18. TUBERCULOSIS SCREENING
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The American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) traditionally provide guidance on the diagnosis, treatment, prevention, and control of tuberculosis (ATS, 1990; CDC, 1990). In addition, the American Academy of Pediatrics (AAP) makes specific recommendations regarding children. This review therefore draws heavily on the published recommendations of these three organizations. Additional sources include the U.S. Preventive Services Task Force's (USPSTF) Guide to Clinical Preventive Services (1989) and textbooks on pediatrics (Starke et al. in Oski et al., 1994), general pediatrics (Niederman in Dershewitz, 1993), and pediatric infectious disease (Smith et al., in Feigin and Cherry, 1992). Several articles were also identified from the bibliographies of the previously described sources and from a MEDLINE search of English-language articles on tuberculosis screening in pediatric and adolescent age groups published between January 1990 and March 1995.

IMPORTANCE

Epidemiology

Mycobacterium tuberculosis is the bacterium responsible for tuberculosis (TB). It can cause significant pulmonary and extrapulmonary disease, but in most otherwise healthy people, untreated infection becomes dormant and never progresses to clinical disease. The risk for developing disease is highest in the first two years after initial infection, but disease may develop months or years later (AAP, 1994a).

Newly-infected children are more likely to progress to disease than newly-infected adults. Without treatment, disease eventually develops in 5 to 10 percent of immunologically normal adults with TB infection. By comparison, disease develops in up to 43 percent of untreated children less than 1 year old, 24 percent of 1-5 year olds, and 15 percent of 11-15 year olds (Starke et al. in Oski et al., 1992). In addition to age,
risk factors for progression of infection to disease include recent close contact with an infected person, recent skin test conversion (see below), intravenous drug use, and medical conditions and treatments that adversely affect the cellular immune system (e.g., HIV infection, Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, and daily corticosteroid therapy) (AAP, 1994a; Starke et al. in Oski et al., 1992).

Transmission is usually by inhalation of droplet nuclei produced by an adult or adolescent with infectious pulmonary TB, though transmission through or across skin, gastrointestinal tract, mucous membranes, placenta, or amniotic fluid has been reported. Children with primary pulmonary TB are usually not contagious (AAP, 1994a).

After decades of consistently declining incidence of TB, the United States has been experiencing a resurgence (Starke et al. in Oski et al., 1992). In 1992, over 26,000 cases of TB were reported, a 13 percent increase per 100,000 population over 1985 (the year with the lowest number of reported TB cases since reporting began). The increase was 25 percent for children 0-4 years old and 21 percent for children 5-14 years old (CDC, 1993). In 1990, the CDC (1990) estimated that there were 10 to 15 million people in the U.S. with latent TB infection.

Case rates of TB for all ages are highest in urban, low-income areas. More than two-thirds of cases are reported in nonwhite racial and ethnic groups (Asians and Pacific Islanders, African Americans, Native Americans and Alaskan Natives, and Latinos) and more than one quarter are reported in people born outside the United States. Rates are also high among the homeless and residents of correctional facilities (AAP, 1994a).

Screening Methods

The purpose of TB screening is to identify asymptomatic infected people so that they can take chemoprophylaxis to prevent the development of TB disease and so their potentially infected contacts can be identified. A tuberculin skin test is used for screening. The incubation period from infection to development of a positive reaction
to a tuberculin skin test is about two to ten weeks. Tuberculin reactivity usually lasts throughout a person's lifetime (AAP, 1994a).

There are two techniques for applying the tuberculin test:

1) The Mantoux technique consists of intracutaneous administration of 5 Tuberculin Units (5-TU) of purified protein derivative (PPD) into the forearm. Two other concentrations of PPD, 1-TU and 250-TU, are not appropriate for routine screening (ATS, 1990). A positive test consists of an indurated area of adequate size (discussed below). This method is generally necessary to make a diagnosis of TB infection, and it is the method recommended by the AAP (1994a), the ATS (1990), and the USPSTF (1989) for screening people with risk factors for TB.

