



TECHNICAL REPORT

Interferon- γ Release Assays for Diagnosis of Tuberculosis Infection and Disease in Children

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KEY WORDS

bacille Calmette-Guérin, interferon- γ release assay, tuberculin skin test, tuberculosis

ABBREVIATIONS

BCG—bacille Calmette-Guérin
ELISA—enzyme-linked immunosorbent assay
ELISPOT—enzyme-linked immunosorbent spot
IGRA—interferon- γ release assay
INF- γ —interferon- γ
LTBI—latent tuberculosis infection
NTM—nontuberculous mycobacteria
PPD—purified protein derivative
QFT—QuantiFERON-TB Gold In-Tube assay
TB—tuberculosis
T-SPOT—T-SPOT.TB assay
TST—tuberculin skin test

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abstract

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Tuberculosis (TB) remains an important problem among children in the United States and throughout the world. Although diagnosis and treatment of infection with *Mycobacterium tuberculosis* (also referred to as latent tuberculosis infection [LTBI] or TB infection) remain the lynchpins of TB prevention, there is no diagnostic reference standard for LTBI. 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 significant cross-reaction with *Mycobacterium bovis*-bacille Calmette-Guérin (BCG) vaccines and many nontuberculous mycobacteria. Interferon- γ release assays (IGRAs) are blood tests that measure ex vivo T-lymphocyte release of interferon- γ after stimulation by antigens specific for *M tuberculosis*. Because these antigens are not found on *M bovis*-BCG or most nontuberculous mycobacteria, IGRAs are more specific tests than the TST, yielding fewer false-positive results. However, IGRAs have little advantage over the TST in sensitivity, and both methods have reduced sensitivity in immunocompromised children, including children with severe TB disease. Both methods have a higher positive predictive value when applied to children with risk factors for LTBI. Unfortunately, neither method distinguishes between TB infection and TB disease. The objective of this technical report is to review what IGRAs are most useful for: (1) increasing test specificity in children who have received a BCG vaccine and may have a false-positive TST result; (2) using with the TST to increase sensitivity for finding LTBI in patients at high risk of developing progression from LTBI to disease; and (3) helping to diagnose TB disease. *Pediatrics* 2014;134:e1763–e1773

INTRODUCTION

Tuberculosis (TB) remains an important disease in the United States and throughout the world. Of the almost 9 million annual cases of TB globally, approximately 10 000 cases occur in the United States.¹ Of the 2660 children and adolescents younger than 18 years with TB disease reported in the United States from 2008 to 2010, 31% were born in other countries.² Among the US-born pediatric patients, 66% had at least 1 foreign-born parent, and 75% of all the pediatric patients had some international connection through family or residence history. Although 52% of these cases occurred in children ages 13 to 17 years,

infants and young children have the highest rate of TB infection progressing to TB disease rapidly after exposure (ie, within a few weeks to several months). Children who immigrated to the United States from countries with high TB burden often received no testing for latent tuberculosis infection (LTBI), expanding the pool of infected children in the United States. Some of these children developed TB disease or were evaluated and treated for LTBI after immigration, but many have untreated LTBI 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, the infection becomes “latent,” and the person remains asymptomatic. However, latent bacilli may remain viable and become active again to cause TB disease. Treatment of LTBI substantially reduces the risk of developing TB disease in both the immediate and distant future.³ Therefore, the goal of testing for LTBI is to identify those individuals who are at increased risk of developing TB disease and will benefit the most from treatment. In the pediatric population, infants and very young children and adolescents are at higher risk of progressing to TB disease than are primary school-aged children. The risk of progression in infants younger than 12 months is 40%; it is decreased to 25% in children 1 to 2 years of age and is 10% to 15% in older children and adolescents. Epidemiologic factors also define risk: 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 LTBI are at higher risk for LTBI than the general population. As

a result, selective testing for LTBI 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 the diagnosis of LTBI.³ Two available but imperfect methods for identification of LTBI are the tuberculin skin test (TST) and interferon- γ release assays (IGRAs). Both methods depend on cell-mediated immunity and provide immunologic evidence of host sensitization to antigens of *M tuberculosis*. Neither method can distinguish between LTBI and TB disease, and both methods display suboptimal performance in immunocompromised patients, who are at greatest risk for progression of TB infection to TB disease. The objective of this technical report is to review the current evidence for the best uses of IGRAs in children.

