Tuberculosis (TB) remains an important problem among children in the United States and throughout the world. There is no diagnostic reference standard for latent tuberculosis infection (also referred to as tuberculosis infection [TBI]). The tuberculin skin test (TST) has many limitations, including difficulty in administration and interpretation, the need for a return visit by the patient, and false-positive results caused by cross-reaction with Mycobacterium bovis–bacille Calmette-Guerin vaccines and many nontuberculous mycobacteria. Interferon-gamma release assays (IGRAs) are blood tests that use antigens specific for M tuberculosis; as a result, IGRAs yield fewer false-positive results than the TST. Both IGRAs and the TST have reduced sensitivity in immunocompromised children, including children with severe TB disease. Both methods have high positive predictive value when applied to children with risk factors for TBI, especially recent contact with a person who has TB disease. The advantages of using IGRAs and diminished experience with the placement and interpretation of the TST favor expanded use of IGRAs in children in the United States. There are now several effective and safe regimens for the treatment of TBI in children. For improved adherence to therapy, the 3 rifamycin-based regimens are preferred because of their short duration. Daily isoniazid can be used if there is intolerance or drug interactions with rifamycins. A TB specialist should be involved when there are questions regarding testing interpretation, selection of an appropriate treatment regimen, or management of adverse effects.

INTRODUCTION
Tuberculosis (TB) remains an important disease in the United States and throughout the world. Approximately 9000 new cases occur each year in the United States.1 Of the 5175 children and adolescents younger than 18 years with TB disease reported in the United States from 2010 to 2017, 32% were born in other countries.2 Infants and young children (younger
than 4 years) have the highest rate for tuberculosis infection (TBI) progressing to TB disease rapidly after exposure, within a few weeks to several months. Children who move to the United States from countries with high TB burden (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union) often receive no testing for TBI, expanding the pool of infected children in the United States. Some of these children developed TB disease or are evaluated and treated for TBI after emigrating, but many have untreated TBI and are at risk for developing TB disease later in life. In addition, many US-born children who have been infected with Mycobacterium tuberculosis within the United States or abroad have gone undetected.

In most children and adolescents, initial infection with M tuberculosis is eliminated or contained by host defenses, and the person remains asymptomatic. However, residual bacilli may remain viable and become active again to cause TB disease. Treatment of TBI substantially reduces the risk of developing TB disease in children who adhere to therapy by 90% in both the immediate and distant future. Therefore, the goal of testing for TBI is to identify individuals who are at risk for developing TB disease and will benefit from treatment.

In the pediatric population, infants and children (younger than 4 years) and adolescents are at higher risk of progressing from TBI to TB disease than are primary school-aged children. The risk of progression in infants younger than 12 months with untreated TBI is 40% to 50%, decreases to 25% in children 1 to 2 years of age, drops to 5% to 10% in school-aged children, and is 10% to 15% in adolescents (Table 1). Epidemiological factors also define risk of infection: children who were born and lived in or have traveled to an area of the world with a high prevalence of TB and those who have had a household or family member with TB disease or TBI are at higher risk for TBI than the general population. As a result, selective testing for TBI of children on the basis of their risk factors has been adopted as the main strategy in the United States.

Although the diagnosis of TB disease is confirmed by the detection of M tuberculosis in a clinical sample, there is no diagnostic gold standard for diagnosis of TBI. Two available but imperfect methods for identification of TBI are the tuberculin skin test (TST) and the interferon-γ release assay (IGRA). Both methods depend on cell-mediated immunity and provide immunologic evidence of host sensitization to antigens of M tuberculosis. Neither method can distinguish between TBI and TB disease, and both methods display suboptimal performance in immunocompromised patients, who are at greatest risk for progression of TBI to TB disease.

**GENERAL TESTING CONSIDERATIONS**

Both the TST and IGRA depend on the host immune response to specific antigens found in M tuberculosis. Determining the sensitivity and specificity of both test types for children is difficult. They were studied and compared initially in children with culture-confirmed TB disease because microbiologic confirmation is the only real proof of TB disease. However, children with culture-proven TB disease tend to have more severe manifestations and clinical illness. Increased severity of disease may result in immunosuppression and diminish the sensitivity of tests that rely on the immune response, such as both the IGRA and TST. As a result, the sensitivity of both test types can be low for TB disease. Children with less severe TB disease often do not have microbiologic confirmation, lacking the absolute proof of infection that is needed to accurately assess test sensitivity and specificity, and many studies have used less reliable methods of clinical diagnosis of TB disease instead. The major difficulty for interpreting studies of the relative performance of the TST and IGRA is that there is no gold standard test, so it is difficult to determine for discordant test results whether the negative test result is more specific or the positive test result is more sensitive.

The TST

The TST is the intradermal injection of 5 TU of purified protein derivative (PPD) or 2 tuberculin units (TU) of PPD-RT23, the latter used predominantly in Europe. PPD tuberculin solution contains dozens of TB antigens, with the exact composition varying among batches and preparations. Many of these antigens also are present in environmental nontuberculous mycobacteria (NTM) prevalent throughout the United States and in the bacille Calmette-Guérin (BCG) vaccines. A patient who mounts a cell-mediated response to tuberculin antigens has a delayed-type hypersensitivity response usually within 48 to 72 hours, causing measurable induration at the injection site.
TST results can be difficult to interpret. The test depends on accurate intradermal injection, which should be performed by an experienced individual. Interpretation requires that the patient returns in 48 to 72 hours. Correct interpretation of the reaction involves careful measurement of induration that should be determined by a provider with experience in this measurement. The measurement should be recorded to the nearest millimeter of the transverse diameter of the induration (Fig 1). Reaction size can vary (on average) within the same individual by 15%, which has been described when the test is placed simultaneously on both arms.13 The variability in measurement observed when experienced observers also varies by about 15% and is much greater among inexperienced personnel and untrained people, especially family members.13 Therefore, family members should not be allowed to interpret a TST result. False-negative TST results can be caused by improper handling of the tuberculin solution, improper placement of the test, and incorrect interpretation of the results.13

Induration at the site of the TST is caused by migration of mostly mononuclear cells to the area and the inflammatory process secondary to these cells’ response. This response can be attributable to infection with *M tuberculosis*, exposure to NTM, or receipt of BCG vaccine. The patient’s history and the size of the induration help to determine which of these 3 potential causes may be likely associated with TST reaction. People with exposure to environmental NTM often have indurations <10 mm, but larger reactions are not uncommon. Among populations with a low prevalence of TB but a high prevalence of exposure to environmental NTM, such as in the United States, the distribution of reactions between individuals who lack a risk factor for TBI and those with NTM exposure overlap to a considerable degree.7 The most effective way to minimize false-positive results is to avoid testing individuals who lack a risk factor for TBI (Table 2).

To improve TST performance, the practice has been to vary the cutoff for the size of the TST reaction considered positive to optimize the sensitivity and specificity of the result. The cutoff is set at ≥15 mm to optimize specificity for people lacking TBI risk factors but who are tested for administrative reasons, ≥10 mm for people with a risk factor for TBI, and ≥5 mm to optimize sensitivity for people at high risk of having or developing TB disease if they have TBI (clinical evidence of TB disease, recent TB exposure, or significant immune compromise).14

BCG vaccines are administered in countries with high TB burden because they reduce the risk of disseminated (miliary) and central nervous system TB in children.15 Interpretation of TST results in BCG recipients who are known contacts of a person with TB disease or at high risk for TB disease is the same as for people who have not received BCG vaccine. For a foreign-born child, history of BCG vaccination should be determined by examination of the vaccination record and the finding of a typical BCG scar, usually located on the deltoid region of either arm. Many of the antigens in PPD also are found in *M bovis*-BCG, the organism in the BCG vaccines. Some individuals who are not infected with *M tuberculosis* may express induration in response to the TST that reflects previous receipt of a BCG vaccination. The size of the TST reaction varies with the strain and dose of vaccine,16 the route of administration,17 age at vaccination,18 the time interval since vaccination,19 and the number of BCG doses. Approximately half of infants who received a BCG vaccination will respond with significant induration to a TST. Although most, perhaps as many as 90%, of children 5 years or older who received a BCG vaccine as an infant will not have a positive response to a TST (unless also infected with *M tuberculosis*, which may not be prevented by BCG vaccination), some will retain this response, causing a false-positive result. The induration often measures <10 mm but can be >15 mm.20 Children born in countries with a high TB burden (Table 2) are candidates for selective testing for TBI, but a large number of false-positive results occur when the TST is used on children who have received a BCG vaccine. Children who have received a BCG vaccination also may be subject to “boosting” from the TST, the immunologic recall of

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**FIGURE 1** Measurement of TST reaction. The technician is marking the widest edges of the patient’s induration (a hard, dense, raised formation) with a pen for accurate measurement of the TST reaction. To locate the skin test site, the arm should be inspected in good light and on a firm surface. A light, gentle motion is used to sweep the fingertips over the surface of the forearm to locate the margins or edges of induration. As in this image, the widest edges of the induration are marked with a pen, using the fingertips as a guide. A millimeter ruler is then used to measure the diameter of the induration between the 2 marks.

