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Evaluation of QuantiFERON-TB Gold In-Tube and Tuberculin Skin Tests Among Immigrant Children Being Screened for Latent Tuberculosis Infection

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Abstract

Background—Centers for Disease Control and Prevention requirements for pre-immigration tuberculosis (TB) screening of children 2- to 14-years old permit a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA). Few data are available on the performance of IGRAs versus TSTs in foreign-born children.

Methods—We compared the performance of TST and QuantiFERON-TB (QFT) Gold In-Tube in children 2- to 14-years old applying to immigrate to the United States from Mexico, the Philippines and Vietnam, using diagnosis of TB in immigrating family members as a measure of potential exposure.

Results—We enrolled 2520 children: 664 (26%) were TST+ and 142 (5.6%) were QFT+. One hundred and eleven (4.4%) were TST+/QFT+, 553 (21.9%) were TST+/QFT− and 31 (1.2%) were TST−/QFT+. Agreement between tests was poor ($\kappa = 0.20$). Although positive results of both tests were significantly associated with older age (relative risks [RR] TST+, 1.64; 95% confidence interval [CI]: 1.36–1.97; RR QFT+, 3.05; 95% CI: 1.72–5.38) and with the presence of TB in at least 1 immigrating family member (RR TST+, 1.40; 95% CI: 1.12–1.75; RR QFT+ 2.24; 95% CI: 1.18–4.28), QFT+ results were more strongly associated with both predictive variables.

Conclusions—The findings support the preferential use of QFT over TST for pre-immigration screening of foreign-born children 2 years of age and older and lend support to the preferential use of IGRAs in testing foreign-born children for latent TB infection.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Keywords

tuberculosis; latent tuberculosis infection; interferon-gamma release assay; tuberculin skin test; foreign birth

Screening for tuberculosis (TB) among immigrants from high-incidence countries is an important part of TB control activities in industrialized nations.[1] Screening also affords an opportunity to identify persons with latent tuberculosis infection (LTBI). LTBI identification and treatment are particularly important in children, who are more likely to progress to TB disease and to develop severe manifestations; those who do not develop disease in childhood are the next generation of adult TB cases.[2–5]

Until 2001, the only LTBI test was the tuberculin skin test (TST), which is associated with relatively high numbers of false positives because the injectable filtrate shares proteins with Bacillus Calmette-Guérin (BCG) TB vaccine, given to 90% of newborns worldwide.[6–8] Interferon-gamma release assays (IGRAs), available since 2001, are an attractive alternative in foreign-born persons because these in vitro blood tests use peptides that do not cross-react with BCG or with most nontuberculous mycobacteria (NTM) antigens.[6,7,9–12] However, questions persist about which test is best for screening foreign-born children because of concerns about IGRA accuracy[13–18] and higher rates of indeterminate results.[18–21] Of note, Centers for Disease Control and Prevention (CDC) instructions permit either TST or IGRA for screening immigrant children aged 2–14 years from high-risk countries.[22]

This study compared the performance of the TST and 1 IGRA, QuantiFERON-TB (QFT) Gold In-Tube, in foreign-born children applying for permanent US residence from Mexico, the Philippines and Vietnam, which accounted for 22% of all immigrants to the United States in 2012,[23] and have historically accounted for 25–50% of pediatric TB cases among foreign-born children.[24,25] Diagnosis of TB in family members applying to immigrate was used as a measure of potential exposure.

MATERIALS AND METHODS

Children 2- to 14-years old applying to immigrate to the United States were prospectively enrolled from July 2010 through April 2011 at 3 clinics: Cho Ray Hospital Visa Medical Unit, Ho Chi Minh City, Vietnam; St. Luke's Medical Center Extension Clinic, Manila, Philippines and Servicios Medicos de la Frontera, Juarez, Mexico. Children from these countries receive BCG at birth; Filipino children receive a second dose at school entry (6- to 7-years old). Participants were recruited consecutively from the pool of applicants during all times when screening is normally conducted, and all children with parental permission were eligible. To increase the likelihood of enrolling participants with positive tests, efforts were made to recruit children from families where at least 1 member had a chest radiograph suggestive of TB. CDC and local institutional review boards approved the study protocol.