TUBERCULIN SKIN TESTS

The TST was first developed by Charles Mantoux in 1907 and has been an important factor in the decline of TB disease in much of the Western world. It has existed in several forms, currently the Mantoux test, which is the intradermal injection of 5 TU of purified protein derivative (PPD) or 2 TU of PPD-RT23. PPD tuberculin solution contains dozens of TB antigens, with the exact composition varying among batches and preparations. Many of these antigens are also present in environmental nontuberculous mycobacteria (NTM) prevalent throughout the United States. A patient who mounts a cell-mediated response to tuberculin antigens has a delayed-type hypersensitivity response usually within 48 to 72 hours, causing measureable induration at the injection site.

TST results can be difficult to interpret. The test depends on accurate

intradermal injection and should be performed by an experienced individual. Interpretation requires that the family return in 48 to 72 hours. Correct interpretation of the reaction involves careful measurement of the induration determined by a provider with clinical experience in this measurement. The measurement should be recorded to the nearest millimeter of the transverse diameter of the induration. The variation in the reaction size of an individual host, determined by placement of the test simultaneously on both arms, averages 15%; the variability in measuring induration among experienced observers also varies by approximately 15% and is much greater among inexperienced personnel and untrained people, such as family members.^{4,5} Therefore, family members should not be allowed to interpret a TST result. False-negative TST results can be caused by improper handling of the PPD solution, improper placement of the test, incorrect interpretation of the results, or advanced TB disease.

Induration at the site of the TST is caused by migration of mostly mononuclear cells to the area and the inflammatory process secondary to the response of these cells. This response can be attributable to infection with *M tuberculosis*, exposure to NTM, or receipt of bacille Calmette-Guérin (BCG) vaccine.⁶ The TST cannot distinguish between TB infection and TB disease. The patient's history and the size of the induration help to determine, to some degree, which of the 3 potential causes is correct. Subjects with exposure to environmental NTM typically 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 among subjects with LTBI and those with NTM exposure will overlap

to some degree. The most effective way to minimize false-positive results is to avoid testing subjects who lack a risk factor for LTBI. When testing is performed, the recommendation has been to vary the cutoff for the size of the TST reaction considered positive. The cutoff is set at 15 mm to optimize specificity for subjects lacking LTBI risk factors, 10 mm for subjects with a risk factor for LTBI, and 5 mm to optimize sensitivity for subjects at high risk of having or developing TB disease if they have LTBI (clinical evidence of disease, recent exposure, or significant immune compromise).⁷

BCG vaccines are administered in countries with high TB burden because these vaccines reduce the risk of TB disease, particularly disseminated (miliary) and central nervous system TB. For a foreign-born child, history of BCG vaccination should be determined by examination of the vaccination record and looking for a typical BCG scar, which is usually found on the deltoid region of either arm. Some of the antigens in PPD are also found in *M bovis*-BCG, the organism in the BCG vaccines. Some subjects who are not infected with *M tuberculosis* 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,⁸ the route of administration,⁹ age at vaccination,¹⁰ the time interval since vaccination,¹¹ and the number of BCG doses. Approximately one-half of infants who received a BCG vaccination will respond with significant induration to a TST. Although most (perhaps as many as 90%) 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), some will retain this response, causing a false-positive result. The induration often measures

<10 mm but can be >15 mm. Children born in most foreign countries are candidates for selective testing for LTBI, but a large number of false-positive results can occur when the TST is used on children who have received a BCG vaccine. Children who have received a BCG vaccination may also be subject to boosting by the TST (ie, the immunologic recall of hypersensitivity to antigens in the PPD that are also present on *M bovis*-BCG), which creates a false-positive TST result on repeat testing.^{12,13}