Image courtesy of CDC/Gabrielle Benenson.
that the positive predictive value of the TST for TBI among foreign-born children younger than 5 years, most of whom had received a BCG vaccine, was 10%, meaning that 90% of the positive results were presumably falsely positive. In addition, the test has poor sensitivity in immunocompromised children, who have the greatest risk of progression to TB disease. Because of these limitations, some experts have called for the "retirement" of the TST in favor of the IGRA.24

The IGRA
IGRAs are ex vivo blood tests that detect interferon-γ (IFN-γ) release from a patient’s CD4+ and CD8+ T lymphocytes after stimulation by antigens found on M tuberculosis complex (which includes M tuberculosis, M bovis, M africanum, M microti, and M canetti). Two IGRAs are available commercially: the QuantiFERON-TB Gold Plus assay (QFT; Qiagen, Hilden, Germany), which has largely replaced the previously used and studied QuantiFERON-TB Gold In-Tube assay, and the T-SPOT.TB assay (T-SPOT; Oxford Immunotec, Abingdon, United Kingdom). However, the studies of QFT published before 2017 used the QuantiFERON-TB Gold In-Tube assay. Both the QFT and T-SPOT use early secreted antigenic target 6 (ESAT-6) and culture filter protein 10 (CFP-10) encoded by genes located within the region of difference 1 (RD1) locus of the M tuberculosis genome. The RD1 antigens used in the 2 IGRAs are not encoded in the genomes of M bovis-BCG strains, although they are present on wild-type M bovis, or most species of NTM, specifically not on the M avium complex organisms that are the most ubiquitous pathogenic environmental NTMs. The RD1 antigens may be found on other NTM strains that are rare causes of human disease (M marinum, M kansasi, M szulgai, and M flavescens). As a result, because the antigens in IGRAs are not found on most clinically relevant NTM and M bovis-BCG strains, one would expect that IGRAs will be more specific than the TST, yielding fewer false-positive results. Like the TST, IGRAs do not distinguish between TBI and TB disease.25

Test Characteristics
Both IGRAs are performed with positive and negative controls. The QFT assay is an enzyme-linked immunosorbent assay (ELISA) whole blood test. The QFT has 2 TB antigen tubes: tuberculosis antigen tube 1 (TB1) and tuberculosis antigen tube 2 (TB2). TB1 contains peptides from ESAT-6 and CFP-10, which are designed to elicit an immune response from CD4+ T-helper lymphocytes. TB2 contains an additional set of peptides targeted for a cell-mediated immune response from CD8+ cytotoxic T lymphocytes, included to bolster overall test sensitivity. The test result is considered positive when the IFN-γ response to the TB antigens (contained in TB1 and

Table 2: Risk Factors for Increased Risk of Acquiring TBI and/or Progressing to TB Disease

| Contacts of people with confirmed or suspected contagious TB (contact investigation) |
| Children with radiographic or clinical findings suggesting TB disease |
| Children immigrating from countries with endemic infection (eg Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees |
| Children with history of significant travel† to countries with endemic infection who have substantial contact with the resident population |
| Children with HIV infection |
| Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, or congenital or acquired immunodeficiencies and children receiving TNF-α antagonists, which may enhance the possibility for progression to severe disease |

† Determination of significant travel should account for the frequency of travel and the duration of time. Testing should be conducted 8–10 wk after completion of travel, to allow for the known incubation period of M tuberculosis.

hypersensitivity to antigens in the PPD that are also present in M bovis-BCG, which creates a false-positive TST result.21,22 False-negative TST results can occur because of limited ability of certain children with TBI or TB disease to mount an appropriate delayed-type sensitivity response, especially those who are immunosuppressed either by disease (such as advanced HIV infection, advanced TB, cancer, or malnutrition) or who receive immunosuppressive treatments (such as corticosteroids, cancer chemotherapy, and immunomodulating biological agents, especially the tumor necrosis factor-α [TNF-α] inhibitors or live-virus vaccines). Unfortunately, children for whom the TST has diminished sensitivity are those individuals most likely to progress to TB disease if infected.4 In summary, there are limitations to both the sensitivity and the specificity of the TST. The positive predictive value of the TST is much greater when it is applied to individuals who have a recognized risk factor for TBI. When the TST is used for individuals lacking risk factors, the vast majority of the positive results may be falsely positive, and this problem is accentuated in children who received a BCG vaccine.7 One large study using latent class analysis (a method of analysis that creates a statistical gold standard when no such test is available) demonstrated

From the American Academy of Pediatrics
TB2) is above the test cutoff of 0.35 IU/mL (after subtracting the negative control value from the test antigen value). If the test result is negative but the positive control also shows a poor response (a positive control failure from immunosuppression), or the background response in the negative control is too high (a negative control failure, perhaps from high baseline IFN-γ production attributable to systemic inflammation26), the result is considered indeterminate (neither negative nor positive). In this situation, testing on a different specimen is recommended.27

The T-SPOT assay is an enzyme-linked immunosorbent spot (ELISPOT) assay performed on peripheral blood mononuclear cells that have been incubated with peptides from ESAT-6 and CFP-10. The result is reported as the number of IFN-γ producing T-cells (spot-forming cells). The test result is considered positive when the number of spots in the test sample, after subtracting the number of spots in the negative control, exceeds a specific threshold of ≥8 spots; the test result is negative if there are 4 or fewer spots. Results with a corrected spot count of 5, 6, or 7 are considered borderline (equivocal), and retesting on a different specimen is recommended by the manufacturer. If the positive control shows a poor response (<20 spots), or if the background response in the negative control is too high (>10 spots), the result is termed invalid or indeterminate (neither negative nor positive).9 In this situation, testing on a different specimen is recommended.27

Although there are standard manufacturer instructions for performing IGRAs, concerns have been raised about the reproducibility of the results on serial performance. Serial testing of health care workers at low risk of TB2 have revealed cases of unexplained cases of low-level positive IGRA results reverting to negative on repeat testing.28 Nkurunungi et al29 performed T-SPOT tests on 405 Ugandan children at age 5 years and then repeated the test 3 weeks later. Of 79 children who had an initial positive T-SPOT result, only 30 (38%) had a positive result 3 weeks later, whereas 96% of the children with an initial negative result had a negative result on repeat testing. The test agreement was better among children who were household contacts of a person with TB (κ = 0.77) than among noncontacts (κ = 0.29). The majority of the reversions and conversions occur among low-level results, usually between 0.35 and 1.0 IU/mL for QFT, although they can occur at higher levels.30,31 The exact cause(s) of low-level false-positive results are unknown, but there appear to be seasonal variations that might explain increased nonspecific reactivity in the assay.32

A further explanation of low-level positive IGRA results is the concept of test-retest variability.33 For example, a test with 80% sensitivity and 70% specificity and a 5% test-retest variability would be associated with a conversion rate of 3.7% in the absence of TBI and a reversion rate of 7.7%. However, a test with 80% sensitivity and 95% specificity but 10% test-retest variability would be associated with a conversion rate of 5.5% and a reversion rate of 57%. T-lymphocyte assays are susceptible to test-retest variability by numerous factors, including manufacturing issues; sample collection issues, such as inconsistencies in specimen collection, inadequate blood volume, delays in isolation and incubation of cells, and inadequate shaking (mixing) of the IGRA collection tubes; and laboratory issues caused by systematic or random error.34 Efforts to reduce test variability through better specimen collection and handling and laboratory standardization will minimize low-level false-positive results.3,33

Published studies have shown a variety of differences in outcomes between the 2 basic IGRA techniques, ELISA (QFT) and ELISPOT (T-SPOT). However, these differences have been small and inconsistent among studies, and the preponderance of evidence supports the conclusion that in terms of accuracy, neither IGRA is strongly preferred over the other.

