Evaluation of the Impact of Interferon-Gamma Release Assays on the Management of Childhood Tuberculosis

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Background: Interferon-gamma release assays are increasingly being used in low-incidence settings, but there is little information on whether test results influence clinical decisions in children.

Methods: In June 2009, the Montreal Children's Hospital began implementing the QuantiFERON-TB Gold In-Tube (QFT) as a follow-up test to the tuberculin skin test (TST). Pediatric respirologists were asked to document how the QFT result changed their initial clinical management based on the TST.

Results: During a 2-year period, 399 children with TST and QFT results were recruited prospectively. The median age was 13 years. In the cohort, 83% were foreign-born and 82% were Bacille Calmette–Guérin vaccinated. The QFT was negative in 5 of 11 (45.5%) children diagnosed with active tuberculosis (TB). Among 55 TST+/QFT− children evaluated as TB contacts, the negative QFT changed the treatment decision in only 3 (5.5%), and isoniazid was prescribed to the remainder. In 201 TST+/QFT− children from targeted school and immigrant screening programs, a negative QFT result was used to withhold isoniazid in 145 (72.1%) children. These children were followed for 1 year, during which no TB cases occurred. In a multivariable analysis, history of TB contact and TST induration ≥20 mm were associated with fewer changes in clinical decisions.

Conclusions: Our cohort study showed that pediatric respirologists used negative QFT results to withhold isoniazid in most low-risk children who were referred for a positive TST found through targeted screening programs. In contrast, in almost all TST-positive children who were evaluated as TB contacts, negative QFT results did not change clinical management.

Key Words: children, diagnostics, interferon-gamma release assay, latent tuberculosis infection, tuberculosis

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Interferon-gamma release assays (IGRAs) are blood-based tests that have been developed to replace the tuberculin skin test (TST) for the diagnosis of latent tuberculosis infection (LTBI). Meta-analyses of IGRA performance in children show that they have increased specificity and similar sensitivity compared to the TST, although the IGRA sensitivity may be lower in high-incidence versus low-incidence settings.[1,2] Many national guidelines in low-incidence countries recommend the use of IGRAs in conjunction with the TST in children.[3]

In Canada, the Canadian tuberculosis (TB) Committee has published an advisory statement on the use of IGRAs in children, allowing for their use as an adjunct diagnostic tool for ruling in suspected active TB, investigating contacts of TB cases, confirming a positive TST in children with low probability of LTBI, confirming a negative TST in immunocompromised children, and targeted screening of recent immigrants.[4–6] Although the use of IGRAs is steadily expanding, there is little evidence on how exactly IGRA results impact clinical management, especially in children. In children, the high specificity of IGRAs may prove to be useful in immigrant children from TB endemic settings, where the TST specificity is compromised by Bacille Calmette–Guérin (BCG) vaccination after infancy, multiple BCG vaccinations or boosting by multiple TSTs.

In 2009, the Montreal Children's Hospital (MCH), a tertiary-care university teaching hospital, began implementing the QuantiFERON-TB Gold In-Tube (QFT; Cellestis Ltd., Victoria, Australia) as a routine clinical test for children with specific indications. The TB Clinic at the MCH sees a substantial number of immigrant children and a majority of them are BCG vaccinated. Using a more specific test in these children may potentially help avoid unnecessary treatment, risks and costs. In contrast, in cases where the diagnosis of TB is difficult (eg, active disease in an immuncompromised child), an additional test may help as part of the diagnostic workup. Our aims were to prospectively determine the concordance between the TST and QFT in children, stratified by clinical subgroups, as well as to measure how the QFT was used to change diagnostic and treatment decisions made by pediatric respirologists in routine practice.