False-negative TST results can occur because of the limited ability of certain children with LTBI or TB disease to mount an appropriate delayed-type sensitivity response, especially those who are immunosuppressed either by disease (eg, advanced HIV infection, advanced TB, cancer, malnutrition) or those who have received immunosuppressive treatments (eg, corticosteroids, cancer chemotherapy, immunomodulating biologic agents [especially the tumor necrosis factor α inhibitors]), or live viral vaccines [particularly measles vaccine]. Unfortunately, children for whom the TST has diminished sensitivity are those subjects most likely to progress to TB disease if infected.⁵

In summary, there are limitations to both the sensitivity and the specificity of the TST.¹⁴ The positive predictive value of the TST is much greater when it is applied to subjects who have a recognized risk factor for LTBI. When the TST is used in subjects lacking risk factors, the vast majority of the positive results are falsely positive, and this problem is accentuated in children who received a BCG vaccine.

INTERFERON- γ RELEASE ASSAYS

IGRAs are ex vivo blood tests that detect interferon- γ (INF- γ) release from a patient's CD4+ T lymphocytes after stimulation by antigens found on the *M tuberculosis* complex (which includes

M bovis, *Mycobacterium africanum*, *Mycobacterium microti*, and *Mycobacterium canettii*). Two IGRAs are available commercially: the QuantiFERON-TB Gold In-Tube assay (QFT; Cellestis/Qiagen, Carnegie, Australia) and the T-SPOT.TB assay (T-SPOT; Oxford Immunotec, Abingdon, United Kingdom). Both tests use early secreted antigenic target 6 and culture filter protein 10 encoded by genes located within the region of difference 1 locus of the *M tuberculosis* genome.¹⁵ The QFT uses a third antigen (TB7.7). The region of difference 1 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 *Mycobacterium avium* complex organisms that are the most ubiquitous pathogenic environmental NTMs. (The antigens are found on several NTM strains, including *Mycobacterium marinum*, *Mycobacterium kansasii*, *Mycobacterium szulgai*, and *Mycobacterium flavescens*.) As a result, one would expect that these tests would be more specific than the TST, yielding fewer false-positive results. Unfortunately, as with the TST, the IGRAs do not distinguish between TB infection and TB disease.

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 result is reported as quantification of INF- γ in international units per milliliter. The test result is considered positive when the INF- γ response to the TB antigen is above the test cutoff of 0.35 IU (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 or the background response in the negative control is too high, the result is considered indeterminate (ie, neither

negative nor positive). The T-SPOT assay is an enzyme-linked immunosorbent spot (ELISPOT) assay performed on peripheral blood mononuclear cells that have been incubated with the 2 antigens. The result is reported as the number of INF- 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 (usually 8 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 test result is negative but the positive control also shows a poor response or if the background response in the negative control is too high, the result is termed invalid (sometimes also called indeterminate [neither negative nor positive]).

Although there are standard manufacturer instructions for performing the IGRAs, concerns have been raised about the reproducibility of the results on serial performance.^{16,17} Serial testing of health care workers at low risk of infection has often revealed unexplained conversion of IGRA results to positive and reversion to negative. Nkurunungi et al¹⁸ 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 TB case ($\kappa = 0.77$) than among noncontacts ($\kappa = 0.29$). T-lymphocyte assays are susceptible to variability by numerous factors, including³: 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 QFT collection tubes; laboratory issues caused by systematic or random error; and immunologic sources, including possible boosting of the response by a recently performed TST.¹⁶ Published studies have shown a variety of differences in outcomes between the 2 basic IGRA techniques, ELISA (QFT) and ELISPOT (T-SPOT). However, in most studies, these differences have been small, and the preponderance of evidence supports the conclusion that, in terms of accuracy, neither IGRA test is preferred over the other.

