopathy.[105] Smuts et al[106] demonstrated that lateral chest radiographs considerably improved the accuracy of detecting hilar adenopathy in children 1 month to 12 years of age. Among 176 culture-confirmed cases of TB disease, 46% (81 of 176) had adenopathy visible on chest radiographs. Adenopathy was visible on both frontal and lateral views in 49% (40 of 81), on only the frontal view in 24% (19 of 81), and on only the lateral view in 27% (22 of 81) of patients. Furthermore, hilar adenopathy was detected only on the lateral view of 19% (27 of 140) of children diagnosed with probable TB disease who had negative cultures for *M tuberculosis*.

CT Scans

In recent years, the role of CT scans in pediatric patients with TB disease has been studied. Because of increased sensitivity when compared with chest radiographs, a chest CT scan may show enlarged or prominent mediastinal or hilar adenopathy that is not demonstrable on chest radiographs and is thought to be of no clinical significance.[107] CT scans may prove useful in children with equivocal chest radiographs or may help further define an alternative pathologic process. CT scans can demonstrate endobronchial disease, pericardial invasion, early cavitation, or bronchiectasis. Neu et al[108] found that 31% (6 of 19) of chest CTs demonstrated mediastinal or hilar adenopathy in children with equivocal or absent adenopathy on chest radiographs. In addition, CT scans provided an alternative diagnosis (eg, a bronchogenic cyst) in some children. However, a pediatric patient with presumptive LTBI generally should not undergo a chest CT.

In summary, there are limited studies demonstrating the yield of lateral chest radiographs for children >6 years of age including adolescents. However, lateral views and chest CTs have been shown to be useful in the assessment of pediatric patients whose frontal views are equivocal for TB diseases.

Cultures for M tuberculosis

If TB disease is suspected, respiratory specimens should be collected. Gastric aspirates or induced sputum may be useful for children who cannot produce sputum. By definition, children with LTBI have a low organism burden, and occasionally such children may have a positive culture from the respiratory

tract.[58] However, cultures are not recommended to assess children or adolescents with LTBI.

Testing for HIV

It is recommended that all patients with TB disease be offered HIV testing, because management may be influenced by coinfection with *M tuberculosis* and HIV. Drug absorption is affected, and the risk of emergence of drug resistance may be increased.[109,110] Coovadia et al[111] reviewed pediatric studies of HIV and TB coinfection and concluded that HIV during infancy increased the risk of developing TB disease. However, no studies have assessed the yield of testing patients with LTBI for HIV coinfection.

Treatment of LTBI

Since the 1950s, numerous studies have been performed to assess the efficacy of treatment regimens for LTBI. The following are brief summaries of these studies.

Clinical Trials With INH

In 1958, the USPHS conducted a randomized trial to prevent TB disease in boarding schools in Alaska.[112] Two dosing regimens of INH were studied, 1.25 vs 5 mg/kg per day given for 6 months to 1701 attendees 5 to 20 years of age either 5 days per week or daily. In 10 years of follow-up, participants who received the higher dose of INH had significantly less progression to TB disease (1.9% [10 of 513]) than participants receiving the lower dose (5.8% [31 of 536]). In addition, the study demonstrated that an intermittent course (ie, 5 days per week) of INH therapy was efficacious.

During the remainder of the 1950s and 1960s, the USPHS performed other randomized, controlled trials of INH treatment for LTBI in industrialized and developing countries.[113] Most studies compared 12 months of INH with placebo, and >100 000 participants at risk for TB disease were studied, including contacts of infectious cases of TB and persons with positive TSTs. When analysis was restricted to participants with higher levels of adherence, the protective efficacy was ~90%. Substantial protection was conferred even with irregular treatment, again suggesting that intermittent treatment could be efficacious.