METHODS

Study Setting

Since June 2009, the TB Clinic at the MCH has implemented the QFT as a clinical test (covered by Quebec government health insurance), based largely on the Canadian IGRA guidelines.[4,5] At the MCH, the QFT is used as a follow-up test to the TST for the following indications:

1. Children (<18 years) with suspected active TB (in combination with other microbiological tests, chest radiography and clinical history);
2. Children in contact with a case of active infectious TB and who have a positive TST;
3. Immunocompromised children defined as receiving prednisone (2 mg/kg/d) for ≥14 days, currently on chemotherapy or have

received chemotherapy in the past 3 months, pre- or post-bone marrow transplant or HIV-positive children;
4. Children with inflammatory diseases prior to starting anti-tumor necrosis factor (TNF) medication;
5. Children with positive TST who are considered to have a low probability of LTBI or, if infected, to have low risk of progression to active disease.

When the QFT was first implemented at the MCH, a memorandum outlining the clinical indications for this new test was circulated among relevant hospital departments. The TB Clinic at the MCH is coordinated by a TB nurse and staffed by 8 attending pediatric respirologists and 2 pediatric respirology fellows. The nurse has 8 years of experience working in TB, whereas the pediatric respirologists have 4–30 years of experience. Attending staff and fellows regularly attend rounds where complex TB cases are discussed. The Canadian IGRA guidelines and MCH indications for the use of QFT were presented at one of the weekly rounds when the hospital began implementing the QFT as a routine test.

Study Design and Enrollment

All children were enrolled at the TB Clinic. Sources of referrals to the TB Clinic included other hospital departments (eg, gastroenterology, infectious diseases, rheumatology and multicultural clinic), public health agencies for child contacts of active TB cases and community health clinics for postlanding immigration screening. As described in a previous study, the TB Clinic also performs an annual school-based TB screening program in elementary and secondary schools that are located in Montreal neighborhoods with large immigrant populations.[7] Only children with positive TST results from the schools were referred to the hospital for further evaluation, and all these children were considered eligible for routine clinical QFT testing.

In children meeting the clinical indications mentioned previously, we conducted a prospective study on how clinical QFT results influenced management decisions made by pediatric respirologists. No informed consent was required, as the tests were performed when clinically indicated, per the hospital guidelines. Our study enrolled children with varying risk of TB, and they were classified into predefined subgroups: active TB suspects, contacts of TB cases, immunocompromised children, children starting anti-TNF treatment and children from targeted screening programs. In addition to TST-positive children from the school-based screening, the targeted screening subgroup consisted of children who were referred to the TB Clinic from community health clinics or the hospital's multicultural clinic for purposes of immigration screening. The multicultural clinic at the MCH provides a general health examination, including TB screening with the TST, for immigrant children who have recently arrived in Montreal. A positive TST result was necessary for a clinical QFT in the TB contacts and targeted screening subgroups, while the QFT was performed regardless of the TST result in active TB suspects, immunocompromised children and children starting anti-TNF treatment. This study was approved by the Research Ethics Board at the MCH (Study Number PED-08-065).

TST and QFT Testing

All the TSTs at the MCH were administered and read by the TB Clinic nurse. The TSTs at school-based screenings were performed by experienced public health nurses and verified by the TB Clinic nurse. The Mantoux technique was used with 0.1 mL or 5 tuberculin unit of purified protein derivative.[8] The cutoff value for a positive TST was ≥5 mm in contacts and immunocompromised children and ≥10 mm for all other subgroups. All TST-positive children received a chest radiograph. For children with suspected active TB, gastric aspirate, sputum induction or bronchoscopy was used for specimen collection, after which smear microscopy and liquid culture were performed on the specimen.

The QFT was done per the manufacturer's recommendations, and results were available within 1–2 weeks for the clinical QFT and 2–4 weeks for the research QFT due to batch processing. The positive cutoff value was TB antigen minus nil ≥0.35 IU/mL, and the results were given as positive, negative or indeterminate. Results were considered indeterminate if the mitogen minus nil was <0.5 IU/mL or the nil was >8.0 IU/mL.