Summary of Studies in Adults

As with most new diagnostic tests, the early studies were conducted on adults. Because there is no reference standard test for LTBI, specificity was estimated among low-risk subjects with no known TB exposure in a low-prevalence setting. Several meta-analyses of studies in adults have demonstrated an IGRA specificity of 95% to 100%, and, as expected, the specificity is not affected by previous BCG vaccination.^{19–21} Although TST specificity is comparable to IGRAs in adults who have not received a BCG vaccine, it is substantially lower (approximately 60%) and variable among BCG-vaccinated populations.³ In contact investigations of adults with pulmonary TB, measures of exposure have often correlated better with IGRA-positive results than with the TST because of more positive TST results in subjects with low intensity of exposure, especially within BCG-vaccinated populations.^{22,23} Test sensitivity is estimated initially among culture-confirmed cases of disease (absolute proof of infection). The sensitivity of the IGRAs in adults with culture-proven TB disease is 80% to 90% (compared with 80% for the TST). As with the TST, the IGRA sensitivity is lower in adults who are immunocompromised, especially those with

poorly suppressed concomitant HIV infection.

General Aspects of Studies in Children

Determining the sensitivity and specificity of the IGRAs for children is more difficult, and fewer studies have been published.²⁴ Most children with clinical TB disease do not have microbiologic confirmation, which means they lack the absolute proof of infection that is needed to accurately assess test sensitivity; many studies have used less reliable methods of clinical diagnosis of TB disease instead. The major difficulty for interpreting studies of LTBI is determining for discordant test results whether the negative test result is more specific or the positive test result is more sensitive. Gradients of exposure to a culture-positive case are frequently used to determine the meaning of discordant results. Four systematic reviews and meta-analyses of the available studies of the use of IGRAs in children were published in 2011 and 2012; as expected, these reviews examined many of the same studies.^{25–28} Analysis of the studies was hampered by the heterogeneous methods used, including varying definitions of a clinical case of TB disease. 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. Some of the published studies used ELISA and ELISPOT techniques that were different from those that are currently available commercially.

Test Specificity in Children

Although there are variable results among individual published studies,

the strongest and most consistent finding is that the IGRAs have a higher specificity for LTBI, especially in settings of low TB burden and for BCG-vaccinated children. This conclusion is based largely on comparison of test results across exposure gradients of contact investigations in schools and the community in otherwise low-burden settings.^{22,29,30} In their meta-analysis, Sun et al²⁷ included 7 studies that assessed IGRA specificity in populations with rates of BCG vaccination ranging from 0% to 100%. The pooled specificity was 100% for ELISA studies, 90% for ELISPOT studies, and 56% for TST. The specificity of ELISPOT was 89% for BCG-vaccinated children and 95% for BCG-unvaccinated children, compared with a TST specificity of 49% for BCG-vaccinated children and 93% for BCG-unvaccinated children. Five of the 7 studies concluded that agreement (measured by using κ scores) between the TST and IGRA results in BCG-unvaccinated children was higher than in vaccinated children, probably because of false-positive TST results caused by previous BCG vaccination. Lighter et al³⁰ found that among 207 children in New York, only 23% with a positive TST result had a positive QFT result and, unlike the TST results, positive QFT results correlated with increased risk of TB exposure. Chun et al³¹ also found that, among 227 BCG-vaccinated children in South Korea, the QFT results were more closely associated with exposure to a TB case than were TST results.

The most convincing evidence of increased specificity of the IGRAs would be a natural history experiment following up untreated children who have positive TST results and negative IGRA results, but these observations are scarce. Ling et al³² evaluated how clinicians in Montreal are using IGRA results to determine management of children. Among 55 children with positive TST results and negative QFT

results who were TB contacts, the negative QFT result changed management in only 3 children; 52 children received isoniazid. In 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. However, given the ages of the children in this study, few cases of TB disease would have been expected even if all these children were infected with *M tuberculosis*. Even given the limitations of available data, the sum of all published studies supports the concept that the IGRAs are more specific than the TST in children. Despite the greater apparent specificity of IGRAs, the decision of whether to treat a patient who has positive TST results and negative QFT results should be based on clinical judgment that takes into consideration the age of the patient, risk stratification, and the degree of exposure.

