The Utility of an Interferon Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection and Disease in Children

A Systematic Review and Meta-analysis

Shingai Machingaidze, BSc,*† Charles Shey Wiyongse, MD,*† Yulieth Gonzalez-Angulo, BSc,*† Mark Hatherill, MD,*† Sizulu Moyo, MB ChB, Willem Hanekom, FCP (Paed),*† and Hassan Mahomed, MMED*†

Background: The utility of interferon gamma release assays (IGRAs) has been assessed in adults, but remains unclear in children. We reviewed the literature on the use of a commercial IGRA in immunocompetent children for the diagnosis of both latent tuberculosis infection (LTBI) and TB disease.

Methods: We searched PubMed for studies published before January 2010 on the diagnosis of TB in children using an IGRA. We compared the specificity and sensitivity of the tuberculin skin test (TST) and the IGRA for LTBI and conducted a random effects meta-analysis on sensitivity of the IGRA for TB disease.

Results: Of 68 studies identified, 20 were included in this review. There was increased specificity of the IGRA for LTBI in children compared with TST, but varying sensitivities. Sensitivity of the IGRA in detecting TB disease in children also varied when compared with TST (mean k score, 0.57). For all TB cases, the pooled sensitivity was 66% (95% confidence interval [CI], 53%–78%) with heterogeneity (\(I^2 = 74.8\%\)). Stratification by background TB incidence highlighted a significantly reduced IGRA sensitivity of 55% (95% CI, 37%–73%) in high incidence settings compared with low incidence settings, 70% (95% CI, 53%–84%).

Conclusions: There was no clear evidence that IGRAs should replace TST for detecting LTBI in children. Sensitivity of the IGRA for TB disease was no different from TST, and a significantly reduced IGRA sensitivity was found in high-burden TB settings compared with low-burden settings. Further studies are needed to determine the value of IGRAs in LTBI and TB disease diagnosis in children.

Key Words: TST, QuantiFERON, tuberculosis, children, systematic review

(Pediatr Infect Dis J 2011;30: 000–000)

Accepted for publication February 8, 2011.

From the *South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine, University of Cape Town, Cape Town, South Africa; and †School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.

Supported by the South African TB Vaccine Initiative (SATVI) (to S. Machingaidze) for the Master’s in Public Health (Epidemiology and Biostatistics) at the University of Cape Town.

Address for correspondence: Hassan Mahomed, MMed, South African Tuberculosis Vaccine Initiative (SATVI), Institute of Infectious Disease and Molecular Medicine (IIDMM), Room N2.10, Wernher and Beit North, Faculty of Health Sciences, University of Cape Town, Anzio Rd, Observatory, 7925, Cape Town, South Africa. E-mail: hassan.mahomed@uct.ac.za.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal’s Web site (www.pidj.com).

It is estimated that one-third of the world’s population is infected with *Mycobacterium tuberculosis* (Mt), resulting in 9 million new cases of tuberculosis (TB) and 1.8 million deaths due to TB being reported in 2007.1 TB in children remains one of the leading causes of mortality globally, responsible for >450,000 child deaths each year.2 Young children are more prone to the development of disseminated disease because of their developing immune systems. Up to 40% of children <2 years of age who are infected with Mt develop TB disease.3,4 A key method of helping to reduce the global TB burden particularly in developing countries is the identification and treatment of latent tuberculosis infection (LTBI). Traditionally, LTBI is diagnosed using the tuberculin skin test (TST), which is dependent on a delayed hypersensitivity response to purified protein derivative of Mt. The TST is a relatively cheap test which requires no laboratory component. However, TST results can be confounded by nontuberculous mycobacteria (NTMs), Bacille Calmette-Guérin (BCG) vaccine, individual’s immune status, competency in the test administration, and reading of results.

The recent identification of Mt antigens absent from BCG, and most NTMs has allowed for the development of more specific diagnostic tests. These tests detect interferon-gamma (IFN-\(\gamma\)) released by T cells when exposed to Mt antigens in vitro.5 The antigens used are the early secreted antigenic target 6 and culture filtrate protein 10. The validity of these IFN-\(\gamma\) release assays (IGRAs) has been examined in adults, but has not been well studied in children or infants.

IGRAs have the following operational advantages over TST: the tests can be completed in 1 visit with the results available within 24 hours; are able to avoid boosting due to repeat testing; and have a standardized interpretation.6 IGRAs have limitations in that they are expensive, require an equipped laboratory with trained personnel, and, like TST, they cannot distinguish between latent and active TB disease.