Data Collection

Information on patient characteristics and TB history were routinely collected for all children by the TB Clinic nurse, using a standard data abstraction form. When BCG vaccination status was unknown, we used the BCG World Atlas to obtain these data according to the child's country of birth.[9] The TB incidence per 100,000 per year in the country of birth was categorized into low (<25), moderate (25–100) and high (>100).[10] The pediatric respirologist was asked to complete a standardized questionnaire (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B300) to document whether or not the QFT had any impact on his or her diagnosis and treatment plan. This questionnaire was administered at the time of the child's follow-up visit when all diagnostic test results were available.

As an example of the data that were captured on the questionnaire, a child from the school-based screening was referred to the TB Clinic due to a positive TST. The QFT test was performed, and it was negative. Based on the complete diagnostic workup, the pediatric respirologist ruled out LTBI, and isoniazid (INH) preventive therapy was withheld. The initial decision from the positive TST would have been to treat the child for LTBI. Thus, this scenario represented a change in the clinical decision making. For children in whom INH was withheld due to a negative QFT, a follow-up phone call was made 1 year after the baseline visit, asking the parents about any presence of TB symptoms, recent contact with a TB case, travel to endemic countries and reasons for doctor or hospital visits within the past year.

Statistical Analysis

The primary study outcome was the proportion of changes in clinical management made within each subgroup of children. We used a logistic regression analysis to determine which factors may be associated with a change in the decision making for children with discordant TST and QFT results. Children with concordant results were excluded from this analysis, as there was no possibility to examine the impact of the QFT on changing clinical decisions. The dependent variable in the model was a change (yes or no) in clinical management based on the QFT result. The covariates were determined a priori and included age, sex, foreign country of birth, recent arrival in Canada (≤2 years), BCG vaccination, TST induration, history of multiple BCG or TST, history of contact with an active TB case, any abnormalities on chest radiography and year of study enrollment.

A multivariable model was used to test the covariates with simultaneous adjustment for potential confounders.[11] Covariates with odds ratios whose 95% confidence interval did not cross the null value were considered to be independently associated with the outcome. Continuous covariates that were not linear on the logit scale were further categorized into quartiles in the multivariable model. Because each pediatric respirologist was likely to have different preferences, levels of TB experience and knowledge about the QFT, we treated each of them as a cluster in the analysis. To account for the correlation in management decisions within each pediatric respirologist as well as between them, we calculated

clustered robust standard errors to ensure that the variability in effect estimates was not underestimated.[12] All analyses were performed using Stata, version 11 (College Station, TX).

RESULTS

Participant Characteristics

Table 1 describes the characteristics of the 399 children in our study sample. The median age was 13 years (range 0–18), and 88% of the children were >5 years of age. Most children were born outside of Canada, and a majority of them were recent arrivals, although the exact date of immigration was not ascertained in all cases. The largest group of children came from high TB incidence countries (45%), while 20% and 35% came from moderate and low TB incidence countries, respectively.

Most of the children were BCG vaccinated, usually with a single dose within 1 year after birth. One-quarter of the children reported a history of contact with a TB case, who was usually a member of the same household or a relative.

In the sample, 92% of the children had TST induration ≥5 mm, while 89% had TST induration ≥10 mm. Using the recommended cutoff points for each subgroup, our sample was predominantly positive on the TST, largely due to children from the school-based screenings who were referred to the TB Clinic on the basis of a positive TST. Only 21% of all children were positive on the QFT according to the manufacturer's recommended cutoff point. The rate of indeterminate results in our study was 1.5%, mostly due to a low response to the mitogen. A vast majority of the children did not have abnormalities consistent with TB on chest radiography. In most children with negative TST results, the chest radiograph was not performed.