2) The multiple-puncture test (MPT) punctures the skin with a pointed applicator that is either coated with dried tuberculin or passes through a film of liquid tuberculin. MPTs use either PPD or Old Tuberculin (OT). The quantity of tuberculin introduced into the skin cannot be precisely controlled so they are not as reliable as the Mantoux and must be interpreted with caution. Though a negative MPT is a good indication that the Mantoux would be negative, an MPT reaction is not adequate evidence that a Mantoux would be positive. An exception is a vesicular MPT reaction, which can be read as positive. Therefore, nonvesicular MPT reactions must be confirmed by a Mantoux (ATS, 1990).

Because of the inferiority of the MPT, the AAP (1994a), the ATS (1990), and the USPSTF (1989) all recommend the Mantoux for screening people with TB risk factors. MPTs are not recommended for screening high-risk populations or for diagnosis (AAP, 1994a; ATS, 1990). The AAP strongly recommends that "MPTs are not appropriate for diagnosis, and their use should be severely restricted if not eliminated" (AAP, 1994b). Because detection of newly infected persons requires accurate testing and reading, multiple-puncture devices should not be used in tuberculin testing surveillance programs designed to detect newly infected persons (ATS, 1990). However, MPTs may be used for surveys or screening among
groups of asymptomatic unexposed persons in whom only a small proportion are expected to have TB infection (ATS, 1990).

**Interpretation of Mantoux Results (AAP, 1994a)**

The definition of a positive Mantoux skin test (5TU-PPD) varies somewhat among the guidelines of different organizations, but there is much overlap. The CDC, ATS, and AAP all interpret an indurated area of at least 15 mm as positive in any person. Interpretation of smaller areas as positive depends on epidemiologic and clinical factors, and recommendations are not uniform. We will base our indicators on the AAP's guidelines (AAP, 1994a) since they are the only ones targeted specifically at the pediatric and adolescent age groups. (The ATS (1990) recommendations are quite similar but are slightly less expansive in the list of reasons for calling a reaction positive when smaller than 15 mm.)

A positive Mantoux includes induration that is (AAP, 1994a):

1) at least 15 mm in anyone;
2) at least 10 mm in a child who:
   a. is less than 4 years old, or
   b. has other medical risk factors putting him/her at increased risk of developing TB disease (e.g., Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition), or
   c. who was born, or whose parents were born, in regions of the world where TB is highly prevalent, or
   d. who is frequently exposed to adults who are HIV-infected, homeless, users of intravenous and other street drugs, poor and medically indigent city dwellers, residents of nursing homes, incarcerated or institutionalized persons, and migrant farm workers.
3) at least 5 mm in a child who:
   a. is in close contact with someone with a known or suspected infectious case of TB (households with active or previously active cases) if: (1) treatment cannot be verified as adequate before exposure, (2) treatment was initiated after
the period of the child's contact began, or (3) reactivation is suspected), or
b. is suspected of having TB disease clinically or by chest x-ray, or
c. has an immunosuppressive condition or HIV infection or is receiving an immunosuppressive treatment.

Tuberculin skin tests should be read 48-72 hours after they are placed (ATS, 1990; USPSTF, 1989; AAP, 1994a). Delayed hypersensitivity reactions to tuberculin (i.e., a positive test) begin at 5 to 6 hours, are maximal at 48-72 hours, and subside over a period of days. In a few persons (who are elderly or have not been tested previously), reactions may develop slowly and may not peak until after 72 hours. Immediate hypersensitivity reactions begin shortly after injection, but disappear by 24 hours and should not be confused with positive tests (ATS, 1990). The AAP (1994a) recommends that qualified medical personnel read positive and negative tuberculin skin tests 48 to 72 hours after placement. In practice, it may be quite difficult to get parents to bring their children back in two or three days to have the test read. This may be even more difficult when the test is negative, and parents believe they can adequately read them. Recent studies have shown that parents often misread positive skin tests (Cheng et al., 1995b) and that parents often do not bring their children back to have the test read even with incentives and reminder phone calls (Cheng et al., 1995a). Studies show that 28-82 percent of skin tests in pediatric patients are not read in the requisite 48-72 hour period (USPSTF, 1989). If tests are read late, positive responses may have subsided enough to be read as negative.