Diagnosis of TB disease in children can be challenging as Mt can only be detected in biologic samples from fewer than 50% of children with TB.6,7 For this reason, TB is generally diagnosed in children based on exposure to an adult confirmed with pulmonary TB disease, TB symptoms, a positive TST, and chest radiography. The question remains whether IGRAs could replace TST in the diagnostic approach to TB disease in children.

There are 2 commercially available IGRAs in clinical use: QuantiFERON TB Gold (Cellestis, Australia) and T-Spot (Oxford Immunotec, United Kingdom). There are also in-house developed versions as well. The QuantiFERON Gold In-Tube (QFT-G IT) is a newer version of the QFT-G and it includes a third antigen, TB7.7, and requires only 3 mL of blood compared with the 16 mL required for the QFT-G assay. The additional antigen is thought to enhance the sensitivity of the assay without reducing its specificity.
Both versions of QFT are based on a 16- to 24-hour whole blood enzyme-linked immunosorbent assay.6

RATIONALE

This systematic review and meta-analysis aimed to examine the available literature on the use of an IGRA (QFT) in immunocompetent young children for the diagnosis of latent TB infection and active TB disease. The South African Tuberculosis Vaccine Initiative based at the University of Cape Town has a TB vaccine clinical trial site where efficacy trials using clinical end points will be conducted. The QFT assay is currently being evaluated as part of its trials. Given the difficulty in diagnosing TB disease in young children, we wanted to determine if the use of IGRA can improve diagnostic accuracy for pediatric LTBI and TB disease. The QFT assay is more widely used, with the most available directly comparable literature compared with other assays, and therefore this review was restricted to the QFT assay only.

METHODS

Search Strategy

We searched PubMed in the period June 2009 to January 2010 for articles published in English, related to the detection and/or diagnosis of TB infection and disease in children using QFT TB Gold (QFT-G) or TB Gold In-Tube (QFT-G IT). The following search phrases were used and combined using the Boolean operator “AND”: (1) Quantiferon OR QFT; (2) Tuberculosis OR TB OR tuberculous; and (3) child* OR pediatric OR paediatric. The electronic literature search was supplemented by 4 recent reviews,3,5,8,9 as well as checking the reference lists of full-text articles included in this review.

Study Selection

After the primary search was conducted by reviewing titles and abstracts of studies, the full texts of eligible studies were screened for inclusion and the study quality of each was assessed (S. Machingaidze). Relevant data were extracted from each study and entered into Microsoft Excel. Study eligibility, quality assessment, and data extraction were checked for validity by a second author (H.M.). An article was included in this review if the article contained original data from children (0 – 18 years) and (1) contained data from children born in countries with a high prevalence of TB (ie, high or low) in the country of the study. For the purpose of this analysis, a TB ‘high-burden’ country is defined as reported by the World Health Organization (studies from 4/22 high-burden TB countries were included in this analysis).1

RESULTS

A total of 68 articles were identified in PubMed. Of total, 48 articles were excluded because of the following main reasons: study reporting data from adults rather than children; article not in English; study including subjects with compromised immune status; and study not comparing QFT and TST. (The numbers per category are shown in Fig., Supplemental Digital Content 1, http://links.lww.com/INF/A778.) Twenty full text articles were selected and included for further analysis.

The Utility of QFT in the Detection of LTBI in Children

The usefulness of IFN-γ assays (QFT) in LTBI detection in children has been explored in a number of studies.10–13 However, only a limited number of studies have carried out a large-scale comparison of QFT and TST in young children (<5 years old) in high-burden TB countries as done by Okada et al in Cambodia.10

Agreement Between TST and QFT in Children

For each study, the agreement (κ) between TST and QFT is indicated in Table 1.5,10–29 QFT is shown to have variable levels of agreement with TST in different pediatric populations. κ scores ranged from 0.17 to 0.86, with certain studies showing good agreement,11,15–17 whereas others showed poor agreement.18,19

Relationship Between Age and QFT

Kampmann et al (2006) showed a significantly lower production of IFN-γ in response to the positive control mitogen phytohaemagglutinin in children younger than 4 years old compared with children 4 to 15 years old (P < 0.0001).30 In addition, Connell et al (2006) showed a significant positive correlation (Spearman coefficient, 0.53; P < 0.001) of the IFN-γ phytohaemagglutinin response (positive control) with an increase in age up to 17 years.18 We found an increased proportion of indeterminate results with QFT in younger children, which supports these findings.