TABLE 1. Characteristics of Children Included in the Study (n = 399)

Characteristic	Frequency (%)
Median age in years (range)	13 (0–18)
≤5	48 (12)
>5	351 (88)
Sex	
Male	215 (54)
Female	184 (46)
Country of birth	
Canada-born	67 (17)
Foreign-born	332 (83)
≤2 yrs since arrival	250
>2 yrs since arrival	56
Unknown	26
TB incidence in country of birth (per 100,000/yr)	
Low (<25)	142 (36)
Moderate (25–100)	79 (20)
High (>100)	178 (44)
BCG vaccination	
No	72 (18)
Yes	327 (82)
Single vaccination at birth	312
Single vaccination after birth	2
Multiple vaccinations	13
History of TB contact	
No	300 (75)
Yes	99 (25)
Close contact with household member or relative	57
Close contact with other person (eg, classmate)	39
Casual contact	3
TST induration (5 mm cutoff)	
≥5 mm	368 (92)
<5 mm	31 (8)
TST induration (10 mm cutoff)	
≥10 mm	354 (89)
<10 mm	45 (11)
TST (recommended cutoffs)*	
Positive	367 (92)
Negative	32 (8)
QFT	
Positive	82 (21)
Negative	311 (78)
Indeterminate	6 (1)
Chest radiography	
Abnormalities present	27 (7)
No abnormalities	367 (92)
Not done (ie, negative TST)	5 (1)
Year of study	
Year 1	202 (51)
Year 2	197 (49)

*5 mm for contacts and immunocompromised children; 10 mm for all others.

Concordance in Predefined Subgroups

Table 2 shows the concordance between the two tests for each of our predefined subgroups. Among 26 suspected active TB cases, 6 children were concordant positive and 9 were concordant negative. In 11 TST+/QFT− children, 5 had a final diagnosis of active disease based mainly on abnormal chest radiography suggestive of active TB, as only 2 of these children were culture-confirmed cases. In 83 TST-positive children who had contact with an active TB case, 29 were positive on both tests. Among 52 TST+/QFT− TB contacts, 7 children converted from a negative result on the first TST done at the end of exposure to a positive result on the second TST done at the end of the treatment window period (12 weeks of INH).

In 5 immunocompromised children, 1 was concordant positive and 3 were concordant negative. One TST-negative child had an indeterminate QFT, which was repeated and negative. In 20 children with a TST done prior to starting anti-TNF treatment, 17 children were concordant negative. One TST+/QFT− child had a history of previous treatment for LTBI. In the final and largest subgroup, 265 TST-positive children were recruited from targeted

TABLE 2. Characteristics of Children Included in the Study (n = 399)

	TST Positive	TST Negative
Active TB suspects (n = 26)		
QFT positive	6	0
QFT negative	11	9
QFT indeterminate	0	0
TST+ contacts with TB case (n = 83)		
QFT positive	29	
QFT negative	52	
QFT indeterminate	2	
Immunocompromised children (n = 5)		
QFT positive	1	0
QFT negative	0	3
QFT indeterminate	0	1
Children starting anti-TNF treatment (n = 20)		
QFT positive	0	0
QFT negative	1	17
QFT indeterminate	0	2
TST+ children from targeted screening programs (n = 265)		
QFT positive	46	
QFT negative	218	
QFT indeterminate	1	

screening programs. Among these children, 46 were concordant positive, and 218 children were negative on the QFT.

Changes in Clinical Management

Since the largest subgroups were TST-positive children from targeted screening programs and children with a history of TB contact, we focused on these 2 major subgroups to determine the impact of the QFT on decision making. In 52 TB contacts with discordant TST+/QFT− results, the negative QFT result did not change the clinical management in 49 children (94.2%). INH was prescribed by the pediatric respirologists based on the positive TST. In the 3 remaining children, the contact was considered minimal and INH was withheld. In 201 TST+/QFT− children from targeted screening programs who returned for their follow-up visits at the TB Clinic, the pediatric respirologists used the negative QFT to consider LTBI unlikely in 145 (72.1%) children and withhold INH therapy. Thus, a change in clinical management was made in a majority of these children.