General Aspects of Studies in Children

The major difficulty for interpreting studies of TBI is determining, for discordant test results between the TST and IGRAs, whether the negative test result is attributable to enhanced test specificity or whether the positive test result is attributable to enhanced test sensitivity. Four systematic reviews and meta-analyses of the available studies of the use of IGRAs in children were published in 2011 and 201235–38; analysis of the studies was hampered by the heterogeneous methodologies used, including varying definitions of a clinical case of TB disease. Some of the early published studies used ELISA and ELISPOT techniques that were different from those that currently are commercially available. More recent rigorous studies using commercially available assays have clarified some issues. Studies have been performed in countries with both low and high TB burden, which often differ greatly in the severity of TB disease, rates of malnutrition in children, availability of TB diagnostic tools, structures of households where transmission often occurs, and the use of various
BCG strains and vaccination techniques.

**Test Specificity in Children**

Although there are variable results among individual published studies, the strongest and most consistent result is that IGRAs have a higher specificity for TBI, especially in settings of low TB burden and for BCG-vaccinated children. This conclusion is based on comparison of test results across exposure gradients of contact investigations in schools and the community in otherwise low-burden settings. In their meta-analysis, Sun et al included 7 studies that assessed IGRA specificity in populations with rates of BCG vaccination ranging from 0% to 100%. The specificity of ELISPOT was 89% for BCG-vaccinated and 95% for BCG-unvaccinated children, compared with a TST specificity of 49% for BCG-vaccinated and 93% for BCG-unvaccinated children: agreement (measured by κ scores) between the TST and IGRA in BCG-unvaccinated children was higher than in vaccinated children, probably because of false-positive TST results caused by previous BCG vaccination. Lighter et al found that among 207 children in New York, only 23% of the children with a positive TST result had a positive QFT, and, unlike the TST results, positive QFT results correlated with increased risk of TB exposure. Chun et al also found among 227 BCG-vaccinated children in South Korea that QFT results were more closely associated with exposure to a TB case than were TST results.

The most convincing evidence of increased specificity of IGRAs would be to determine rates of progression to TB disease among untreated children who have positive TST results and negative IGRA results. Ling et al evaluated how clinicians in Montreal used IGRA results to determine management of children. Among 55 children with positive TST results and negative QFT results who were part of TB contact investigations, the negative QFT result changed management in only 3 children; 52 children received isoniazid. However, of 201 children with positive TST results and negative QFT results who were tested in school and immigration screenings, 145 did not receive treatment, and none developed TB disease in 1 year of follow-up.

Researchers in a prospective multicenter trial in the United Kingdom studied 431 children who were recently exposed in their household to an infectious case of TB; 18 children with a positive TST but negative IGRA result went untreated, and none developed TB disease. A large multicenter trial in the United States performed a TST and IGRA on 3593 children at risk for TBI and/or progression to TB disease (mostly because of birth in a country with high burden of disease). Of 533 children with positive TST and negative IGRA results who were not treated for TBI, including 54 children younger than 2 years, none progressed to disease over a 2-year period. Lowenthal et al reviewed the results from California of testing for TBI among children moving to the United States from 2002 to 2013. Among 4035 children who had a positive TST result before entry, only 23% had a positive IGRA result after entry, and as expected, the proportion with a positive IGRA increased with age, reflecting higher risk of true infection over time. Finally, among 762 healthy children with a premigration positive TST result arriving to Sweden, only 33% with a BCG scar had a positive QFT result, compared with 76% without a BCG scar. However, low-level (<1.00 IU/mL for QFT, <8 spots for T-SPOT) false-positive IGRA results do occur, not because of cross-reaction with BCG vaccination or NTM but caused by nonspecific reactivity or technical factors in testing. Low-level IGRA test conversions (negative to positive) and reversions (positive to negative) occur frequently among low-risk health care workers in serial testing programs and do not represent TBI. Although there are no specific data for children, it is recommended that if a patient has an unexpected low-level positive IGRA result, either the same test should be repeated or a different test should be performed, and action should be taken on the second result. The best way to minimize false-positive results with any test of TBI is to test only children with legitimate risk factors for TBI.

The sum of all published studies supports the concept that IGRAs are more specific than TST in children of all ages. Despite the greater apparent specificity of IGRAs, the decision to treat or not in a patient with a positive TST result and a negative IGRA result should be based on clinical judgment that takes into consideration the risk of progression to disease and the degree of exposure. For example, children who were recently exposed to a case of contagious TB disease should be considered to have TBI if either the TST or IGRA result is positive, because they have a high risk of progressing rapidly to TB disease.

**Test Sensitivity in Children**

The analysis of studies in children of the sensitivity of IGRAs compared with TST is far more difficult, and the results have been highly variable. The earliest information came from the meta-analyses of studies of children with TB disease, diagnosed by either culture or clinical diagnosis. Sun et al found a sensitivity for all TB disease...
in children of 70% for ELISA (mostly QFT [range, 57% to 96%]), 62% for ELISPOT (mostly T-SPOT [range, 40% to 100%]), and 71% for TST (range, 43% to 100%). When the analysis was divided into cases of culture-confirmed TB and clinically diagnosed TB, the sensitivities were 85% and 64% for ELISA (mostly QFT), 76% and 58% for ELISPOT (mostly T-SPOT), and 85% and 66% for the TST, respectively. All 3 tests had lower sensitivity in clinically diagnosed cases; there are many possible explanations, including misdiagnosis of TB in the clinically diagnosed group.52 Another study conducted in a setting with high TB burden also found low sensitivity of IGRAs and the TST for TB disease, which did not add value to the clinical data and conventional tests for diagnosis of TB disease in these children.53 A systematic review and meta-analysis (15 studies included) of the performance of TST and IGRAs in immunocompetent children with microbiologically confirmed TB disease calculated the sensitivities of the TST, QFT, and T-SPOT to be 88.2%, 89.6%, and 88.5%, respectively.54 Kay et al55 analyzed California TB registry data for 778 patients 18 years or younger with laboratory-confirmed TB. Among children ages 5 to 18 years, the sensitivity of the IGRA was 96% vs 83% for the TST; IGRA sensitivity compared with TST in children ages 2 to 4 years was 91% vs 91% (so equivalent), and the sensitivity compared with TST in children younger than 2 years was 80% vs 87%. A smaller study in Italy of children with TB disease demonstrated the sensitivity of QFT to be 93.3% vs 86.5% for the TST.56 The sum of all published studies suggests that the sensitivity of IGRAs in settings of low TB burden is comparable to the TST, with both being less sensitive in settings of high TB burden and for extrapulmonary TB disease.11,39

There is some evidence that the sensitivity is increased when both a TST and IGRA are performed and the child is considered infected if either test result is positive. Hill et al52 investigated child household contacts of adult TB cases in the Gambia. Overall agreement between the TST and ELISPOT was 83%, with each test result being positive in 32% of the children, and neither test was affected by BCG vaccination. An additional Gambian study demonstrated a 10% sensitivity benefit for using both a TST and IGRA in children at high risk.58