Specificity of QFT Versus TST for LTBI

Several studies show QFT to be more specific than the TST for Mtb detection in children.6,13,15,20,21 Specificity is interpreted here as the degree to which a positive QFT is associated with exposure implying that that this is a true rather than false positive result. In a prospective study carried out by Lighter et al (2009), 207 children receiving health care in New York were assessed.6 QFT-G IT was positive in only 23% of children with a positive TST and a positive QFT-G IT was associated with increased Mtb exposure suggestive of superior specificity of QFT when compared with TST. It is important to note that an alternative explanation could be that QFT is less sensitive than the TST with particular reference to children with less recent exposure meaning that children with a positive TST without a reported recent exposure may have been exposed at a more remote time. In another prospective study carried out by Bianchi et al (2009), 336 children at risk for TB in Italy were assessed. Of the 336 children tested, the number of positive TST and QFT results were 58 and 60, respectively. Half of the children with a positive TST (defined as TST ≥5 mm for children in contact with TB cases and TST ≥10 mm for children born in countries with a high prevalence of TB) had a negative QFT (22/44). Again, this result suggests that either QFT is more specific than TST or alternatively that TST is more sensitive.20

In yet another prospective study carried out by Chun et al (2008) in 227 children <15 years old in South Korea, children were divided into 4 groups as follows: close contact, casual
Contact, TST positive with no contact history (control group), and those with symptoms suggestive of TB. In children with close contacts with TSTs ≥10 mm, 7 of 14 were QFT-G IT positive (moderate agreement κ = 0.53). In children with casual contacts with TST ≥10 mm (n = 7), 2 were QFT-G IT positive (low agreement κ = 0.38). In children in the control group with TST ≥10 mm (n = 42), only one had a positive QFT-G IT result. Their results show QFT-G IT is more closely associated with exposure to a TB contact than TST and therefore better at indicating LTBI. These results may also suggest that QFT is better at detecting more recent infections when compared with TST.21

In a study carried out by Tsiouris et al (2006) in Gugulethu, South Africa; 184 school children (5–15 years old) at high risk for LTBI underwent both TST and QFT-G IT testing. Overall, they found 43.5% of the children had TST ≥10 mm and 33.2% had a positive QFT-G IT result. An increasing agreement and accuracy of TST that they reported to be 0.90, 0.95, and 0.95, respectively.17

In a prospective study in children at risk for LTBI in Melbourne, Connell et al (2008) found a moderate agreement of 75% between QFT-G IT and TST (κ = 0.50; 95% CI, 0.34–0.56). For children with TST-defined LTBI and accuracy of TST that they reported to be 0.90, 0.95, and 0.95, respectively.17 In a study with children with close contact, TST positive with no contact history (control group), and those with symptoms suggestive of TB. In children with close contacts with TSTs ≥10 mm, 7 of 14 were QFT-G IT positive (moderate agreement κ = 0.53). In children with casual contacts with TST ≥10 mm (n = 7), 2 were QFT-G IT positive (low agreement κ = 0.38). In children in the control group with TST ≥10 mm (n = 42), only one had a positive QFT-G IT result. Their results show QFT-G IT is more closely associated with exposure to a TB contact than TST and therefore better at indicating LTBI. These results may also suggest that QFT is better at detecting more recent infections when compared with TST.21

In a study carried out by Tsiouris et al (2006) in Gugulethu, South Africa; 184 school children (5–15 years old) at high risk for LTBI underwent both TST and QFT-G IT testing. Overall, they found 43.5% of the children had TST ≥10 mm and 33.2% had a positive QFT-G IT result. An increasing agreement and accuracy of TST that they reported to be 0.90, 0.95, and 0.95, respectively.17

In a prospective study in children at risk for LTBI in Melbourne, Connell et al (2008) found a moderate agreement of 75% between QFT-G IT and TST (κ = 0.50; 95% CI, 0.34–0.56). For children with TST-defined LTBI and accuracy of TST that they reported to be 0.90, 0.95, and 0.95, respectively.17