Secondary analysis of 2 USPHS household contact studies provided insight into the optimal duration of INH therapy.[114] TB case rates among contacts were compared with the estimated duration of INH use. Efficacy plateaued at 9 to 10 months of treatment, suggesting that more prolonged INH therapy offered no additional benefit. Similarly, in a study among the Inuit in Alaska, a second year of INH treatment did not result in additional benefit beyond that conferred by the first year of treatment.[115,116]

The International Union Against Tuberculosis and Lung Disease evaluated the efficacy of various durations of INH therapy (3, 6, and 12 months) in 27 730 adults with a positive (defined in this study as >6 mm) TST and "fibrotic pulmonary lesions."[117] During 5 years of follow-up, 1.4% (97 of 6990) of participants in the placebo group developed TB disease compared with 1.1% (76 of 6956) of persons treated with the 3-month course, 0.5% (34 of 6965) of those treated for 6 months, and 0.4% (24 of 6919) of those treated for 12 months. Among persons thought to have taken ≥80% of their dosages of INH, efficacy for the 6- and 12-month regimens increased: only 0.5% (25 of 5437) and 0.1% (5 of 4543) of participants developed TB disease. Overall, participants receiving the 6-month regimen had a fourfold higher risk of TB disease than those receiving the 12-month regimen. Similar studies have not been performed in children.

Regimens With Rifampin

In the United States, daily rifampin has been used for the treatment of LTBI in children and adolescents when INH was not tolerated or the child was exposed to an INH-resistant, rifampin-susceptible source case. Villarino et al[118] examined the adverse effects and acceptability of rifampin therapy for LTBI (10 mg/kg per day for 24 weeks) in 157 adolescents. One or more adverse effects including anorexia, nausea, fatigue, and rash were reported by 26% (41 of 157) of patients, and of these, 18 of 41 discontinued therapy temporarily and 2 of 41 discontinued therapy permanently. Eighty-seven percent of the participants received telephone follow-up 18 to 24 months after enrollment (240 person-years), and none reported illness compatible with TB disease and none were listed in the TB disease registry.

Ormerod[119] suggested that 3- and 4-month regimens of rifampin (10 mg/kg per day) plus INH (10 mg/kg per day) were effective in the treatment of LTBI in children and adolescents ≤15 years of age. In this observational study conducted in England, pediatric contacts of infectious cases of TB disease and children emigrating from countries with a high prevalence of TB disease were treated for LTBI. The duration of recommended therapy (INH plus rifampicin) was reduced gradually over a 15-year period. From 1981 to 1983 the duration of treatment was 9 months (n = 220 children), from 1984 to 1986 the duration was 6 months (n = 119), from 1987 to 1988 the duration was 4 months (n = 53), and from 1989 to 1996 the duration was 3 months (n = 213). The reduction in the proportion of pediatric cases of TB disease, noted after the introduction of LTBI treatment in 1981, was maintained even with the use of shorter-duration regimens. This study was limited by a small sample size and lack of controls but did not seem to be confounded by potential epidemiologic changes such as changing immigration patterns or a decrease in cases of infectious TB disease.

Recent studies in adults attempted to shorten LTBI regimens further by using rifampin and pyrazinamide for 2 months. Unexpectedly high rates of hepatotoxicity including fatalities were noted: 21 cases were reported, of whom 5 died of liver failure.[5] Thus, this regimen is not recommended for general use.[6]

Contacts of Patients With MDR TB

The occurrence of outbreaks of MDR-TB disease and the worldwide rise in resistance rates have focused attention on treatment of persons with LTBI

caused by such organisms.[120,121] However, there are few published data on treatment of MDR LTBI in children and adolescents. Schaaf et al[122] evaluated the pediatric contacts <5 years of age (median: 28 months old) of adults with MDR-TB disease in South Africa. From April 1994 to January 2000, 41 exposed children (all infected or uninfected <2 years of age) were treated for MDR LTBI for 6 months by using DOT. The regimens consisted of ≥2 active drugs guided by the susceptibility of the source case's isolate. During 30 months of follow-up, 5% (2 of 41) of children developed TB disease, compared with 20% (13 of 64) of children who did not receive LTBI therapy. Two factors may have contributed to the treatment failures. First, the definition of LTBI used in the study included asymptomatic children with a TST ≥15 mm with a normal chest radiograph, calcifications in the lung parenchyma, or regional lymphadenopathy and 2 negative gastric aspirate cultures. In the United States, regional lymphadenopathy is thought to represent TB disease, and treatment would consist of more prolonged multidrug therapy. Second, the 6-month treatment course may have been inadequate for LTBI caused by MDR strains.