Medical examinations were conducted according to CDC instructions,[22] except participants received both TST and QFT. As per the instructions, children with a positive result or who have TB symptoms or HIV infection receive chest radiographs. Clinics used the purified

protein derivative (PPD) solutions routinely used for screenings (Tubersol by Sanofi Pasteur in Mexico and Vietnam; Tuberculin PPD by Japan BCG Laboratory in the Philippines). TST was administered by the Mantoux method and preparations used were equivalent to 5TU PPD-S. Participants/parents were instructed to return 48–72 hours later for measurement of any induration. Experienced clinicians placed and read the TSTs. Reactions were considered positive if the diameter of the induration was ≥10 mm, regardless of BCG vaccination status.[22] Blood for the QFT was drawn prior to TST placement. The QFT was processed on-site according to manufacturer's instructions (Cellestis LTD, Carnegie, Australia). When indeterminate, the QFT was repeated using the same specimen and the repeat result was used. TST and QFT training and quality assurance were conducted on-site prior to and during the study.

The applicant medical examination collects demographics, medical history, physical examination and TB classification data in an electronic database. Information on BCG vaccination is not part of the medical examination. Test results were entered in a separate database; the 2 were linked for analysis.

Screening results of each participant's family members who applied to immigrate to the United States with the child were used to identify potential exposure to TB cases. Children were classified into mutually exclusive groups: (1) children with immigrating family members diagnosed with culture-confirmed pulmonary TB; (2) children with immigrating family members who had a medical history, physical examination or chest radiograph suggestive of pulmonary TB but not culture-confirmed TB (TB suspect) and (3) children whose family members had normal chest radiographs.

Categorical data were compared using the Pearson χ^2 test. Wilcoxon-rank sum and Kruskal–Wallis tests were used to determine whether the distribution of continuous variables differed between groups. Kappa statistic (κ) and McNemar test assessed test concordance. Annual risk of a positive test was calculated using $R = 1 - (1-P)^{1/a}$, where R is annual risk of a positive test, P is observed prevalence of test positivity and a is average age.[26,27]

Multivariate log-binomial regression identified predictors of TST and QFT positivity, and of discordant results. Model building started with all variables (age, gender, country of examination, TB results of immigrating family members) and used backward elimination. Variables with a Wald P value ≤ 0.05 were retained, as were variables deemed to be clinically significant. The analysis for predictors of TST and QFT positivity excluded those with a final indeterminate QFT. The analysis for predictors of discordance excluded children who were positive on both tests or had a final indeterminate QFT, and compared each type of discordance (QFT+/TST−, TST+QFT−) to all others. Analysis used SAS (9.2; SAS Inc, Cary, NC) and R (2.13.1; Auckland, New Zealand).

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RESULTS

The study enrolled 2564 children and analyzed 2520 records. Of the 44 excluded, 20 were in the study-specific database but not the visa applicant database, 6 were outside the age range, 16 lacked documentation of parental permission and 2 did not complete both tests.

During the study period, clinics reported TB diagnoses for 14 of 34,856 applicants from Mexico (prevalence rate of 40/100,000 applicants), 115 of 14,613 applicants from the Philippines (787/100,000) and 161 of 16,304 Vietnamese applicants (987/100,000). These are higher than 2012 WHO rates, which estimated TB prevalence of 33/100,000 persons in Mexico, 461/100,000 in the Philippines and 218/100,000 in Vietnam.[28] No TB cases were detected among the 6470 Mexican, 2903 Filipino and 2776 Vietnamese children screened during the study period.

The final analysis included 970 (38.5%) from Mexico, 952 (37.8%) from the Philippines and 598 (23.7%) from Vietnam (Table 1). The majority (51.8%) were 10- to 14-years old. Two hundred eighty-eight children (11.4%) had a family member who was a TB suspect, and 75 (3.0%) had a family member with culture-confirmed TB. Children from the Philippines and Vietnam were more likely to have a family member who was a TB suspect or had culture-confirmed TB ($P < 0.0001$).

Of the 2520 children, 664 (26.3%) were TST-positive, 142 (5.6%) were QFT-positive, 1812 (71.9%) were negative on both tests and 111 were positive on both tests (Fig. 1). Of the 142 QFT-positive children, 78% were positive on both tests. Of the 664 TST-positive children, 17% were positive on both tests.