Table 2 lists 6 studies which measured the sensitivity of QFT in detecting active TB disease in children. Two of these studies performed in high TB incidence settings,10,11 whereas 4 were carried out in low TB incidence settings.20,22,24 QFT and TST sensitivities were similar for diagnosing active TB disease and ranged from 53% to 94%. The results suggested that QFT did not perform significantly better nor significantly worse than TST in identifying active TB disease in pediatric populations.10,20,23,31 However, Okada et al observed a significantly reduced sensitivity of QFT when compared with TST in children <5 years diagnosed with active TB disease in Cambodia. Of the 19 children identified to have active TB disease, 15 (79%) were TST positive, whereas only 10 (53%) were QFT positive.10

Although both Kampmann et al (2009) and Bramford et al (2009) showed QFT did not perform significantly better than TST in identifying active TB disease, they did find that combining the 2 tests improved the test sensitivity with both reporting an improved sensitivity of 91% compared with QFT sensitivities of 80% and 78% in the 2 studies, respectively, when QFT was used in isolation.23,24

Can QFT be Used to Aid in the Diagnosis of Active TB Disease in Children?

Table 2 lists 6 studies which measured the sensitivity of QFT in detecting active TB disease in children. Two of these studies performed in high TB incidence settings,10,11 whereas 4 were carried out in low TB incidence settings.20,22,24 QFT and TST sensitivities were similar for diagnosing active TB disease and ranged from 53% to 94%. The results suggested that QFT did not perform significantly better nor significantly worse than TST in identifying active TB disease in pediatric populations.10,20,23,31 However, Okada et al observed a significantly reduced sensitivity of QFT when compared with TST in children <5 years diagnosed with active TB disease in Cambodia. Of the 19 children identified to have active TB disease, 15 (79%) were TST positive, whereas only 10 (53%) were QFT positive.10

Although both Kampmann et al (2009) and Bramford et al (2009) showed QFT did not perform significantly better than TST in identifying active TB disease, they did find that combining the 2 tests improved the test sensitivity with both reporting an improved sensitivity of 91% compared with QFT sensitivities of 80% and 78% in the 2 studies, respectively, when QFT was used in isolation.23,24

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>Age (yr)</th>
<th>Test Type</th>
<th>TB Burden</th>
<th>TST Cutoff (mm)</th>
<th>Overall Agreement Between TST and QFT (κ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al10</td>
<td>2008</td>
<td>Cambodia</td>
<td>195</td>
<td>&lt;5</td>
<td>QFT-G</td>
<td>High</td>
<td>10</td>
<td>0.63</td>
</tr>
<tr>
<td>Hesseling et al25</td>
<td>2007</td>
<td>South Africa</td>
<td>29</td>
<td>&lt;5</td>
<td>QFT-G</td>
<td>High</td>
<td>10</td>
<td>0.78</td>
</tr>
<tr>
<td>Nakaoka et al12</td>
<td>2006</td>
<td>Nigeria</td>
<td>207</td>
<td>&lt;5</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.50</td>
</tr>
<tr>
<td>Dogra et al13</td>
<td>2006</td>
<td>India</td>
<td>105</td>
<td>1–12</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.73</td>
</tr>
<tr>
<td>Tsiouris et al13</td>
<td>2006</td>
<td>South Africa</td>
<td>184</td>
<td>5–15</td>
<td>QFT-G IT</td>
<td>High</td>
<td>10</td>
<td>0.56</td>
</tr>
<tr>
<td>Lighter et al6</td>
<td>2009</td>
<td>United States</td>
<td>207</td>
<td>&lt;18</td>
<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.17</td>
</tr>
<tr>
<td>Connell et al14</td>
<td>2009</td>
<td>Australia</td>
<td>106</td>
<td>&lt;18</td>
<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.3</td>
</tr>
<tr>
<td>Dominguez et al25</td>
<td>2007</td>
<td>Spain</td>
<td>134</td>
<td>&lt;18</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>5</td>
<td>0.71</td>
</tr>
<tr>
<td>Bianchi et al20</td>
<td>2009</td>
<td>Italy</td>
<td>336</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>0.53</td>
</tr>
<tr>
<td>Haustein et al22</td>
<td>2009</td>
<td>United Kingdom</td>
<td>237</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>6</td>
<td>0.71</td>
</tr>
<tr>
<td>Bergamini et al19</td>
<td>2009</td>
<td>Italy</td>
<td>496</td>
<td>&lt;19</td>
<td>QFT-G</td>
<td>Low</td>
<td>10</td>
<td>0.35</td>
</tr>
<tr>
<td>Connell et al14</td>
<td>2008</td>
<td>Australia</td>
<td>96</td>
<td>&lt;19</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>Nsutebu et al26</td>
<td>2008</td>
<td>United Kingdom</td>
<td>190</td>
<td>13–14</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tavast et al17</td>
<td>2009</td>
<td>Finland</td>
<td>99</td>
<td>&lt;18</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>0.86</td>
</tr>
<tr>
<td>Higuchi et al17</td>
<td>2009</td>
<td>Japan</td>
<td>61</td>
<td>8–12</td>
<td>QFT-2G</td>
<td>Low</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Chiu et al24</td>
<td>2008</td>
<td>South Korea</td>
<td>297</td>
<td>&lt;15</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>5</td>
<td>0.53</td>
</tr>
<tr>
<td>Higuchi et al29</td>
<td>2009</td>
<td>Japan</td>
<td>313</td>
<td>&lt;16</td>
<td>QFT-G</td>
<td>Low</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bramford et al24</td>
<td>2009</td>
<td>United Kingdom</td>
<td>333</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>15</td>
<td>0.54</td>
</tr>
<tr>
<td>Kampmann et al23</td>
<td>2009</td>
<td>United Kingdom</td>
<td>209</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>15</td>
<td>0.57</td>
</tr>
<tr>
<td>Hermann et al28</td>
<td>2009</td>
<td>France</td>
<td>131</td>
<td>&lt;16</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>10</td>
<td>—</td>
</tr>
</tbody>
</table>