Persons infected with INH- and rifampin-resistant organisms are unlikely to benefit from treatment of LTBI with regimens containing these agents. The combination of pyrazinamide and ethambutol for 9 to 12 months has been recommended for treatment of LTBI in adults if the MDR isolate is susceptible to both drugs.[123] Ethambutol at 15 mg/kg is safe in children and may be prescribed without routine ophthalmologic examinations.[124] When pyrazinamide and ethambutol cannot be used, many experts recommend treatment with 2 other drugs (eg, ethionamide, cycloserine, para-amino salicylic acid, or fluoroquinolones) to which the infecting organism is susceptible.[125–127] However, hepatitis has been observed in adolescents and adults treated with pyrazinamide and ofloxacin.[127]

Toxicities Associated With INH

In general, INH is very well-tolerated by children and adolescents. However, potential toxicities are hepatitis (which can progress to hepatic failure), gastrointestinal disturbances, and neurologic complaints including peripheral neuropathy.

Hepatitis

Three types of hepatotoxicity can occur secondary to INH[128]: (1) most commonly, an asymptomatic, transient elevation of transaminases; (2) a relatively rare clinical hepatitis that resolves when INH is discontinued; and (3) a very rare, fulminant hepatitis and liver failure leading to death or liver transplant.

Persons at risk for hepatitis include those with preexisting liver disease, older age (particularly elderly adults), malnutrition, alcoholics, or those receiving other potentially hepatotoxic drugs (eg, anticonvulsant medications). In addition, pregnant women (including adolescents) and women in the first several weeks postpartum are at increased risk of hepatitis. Many experts recommend delaying treatment of pregnant women until they are 2 to 3 months postpartum unless the woman is HIV-infected or a close contact.[129]

The risk of hepatitis increases with age. In adults, the risk of elevated liver-function tests secondary to INH is estimated to be 10% to 20%, the risk of clinical hepatitis is 1%, and the overall risk of death from hepatic failure is 0.1%. Severe effects are more likely in women and individuals continuing to take INH despite symptoms of hepatotoxicity.[130] Children and adolescents receiving INH for treatment of LTBI are at decreased risk of developing hepatitis when compared with adults.

Several studies have prospectively evaluated the risk of hepatitis secondary to INH among pediatric patients. These studies varied in sample size, treatment regimens, and methodologies used to assess toxicity. Mount and Ferrebee[131] studied 2750 children with LTBI from 1955 to 1957 who were randomized to receive either INH 4 to 6 mg/kg per day (rather than the currently recommended dose of 10–15 mg/kg per day) or placebo. In all, 1394 received INH, of whom 60% (843 of 1394) were <3 years of age. Only 0.14% (2 of 1394) of children developed nausea and vomiting attributed to INH. However, no liver-function tests were reported in this study.

Hsu[132] studied 1881 children with LTBI, of whom 18% (460 of 1881) were <3 years of age. In this trial, 394 were prescribed 6 to 10 mg/kg per day of INH for 18 months, and 1487 were prescribed 10 to 20 mg/kg per day of INH for 12 months. Only 4 cases of adverse events were attributed to INH and included rash, vomiting, and diarrhea. Clinical hepatitis did not occur.

Palusci et al[133] reviewed data from various studies to assess the frequency of hepatitis secondary to INH. In a pooled analysis of 965 children, 8% (75 of 965; range: 0%–13.6%) developed transient elevations of liver-function tests, and INH was discontinued in only 0.4% (4 of 965). There were no cases of hepatic failure. The authors performed an additional pooled analysis and found that 1.3% (58 of 4473) of children had liver-function tests obtained because of symptoms suggestive of clinical hepatitis.[133] However, only 0.07% (3 of 4473) had elevated transaminases. Despite the low risk of clinical hepatitis, hepatic failure secondary to INH has occurred in pediatric patients.[133–135] Several questions should be asked of the patient and their families to identify risk factors for hepatotoxicity and allow appropriate monitoring of liver function (Table 16).