Thirteen children (0.5%) had final indeterminate QFT results; all were TST-negative. The indeterminate result of 1 child was due to a high nil value; all others were due to low mitogen responses. Eleven of the 13 (84.6%) were from Mexico and 2 (15.4%) were from Vietnam ($P = 0.0019$). One had a family member who was a TB suspect. Seven (53.8%) were 2- to 5-years old, 2 (15.4%) were 6- to 9-years old and 4 (30.8%) were 10- to 14-years old. Indeterminate results were more common among the youngest children compared with both 6- to 9-year olds (RR, 4.80; 95% CI: 1.0–23.0) and 10- to 14-year olds (RR, 4.5; 95% CI: 1.3–15.2).

After excluding children with final indeterminate QFT results, 26.5% were TST-positive and 5.7% were QFT-positive (Table 2). The percentages of children with positive QFTs ranged from 4.4% in Vietnam to 6.3% in the Philippines. The percentages of children with positive TSTs ranged from 9.8% in Mexico to 42.7% in the Philippines. Excluding those with final indeterminate results, 76.7% had concordant results: 111 (4.4%) with positive and 1812 (72.3%) with negative results. Almost all (94.7%) of the 584 children with discordant results were QFT-negative/TST-positive. Agreement was low (κ: 0.20; 95% CI: 0.16–0.24).

In multivariate analysis, positive QFT results were associated with older age and with having a family member with culture-confirmed TB (for details, see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B961). Children in the oldest age group (10- to 14-years old) were 3 times as likely to be QFT-positive as those in the youngest group (2- to 5-

year olds) (RR, 3.05; 95% CI: 1.72–5.38). Children with a family member who had culture-confirmed TB were more than twice as likely to be QFT-positive as children whose family members had normal chest radiographs (RR, 2.24; 95% CI: 1.18–4.28).

Positive TST results were also associated with older age and having a family member with culture-confirmed TB, although the associations were generally weaker than with QFT positivity (for details, see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B961). In addition, positive TST results were associated with having a family member who was a TB suspect (RR, 1.18; 95% CI: 1.01–1.37). Children from Vietnam (RR, 2.85 95% CI: 2.26–3.60) and the Philippines (RR, 4.28; 95% CI: 3.47–5.27) were more likely to be TST-positive than Mexican children. In all countries, the proportion of children who tested positive on either test increased with age (Fig. 2). The proportion of children at each age who were TST-positive varied greatly by country, but the proportion who were QFT-positive varied only modestly. The annual risk of a positive TST was 1.05% in Mexico, 5.98% in the Philippines and 3.67% in Vietnam. The annual risk of a positive QFT was 0.62% in Mexico, 0.72% in the Philippines and 0.52% in Vietnam.

In country-specific risk models, the model for Vietnam was unstable due to small numbers; the model for the Philippines showed risks similar in magnitude and direction to the overall model (data not shown). However, the age-specific risk of QFT positivity in Mexican children was much higher than the risk in the overall model. Mexican children 10- to 14-years old were 13 times as likely to be QFT-positive compared with 2- to 5-years olds (RR, 12.7; 95% CI: 1.76–91.0) and, while not statistically significant, 6- to 9-year olds were 7 times as likely to be QFT-positive compared with 2- to 5-years olds (RR, 6.82; 95% CI: 0.88–52.7).

Test discordance was associated with age, family TB exposure and country of origin (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/B962). Children in the oldest group who were TST-negative were more likely than those in the youngest group to be QFT-positive (RR, 8.8; 95% CI: 1.20–65.7). Among those who were QFT-negative, children with a family member with culture-confirmed TB (RR, 1.36; 95% CI: 1.04–1.79) and those with a family member who was a TB suspect (RR, 1.20; 95% CI: 1.02–1.42) were more likely to be TST-positive. Children from the Philippines (RR, 6.16; 95% CI: 4.79–8.02) and Vietnam (RR, 3.97; 95% CI: 2.97–5.30) who were QFT-negative were more likely than children from Mexico to be TST-positive. Children 10- to 14-years old who were QFT-negative were more likely to be TST-positive than 2- to 5-years olds (RR, 1.59; 95% CI: 1.31–1.95).