*Year of publication.
†Values between 0.61 and 0.80 imply good agreement (adapted from Landis and Kock, 197714).

QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

**Table 1.** Studies Comparing the Performance of QFT With TST in Children

**Table 2.** Sensitivity of QFT Versus TST for LTBI

The sensitivity of QFT when compared with TST in children has been assessed in a limited number of studies.12,16,17 In Abuja, Nigeria (n = 207; <5 years old), it was found that children at high risk for LTBI who were in contact with confirmed adult cases of pulmonary TB, generally disagreement was due to a TST negative result and a positive QFT-G IT result—a finding indicative of a higher sensitivity of QFT.12

However, a retrospective, nonblinded study carried out by Tavast et al (2009) in a pediatric population in Finland (n = 99; 0–18 years old) showed the sensitivity and specificity of QFT-G compared well with that of TST. The sensitivity, specificity, and accuracy of the QFT-G were found to be 0.92 (95% CI, 0.67–0.99), 0.91 (95% CI, 0.77–0.97), and 0.91 (95% CI, 0.80–0.97), respectively. This compared well with the sensitivity, specificity,
Comparison of QFT Sensitivity in High-Burden Versus Low-Burden TB Settings

Figure 1 shows the results of a meta-analysis of the sensitivity of QFT in detecting active TB disease in children specifically. QFT sensitivity in culture confirmed TB cases was reported in 5 studies. The pooled sensitivity was 75% (95% CI, 63%–85%), with a moderate amount of statistical heterogeneity observed across the studies (I² = 49.2%). A possible explanation for this heterogeneity was thought to be the background TB incidence. However, 4 low-burden TB countries and only one high-burden TB country were included meaning further analysis by stratification was not possible.

Figure 2 shows the results of a meta-analysis of QFT sensitivity for all cases of TB disease. The pooled sensitivity of the 6 studies included was 66% (95% CI, 53%–78%) shown in Figure 2. However, there was a significant amount of statistical heterogeneity in QFT sensitivity across the studies (I² = 74.8%). Further analysis by stratification showed that in a high-burden TB setting (n = 2), the pooled sensitivity was 55% (95% CI, 37%–73%) with homogenous study results (P = 0.66; I² = 0%). However, in a low-burden TB setting (n = 4), the pooled sensitivity was 70% (95% CI, 53%–84%) although heterogeneity in QFT sensitivity was still observed across these studies (I² = 64.6%).

DISCUSSION

Our review found variable agreement between TST and QFT. In general, QFT had better specificity for LTBI than TST in that it was more closely associated with TB exposure. Sensitivity for LTBI varied between TST and QFT. Sensitivity for TB disease also varied between TST and QFT, but we found that QFT had better sensitivity in low TB burden compared with high-burden TB countries.