Symptoms of hepatitis include anorexia, nausea, vomiting, malaise, fatigue, abdominal discomfort, and/or fever. Signs of hepatitis include scleral icterus, jaundice, brown urine (often described as coffee-, cola-, or mud-colored), or clay-colored stools.

In summary, children and adolescents who are being assessed for treatment of LTBI with INH should have a history and physical examination performed to elicit risk factors for potential hepatitis secondary to INH. Although transient elevations of transaminases can occur in children and adolescents receiving INH, clinical hepatitis and fulminant hepatitis are rare.

TABLE 16. Elements of History That Should be Assessed Before Initiating INH

Question	Action
1. Has the patient ever taken INH previously and had any side effects, including hepatotoxicity?	If so, INH should not be prescribed.
2. Is the patient currently taking any concurrent medications that increase the risk of hepatotoxicity?	If so, obtain liver-function tests before initiating INH; may require dose adjustment of the concurrent medication and additional monitoring.
3. Does the patient consume alcohol?	If so, obtain liver-function tests before initiating INH; alcohol increases the risk of hepatotoxicity and should be avoided.
4. Does the patient currently have any signs or symptoms of acute or chronic liver disease?	If so, INH should be avoided until the acute illness has resolved; obtain liver-function tests before initiating INH.
5. Has the patient ever been diagnosed with hepatitis?	If so, INH should be deferred until liver-function tests are obtained and reviewed; if ongoing liver disease, liver-function tests should be monitored during treatment.

Peripheral Neuropathy

INH can also cause toxicities related to the nervous system, including peripheral neuropathy and, less commonly, optic neuritis, encephalopathy, ataxia, seizures, or psychiatric symptoms. These symptoms occur because of interference with niacin metabolism and are thought to be dose-related and caused by increased excretion of pyridoxine (vitamin B_6). Peripheral neuropathy is a distal sensory-motor axonopathy and manifests as tingling in the fingers and toes. Peripheral neuropathy is rare in children and adolescents but is increased in patients with certain risk factors. These risk factors include diabetes, uremia, a diet low in milk and meat, nutritional deficiencies, symptomatic HIV infection, pregnancy, alcoholism, and breastfeeding infants and their mothers.

Hypersensitivity Reactions

Skin rashes including maculopapular or morbilliform rashes can occur secondary to INH. Discontinuing the drug and rechallenging may clarify the etiology of the skin rash if it is INH-related. Fever, pruritis, and arthralgias secondary to INH have been described also.

Adherence to Treatment

Children who have been diagnosed with LTBI must complete the prescribed regimen to maximize the protective effects of therapy. However, data reveal that adherence to treatment for LTBI is generally suboptimal. In 1996, the CDC evaluated the completion rates of treatment in 5 health departments.[136] In all, 398 patients were identified by contact investigations, of whom only 51% completed therapy. Of the 52 contacts <15 years of age, 63% completed therapy. Reported completion rates ranged from 13% to 91%.[137,138]

Measures of Adherence

Both indirect and direct measures of adherence to LTBI therapy have been described (Table 9). Indirect measures include self-/caregiver reports, provider assessments, pharmacy records, or pill counts. Direct measures include detection of INH metabolites in the urine or DOT records. Perry et al[139] compared the reliability and validity of an INH metabolite test with the self-reports of adolescents in California. In this study, self-reports correlated well with the detection of urine metabolites; 85% (546 of 646) of the participants who reported taking INH within 2 days had a positive urine test and 91% (104 of 114) who reported not taking INH within 2 days had a negative urine test.

Strategies to Improve Adherence

To improve adherence to treatment, including initiation of treatment for LTBI, it is necessary to overcome a variety of barriers. For instance, interviews conducted with recent Vietnamese refugees identified misconceptions about LTBI in that 29% (15 of 51) of respondents did not believe that asymptomatic infection was possible.[140] In adults, patient education, the use of lay workers from the patient's social and/or cultural group, and DOT promoted adherence. Enablers (ie, strategies to overcome logistic barriers such as funds for transportation or extended clinic hours) and incentives (ie, strategies to enhance motivation such as snacks, food coupons, or movie tickets) also proved effective.[140,141]