Factors Associated With Changes in Clinical Management

There were 282 children with discordant TST+/QFT− results in the entire study sample. Children with concordant results and those with indeterminate QFT results were not included in this analysis because the QFT was not expected to change the clinical management. In addition, 10 children with previous treatment for active or latent TB were excluded for the same reason. Furthermore, in 17 children the decision about clinical management could not be obtained and in 5 children the date of arrival was missing. Thus, 250 children were included in the logistic regression analysis. There were a total of 11 clusters, consisting of 10 respirologists who evaluated children during the study period and 1 cluster of physicians from other hospital departments who had ordered the QFT. In the multivariable model, the TST induration was categorized into quartiles based on established cutoffs (5–9 mm, 10–14 mm, 15–19 mm and ≥20 mm) to account for its nonlinear effect. Because the 5–9 mm quartile applied only to TB contacts in whom there was no change in clinical management, it was not retained in the model. Thus, the 10–14 mm quartile was used as the reference category. The results from the multivariable analysis are presented in Table 3.

In the multivariable analysis, age in years was not associated with the decision to change clinical management based on the QFT result. This did not change when age was dichotomized as a binary variable (≤5 vs. >5 years). Neither foreign birth nor BCG vaccination status affected the clinical management. Only history of contact with an active TB case and a TST result ≥20 mm had independent effects on reducing the likelihood of a change in clinical management. In other words, when the child was a TB contact and/or had a large TST reaction, the pediatric respirologists did not change their management decisions because of the negative QFT result.

Follow-up Results

Follow-up phone calls were made by a nurse to the homes of 96 TST-positive children who did not receive INH therapy due to a negative QFT result. Parents of 59 (61.5%) children were successfully contacted. One-quarter of the children could not be reached after 3 separate calls were made at different times of the day. In 13 (13.5%) children, the phone number was no longer in service and they could not be reached. As of January 2012, we are not aware of any child who has developed active disease.

TABLE 3. Results From Multivariable Logistic Regression Analysis for Factors Associated With a Change in Clinical Management (n = 250)

Covariate	Odds Ratio	95% Confidence Interval
Age in years	0.98	0.90–1.07
Male	0.60	0.33–1.08
Foreign-born	1.01	0.29–3.57
Recent arrival (≤2 yr)	0.70	0.27–1.82
BCG vaccinated	0.48	0.16–1.45
Multiple BCG/TST	3.93	0.68–22.55
History of contact	0.01	0.003–0.08
TST 10–14 mm	1	—
TST 15–19 mm	0.57	0.30–1.09
TST ≥20 mm	0.27	0.15–0.49
Any chest radiograph abnormalities	2.52	0.68–9.32
Year of study (1st vs. 2nd)	0.87	0.25–3.03

DISCUSSION

The evidence based on TB diagnostics is mostly focused on test accuracy (ie, sensitivity and specificity), and many studies have evaluated the sensitivity and specificity of IGRAs. Studies that evaluate the factors associated with discordant TST and IGRA results are also very common in the literature. However, there are few published data on how IGRA results impact patient-important outcomes,[13] such as changes in diagnostic and treatment decisions, and which factors are associated with these changes. A change in clinical management can be considered an intermediate outcome that impacts long-term patient outcomes.[14]

In our prospective cohort study, we found that in a majority of children with TST+/QFT− results from targeted screening programs, pediatric respirologists withheld INH based on the negative QFT, presumably because they judged the children to be at low risk for LTBI. In contrast, it was assumed that TST-positive children in close contact with an active TB case were deemed at high enough risk to warrant preventive therapy regardless of the negative QFT result. As expected, the effect of history of TB contact on the reluctance to change clinical management was confirmed in a logistic regression analysis that also accounted for differences among the pediatric respirologists. A larger TST induration size was also associated with not changing the clinical decision. Al Zahrani et al[15] reported that above a 5-mm cutoff point in close contacts and active TB suspects, the induration size did not matter in predicting active disease. However, this study was conducted in adults and it remains to be seen whether this finding holds true in children.

Several published studies from low-incidence settings have also reported higher sensitivity for active TB with the TST compared with the QFT, and these have been summarized in meta-analyses on the performance of the IGRAs in children.[1,2] In our study, the QFT missed 5 of 11 active TB cases. Two of these children were culture confirmed, and all of them had chest radiographs suggestive of pulmonary disease and a history of contact with an active TB case. Based on the diagnostic workup, the pediatric respirologist prescribed TB therapy. Given the suboptimal sensitivity, a negative QFT result cannot be used to rule out active disease in children, which is consistent with the Canadian IGRA guidelines.[4–6] Furthermore, the fact that all 7 child contacts who had converted on the TST remained negative on the QFT after 12 weeks suggests that the QFT may require an even longer period to convert after documented exposure.