Test Sensitivity in Children

The analysis of studies in children regarding the sensitivity of the IGRAs compared with TST is far more difficult, and the results have been highly variable. The best information comes from the meta-analyses of studies of children with TB disease, diagnosed either by using culture results or clinical diagnosis.^{25–28} Sun et al²⁷ found a sensitivity for all TB disease in children of 70% for ELISA (range: 57%–96%), 62% for ELISPOT (range: 40%–100%), and 71% for the TST (range: 43%–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. Although this meta-analysis found no significant difference in test performance between settings of high and low TB burden, 2 other meta-analyses found the sensitivity of IGRAs to be lower in settings with high TB burden, although the number of studies was small.^{25,26} Two more recent studies conducted in settings with high TB burden also found low sensitivity of IGRAs for TB disease, and they did not add value to the clinical data and conventional tests for diagnosis of TB disease in these children.^{33,34}

The sum of all published studies suggests that the IGRAs are not more sensitive than TST (likely less sensitive in settings of high TB burden) or other measures of determining TB disease in children and cannot be used to rule out TB disease. However, there is some evidence that the sensitivity is increased when both a TST and IGRA are performed, and the use of both tests will increase the rate of positive results in high-risk settings. Hill et al³⁵ investigated child household contacts of adult TB cases in The Gambia. Overall agreement between the TST and ELISPOT was 83%, with each test 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.³⁶

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; however, they also occur when the background activity in the negative control is too high. Indeterminate/invalid results may occur because of technical factors, most frequently inadequate shaking of the QFT tubes after the patient's sample has been added. Rates of indeterminate/

invalid results among children have varied between 0% and 35%, but most studies have reported rates in the range of 0% to 10%.^{26,37–42} The rates have been slightly lower with the more recent versions of the commercially available tests. Indeterminate/invalid rates generally are higher among subjects with compromised immune systems whose T lymphocytes cannot mount an adequate response to the positive control, especially people with HIV infection⁴³; they have also been noted to be higher in children with poorly controlled inflammatory bowel disease, hepatitis, malaria, and helminthic infection.^{44,45} Many, but not all, studies have found that otherwise healthy children younger than 5 years are more likely to have indeterminate/invalid test results than older children and adolescents.^{40,46–49}

Test Performance in Immunocompromised Children

Data are scarce for determining the sensitivity and specificity of the IGRAs for immunocompromised children who are at increased risk of developing TB disease if they are infected with *M tuberculosis*. Three systematic reviews of the performance of IGRAs in HIV-infected subjects, mostly adults, 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.^{43,50,51} Several small studies have included children with HIV infection and produced varied results; in general, the IGRAs perform poorly and have less concordance with the TST in children with advanced HIV infection, especially if they have concomitant malnutrition.^{52,53} Two small studies have examined the performance of the IGRAs and the TST in children with cancer. Stefan et al⁵⁴ 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 cell counts. During a contact investigation of 18 children in a pediatric hematology-oncology ward 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.⁵⁵

Screening for TB risk factors should be performed before any immunosuppressing therapy is given, but it is especially important before therapy with immunomodulating biologic agents, such as monoclonal antibodies against tumor necrosis factor α .³ This topic has been the subject of many small studies in adults that were reviewed in 2 papers.^{56,57} Unfortunately, there are no published studies involving children. For these patients, test sensitivity is more important than specificity because of the increased risk of progression of LTBI to TB disease. In most of the published studies, adult patients had already been treated with a variety of immunosuppressing agents, which may have affected the results of the TST or IGRAs. Rates of indeterminate/invalid results were higher than usual in these patients because of immunosuppression by both disease and drugs. The current evidence does not consistently suggest that IGRAs are better than the TST in identifying subjects who will benefit from treatment of LTBI. It is commonly recommended that all patients, regardless of specific TB risk factors, who will be receiving an immunomodulating biologic agent should be tested for LTBI before starting the therapy. Many experts have suggested that both the TST and an IGRA should be performed for patients who also have a risk factor for LTBI, and appropriate treatment of LTBI should be started if either test result