Morisky et al[142] assessed the effects of educational strategies to improve treatment of LTBI among adolescents (mean: 15.2 years of age) in Los Angeles. Participants were assigned randomly to 1 of 4 intervention groups: (1) peer counseling, (2) negotiated incentive, whereby the adolescent selected their reward for adherence in advance, (3) combined peer counseling and incentives, or (4) usual care. There was no difference in the rates of completion of LTBI treatment among the 4 groups, but participants who were <15 years of age, of Asian ethnicity, or foreign-born were more likely to complete treatment. Salabarria-Pena et al[143] assessed the effects of acculturation and psychosocial factors on adherence to treatment for LTBI in the same population. Adolescents with high linguistic acculturation, strong ethnic identification, and parental support were more likely to complete therapy. Younger age and ease in getting to clinic also predicted adherence.

In 2 high-school–based LTBI treatment programs in New York City, Kohn et al[144] compared completion rates for adolescents being treated by DOT versus traditional daily home therapy. Significantly

higher rates of completion occurred in patients who received DOT (87.6% [19 of 22]) as compared with home therapy (50% [52 of 105]). Similarly, Sass et al[145] reported a significantly higher rate of completion among students receiving DOT (54% [51 of 94]) compared with those on home therapy (26% [42 of 61]).

A unique component of the San Diego school-based programs described above (see "School-Based Screening for LTBI") was the follow-up and treatment of students with positive TSTs (K. Moser, MD, MPH, written communication, 2003). Overall, 73% (115 of 158) of students eligible for treatment started LTBI therapy, of whom 57% (65 of 115) completed treatment and 31% (36 of 115) were continuing at last report. For such programs to enjoy sustained success, several key components are needed (Table 17). The support and participation of school staff, mobilization of community resources including outreach from a multidisciplinary team, and outcomes assessment are critical.

Most children are not responsible for administering their own medication; therefore, adherence to a regimen will be determined largely by the caregiver. In other chronic illness in children, Thompson and Gustafson[146] found an association between poor adherence and the caregiver's understanding of the regimen and its complexity. Successful interventions to overcome barriers to adherence in pediatric asthma, rheumatoid arthritis, diabetes, and HIV/AIDS have included educational, organizational, and behavioral strategies.[147–149] Such strategies are most likely applicable to the treatment of LTBI (Table 9).

RECOMMENDATIONS

The following consensus recommendations were developed by the Pediatric Tuberculosis Collaborative Group. The recommendations represent a consensus, but not all members agreed with all the recommendations. The strength of the treatment recommendations and the quality of the evidence are graded using the USPHS's rating system (Table 7).[2] The remainder of the recommendations are not graded but reflect the committee's guidelines for care. These recommendations are intended for all health care providers caring for children and adolescents, including primary care pediatricians, nurse practitioners, family practitioners, and health departments. Several recommendations stress the importance of educating the patients and their families and the need for careful documentation of testing and treatment.

Delineating the Role of the Health Department

- Timely, effective contact investigations remain an important priority of health departments. Contact investigations are an effective strategy to prevent TB disease and detect children and adolescents with LTBI and TB disease.
- Pediatric health care providers must be familiar and comply with state and local health department reporting guidelines for TB disease and LTBI. All jurisdictions require reporting of cases of suspected TB disease. Some jurisdictions require reporting of all cases of LTBI, whereas most others restrict reporting to younger children.

Screening for Risk Factors for LTBI in Children and Adolescents

- Pediatric health care providers should be familiar with local epidemiology for TB disease.
- Primary care providers should screen children and adolescents for LTBI risk factors by using a risk-assessment questionnaire (Table 3). This questionnaire should assess at least 4 major risk factors:
  - contact with TB disease;
  - foreign birth;
  - foreign travel to TB endemic countries (see www.who.int/gtb/publications/globrep02/contents.html); and
  - household contact with LTBI.
- Educate children and adolescents and/or their families about risk factors for TB and LTBI including the need for reassessment if a new risk factor occurs.
- Perform risk assessment once a year to assess acquisition of any new risk factors since last assessment.
- A TST should not be routinely required for school entry, day care attendance, Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) eligibility, or camp attendance for a child or adolescent at low risk for LTBI. The provider should write "TST not indicated" and explain to the child, adolescent, and/or the family the rationale for not performing a TST.
- Local regulations should be reviewed and updated to reflect these guidelines.