For each tuberculin test, a record should be made of the technique of administration (Mantoux or multiple-puncture), the kind and dose of tuberculin, and the size of reaction in millimeters of induration (ATS, 1990). In a clinic in which only one type of tuberculin is used, it would be unnecessary to document these in each chart. However, the size of reaction would be important.
The frequency of false-positive and false-negative tests depends on a number of variables, including immunologic status, the size of the hypersensitivity reaction, and the prevalence of atypical mycobacteria (nontuberculosis mycobacteria that cross-react with the tuberculin skin test) (USPSTF, 1989). Vaccination with BCG (a TB vaccine rarely given in the U.S. but common among immigrants from some parts of the world) can produce a false positive. Guidelines for interpreting skin tests take this into account (ATS, 1990). Anergy testing can help distinguish true from false negatives in HIV-infected and immunosuppressed people (ATS, 1992; CDC, 1991).

**Populations To Be Screened**

The AAP and ATS recommend a strategy of identifying high-risk populations for annual Mantoux skin-testing rather than routinely testing all persons, many of whom would be at low risk (AAP, 1994b; ATS, 1990).

Specifically, the AAP (1994a) defines as high risk children or adolescents who:

- are contacts of adults [or adolescents] with infectious tuberculosis, or
- are from or have parents [or household contacts] from regions of the world with high prevalence of tuberculosis, or
- have abnormalities on chest X-ray suggestive of tuberculosis, or
- have clinical evidence of tuberculosis, or
- are HIV-infected, or
- have immunosuppressive conditions, or
- have other medical risk factors, e.g., Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, or
- are incarcerated, or
- are frequently exposed to adults [or adolescents] who are HIV-infected, homeless, users of intravenous and other street

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1Material that seems consistent with the AAP list has been added in brackets.
drugs, poor and medically-indigent city dwellers, residents of nursing homes, migrant farm workers.

If no household contacts have current TB disease but one or more contacts have a positive tuberculin skin test, an infant should be tested with a Mantoux skin test at 3 to 4 months of age (AAP, 1994a). The AAP (1994a) provides guidelines for what to do if a contact does have current disease or if all contacts cannot be promptly tested. These detailed guidelines will not be incorporated into the indicators because they will not apply to many patients in the current study and because they fit better in a review of management of adult TB rather than a review of routine screening.

The ATS (1990), the CDC (1990), and the USPSTF (1989) do not define high-risk specifically for children and adolescents, but their general recommendations are essentially the same as the AAP's.

The CDC and ATS do not recommend routine skin testing in low-risk groups in communities with a low prevalence of tuberculosis except for one-time testing during childhood for epidemiologic assessment of tuberculosis infection in the area. Positive skin tests in such populations would be more likely to be false than true positives (AAP, 1994a). The AAP (1994a) makes an additional recommendation for children with no risk factors living in high-prevalence regions and for children whose risk factor history is incomplete or unreliable: periodic Mantoux tests (e.g., 1, 4, 6, and 11-16 years) may be performed depending on local epidemiology. These recommendations will not be incorporated into an indicator because of the variability of local epidemiology and because the timing of testing for this recommendation is left to the discretion of the clinician.

Many people who should receive skin-testing do not. In one study, three-quarters of TB patients had had contact with a health-care provider within the 5 year period prior to diagnosis, but less than one-third had been skin-tested, even though many had risk factors for TB (ATS, 1992). The CDC estimates that more than 90 percent of persons reported to have clinical TB disease have been infected for at least a year (CDC, 1990).
Chemoprophylaxis

Screening is important because chemoprophylaxis can be given to asymptomatic people to prevent progression from TB infection to disease and to prevent spread to others.