The identification and treatment of children with LTBI are important for the following reasons: it is known that children with LTBI face a high risk of progression to active TB disease3,4; accurate diagnosis and treatment of LTBI in children may prevent many future cases of adult reactivation TB disease; and TB disease in children has epidemiological significance in that it signals recent transmission of Mtb in the community.8 However, due to the lack of a gold standard for the diagnosis of LTBI, determining whether a diagnostic test is better than TST becomes very difficult. In practice, a TST ≥15 mm measurement is considered a reliable or more specific cut-off as BCG and NTM infections are unlikely to cause indurations ≥15 mm. However, this does not imply that measurements >15 mm are diagnostic of LTBI.20 In the absence of a recognized gold standard for

### TABLE 2. Studies Comparing the Sensitivity of QFT With That of TST in the Diagnosis of Active TB Disease (All Cases) in Children

<table>
<thead>
<tr>
<th>Author, Year*</th>
<th>Test Type</th>
<th>TB Burden</th>
<th>Age (yr)</th>
<th>Sample Size</th>
<th>No. TB Cases</th>
<th>TST Cutoff (mm)</th>
<th>Sensitivity (%)</th>
<th>TST</th>
<th>QFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okada et al,10 2008</td>
<td>QFT-G</td>
<td>High</td>
<td>&lt;5</td>
<td>195</td>
<td>19</td>
<td>10</td>
<td>79%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>Dogra et al,11 2006</td>
<td>QFT-G IT</td>
<td>High</td>
<td>1–12</td>
<td>105</td>
<td>8</td>
<td>10</td>
<td>63%</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>Bianchi et al,12 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>336</td>
<td>15</td>
<td>10</td>
<td>86%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Haustein et al,13 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>237</td>
<td>27</td>
<td>6</td>
<td>72%</td>
<td>78%</td>
<td></td>
</tr>
<tr>
<td>Bramford et al,14 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>333</td>
<td>195</td>
<td>15</td>
<td>55%</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>Kampmann et al,15 2009</td>
<td>QFT-G IT</td>
<td>Low</td>
<td>&lt;16</td>
<td>209</td>
<td>63</td>
<td>15</td>
<td>60%</td>
<td>63%</td>
<td></td>
</tr>
</tbody>
</table>

*Year of publication.
QFT indicates QuantiFERON; TST, tuberculin skin test; TB, tuberculosis; QFT-G, QuantiFERON Gold; QFT-G IT, QuantiFERON Gold In-Tube.

FIGURE 1. Meta-analysis of QFT sensitivity for diagnosing active TB disease (culture positive) in children. QFT sensitivity: pooled proportion = 75% (95% CI, 63%–85%); heterogeneity tests: Cochran Q = 7.875 (df = 4), P = 0.0962; Moment-based estimate of between studies variance = 0.04435, I² (inconsistency) = 49.2% (95% CI, 0%–80%).
LTBI detection, the analysis of study results with respect to TB contact history is a method that is used to deduce the possible superiority of one test over another.1,6

The observation of varying levels of agreement in the different studies might be explained in several ways including varying BCG vaccination status, differential exposure to Mtb and other NTMs, time since exposure, and the age of the children included in the studies.9 A greater specificity by QFT or a greater sensitivity by TST are the 2 main approaches to understand TST/QFT discordance.

Lalvani et al suggested that a test that is more accurate than TST should be more closely associated with the degree of TB exposure than the TST. However, its performance should be independent of the BCG vaccination status of the individual.31 QFT appears to be more specific than TST for LTBI in children (including in children <5 years old),6,13,15,20,21 since QFT was more closely associated with exposure in the studies we reviewed, but there was no clear trend in the sensitivity of QFT in children.12,16,17 With all the above-mentioned factors considered, Okada et al concluded QFT to be a suitable substitute for TST in detecting LTBI in young children, particularly in those who may have false-positive TSTs due to BCG vaccination or NTM infection.10 Thus, there is evidence to support the use of QFT in children in situations where improved specificity is needed. As an alternative, a higher cutoff improves the specificity of the TST so where a QFT is not possible, a higher cutoff of 15 mm for TST may be used. However, in a high-burden TB setting for young children living in the same household with a newly diagnosed pulmonary TB patient for 1 month or more, given the inconsistent results with respect to sensitivity obtained in various studies, it may be premature to definitively say that QFT should replace the TST.