DISCUSSION

This study, the largest to date, assessed 2 LTBI tests in 2520 children applying to immigrate to the United States from Mexico, the Philippines and Vietnam. These findings are consistent with other research that suggests QFT is a more accurate test for LTBI in foreign-born children because of problems with TST cross-reactivity.[29–36]

A major obstacle to the development and assessment of LTBI tests is the lack of a gold standard to measure sensitivity and specificity, particularly when none of the sample population has TB. We addressed this with 3 proxy measures for exposure: (1) the presence of suspected or confirmed TB in family members, (2) the expected low prevalence of LTBI in the very young and (3) the expected increases in TB exposure and, therefore, positive results with age. For both tests, positive results were significantly associated with the presence of TB in an immigrating family member, but the association was stronger for QFT. None of the 2-year olds in our study were QFT-positive, compared with 13 (13%) who were TST-positive. The lower prevalence of QFT-positives compared with TST-positives in 2-year olds is more consistent with the expected prevalence of LTBI in young children with limited exposure outside immediate family members. Although both QFT-positive and TST-positive results showed significant increases with age, this association was stronger for QFT.

If our conclusion is correct that QFT is associated with fewer false-positive test results than TST in pre-immigration screening of foreign-born BCG-vaccinated children, the use of QFT during pre-immigration screening would have substantial benefits. Since fewer children were QFT-positive, the number requiring radiography would decrease, resulting in lower costs and reduced radiation exposure. The use of QFT would also reduce the number of children considered for LTBI treatment once in the United States. Relying on QFT alone would reduce the percentage of children who were LTBI positive by 85% in the Philippines, 84% in Vietnam and 41% in Mexico. This reduction might lead to reduce exposure to radiographs and improved LTBI treatment in foreign-born children, since clinicians and health departments would be less burdened by children who are likely not infected, allowing for prioritization of care and treatment for patients most likely to benefit. Clinicians and health departments in the United States may be more confident with the results of QFT performed abroad, decreasing the need for, and costs of, repeat testing among these children.

Some children with only positive TSTs may have LTBI. However, because of the concerns about high false-positive TST rates among BCG-vaccinated children, some US health departments already re-test these children with QFT and treat only those who are positive.[37] Moreover, no TB cases were detected among 12,149 children screened during the study period, providing reassurance that the prevalence of true LTBI is probably closer to the 5.7% found with QFT than the 26.5% with TST.

Clinicians have been concerned that using QFT in children might yield a high proportion of indeterminate results, particularly among children younger than 5 years of age. However, we found few indeterminate results in the study population (0.5%) and among the youngest children (1.4%). Since more than 98% of the youngest children had interpretable QFT results, the fear of high indeterminate rates may be unwarranted. Similar to previous findings, all indeterminate results occurred in children who were TST-negative,[31] suggesting the risk of developing TB among children with indeterminate results is low.

The findings from Mexico were surprising given that the TB prevalence rate in Mexico is 15% of the rate in Vietnam and 7% of the rate in the Philippines.[28] Compared to the much higher percentages of TST-positive results in the Philippines (42.7%) and Vietnam (27.5%), the lower percentage of children from Mexico who were TST-positive (9.8%) was expected

and consistent with previous reports.[37,38] However, the percentage of QFT-positive Mexican children (5.8%) was unexpectedly similar to the percentages seen in the Philippines (6.3%) and Vietnam (4.4%). Although we expected the reduction in Mexico to be greater, a 41% reduction is important, particularly considering that over 14% of immigrants entering the United States are Mexican.[23] Unexpectedly, smaller discordance between QFT and TST results among Mexican compared with Filipino children has been reported.[37] Potential explanations include the prevalence of NTMs, differences in BCG vaccination strains, immunologic response differences and differences in *Mycobacterium tuberculosis* strains.[37]

Another unexpected result was that the higher proportion of QFT-positive/TST-negative children was higher in Mexican (2.2%) compared with Vietnamese (0.5%) and Filipino children (0.9%). This relates to the lower prevalence of TB in the population, which affects test sensitivity and specificity. Assuming that some of these children are truly LTBI-negative, relying on QFT alone would result in a slightly higher proportion of Mexican children who receive radiographs and treatment unnecessarily. Nevertheless, this proportion is smaller than the proportion potentially receiving radiographs and treatment with TST alone.