Isoniazid (INH) is the primary drug used for prophylaxis. When taken as prescribed, preventive therapy with INH is highly effective. In controlled trials conducted by the U.S. Public Health Service, 12 months of INH preventive therapy reduced the incidence of disease by 54-88 percent. The main reason for variation appears to have been the amount of medication actually taken. In a large trial in eastern Europe among infected adults with abnormal chest x-rays, a 12-month course of INH was 75 percent effective among all persons assigned to the regimen and 93 percent effective among those who were compliant with therapy. A six month course was 69 percent effective among those who were compliant (ATS, 1992). The AAP (1994a) reports that efficacy of chemoprophylaxis is almost 100 percent when the medication is taken properly. The current recommendation for children without HIV is 9 months and with HIV is at least 12 months (AAP, 1994a). INH is not without risks, primarily a risk of hepatotoxicity that increases with age, but the benefits are generally considered to outweigh the risks until a person is at least 35 years old. Other prophylaxis regimens may be necessary when there is reason to believe the organisms are resistant to INH (ATS, 1992). If INH-resistance is suspected, Rifampin should be given along with INH until the suspected source of infection can be tested for susceptibilities. If the index case is susceptible to INH, Rifampin would be discontinued; if the index case is susceptible only to Rifampin, the INH should be discontinued. If the index case is susceptible to neither, an (infectious disease) expert should be consulted (AAP, 1994a).

Children receiving chemoprophylaxis should have a visit with medical personnel at least monthly during therapy so they can be checked for symptoms of side effects. Because of possible visual impairment, children who are old enough should have a baseline visual acuity test done. Follow-up tests are only necessary if indicated by symptoms of changing vision (ATS, 1986). Children should receive a chest x-ray when
chemoprophylaxis is begun. If it is normal and the child remains asymptomatic, it does not need to be repeated (AAP, 1994a).

Hepatotoxic reactions to INH are rare in children and adolescents, so routine monitoring of liver enzymes is not necessary. Pyridoxine helps prevent peripheral neuritis and should be given daily (Niederma in Dershewitz, 1993).
RECOMMENDED QUALITY INDICATORS FOR TUBERCULOSIS SCREENING AND TREATMENT

The following criteria apply to tuberculosis screening for infants, children, and adolescents.

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<th>Indicator</th>
<th>Quality of evidence</th>
<th>Literature</th>
<th>Benefits</th>
<th>Comments</th>
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<td>1. By the time a child is four months old, there should be documentation of whether or not the child has tuberculosis risk factors* or documentation that the child has had a Mantoux test.</td>
<td>III</td>
<td>Inferred from AAP, 1994a; ATS, 1990</td>
<td>Prevent development of TB disease and its complications.** Prevent spread of TB.</td>
<td>Though guidelines call for annual screening in people at risk for TB, they do not say how often or at what interval a clinician should ask about TB risk factors. Setting the time at one year old should provide ample opportunity to have asked about risk factors at least once. By asking about risk factors, the clinician can determine the need for testing, prophylaxis to prevent infection from developing into disease, and treatment. Clinicians would often know that a child's parents were not from regions of the world with high prevalence of TB and therefore would not typically ask about this risk factor. However, they would not necessarily know whether there was another relative, boarder, household employee, or other contact from another part of the world. Therefore, it seems appropriate to ask about household contacts and to document it. TB risk factors include: - whether the child has had contact with an adult/adolescent with infectious TB; - whether the child or household contacts are from a region of the world with high TB prevalence; and - whether the child is frequently exposed to adults or adolescents who are HIV-infected, homeless, users of injection and other street drugs, poor and medically-indigent city dwellers, residents of nursing homes, or migrant farm workers.</td>
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<td>2. If no contacts have evidence of current TB disease but at least one has a positive tuberculin skin test, newborns should be Mantoux tested by the end of the fourth month of life.</td>
<td>III</td>
<td>AAP, 1994a</td>
<td>Prevent development of TB disease and its complications.** Prevent spread of TB.</td>
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3. If a child has any of the TB risk factors listed below, he/she should receive an annual Mantoux skin test during the duration of the risk factor:
   a. has abnormalities on chest X-ray suggestive of TB; or
   b. has clinical evidence of TB; or
   c. has HIV-infection, Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition, or another immunosuppressive condition; or
   d. has had contact with an adult/adolescent with infectious TB; or
   e. is from, or household contacts are from, a region of the world with high TB prevalence; or
   f. is frequently exposed to adults or adolescents who are HIV-infected, homeless, users of injection and other street drugs, poor and medically-indigent city dwellers, residents of nursing homes, or migrant farm workers.