Associate Investigations

- Associate testing of the associates of children <4 years of age with LTBI is recommended for persons sharing a residence with the child or those with equally close contact. Such investigations can

TABLE 17. Elements of a Successful School-Based TST Program

Administrative	Targeted tuberculin testing emphasizing treatment outcomes
	Support of program by school administration
	Collaboration with school nurse
	TB-control program coordinator involvement
Education/incentives	Educating students, parents, and staff
	Incentives for students to complete treatment
Medical management	Referrals for treatment of LTBI
	DOT for LTBI in school if feasible
Performance indicators	Sustainability of program emphasized
	Outcomes measured
	Track completion rates for treatment for LTBI

be performed by health departments and/or primary care providers.
- Criteria for evaluation and treatment of an adult associate with a positive TST should be based on the LTBI risk factors for that individual as described in the current American Thoracic Society/CDC guidelines.[2]
- Criteria for evaluation and treatment of a pediatric associate with a positive TST should follow the recommendations outlined in this article.
- The rationale for associate investigations should be explained to the child, adolescent, and/or the family.

School-Based Programs
- Develop school-based screening programs following the principles outlined in this article; adolescents and foreign-born children have higher rates of LTBI.
- Undertake school-based screening programs only if sufficient programmatic infrastructure resources are available to complete all aspects of screening, testing, evaluation, and treatment of LTBI.
- Periodically assess the yield and treatment outcomes of screening programs.

Testing for LTBI
- Explain the rationale for placing a TST to the child, adolescent, and/or the family.
- A decision to place a TST is a commitment to evaluate the patient completely and to provide treatment for LTBI if indicated.
- A trained health care provider must place the TST by the Mantoux method using a 5-TU PPD if:
  - a risk factor is identified by the risk-assessment questionnaire; or
  - a new risk factor has been acquired since the last assessment.
- If a patient has a history of a previously positive TST without written documentation of the millimeters of induration, the TST should be repeated.
- Place a TST regardless of a history of BCG immunization.
- Perform a TST in children and adolescents before starting immunosuppressive medications that could increase their risk of progressing from LTBI to TB disease (eg, steroids, chemotherapy, TNF-α antagonists).
- A TST can be placed at the same time as systemic corticosteroids are initiated; both positive and negative TSTs are reliable.
- If the TST is placed after initiating systemic corticosteroid therapy, then a positive TST is reliable, but the significance of a negative TST is unknown.
- A TST can be administered at the same time as live vaccines (eg, measles, varicella). If not administered at the same time, wait 6 weeks to administer the TST.
- Perform a TST annually in children with HIV/AIDS or in incarcerated adolescents.
- Rarely, a severe, immediate reaction may occur to a TST. It may be prudent to avoid repeat testing in such an individual. Screening such an individual for symptoms of TB disease is recommended if risk factors for LTBI or TB are present.
- The QFT test is not currently approved for use in children and adolescents <17 years of age.
- Explain the need to return for the reading and interpretation of the TST within 48 to 72 hours to the child, adolescent, and/or the family and the consequences of not doing so (ie, the need to repeat the test).

TST Interpretation
- A trained health care professional must measure and interpret the TST.
- Record the results of negative (eg, 00 mm) or positive (eg, 12 mm) tests in millimeters of induration in the medical record and on the immunization card, which provides the family with written documentation of the TST reaction.
- Interpret the TST as described in the AAP guidelines by using the 3 cutoff levels (Table 4).
- Ignore the history of BCG immunization when interpreting a TST.
- Do not administer control antigens (eg, *Candida* or tetanus toxoid) to assess for anergy.

History
- Obtain an appropriate medical history for all children and adolescents with a positive TST (Table 5).

Physical Examination
- Perform a directed physical examination for all children and adolescents with a positive TST to assess for pulmonary or extrapulmonary TB disease or risks for TB-drug toxicity (Table 6).