This study has limitations. No children were diagnosed with TB, so we could not calculate sensitivity or specificity of either test. We did not prospectively follow children to determine if either test was associated with progression to TB disease. We were unable to control for other health problems in the children. Although some health variables were self-reported, they were considered unreliable because few applicants reported any health problems.

Individual BCG vaccination status is not obtained at the examinations of visa applicants; we assumed participants were immunized at birth based on BCG guidelines in each country.[39] BCG guidelines in the Philippines require a second dose of BCG at school entry, which could have affected TST results. It is hard to separate the effect of a second BCG dose from that of older age (both of which may increase TST positivity). However, Figure 2 shows that the proportion of children who were TST-positive in the Philippines is similar to the proportion in Vietnam, suggesting that the second dose of BCG did not substantially affect our findings.

Although both tests have been approved for use in this population,[22] CDC guidance indicates a preference for IGRAs in BCG-vaccinated persons older than 5 years due to IGRAs' higher specificity and ability to exclude reactions caused by BCG and NTMs.[21] For children younger than 5 years, CDC guidelines indicate a preference for TST over IGRA.[21] However, this study's findings support the use of QFT for pre-immigration screening of children 2 years and older and support the preferential use of IGRAs over TSTs for LTBI testing of foreign-born BCG-vaccinated children in the United States.

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References

1. Pareek M, Baussano I, Abubakar I, et al. Evaluation of immigrant tuberculosis screening in industrialized countries. Emerg Infect Dis. 2012 [Accessed June 23, 2014] serial on the Internet.
2. Menzies HJ, Winston CA, Holtz TH, et al. Epidemiology of tuberculosis among US- and foreign-born children and adolescents in the United States, 1994–2007. Am J Public Health. 2010; 100:1724–1729. [PubMed: 20634457]
3. Marais BJ, Obihara CC, Warren RM, et al. The burden of childhood tuberculosis: a public health perspective. Int J Tuberc Lung Dis. 2005; 9:1305–1313. [PubMed: 16466051]
4. Marais BJ. Tuberculosis in children. Pediatr Pulmonol. 2008; 43:322–329. [PubMed: 18306338]
5. Munoz, FM.; Starke, JR. Tuberculosis in Children. In: Reichman, LB.; Hershfield, ES., editors. Tuberculosis: A Comprehensive International Approach. 2. New York, NY: Marcel Dekker, Inc; 2000. p. 516-555.
6. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2000; 49(RR-6)
7. Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med. 2007; 146:340–354. [PubMed: 17339619]
8. World Health Organization. [Accessed August 23, 2013] Global and Regional Immunization Coverage, 1980–2007. 2011. Available at: http://www.who.int/immunization_monitor-ing/diseases/BCG_coverage.jpg
9. Lalvani A, Millington KA. T cell-based diagnosis of childhood tuberculosis infection. Curr Opin Infect Dis. 2007; 20:264–271. [PubMed: 17471036]
10. Vincenti D, Carrara S, Butera O, et al. Response to region of difference 1 (RD1) epitopes in human immunodeficiency virus (HIV)-infected individuals enrolled with suspected active tuberculosis: a pilot study. Clin Exp Immunol. 2007; 150:91–98. [PubMed: 17680823]
11. Mahairas GG, Sabo PJ, Hickey MJ, et al. Molecular analysis of genetic differences between *Mycobacterium bovis* BCG and virulent *M. bovis*. J Bacteriol. 1996; 178:1274–1282. [PubMed: 8631702]
12. Gey van Pittius NC, Sampson SL, Lee H, et al. Evolution and expansion of the *Mycobacterium tuberculosis* PE and PPE multigene families and their association with the duplication of the ESAT-6 (esx) gene cluster regions. BMC Evol Biol. 2006; 6:95. [PubMed: 17105670]
13. Bergamini BM, Losi M, Vaienti F, et al. Performance of commercial blood tests for the diagnosis of latent tuberculosis infection in children and adolescents. Pediatrics. 2009; 123:e419–e424. [PubMed: 19254978]
14. Mandalakas AM, Detjen AK, Hesseling AC, et al. Interferon-gamma release assays and childhood tuberculosis: systematic review and meta-analysis. Int J Tuberc Lung Dis. 2011; 15:1018–1032. [PubMed: 21669030]
15. Chiappini E, Bonsignori F, Accetta G, et al. Interferon-γ release assays for the diagnosis of *Mycobacterium tuberculosis* infection in children: a literature review. Int J Immunopathol Pharmacol. 2012; 25:335–343. [PubMed: 22697065]
16. Machingaidze S, Wiysonge CS, Gonzalez-Angulo Y, et al. The utility of an interferon gamma release assay for diagnosis of latent tuberculosis infection and disease in children. Pediatr Infect Dis J. 2011; 30:694–700. [PubMed: 21427627]
17. Kakkar F, Allen U, Ling D, et al. Tuberculosis in children: new diagnostic blood tests. Paediatr Child Health. 2010; 15:529–538. [PubMed: 21966239]
18. Connell TG, Ritz N, Paxton GA, et al. A three-way comparison of tuberculin skin testing, QuantiFERON-TB gold and T-SPOT.TB in children. PLoS One. 2008; 3:e2624. [PubMed: 18612425]
19. Haustein T, Ridout DA, Hartley JC, et al. The likelihood of an indeterminate test result from a whole-blood interferon-gamma release assay for the diagnosis of *Mycobacterium tuberculosis* infection in children correlates with age and immune status. Pediatr Infect Dis J. 2009; 28:669–673. [PubMed: 19633512]