is positive once TB disease has been ruled out.^{56–60}

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 are more likely than older children to have progression from untreated LTBI to TB disease and young children are more prone to develop serious forms of TB, failure to accurately diagnose TB infection in this age group can have dire consequences.⁷ Resolution of this issue has been hampered by the lack of a reference standard for LTBI. The earliest studies suggested that IGRA sensitivity is diminished in young children, but the results were inconsistent.^{26,41} However, several more recent studies have demonstrated better performance of the commercially available IGRAs in young children. Debord et al⁶¹ found that among 19 children with TB disease, 6 of 10 children younger than 2 years and 9 of 9 children 2 to 5 years of age had a positive QFT result. Moyo et al⁶² 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 TB infection in otherwise healthy children. Pavić et al⁶³ studied 142 healthy BCG-vaccinated children in Croatia who had recently been exposed to infectious TB disease. Both

the QFT and the TST had rates of positive results that were associated with degree of exposure, and there was no evidence that age affected QFT performance. Critselis et al⁴⁹ 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 were younger than 2 years), infants with positive QFT results produced a greater mean titer of INF- γ than older children and adolescents. Agreement between the TST and QFT results was not significantly different between younger and older children. However, the rate of indeterminate results was significantly greater in younger (8.1%) than in older (2.7%) children. It is clear that the use of the TST in infants and young children who received a BCG vaccine will lead to some false-positive results caused by cross-reaction with the BCG. Although some experts support the use of IGRAs to test for LTBI in infants and young children, especially those at low risk of TB infection who have received a BCG vaccine, others do not recommend their routine use in children younger than 5 years until more supportive data are available.

In summary, if an IGRA is performed in an infant or young child, a positive result likely indicates infection with *M tuberculosis*, but a negative result does not rule it out. The rates of indeterminate/invalid results seem to be higher in infants and toddlers than in older children.

Strategies for the Use of IGRAs in Children

Some of the major differences between the TST and the IGRAs are summarized in Table 1. 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 LTBI and TB disease. When testing otherwise healthy subjects, the purpose of the TST or an IGRA is to determine

whether the person is infected with *M tuberculosis* and will benefit from treatment. In truth, the positive predictive value of both tests for the development of TB disease is poor in adults and children 5 years or older because, at most, 5% to 10% of those who test positive and go untreated will develop TB disease in their lifetime. In this regard, there is little difference between the TST and the IGRAs. However, children younger than 2 years with untreated TB infection have a 30% to 40% risk of developing TB disease within 1 year; therefore, optimizing test sensitivity is important for this age group. In addition, because children tend to tolerate the treatment of LTBI much better than adults, their risk of adverse events caused by treatment is less. However, test specificity is also an issue, especially for children who have received a BCG vaccine or who have a likelihood of exposure to NTM in their environment; testing them by using the TST will lead to an appreciable proportion of false-positive results when the prevalence of TB infection is low, as in the United States.

Both the TST and the IGRAs are imperfect methods. As a result, **only children who have a risk factor for**

TB infection, have a disease or condition that may require significant therapeutic immunosuppression, or are suspected of having TB disease should be tested with either method. 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 (eg, otherwise low-risk BCG-vaccinated children), the IGRAs are the superior tests. Neither method has a clear advantage in sensitivity; when sensitivity is the main concern, a positive result with either the TST or IGRA should be considered indicative of infection with *M 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 biologic agent, both an IGRA and a TST should be performed. Performing both tests will lower the overall specificity and lead to some false-positive results, but in children with a high risk of progression to TB disease, this outcome is often an acceptable trade-off.

TABLE 1 Comparison of the TST and IGRAs

Characteristic	TST	IGRA
Antigens used	Many; PPD	3 (QFT) or 2 (T-SPOT)
Sample	Intradermal injection	Blood draw
Patient visits required	2	1
Distinguish between LTBI and TB disease	No	No
Cross-reactivity with BCG	Yes	No
Cross-reactivity with NTM	Yes	Only rare species ^a
Differing positive values by risk	Yes (5-10-15)	No
Causes boosting	Yes	No
Subject to boosting by previous TST	Yes	Possible
Durability over time (stays positive with or without treatment)	Yes	Unknown
Difficulties with test reproducibility	Yes	Yes
Relative cost	Lower	Higher
Location of need for trained staff	"Bedside"	Laboratory
Estimated specificity in BCG-unvaccinated children	95% to 100%	90% to 95%
Estimated specificity in BCG-vaccinated children	49% to 65%	89% to 100%
Estimated sensitivity (confirmed TB disease)	75% to 85%	80% to 85%
Estimated sensitivity (clinical TB disease)	50% to 70%	60% to 80%

^a *M marinum*, *M kansasii*, *M szulgai*, and *M flavescens*.