4. Children with immunodeficiency or HIV-infection should have anergy testing (e.g., Candida or Mumps antigen) at the same time as TB testing.

5. Mantoux skin tests in children with risk factors should be read by a health professional or other trained personnel within 48-72 hours.

6. Results of tuberculin skin tests in children with risk factors should be documented within 96 hours of placing the test.

7. All Mantoux skin tests read as positive should document that there was induration and should document the diameter of the induration in millimeters.

8. A Mantoux skin test with $\geq 15$ mm should be read as positive.
9. A Mantoux skin test should be read as positive if there is induration that is at least 10 mm in a child who:
- is less than 4 years old;
- has other medical risk factors for developing TB disease (Hodgkin's disease, lymphoma, diabetes mellitus, chronic renal failure, malnutrition);
- who was born, or whose parents were born, in regions of the world where TB is highly prevalent; or
- who is frequently exposed to adults who are HIV-infected, homeless, users of intravenous and other street drugs, poor and medically indigent city dwellers, residents of nursing homes, incarcerated or institutionalized persons, and migrant farm workers.

10. A Mantoux skin test should be read as positive if there is induration that is at least 5 mm in a child who:
- is in close contact with someone with a known or suspected infectious case of TB (households with active or previously active cases) if (a) treatment cannot be verified as adequate before exposure, (b) treatment was initiated after the period of the child’s contact began, or (c) reactivation is suspected;
- is suspected of having TB disease clinically or by chest X-ray; or
- has an immunosuppressive condition or HIV infection or is receiving immunosuppressive treatment.

11. All children with positive Mantoux skin tests should have a chest x-ray within two weeks.

12. Children with a positive Mantoux test and negative chest x-ray and no other symptoms of TB should receive prophylaxis with INH and/or Rifampin.

13. Children with a positive Mantoux test and negative chest x-ray and no other symptoms of TB, whose presumed index case (source of infection) has TB resistant to INH and Rifampin, should have a referral made to an infectious disease specialist.
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<td><strong>14.</strong></td>
<td>Prophylaxis with INH should be given for 9 months to asymptomatic children without HIV and 12 months to asymptomatic children with HIV.</td>
<td>III</td>
<td>AAP, 1994a</td>
<td>Prevent development of TB disease and its complications.**</td>
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<td><strong>15.</strong></td>
<td>Children receiving TB chemoprophylaxis should have contact with a clinician at least once every 5 weeks during therapy.</td>
<td>III</td>
<td>ATS, 1986; Niederman in Dershewitz, 1993</td>
<td>Prevent development of TB disease and its complications.** Prevent toxicities from medications. Periodic visits ensure patients are taking medications and check for side effects. Side effects are rare in children and include hepatitis and peripheral neuritis or convulsions (due to inhibition of pyridoxine metabolism). The ATS recommendation is for once a month. This indicator allows a grace period.</td>
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<td><strong>16.</strong></td>
<td>All children three years and older who are receiving TB chemoprophylaxis with INH should have a baseline visual acuity test performed or attempted.</td>
<td>III</td>
<td>ATS, 1986</td>
<td>Prevent vision loss. Vision loss is an uncommon side effect of INH. Three-year olds will not always participate in a visual acuity test, but they are young enough to try. Most four-year olds will participate.</td>
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**TB risk factors include:**
- whether the child has had contact with an adult/adolescent with infectious TB;
- whether the child or household contacts are from a region of the world with high TB prevalence; and
- whether the child is frequently exposed to adults or adolescents who are HIV-infected, homeless, users of injection and other street drugs, poor and medically-indigent city dwellers, residents of nursing homes, or migrant farm workers.

**Disease can cause serious and disabling illness affecting lungs and most other parts of the body.**

**Quality of Evidence Codes:**
I: RCT
II-1: Nonrandomized controlled trials
II-2: Cohort or case analysis
II-3: Multiple time series
III: Opinions or descriptive studies
REFERENCES - TUBERCULOSIS SCREENING AND TREATMENT