Indeterminate/Invalid Results in Children

Indeterminate (preferably called invalid in relation to the T-SPOT test) results occur most commonly when the test sample is negative but the positive control has insufficient activity but also occur when the background activity in the negative control is too high. Indeterminate/invalid results often occur because of technical factors, most frequently inadequate shaking of the IGRA tubes after the patient’s sample has been added.3 Rates of indeterminate/invalid results among children varied in early studies between 0% and 35%,36,59–61 but the reported rates have been lower (0% to 8%) with the more recent versions of the commercially available tests.32,34,62–64 Rego et al65 reviewed 645 947 T-SPOT assays, finding 0.6% invalid and 1.8% borderline results. When 5044 borderline tests were repeated, 59.2% were negative, 20.0% were positive, and 20.2% remained borderline; the subject’s age did not affect the results. Indeterminate/invalid rates generally are higher among individuals with compromised immune systems whose T lymphocytes cannot mount an adequate response to the positive control, especially people living with HIV infection66,68; these rates also have been noted to be higher in children with poorly controlled inflammatory bowel disease, hepatitis, malaria, and helminthic infection.67,68 Some researchers have found that otherwise healthy children younger than 3 years are more likely to have indeterminate/invalid test results than older children and adolescents.69–72 However, authors of a recent systematic review and meta-analysis of 133 studies using IGRAs to diagnose TB found a 4% rate of invalid results and no difference between children 0 to 7 years of age and those 8 years or older.73

Test Performance in Immune-Compromised Children

Data are scarce for determining the sensitivity and specificity of IGRAs for immune-compromised children, who are at increased risk of developing TB disease if they are infected with M tuberculosis. There are scant data for children living with HIV infection, because IGRAs are generally not available in areas with high TB burden where there is also a high burden of HIV infection. Systematic reviews of the performance of IGRAs in people living with HIV infection, mostly adults, have concluded that the T-SPOT test may be slightly more sensitive than the QFT (72% vs 61%), but neither was more sensitive than the TST.66,74,75 Several small studies have included children living with HIV infection with varied results; in general, the IGRAs have less concordance with the TST in children with advanced HIV infection, especially if they have concomitant malnutrition.76–78 The risk of TB disease among people with HIV infection remains higher than that of the general population, and the cadence of TB testing in
HIV-infected patients is discussed elsewhere.79

Researchers in 2 small studies have examined the performance of IGRAs and the TST in children with cancer. Stefan et al found that among 37 children with untreated cancer in Cape Town, South Africa, a region with extremely high rates of TB, 7 had positive results with at least 1 test; there was a higher rate of positive results with the T-SPOT, poor concordance among the TST and IGRAs, and a high rate of test failure because of low lymphocyte counts in patients.80 During a contact investigation of 18 children in a pediatric hematology-oncology hospital unit after a patient was found to have pulmonary TB, only 2 patients had a positive T-SPOT result, and this test had more invalid/indeterminate results than the QFT.81

Screening for TB risk factors should be performed before any immunosuppressing therapy is given, but it is especially important before therapy with immunomodulating biological agents, such as monoclonal antibodies against TNF-α.3 This topic has been the subject of many small adult studies.82,83 Most of the adult patients in these studies also had been treated with a variety of other immunosuppressing agents, which may have affected the results of the TST or IGRAs. Rates of indeterminate/invalid results were higher than usual in the adult patients because of immune suppression by both disease and drugs. Within one small study of 79 children in Greece receiving antirheumatic treatment (only 18 were tested before treatment with an anti-TNF-α drug), patients with a risk factor for TBI were 27.6 times more likely to have a positive QFT result, and no child had a positive TST result.84 For these children, test sensitivity is more important than specificity because of the increased risk of progression of TBI to TB disease. The current evidence does not consistently suggest that IGRAs are better than the TST in identifying immunosuppressed individuals who will benefit from treatment of TBI. It is commonly recommended that all patients who will be receiving an immunomodulating biological agent, regardless of specific TB risk factors, should be tested for TBI before starting the therapy. Many experts have suggested that to increase sensitivity, both the TST and an IGRA should be performed initially for patients who also have a risk factor for TBI, and appropriate treatment of TBI should be started if either test result is positive once TB disease has been ruled out.82–85

Patients whose initial test results for TBI are negative should be screened annually for new TBI risk factors, but annual testing is not generally recommended in the absence of a new risk factor while on continued immunosuppression.

**Effect of Age on Test Results**

There has been a hesitancy to use IGRAs in children younger than 5 years because of a lack of data for this age group and concerns about inadequate sensitivity of the IGRAs. Because infants and young children (younger than 4 years) are more likely than older children to have progression from untreated TBI to TB disease and younger children are more prone to develop serious forms of TB, failure to accurately diagnose TBI in this age group can have dire consequences.14 Resolution of this issue has been hampered by the lack of a reference standard for TBI. The earliest studies suggested that IGRA sensitivity is diminished in young children, but the results were inconsistent.16 However, subsequent studies have demonstrated better performance of newer versions of the commercially available IGRAs in young children than previously reported. Debord et al89 found that among 19 children with TB disease, 6 of 10 children younger than 2 years and 9 of 9 children who were 2 to 5 years of age had a positive QFT result. Moyo et al90 studied 397 children in South Africa who were younger than 3 years and were suspected of having TB disease. Agreement between the QFT and TST was 94%, but both tests had lower sensitivity for TB disease (38% for QFT and 35% for the TST) than has been reported in older age groups.

Although the IGRAs have low sensitivity for detecting TB disease in young children whose immune responses may be blunted by malnutrition and TB itself, it is not clear whether they have a higher sensitivity for detecting TBI in otherwise healthy young children. Pavic et al91 studied 142 healthy BCG-vaccinated children in Croatia who recently had been exposed to infectious TB disease. Both the QFT and TST had proportions of positive results that were associated with degree of exposure, and there was no evidence that age affected QFT performance. Critselis et al72 performed a TST and QFT in 761 healthy Greek children in 4 age groups who were referred for several indications. Among the 198 children younger than 5 years (74 children were younger than 2 years), infants with positive QFT results produced a greater mean titer of IFN-γ than older children and adolescents. Agreement between the TST and QFT results was not significantly different between younger and older children. Velasco-Arnaiz et al92 found that among 39 children younger than 5 years with confirmed TB disease (15 children were younger than 2 years), the sensitivity of QFT was 93%, and in 79 children with either...
TBI or TB disease, there was no correlation between age and antigen-stimulated IFN-γ responses. From 2005 to 2008, the San Francisco TB program followed 146 untreated TST-positive/QFT-negative children, including 44 children younger than 2 years, and none developed TB disease.

It is clear that the use of the TST in infants and young children who received a BCG vaccine will lead to many false-positive results caused by cross-reaction with the BCG. Although some experts currently support the use of IGRAs to test for TBI in infants and toddlers, especially those at low risk of TBI who have received a BCG vaccine, others do not recommend their routine use in children younger than 2 years until additional supportive data are available. In summary, if an IGRA is performed in an infant or young child, a positive result likely indicates infection with Mycobacterium tuberculosis, but a negative result does not rule it out. A negative result for either a TST or an IGRA should be considered especially unreliable in a child younger than 3 mo.

**Strategies for the Use of IGRAs in Children**

Some of the major differences between the TST and IGRAs are summarized in Table 3. The basis for deciding which diagnostic test to use is fundamentally different for a child than for an adult, and it differs between the diagnosis of TBI and TB disease. When testing otherwise healthy individuals, the purpose of the TST or an IGRA is to determine if the person is infected with Mycobacterium tuberculosis and will benefit from treatment. The positive predictive value of both tests for the development of TB disease is low in adults and children 5 years or older, because only 5% to 10% of those who test positive and go untreated will develop TB disease in their lifetime. In these groups, test specificity is important to avoid massive overtreatment of individuals with false-positive results. However, children younger than 2 years with untreated TBI have a 25% to 50% risk of developing TB disease within 1 year, so optimizing test sensitivity is important for this age group. In addition, children tend to tolerate the treatment of TBI much better than adults, so their risk of adverse events caused by treatment is less. However, test specificity is also an issue for the youngest children, especially if they have received a BCG vaccine or have a likelihood of exposure to NTM in their environment; testing them with only the TST will lead to an appreciable proportion of false-positive results when the prevalence of TBI is low, as in the United States.