Radiographic Studies
- Obtain a chest radiograph in children and adolescents with a positive TST (using 3 cutoff levels) to document that there are no findings of TB disease before starting treatment for LTBI.
- Explain to the child, adolescent, and/or the family the rationale for the chest radiograph.
- A radiograph should be obtained in pediatric patients who are contacts of infectious TB cases or who are immunocompromised. However, chest radiographs should not be obtained routinely in pediatric patients whose TST is 5 to 9 mm.
- Obtain frontal and lateral chest radiographs in children ≤6 years of age with a positive TST to evaluate for TB disease. If resources permit, it is preferable that frontal and lateral chest radiographs be obtained in all pediatric patients. The lateral view may be particularly useful if the frontal view is equivocal.
- A physician who is familiar with the subtle radiographic findings of pediatric pulmonary TB should interpret such chest radiographs.
- Do not obtain a CT scan to evaluate an asymptomatic child or adolescent with a normal chest radiograph.
- Do not obtain a repeat chest radiograph during the treatment course for LTBI in the absence of signs and symptoms of TB disease.
- If LTBI therapy is not started within 3 months of obtaining a chest radiograph, a repeat radiograph

should be obtained to ensure that TB disease has not developed.
- For children and adolescents at increased risk of progression to TB disease, if LTBI therapy is not started within 1 month of obtaining a chest radiograph, consideration should be given to repeating the chest radiograph to ensure that TB disease has not developed. High-risk children could include infants <1 year of age, those coinfected with HIV, or those receiving immunosuppressive therapy.
- Children and adolescents with fibrotic scars detected on chest radiographs should be evaluated further. Evaluation could include sputum cultures, serial chest radiographs, and/or treatment for TB disease until culture results of the respiratory tract are known.

Pretreatment Laboratory Evaluations
- Routine testing for HIV is not indicated for children or adolescents with LTBI in the absence of risk factors for HIV infection.
- Phenytoin or carbamazepine levels should be obtained and monitored in patients receiving these agents and INH.
- Baseline liver-function tests:
  - are not indicated in the absence of risk factors for liver disease.
  - are indicated for children and adolescents with a history or physical findings of liver disease, alcohol or drug abuse, symptomatic HIV/AIDS, or those treated with potentially hepatotoxic drugs.

Treatment of LTBI in Children
- Treatment for LTBI is not indicted for a child or adolescent without risk factors who has a reactive TST. Such a reaction is considered false-positive.
- Exclude TB disease before treatment for LTBI is initiated; the chest radiograph must be obtained and interpreted before starting treatment.
- If possible, identify the source case and the drug-susceptibility pattern of the source case's isolate of *M tuberculosis*.
- Explain to the child, adolescent, and/or the family the need to initiate treatment, the importance of adhering to treatment, and the consequences of not doing so.
- Use INH if the source case has an INH-susceptible organism or the susceptibility is unknown.
- Use INH daily for 9 months (Tables 7 and 8) (A[II]).
  - Use INH daily for 9 months (270 doses) within a 12-month period (A[III]).
  - Re-treat if the patient received <6 months of INH within a 9-month period (A[III]).
- Intermittent (two or three times per week) INH for 9 months can be used if DOT is used (B[II]).
- If a dose is missed, it should not be added to the subsequent day's dose if the patient is receiving daily therapy. However, the treatment course must be extended to include these missed doses.
- Liquid INH may cause abdominal pain and/or diarrhea. INH is available as scored 100- and 300-mg tablets that are easily crushed and dispensed in soft foods (eg, pudding, Jell-O, or infant food).
- Use rifampin daily for 6 months if the source case has an INH-resistant and rifampin-susceptible organism or if INH is not tolerated despite careful education and efforts to alleviate mild side effects with INH (Tables 7 and 8) (A[III]).
- Rifampin/pyrazinamide for 2 months is not recommended (D[II]).
- Provide vitamin B_6 to breastfed infants, to children or adolescents on milk- and meat-deficient diets, those with HIV/AIDS, or those who experience paresthesias while taking INH (A[II]).

Treatment of MDR LTBI
- Consult an expert in pediatric TB for treatment of LTBI in a child exposed to an infectious source case with MDR TB.
- Strongly consider the use of DOT for treatment of all children and adolescents with MDR LTBI.