Figure 1 and Table 2 show potential strategies for testing. Some specific points are:

- Only children who have a risk factor for TB infection, are about to undergo significant immunosuppression, or are suspected of having TB disease should be tested with a TST or an IGRA.
- There is no compelling evidence to support the use of one IGRA over the other.
- If the child has been exposed recently to an infectious case of TB disease, he or she should be evaluated and treated accordingly 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

should be retested in 8 to 10 weeks regardless of whether the initial test used was a TST or IGRA.

- For children 5 years or older, either the TST or an IGRA can be used.
- For children 5 years or older who have received a BCG vaccine, 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 can be performed, and its result acted on.
- When testing for LTBI, some experts will use an IGRA in children 2 to 4 years of age, especially if they have received a BCG vaccine. Most experts

do not currently use an IGRA when testing for LTBI for children younger than 2 years because of lack of data for this age group and the high risk of progression to disease.

- When evaluating a child of any age for TB disease, both a TST and one or both IGRAs can be performed to maximize sensitivity. However, neither method can be used to rule out TB disease.
- For children diagnosed with an immunosuppressing disease or who are about to start immunosuppressive therapy of any kind, testing should be performed with either a TST or IGRA, even in the absence of a recognized TB risk factor. If the child does have a TB risk factor,

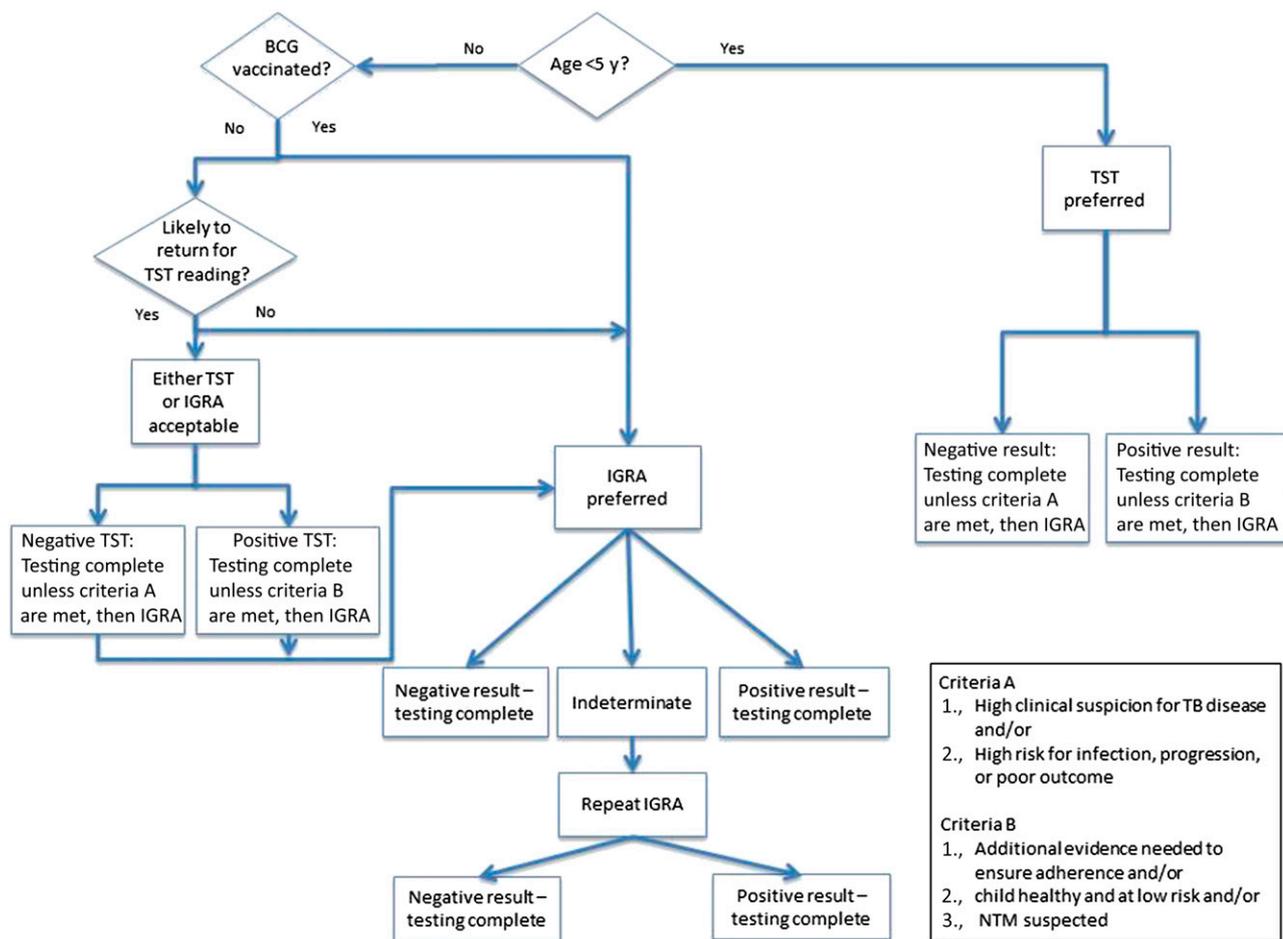


FIGURE 1

An algorithm for the use of the TST and IGRAs in children. Entry into the algorithm assumes that the child has at least 1 risk factor for TB infection.

TABLE 2 Suggested Uses of TST and IGRA in Children

TST preferred
• Children younger than 5 y ^a
IGRA preferred, TST acceptable
• Children 5 y or older who have received BCG vaccine
• Children 5 y or older who are unlikely to return for the TST reading
Both the TST and an IGRA should be considered when:
• The initial and repeat IGRA results are indeterminate/invalid
• The initial test (TST or IGRA) result is <i>negative</i> and:
• There is clinical suspicion of TB disease ^b