One study has described the impact of the QFT for children in a clinical setting based on national guidelines that incorporate the IGRAs. Taylor et al[16] compared management decisions under the local Newcastle guidelines with the UK National Institute for Health and Clinical Excellence guidelines, which call for a 2-step algorithm in which the IGRA is used to confirm a positive TST. During a period of 18 months, a change in clinical management was observed for 22% of the children using the QFT. In total, 85%

fewer children would have been treated with INH under the new National Institute for Health and Clinical Excellence guidelines on an "inform and advise" basis. However, 2 probable TB cases would have been missed, both of whom were close contacts and had abnormal chest radiographs suggestive of active disease.

In Canada, Kunimoto et al[17] performed a study in adults seen at a centralized provincial TB clinic. Similar to our setting, their sample consisted of large proportions of contacts and screening referrals. In the study, 60% of TST-positive subjects were negative on the QFT, and presumably INH was withheld in most of these individuals. Using the QFT as a confirmatory tool for potentially false-positive TST results could help cut the costs associated with INH preventive therapy. Oxlade and colleagues[18] have shown that the 2-step diagnostic strategy where the QFT is performed only in TST-positive individuals is the most cost-effective use of the QFT for immigrants and contacts in Canada.

Strengths and Limitations

Our study evaluated the impact of the QFT on decision making in routine practice. By asking the pediatric respirologists for their diagnostic and treatment decisions before and after the QFT, our study documented the rationale behind their clinical management in an explicit way. We were able to go beyond the information contained solely in medical charts by providing some justification for their final management decisions. One potential limitation is the Hawthorne effect, in which participants of a study behave differently when they are being observed. While the study may have made the pediatric respirologists more aware of the introduction of this new test, we believe that the Hawthorne effect was not a major issue. One pediatric respirologist relied on the TST alone and did not use the QFT result in making his clinical decisions. Furthermore, if intention to test means intention to treat or not treat depending on the result, then in the case of child contacts the QFT was not being used in strict accordance with the clinical indications.

Because the clinical indications followed the Canadian IGRA guidelines, the study design did not allow us to evaluate what would happen if QFT results were available first followed by the TST. That is, we cannot answer the question: Is the QFT useful because of the effect of having an additional test result or is it really a better test? In addition, as most children from targeted screening programs were of school age and referred to the TB Clinic on the basis of a positive TST, our study sample is not reflective of all children investigated for LTBI or all age groups. The low number of active TB suspects, immunocompromised children and children starting anti-TNF treatment in the sample also limits the generalizability of our results to these important subgroups. Furthermore, our study was conducted in a tertiary-care pediatric hospital, and all cases were seen by trained respirologists. Thus, our findings may not be generalized to primary-care settings or pediatricians who are not highly experienced in investigating and treating TB.

Our study suggests that the high specificity of the QFT may be useful in reducing the number of low-risk children who need INH. While this is a short-term finding, it is not necessarily a good surrogate for long-term patient outcomes. Our study cannot determine whether the change in decision making necessarily leads to a better long-term outcome. If some of the TST+/QFT− children in whom INH was withheld progressed to active disease during follow-up, then the change in clinical management would have resulted in a worse outcome. While no cases of active TB were detected through the follow-up phone calls, our study had limited ability to assess such long-term patient outcomes.

Other studies have evaluated the prognostic (predictive) value of IGRAs, and a recent meta-analysis found that neither IGRAs nor the TST have high accuracy for the prediction of active TB, although IGRAs may be useful for reducing the number of people considered for preventive treatment in some populations.[19] Thus, further research is needed to discover new biomarkers that will identify individuals who will benefit most from preventive therapy.

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