Highly Active Antiretroviral Therapy
- Consult an expert in pediatric TB and pediatric HIV for treatment of LTBI in a child with HIV/AIDS on highly active antiretroviral therapy.

Monitoring Treatment
- Educate parents and patients at each visit about signs and symptoms of hepatotoxicity (Section "Hepatitis") and other adverse reactions.
- Instruct parents and patients to stop medications immediately if symptoms consistent with hepatotoxicity develop and to return immediately to provider for assessment.
- Perform monthly face-to-face evaluations to assess adherence, missed doses, potential hepatotoxicity, or progression to TB disease.
- Do not obtain liver-function tests during therapy for LTBI in children and adolescents unless signs or symptoms of hepatotoxicity develop.
- Perform liver-function tests after the first and third month of treatment for LTBI in patients at risk for hepatotoxicity.

Measures to Increase Adherence
- Promote and monitor adherence to treatment of LTBI in all patients.
- Provide education about the importance of adhering to treatment and potential side effects of treatment.
- Consider the use of adherence-enhancing strategies including enablers and incentives for all patients being treated for LTBI.
- Prioritize DOT for:
  - children <3 years of age;
  - LTBI caused by an MDR-TB strain;
  - HIV-infected children and adolescents;
  - close contacts of cases of TB disease;
  - those who are immunocompromised; and/or
  - those with a history of poor adherence
- If resources allow, all children should be on DOT.
- Consider school-based DOT, if available.

Completion of Therapy

- Provide written documentation of TST results and completion of therapy for LTBI to the child, adolescent, and/or the family.
- Educate parents and patients about signs and symptoms of TB disease.
- Do not obtain a chest radiograph at the completion of treatment unless signs and symptoms of TB disease develop.
- Inform the parents and patients that future tuberculin skin testing is unnecessary if documentation of testing and treatment is kept. However, if a TST is performed in the future, it is safe.

PRIORITIES FOR FUTURE RESEARCH

Additional Validation of the Risk-Assessment Questionnaire

1. Validate the risk-assessment questionnaire in different populations and different clinical settings, including special populations such as refugee and immigrant children and adolescents.
2. Determine the optimal frequency for administering the risk-assessment questionnaire in different populations.
3. Determine the yield and cost-effectiveness of administering the risk-assessment questionnaire in various settings (eg, private offices, health clinics, or schools).
4. Evaluate barriers to implementation of the questionnaire.
5. Determine the duration of foreign travel that confers a risk for LTBI.

Studies of Associate Investigation

1. Study the yield of associate testing in areas of medium or low prevalence of TB disease.
2. Prospectively study the outcomes of associate testing in different populations.
3. Develop a more comprehensive, evidence-based definition of "associate" to address the various circumstances in which children and adolescents live.
4. Assess the cost-effectiveness of associate investigations in different settings.

Studies for School-Based Screening

1. Study the cost-effectiveness of school-based programs for identifying LTBI in students, particularly adolescents.
2. Compare the effectiveness of routine TSTs for all new high school entrants versus the use of the risk-assessment questionnaire in different populations.

Evaluation of a Child With a Positive TST

1. Analyze existing databases and results of multicenter studies of children and adolescents with LTBI to determine the contribution and cost-effectiveness of specific elements of the medical history, physical examination, and radiographic studies, particularly the relative contribution of the lateral chest radiograph for pediatric patients >6 years of age.
2. Assess the usefulness of the QFT test, ELISPOT, and other newer tests in children.

Optimal Treatment of LTBI

1. Design and conduct studies of shorter courses of LTBI treatment in children and adolescents.
2. Assess the rate of completion of treatment for LTBI among associates.
3. Assess the role of rifapentine (a long-acting rifamycin) in treatment of LTBI in children and adolescents.

Adherence

1. Assess factors associated with completion rates of treatment for LTBI in children and adolescents.
2. Determine the effectiveness and feasibility of DOT in all children and adolescents with LTBI.
3. Evaluate methods to improve adherence (eg, incentives, enablers, educational efforts) among different age groups and populations.
4. Evaluate measures of adherence.

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