Both the TST and IGRAs are imperfect methods. As a result, only children who have a risk factor for TBI or TB disease, have a disease or condition that may require immunosuppression, or are suspected of having TB disease should be tested. However, a negative result from either type of test is not reliable for excluding the presence of TB disease. Deciding which test to use involves a consideration of sensitivity and specificity. When high specificity is desired (for example, otherwise low-risk BCG-vaccinated children), the IGRAs are the clearly superior tests. Neither method has a clear advantage in sensitivity; when sensitivity is the main concern, such as when contact with a contagious case of TB disease, a positive result with either the TST or IGRA should be considered indicative of infection with Mycobacterium tuberculosis. When sensitivity is paramount, such as high suspicion of TB disease or testing a child who has a TB risk factor and who will soon receive an immunomodulating biological agent, performing both an IGRA and a TST should be strongly considered, with a positive result for either test leading to the child being diagnosed with TBI. Performing both tests will lower the overall specificity and lead to some false-positive results, but in children with a high risk of

### Table 3: Comparison of the TST and IGRAs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigens used</strong></td>
<td>Many: PPD</td>
<td>3 (QFT) or 2 (T-SPOT)</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>Intradermal injection</td>
<td>Blood draw</td>
</tr>
<tr>
<td><strong>Patient visits required</strong></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>Distinguish between TBI and disease</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cross-reactivity with BCG</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Cross-reactivity with NTM</strong></td>
<td>Yes</td>
<td>Only rare species</td>
</tr>
<tr>
<td><strong>Differing threshold for positive values by level of risk for TBI</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Causes boosting</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Subject to boosting by previous TST</strong></td>
<td>Yes</td>
<td>Unknown but possible</td>
</tr>
<tr>
<td><strong>Durability over time (stays positive with or without treatment)</strong></td>
<td>Yes</td>
<td>Unknown but likely</td>
</tr>
<tr>
<td><strong>Difficulties with test reproducibility</strong></td>
<td>Yes (Bedside)</td>
<td>Yes (Laboratory)</td>
</tr>
<tr>
<td><strong>Location of need for trained staff</strong></td>
<td>Recommended</td>
<td>Acceptable</td>
</tr>
<tr>
<td><strong>Age &lt;2 y</strong></td>
<td>95–100 (unvaccinated children)</td>
<td>90–95 (vaccinated children)</td>
</tr>
<tr>
<td><strong>Estimated specificity in BCG-unvaccinated children, %</strong></td>
<td>45–85</td>
<td>89–100</td>
</tr>
<tr>
<td><strong>Estimated sensitivity (confirmed TBI disease), %</strong></td>
<td>75–85</td>
<td>80–85</td>
</tr>
<tr>
<td><strong>Estimated specificity (clinical TB disease), %</strong></td>
<td>50–70</td>
<td>60–80</td>
</tr>
</tbody>
</table>

a: Negative result of either the TST or an IGRA should be considered especially unreliable in a child younger than 3 mo.

b: Mycobacterium marinum, Mycobacterium kansasii, Mycobacterium szulgai, and Mycobacterium flavescens.

c: All rates of indeterminate/invalid results are higher in infants and young children.
progression to TB disease, this is an acceptable trade-off.

**Summary of Recommendations Regarding Testing**

Table 4 shows potential strategies for testing. Some specific points are as follows:

- Only children who have a risk factor for TBI or are at risk for progressing to disease, are suspected of having TB disease, or who have an immunosuppressive disease or about to start immunosuppressive therapy should be tested with a TST or an IGRA.
- There is no compelling evidence to support the use of one IGRA (QFT, T-SPOT) over the other.
- If the child of any age has been exposed to an infectious case of TB disease, he or she should be evaluated and, if determined not to have TB disease, given a full course of treatment of TBI if either a TST or IGRA result is interpreted to be positive.
- Even with a negative initial test result, contacts of a person with known TB disease should be retested in 8 to 10 weeks, usually with the same test, regardless of whether the initial test used was a TST or IGRA.

^ For exposed contacts with impaired immunity (eg, HIV infection) and all contacts younger than 5 years, treatment of possible TBI should be initiated, even if the initial TST or IGRA result is negative, once TB disease is excluded (often referred to as “window prophylaxis”). If the TST or IGRA result still is negative with repeat testing in 8 to 10 weeks, treatment can be discontinued. If a TST or IGRA result of a contact becomes positive, the regimen for TBI should be completed.

- For children who have received a BCG vaccine and have no known exposure to a contagious TB case and no other TB risk factor other than birth in a foreign country, 2 strategies can be used:
  1. an IGRA can be used and the result acted on; or
  2. a TST can be performed, and if the result is negative, no further testing is necessary; if the result is positive, an IGRA should be performed and its result acted on.
- When evaluating a child of any age for TB disease, both a TST and one or both IGRAs can be performed to maximize sensitivity.

**TABLE 4 Suggested Uses of TST and IGRA in Children**

<table>
<thead>
<tr>
<th>Suggested Uses of TST and IGRA in Children</th>
<th>TST preferred, IGRA acceptable*&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TST preferred&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children younger than 2 y&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Children younger than 2 y&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Children younger than 2 y&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IGRA preferred&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IGRA preferred&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IGRA preferred&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children 2 y or older, especially those who have received BCG vaccine</td>
<td>Children of any age who are unlikely to return for the TST reading&lt;br&gt;Both&lt;sup&gt;d&lt;/sup&gt; the TST and an IGRA should be considered when:</td>
<td>Both&lt;sup&gt;d&lt;/sup&gt; the TST and an IGRA should be considered when:</td>
</tr>
<tr>
<td></td>
<td>The initial and repeat IGRA results are indeterminate or invalid&lt;br&gt;The initial test (TST or IGRA) result is negative and:</td>
<td>The initial and repeat IGRA results are indeterminate or invalid&lt;br&gt;The initial test (TST or IGRA) result is negative and:</td>
</tr>
<tr>
<td></td>
<td>There is clinical suspicion of TB disease&lt;sup&gt;e&lt;/sup&gt; (to maximize sensitivity)&lt;br&gt;The child has a risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biological agent, such as a TNF-α antagonist)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>There is clinical suspicion of TB disease&lt;sup&gt;e&lt;/sup&gt; (to maximize sensitivity)&lt;br&gt;The child has a risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biological agent, such as a TNF-α antagonist)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>An initial TST is positive and:</td>
<td>An initial TST is positive and:</td>
</tr>
<tr>
<td></td>
<td>The child has a history of BCG vaccination&lt;br&gt;Additional evidence is needed to increase adherence with therapy</td>
<td>The child has a history of BCG vaccination&lt;br&gt;Additional evidence is needed to increase adherence with therapy</td>
</tr>
</tbody>
</table>

* In situations of testing obligated by law or credentialing bodies in person unlikely to be uninfected with TB, IGRA is preferred.<sup>a</sup>

<sup>b</sup> Many experts will use an IGRA in children of any age, especially if the child has received a BCG vaccine but have no other significant risk factors other than foreign birth. However, data from children in this age group are few.<sup>b</sup>

<sup>c</sup> A positive result of either test is considered significant in these groups.<sup>c</sup>

<sup>d</sup> The clinician should obtain the complementary test (eg, if a TST was initially performed, then IGRA should be obtained for a complete set).<sup>d</sup>

**Rationale**

The goal of treatment is to prevent TBI from progressing to TB disease and to diminish the reservoir for future TB cases. All children who have TBI should receive a course of therapy. The risk of developing TB disease is highest during the 6 months after infection and remains high for 2 years.<sup>95</sup> Not all people with TBI have the same level of risk of progression to disease. Three
high-risk groups bear special attention for disease progression:

1. Infants and young children (particularly those younger than 2 years) may progress rapidly to disease (40% to 50% of infected children younger than 1 year; 25% of infected children 1–2 years of age) including meningitis or miliary disease (15% of infected children younger than 1 year; 5% to 7% of infected children 1–2 years of age).

2. Postpubertal adolescents (older than 12 years) who also have the risk of progression to adult-type disease.

3. Children and adolescents with immunocompromising conditions or receiving certain immunosuppressing treatments, including patients with diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies; patients with malignancy; patients receiving TNF-α antagonists or blocking agents; and patients preparing for or experiencing organ or hematologic transplant.