The high risk of progression from LTBI to active TB disease in infants is indicative of less effective protective T cell-mediated immune responses in infants. Infants rely on their own cell-mediated response to fight against and/or contain infections caused by pathogens such as Mb.8,32 Since it is known that cell-mediated immunity matures from infancy through to early childhood, an important question that we asked was whether age affected the IFN-γ production measured by QFT. The results of studies18,30 show that age does affect the IFN-γ production that is measured by QFT. This has implications for the measurements of QFT specificity and sensitivity as well as in the frequency of indeterminate results obtained in studies involving young children. The increased frequency of indeterminate results in this age group may undermine the value of QFT as a more specific test.

Can QFT be Used to Aid in the Diagnosis of Active TB Disease in Children?

Untreated active TB disease is associated with significant morbidity and mortality in all age groups with younger children being most vulnerable after exposure to a household contact. While neither TST nor QFT (and other IGRAs) can distinguish between LTBI and active TB disease, Mtb infection must precede TB disease meaning that QFT may assist in the diagnosis of TB disease in the same way as the TST.8,5

The results of our sensitivity analysis show that QFT sensitivity is not significantly better or worse than that of TST in detecting active TB disease in children. However, we have shown that the performance of QFT in the detection of active TB disease in children differs significantly in high-burden versus low-burden TB settings. Typically, low-burden TB countries are developed countries where the population is at a low risk for LTBI with children in only some of these countries having received BCG at birth. In comparison, high-burden TB countries are typically developing countries, where the population is at a high risk for LTBI, with most countries administering BCG at birth.

The available literature on this subject suggests QFT to have a lower sensitivity and specificity in high TB incidence settings for diagnosing active TB disease when compared with low TB incidence settings.7,9 A recent meta-analysis (not specific to children) showed an overall pooled QFT sensitivity of 77%; however, in high-burden settings (n = 4) sensitivity was 69% compared with low-burden settings (n = 7) where sensitivity was 83%.3,9

The results of our meta-analysis which show QFT to have a reduced sensitivity in diagnosing active TB disease in children in a high-burden TB setting when compared with a low-burden TB setting.
setting are in line with the findings of previous reviews. There are a number of factors that may influence the observed difference in sensitivity of QFT (and other IGRAs) between high-burden TB countries and low-burden TB countries, and these include high exposure to MtB, transmission dynamics, repeat exposures, malnutrition, infection of human immunodeficiency virus (HIV), exposure to NTMs and helminth infection among others. Further investigation is required to clarify which of these factors affect the sensitivity of QFT most.

Limitations

Despite a good range of sample sizes (range, 29–496 children), the major limitation of this review is the number of culture confirmed TB disease cases reported in the various studies included (range, 6–49 cases). Study designs and definitions for TB diagnosis differed among the studies although an analysis of QFT sensitivity for active TB disease made use of culture-confirmed TB cases. Since the studies that included HIV-positive children in their analyses were excluded, therefore the performance of QFT in the presence of HIV infection was not assessed. Only QFT was evaluated in this review, and results for other IGRAs may be different.

CONCLUSIONS

The performance of QFT in children for both LTBI and active TB disease has been better assessed in low-burden TB countries than in high-burden TB countries. In both high- and low-burden TB settings, strong evidence is available to support increased LTBI specificity of QFT in children when compared with TST. However, the sensitivity of QFT was variable when compared with TST. Before QFT can replace TST for the identification of LTBI, this variable sensitivity must be addressed and other considerations such as the cost as well as the need for laboratories and personnel are necessary to establish whether the use of QFT is feasible within a given setting. It must be noted that in general, the treatment of LTBI is not a priority in high-burden TB settings due to overburdened health systems and limited resources.

The sensitivity of QFT in detecting active TB disease in children does not seem to be significantly better than that of TST. Our meta-analysis of QFT sensitivity specifically in children showed a significantly reduced sensitivity of QFT in detecting active TB disease within high-burden TB settings when compared with low-burden TB settings. However, further prospective studies are required to determine a true measure of QFT diagnostic accuracy for active TB disease where clearly laid out case definitions and standardized study designs are used so as to allow for comparison. Use of a combination of both QFT and TST (with either test positive) where applicable, should be explored further, as these results in an increased sensitivity for the diagnosis of TB disease in children.

Within a vaccine trial environment, the diagnosis of LTBI and active TB disease in children could include a combination of both TST and QFT (among other diagnostic tools). At this stage, given the above-mentioned results, caution must be exercised with the sole use of a positive QFT result in diagnosing active TB disease in young children as part of a clinical end point especially within a high TB incidence setting.

REFERENCES

20. Machingaidze et al

© 2011 Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.