• The child has a TB risk factor and is at high risk of progression and poor outcome (especially therapy with an immunomodulating biologic agent, such as a TNF- α antagonist) ^b
• The initial TST is <i>positive</i> and:
• The patient is 5 years or older and has a history of BCG vaccination
• Additional evidence is needed to increase adherence with therapy

TNF- α , tumor necrosis factor α .

^a Some experts will use an IGRA in children 2 to 4 years of age, especially if they have received a BCG vaccine but have no other significant risk factors. Most experts do not use an IGRA for children younger than 2 years because of lack of data for this age group and the high risk of progression to disease.

^b A positive result of either test is considered significant in these groups.

testing should be performed with both the TST and an IGRA.

- When an IGRA result is indeterminate/invalid, either a repeat IGRA test using the same or the other IGRA can be performed, ensuring proper technique of specimen collection and processing, or a TST can be performed.

CONCLUSIONS

The IGRAs are an advance in the diagnosis of TB infection and disease in children. They have greater specificity than the TST and can greatly reduce the number of false-positive results and unnecessary treatment in children who have received a BCG vaccine or who have been exposed to NTM. The sensitivity of the IGRAs seems to be no better than the TST, but combining them with a TST may increase sensitivity for the diagnosis of TB disease or the detection of TB infection in children at particularly high risk of having progression from TB infection to TB disease. For children 5 years or older, IGRAs can be

used in any situation in which a TST would be used. Because of the relative lack of data concerning the reliability of negative IGRA results in young children and the need for sensitivity in these children because of their increased risk of progression to disease, the IGRAs should not be used to detect LTBI in children younger than 2 years. The IGRAs have the advantages of requiring only a single health visit and have more objective measurement in the laboratory. Although these tests are more expensive than the TST, their use may be more economical than the TST because of the elimination of many false-positive results.⁶⁴

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