There are several barriers to completion of treatment of TBI. Children with infection are asymptomatic, and families do not readily observe a response to treatment and often do not appreciate a clear need to continue medications. Pediatric formulations of anti-TB medications are not generally available in the United States, requiring compounding or adaptation of adult formulations such as crushing pills or opening capsules (see “Administration of Antituberculosis Medication to Children”). Medical providers for children and adolescents should be familiar with all the regimens available to treat TBI to select the best regimen for the individual child and family. The regimen ultimately prescribed for children should be safe, effective, and relatively inexpensive, allow easy administration to young children, and result in a high completion rate. The one characteristic that consistently inversely correlates with completion of treatment is the length of treatment: the shorter the duration, the higher the completion rate.

**General Principles**

The practitioner should be cognizant of the following principles and assumptions when caring for pediatric patients with TBI:

- Infants and children with TBI who have been recently infected have an increased risk of rapid disease development, and young age at infection predicts more years at risk for disease progression into adulthood.

- Assume that the causative *M tuberculosis* is susceptible to multiple drugs unless specific knowledge of drug resistance is available. The incidence of isoniazid resistance among TB isolates from US patients is approximately 9%, and the incidence of rifampin resistance is <1%. The assumption is negated if the source case is known to have a drug-resistant isolate.

- A thorough physical examination and high-quality chest radiographs (posterior-anterior and lateral views) should be performed before starting treatment. It is crucial to ensure that TB disease is not inadvertently treated with an inadequate drug regimen; otherwise, the risk of developing drug-resistant TB while on therapy is high (particularly with monotherapy with isoniazid or rifampin). Chest radiographs rule out lung parenchymal disease and any enlarged thoracic adenopathy. The physical examination helps to exclude extrapulmonary TB (including adenopathy and hepatosplenomegaly). If evidence of TB disease is found, additional diagnostic procedures should be performed, and the treatment regimens will be different from those for TBI.

- Anti-TB treatment regimens that are efficacious in adults will be effective in children. Performing efficacy trials exclusively in children is not ethically or scientifically justifiable. Extensive experience has shown that treatment regimens for both TBI and TB disease that are effective in adults also will be effective in children. As such, rather than focusing on efficacy alone, studies regarding TB regimens in children are designed to assess and improve medication safety, tolerability, pharmacokinetics, and adherence.

- Laboratory testing before or during treatment is not necessary in otherwise healthy pediatric patients. The use of isoniazid monotherapy for pediatric TBI causes low rates of hepatotoxicity (<1%). Alternate regimens, which may include 2 drugs but for a shorter duration, are even less hepatotoxic than the 9 months of isoniazid monotherapy. This reduced toxicity stems, in part, from the overall decreased time of drug exposure. However, increased risk of hepatotoxicity can be experienced by children who are obese and have nonalcoholic steatohepatitis, are taking other potentially hepatotoxic medications (especially anticonvulsants), are pregnant in the first 12 weeks of gestation, or have underlying liver disease. These children should have baseline hepatic function tests (alanine transaminase, aspartate...
transaminase) and periodic laboratory monitoring (eg, monthly) during therapy.

- Completion of regimens for TBI in high-risk groups (including children and adolescents) is imperative. Historically, medication regimens for TBI have been through self-administered therapy (SAT). Although completion of isoniazid by SAT was >80% within the context of a research study, completion rates decrease to approximately 60% in the real world because of patient fatigue or drug intolerance. Adherence may be improved by directly observed therapy (DOT), when medications are administered directly to the patient by a health care professional or trained third party (not a relative or friend) who observes and documents that the patient ingests each dose of medication. There has been success in administering DOT through school-based health centers. DOT is considered directly to the patient by a health care professional or trained third party (not a relative or friend) who observes and documents that the patient ingests each dose of medication. There has been success in administering DOT through school-based health centers. DOT should be considered for treatment of children and adolescents with TBI who are at high risk of rapid progression to disease. When well conducted, DOT is a package of services, including enablers and reinforcements, designed to help the patient and family complete therapy.

- DOT provides the highest rates of medication completion (approximately 80% to 95%). It requires both financial and staff resources, usually from the local health department, and can be time consuming for the staff and families. The time and resources required often make DOT unacceptable to patients and providers.

- SAT-hybrid models may be alternate methods for improving patient compliance. One example is self-administration, with text reminders from providers. A successful program in Houston, Texas, has been SAT-based, but the health department delivers the medications to the patient’s home on a monthly basis and contacts the family weekly to support the treatment. Video DOT may be used in lieu of the traditional in-person DOT strategy, provided the patient has a personal device and that privacy restrictions of the Health Insurance Portability and Accountability Act are applied. Video DOT may be synchronous (in real time) or asynchronous (video clips are recorded and then uploaded for later review).

- Children with adequate anti-TB treatment need not be retested. The test of infection (either TST or IGRA) remains positive after adequate treatment and should not be used as a test of cure or as surveillance for emergence of TB disease.

### Treatment Selection

Anti-TB drugs kill or inhibit multiplication of *M. tuberculosis*, thereby arresting progression of infection and preventing most complications. Historically, the dominant regimen was 6 to 9 months of isoniazid monotherapy by SAT. Other alternatives to treatment of TBI have emerged, with similar rates of efficacy to protect against development of disease. Factors to consider in regimen selection include the child’s age and requirement for liquid formulations, need for speedy treatment (such as a pending stem cell or solid organ transplant), use of concomitant hepatotoxic medications, concurrent HIV infection, and suspected infection with drug-resistant *M. tuberculosis*. If therapy is completed successfully, there is no need to perform additional tests or chest radiographs unless a new exposure is documented or the child develops a clinical illness consistent with TB, the latter being extremely rare in North America. A TB specialist should be involved if questions arise regarding selection of an appropriate treatment regimen or management of adverse effects.

#### Specific Drugs

**Isoniazid**

Pediatric experience with isoniazid is extensive and well published. Isoniazid can inhibit pyridoxine metabolism; however, otherwise healthy children and adolescents in the United States given recommended doses rarely develop associated peripheral neuritis or seizures and do not need pyridoxine supplements as a preventive measure. However, isoniazid overdose, as in a suicide attempt, can lead to generalized seizures that are difficult to control unless large doses of pyridoxine are administered. Routine pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic children living with HIV infection; and pregnant adolescents and women. Bioavailability of isoniazid is improved with administration on an empty stomach, although dyspepsia may be alleviated with small amounts of food.

Hepatotoxicity caused by isoniazid is rare in otherwise healthy children, and routine laboratory testing is not necessary (Table 5). There can be transiently mild elevations of transaminases, with no clinical consequence given that these resolve spontaneously. When testing is indicated because of development of clinical signs or symptoms (eg, abdominal pain, vomiting, jaundice) that could be caused by hepatitis, hepatotoxicity may be defined as...
transaminase elevations of 2 to 3 times the upper limit of normal if the patient is symptomatic, or >5 times the upper limit of normal if the patient is asymptomatic.\textsuperscript{106}

\textbf{Rifampin}

Rifampin is a rifamycin that, because of its short half-life, must be administered daily. Rifampin is readily available by prescription, including a standard compounded liquid formulation for young children. Bioavailability of rifampin is improved with administration on an empty stomach, although dyspepsia may be alleviated with small amounts of food (Table 5).

A major concern with using any rifamycin-containing regimen is drug–drug interactions. These interactions should be appreciated as the number of pediatric immunocompromised patients (such as those undergoing treatment of HIV infection, with oncologic diseases, or who are transplant recipients) increases. The rifamycins are potent inducers of the hepatic CYP 450 enzyme. This increased enzymatic activity will heighten metabolism of classes of antiretroviral drugs such as the protease inhibitors. Conversely, the rifamycins may increase the exposure to specific immunosuppressive drugs, necessitating a dose reduction of agents such as tacrolimus and cyclosporine.

An additional drug interaction concern with rifampin is that it can lower the effectiveness of oral contraceptives. Female adolescents taking rifampin must be counseled that they should rely on other forms of birth control while taking this medication. Also, patients should be warned that rifampin will cause urine, sweat, saliva, and tears to turn a red-brown color and can cause staining of contact lenses.

\textit{Rifapentine}

Rifapentine is a rifamycin with a long half-life allowing for weekly administration, versus the daily dosing of rifampin. The bioavailability of rifapentine is enhanced by food (particularly products containing fat, such as milk or egg), and this medication should be given as possible with fatty food. The dosing of the 2 components (isoniazid, rifapentine) varies by weight and age of the patient (Table 6). The drug–drug interactions with rifapentine appear less when compared with those of rifampin.

\textbf{Treatment Regimens for TBI}

\textbf{Once-Weekly Dosing of Isoniazid and Rifapentine (3HP) (12 Doses)}

This regimen includes the use of isoniazid and rifapentine, given once weekly, for 12 doses. The regimen is commonly referred to as once-weekly dosing of isoniazid and rifapentine (3HP): the H is the international symbol for isoniazid, the P is the symbol for rifapentine, and the 3 refers to a treatment length of 3 months. The 3HP regimen is considered complete if at least 11 doses have been taken over 16 weeks. This regimen has similar efficacy to 9 months of isoniazid (see below) but is associated with higher completion rates in adults, children, and adolescents.\textsuperscript{100,107}

When first introduced, 3HP was prescribed under DOT, and rifapentine was available only through local health departments. However, an open-label, phase 4 clinical trial of adult patients (18 years or older) demonstrated noninferiority for completion rates and safety of 3HP given by SAT compared with DOT.\textsuperscript{103} As a result, the Centers for Disease Control and Prevention (CDC) has recommended that 3HP may be given via SAT when DOT is not available or feasible.\textsuperscript{108,109} Because the study did not include children or adolescents, it is not known whether the similarity of completion rates observed in adults given 3HP by SAT or DOT would be seen in children and adolescents. Use of DOT may be preferred for patients at increased risk of rapid progression to TB disease (recent contacts of infectious cases, immune-compromised patients, age younger than 5 years, some adolescents).

The 3HP regimen, despite the use of 2 agents, appears to be equally or less hepatotoxic than 9 months of isoniazid monotherapy.\textsuperscript{100} Providers should be cognizant that the pill burden of this regimen may be high; a child weighing 25 kg would need to take 6 tablets (4 of rifapentine, 2 of isoniazid) simultaneously.

This regimen is recommended for children 2 years or older (there is a paucity of data on rifapentine pharmacokinetics in very young children). 3HP can be used in HIV-infected individuals barring drug–drug interactions with antiretroviral medications.

\textbf{4 Months of Daily Rifampin (4R) (120 Doses)}

The 4-month regimen of daily rifampin (4R) is usually taken by SAT (15–20 mg/kg per dose, maximum 600 mg per dose). Rifampin is bactericidal against \textit{M tuberculosis}. Therapy is deemed completed if 120 doses have been administered within 6 months. Efficacy is similar to 9 months of isoniazid, but the shorter period allows for a significantly higher rate of completion.\textsuperscript{110–112}

Drug–drug interactions preclude it as a regimen for HIV-infected individuals. Because HIV-infected individuals with low CD4\textsuperscript{+} T-lymphocyte counts may have subclinical TB disease, using
rifampin monotherapy may inadvertently increase TB resistance in those people.

There is no age restriction for the use of 4R. The adverse effect profile of 4R is excellent, with similar transaminase elevations as with 9 months of isoniazid (see below).110–112 Hence, 4R is preferred in children without HIV infection of all ages who are not able to undergo DOT, or if there is a concern of an isoniazid-resistant isolate as judged from the exposure history.

### 3 Months of Daily Therapy With Isoniazid and Rifampin (3HR) (90 Doses)

This regimen consists of 3 months of daily isoniazid and rifampin (3HR). The use of 3HR is considered the best option for isoniazid-resistant isolates. The regimen can be used for children under 12 years of age and adults. There are no age restrictions for the use of 3HR.

### 6 or 9 Months of Isoniazid (6H) (9H)

Isoniazid monotherapy has been the most widely recommended and used treatment of pediatric TBI. Isoniazid is bactericidal against *M. tuberculosis*. Isoniazid may be given daily by SAT (10–15 mg/kg per dose, maximum 300 mg per dose) or twice weekly, via DOT (20–30 mg/kg per dose) or twice weekly, via DOT (20–30 mg/kg per dose) or twice weekly.

There is no age restriction for the use of 6H. The adverse effect profile of 6H is excellent, with similar transaminase elevations as with 9 months of isoniazid (see below).14–18 Hence, 6H is preferred in children without HIV infection of all ages who are not able to undergo DOT, or if there is a concern of an isoniazid-resistant isolate as judged from the exposure history.

### TABLE 5 Characteristics of Medications Used in Pediatric Patients With TBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Common Adverse Effects</th>
<th>Bioavailability</th>
<th>Drug Safety Monitoring for All Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Hepatotoxicity, Peripheral neuropathy, Gastrointestinal upset (common, particularly if isoniazid is taken on empty stomach), Diarrhea, Rash</td>
<td>Best if on empty stomach, although small amounts of food may alleviate dyspepsia</td>
<td>• Otherwise healthy patient: no baseline LFTs needed. If symptomatic on treatment, obtain LFTs.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Gastrointestinal upset (common, particularly if these are taken on empty stomach), Hepatotoxicity, Rash, Thrombocytopenia, Hypersensitivity response (rare in children), Orange discoloration of body fluids (urine, sweat, tears)</td>
<td>Best if on empty stomach, although small amounts of food may alleviate dyspepsia</td>
<td>• Patient with existing liver disease or with concomitant hepatotoxic drugs: baseline and periodic (often monthly) LFTs recommended</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Should be given with fatty food to enhance absorption</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Agent(s)</th>
<th>Dose and Age Group</th>
<th>Administration</th>
<th>Duration, mo</th>
<th>No. Doses Needed for Completion</th>
<th>Rates of Completion, %</th>
<th>Age Restriction</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>3HP</td>
<td>Isoniazid + Rifapentine</td>
<td>Age ≥12 y</td>
<td>Weekly (SAT or DOT)</td>
<td>3</td>
<td>12</td>
<td>83–97</td>
<td>Not for children &lt;2 y</td>
<td>Take with food, containing fat if possible; pyridoxine for selected patients&lt;sup&gt;a&lt;/sup&gt;</td>
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</table>
| 4R      | Rifampin | Adult: 10 mg/kg (max 600 mg)  
Child: 15–20 mg/kg (max 600 mg) | Daily (SAT) | 4 | 120 | 72–96 | None | Drug–drug interactions |
| 3HR     | Isoniazid + rifampin | Same doses as when drugs are used individually | Daily (SAT) | 3 | 90 | 82 | None | Not considered unless 3HP or 4R are not feasible |
| 6H      | Isoniazid | Adult: 5 mg/kg (max dose 300 mg)  
Child: 10–15 mg/kg (max 300 mg)  
Adult: 15 mg/kg (max dose 900 mg)  
Child: 20–30 mg/kg (max 900 mg) | Daily (DOT) | 6 | 180 | 20–93 | None | Seizures with overdose; pyridoxine for selected patients<sup>a</sup> |
| 9H      | Isoniazid | Adult: 5 mg/kg (max dose 300 mg)  
Child: 10–15 mg/kg (max 300 mg)  
Adult: 15 mg/kg (max dose 900 mg)  
Child: 20–30 mg/kg (max 900 mg) | Twice weekly (DOT) | 9<sup>b</sup> | 270 | 20–93 | None | Seizures with overdose; pyridoxine for selected patients<sup>a</sup> |

<sup>a</sup> Exclusively breastfed infants and for children and adolescents on meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic children living with HIV; pregnant adolescents and women.

Table adapted from Cruz AT, Ahmed A, Mandalakas AM, Starke JR. Treatment of latent tuberculosis infection in children. J Pediatr Infect Dis. 2013;2(3):248–258. 6H, 6 months of isoniazid; 9H, 9 months of isoniazid; —, not applicable.
The efficacy of isoniazid monotherapy reaches 98% against development of TB disease.\textsuperscript{106} The World Health Organization recommends a treatment duration of 6 months\textsuperscript{114} to provide high coverage of the population in countries with a high disease burden. A 9-month regimen gives an additional 20% to 30% increase in efficacy.\textsuperscript{97} The CDC and National TB Controllers Association recommends 6-month or 9-month durations of isoniazid monotherapy, if shorter-course rifamycin-based regimens cannot be used.\textsuperscript{108}

Although isoniazid is readily available, the long duration of isoniazid monotherapy results in poor adherence and low completion rates. This option may be unattractive to patients and families. Many TB care providers and clinics use this regimen only when a rifamycin-containing regimen cannot be used because of drug interactions.

**Administration of Antituberculosis Medication to Children**

Given the common inability of young children to swallow pills and to mitigate the common adverse effect of gastrointestinal tract upset right after taking the medication, guidance for administering medication (particularly isoniazid) is warranted. Commercially available isoniazid suspension contains large amounts of sorbitol and often causes nausea and diarrhea if the volume exceeds 5 mL and/or if it is taken when the child has fasted. If the child is unable to swallow pills, the pills can be crushed and mixed into syrup or other palatable liquid to appeal to the young child, and in the smallest volume possible to ensure the entire dose is taken (ie, not in a full bottle of milk). Rifampin should be given on an empty stomach or with a small amount of food. Rifapentine should be administered with food, particularly with a high fat content, to enhance absorption.

For mothers receiving treatment for TBI or TB disease who are also breastfeeding, their infants may be indirectly receiving TB medications. The amount being received is miniscule and is the basis for recommendations for mothers to continue breastfeeding even while receiving TB treatment with first-line agents.\textsuperscript{115}

**Evaluation and Management of Adverse Reactions**

Regardless of the treatment regimen selected, all children should be clinically monitored on a regular basis. This allows the medical provider to assess for medication adverse effects, determine if there is advancement of the TBI to disease, and continue to educate patients and families on the importance of treatment and adherence. Monthly clinical evaluation (at a minimum) to observe for signs or symptoms of hepatitis and other adverse effects of drug therapy is appropriate and can be done without routine laboratory monitoring of serum transaminase concentrations. Children receiving other known potentially hepatotoxic medications or who have known or suspected liver dysfunction (including obese children at risk for nonalcoholic steatohepatitis) should have baseline transaminase levels determined and followed closely for clinical signs or symptoms of hepatitis. The increasing use of telehealth visits in ambulatory care settings may allow increased access for monitoring but has the disadvantage of not allowing a thorough physical examination in a child who is taking hepatotoxic drugs.

**End-of-Therapy Assessment**

Families should be advised that either test of infection (TST or IGRA) will remain positive after treatment completion because of immunologic memory and is not a sign of treatment failure. Patients and their parents also should be aware that the child should not receive a TST in the future, because there may be an accelerated reaction that can result in a blister or even a scar at the site of the injection. Repeat chest radiography after treatment completion is not necessary. If there is a clinical change or a new risk factor has emerged, then a complete physical examination and chest radiography should be performed for assessment of TB disease.

**Common Drug-Related Adverse Reactions**

**Hepatotoxicity**

If any patient, while on treatment, exhibits clinical signs and symptoms concerning for a significant adverse reaction from the medication (including but not limited to abdominal pain, anorexia, jaundice, dark-colored urine, pale stools), the medication should be stopped immediately while the clinician is contacted and directs evaluation. Many patients who eventually suffer severe hepatotoxicity had continued to take the medications even after clinical signs or symptoms became apparent. Transaminases should be assessed and, if elevated, measured weekly until either resolution or concern prompting gastroenterology consultation. Resolution of clinical symptoms and/or laboratory abnormalities may allow rechallenge with the same regimen. In situations in which resolution does not occur after medication discontinuation, or previously resolved abnormalities resurface at the time of rechallenge, a different regimen not containing the suspected offending drug should be started. This decision to use drugs other than isoniazid or a
that gastrointestinal tract upset, if not easily relieved with above measures, is not secondary to medication-induced hepatotoxicity.

**Interruptions in Therapy**

Questions may arise regarding how to manage patients who experience interruptions in therapy because of poor adherence, assessment of possible drug-related toxicity, or temporary lack of available medications. No formal trials of interrupted treatment courses and efficacy have been conducted. Published guidance and medical expert opinion have put forth acceptable options for completion of certain regimens (see specifics in drug regimens above).

Interruptions in treatment regimens with already short duration of the rifamycin-based regimens likely have more detrimental impact on effectiveness. The clinician needs to determine if to restart the regimen or extend the date of completion. If the interruption occurred early or over an extended time (over a month), it may be prudent to restart courses of rifamycin-based regimens.

**Special Considerations**

**Treatment of Multidrug-Resistant TBI**

Multidrug-resistant TB is defined as infection or disease caused by a strain of *M tuberculosis* that is resistant to at least isoniazid and rifampin, the 2 first-line drugs with greatest efficacy. Optimal therapy for multidrug-resistant TBI has not been established and needs to be individualized on the basis of the exact drug resistance pattern of the isolate. Although there have been no randomized controlled trials, many experts recommend that a fluoroquinolone antibiotic, either levofloxacin or moxifloxacin, alone or in combination with a second drug to which the isolate is susceptible, is the best currently available regimen. The optimal length of therapy is unknown, with most experts recommending treatment duration between 6 and 12 months. These cases should be managed in consultation with a specialist with expertise in managing pediatric TB.

**Children Living With HIV Infection**

The CDC and National TB Controllers Association prefer short-course rifamycin-based regimens for TBI if there are no prohibitive drug-drug interactions with antiretroviral medications. Specifically, 3HP is recommended for children 2 years and older in this situation, followed by 3HR in children of all ages. The combination of isoniazid and rifapentine has been given successfully to adults living with HIV infection, and some data are available for children. Treatment of coinfected individuals should be guided by clinicians experienced in the management of both conditions.

**SUMMARY OF RECOMMENDATIONS REGARDING TREATMENT REGIMENS**

- The risk of a child progressing from having TBI to TB disease depends on the child’s age and immune status. Young children (younger than 4 years), adolescents, and immunocompromised individuals are at higher relative risk to progress from infection to disease.
- Short-course rifamycin-based regimens are preferred for treatment of TBI. On the basis of safety, adherence and completion, and effectiveness, many experts prefer 3HP, by DOT, in patients 2 years or older. When DOT is not available or the child cannot handle the pill burden of 3HP, 4R or 3HR may be the best regimen.
- Patient monitoring for adherence (DOT or SAT-hybrid) should be...
strongly considered for patients at high risk for progression to TB disease.

- Routine laboratory monitoring is not needed for healthy patients but should be considered for patients with immune compromise, those with existing liver disease, or those who are taking other potentially hepatotoxic medications.
- Respiratory illnesses are rarely a harbinger of progression to disease but likely represent intercurrent community-acquired infections.

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ABBR EVIATIONS

3HP: once-weekly dosing of isoniazid and rifapentine
3HR: 3 months of daily isoniazid and rifampin
4R: 4-month regimen of daily rifampin
BCG: bacille Calmette-Guérin
CDC: Centers for Disease Control and Prevention
CFP-10: culture filter protein 10
DAT: directly observed therapy
ELISA: enzyme-linked immunosorbent assay
ELISPOT: enzyme-linked immunosorbent spot
ESAT-6: early secreted antigenic target
IFN-γ: interferon-γ
IGRA: interferon-γ release assay
NTM: nontuberculous Mycobacterium
PPD: purified protein derivative
QFT: QuantiFERON-TB Gold In-Tube assay
RD1: region of difference 1
SAT: self-administered therapy
TB: tuberculosis
TB1: tuberculosis antigen tube 1
TB2: tuberculosis antigen tube 2
TNF-α: tumor necrosis factor-α
T-SPOT: T-SPOT.TB assay
TST: tuberculin skin test
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