20. Thomas B, Pugalenthi A, Patel H, et al. Concordance between tuberculin skin test and interferon-γ assay and interferon-γ response to mitogen in pediatric tuberculosis contacts. Pediatr Pulmonol. 2011; 46:1225–1232. [PubMed: 21681979]
21. Centers for Disease Control and Prevention. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection — United States, 2010. MMWR Morb Mortal Wkly Rep. 2010; 59(RR-5):1–25. [PubMed: 20075837]
22. Centers for Disease Control and Prevention. [Accessed June 20, 2013] CDC immigration requirements: technical instructions for tuberculosis screening and treatment. 2009. Available at: http://www.cdc.gov/immigrantrefugeehealth/pdf/tuberculosis-ti-2009.pdf
23. Department of Homeland Security. [Accessed June 20, 2013] 2012 Yearbook of Immigration Statistics. Table 2 Available at: http://www.dhs.gov/yearbook-immigration-statistics
24. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2012. Atlanta, GA: U.S. Department of Health and Human Services, CDC; Oct. 2013
25. Centers for Disease Control and Prevention. [Accessed June 18, 2014] Slide set–epidemiology of pediatric tuberculosis in the United States, 1993–2012. Available at: http://www.cdc.gov/tb/publications/slidesets/pediatricTB/default.htm
26. Cauthen, GM.; Pio, A.; ten Dam, HG. Annual risk of tuberculous infection. Geneva: World Health Organization; 1988. WHO/TB/88.154
27. Rieder H. Annual risk of infection with *Mycobacterium tuberculosis*. Eur Respir J. 2005; 25:181–185. [PubMed: 15640340]
28. World Health Organization. Global tuberculosis control 2013. Geneva: World Health Organization; 2013. Available at: http://www.who.int/tb/country/data/profiles/en/index.html [Accessed November 4, 2013]
29. Bianchi L, Galli L, Moriondo M, et al. Interferon-gamma release assay improves the diagnosis of tuberculosis in children. Pediatr Infect Dis J. 2009; 28:510–514. [PubMed: 19504735]
30. Cruz AT, Geltemeyer AM, Starke JR, et al. Comparing the tuberculin skin test and T-Spot. TB in Children. Pediatrics. 2011; 127:e31. [PubMed: 21135009]
31. Okada K, Mao TE, Mori T, et al. Performance of an interferon-gamma release assay for diagnosing latent tuberculosis infection in children. Epidemiol Infect. 2008; 136:1179–1187. [PubMed: 17988427]
32. Lighter J, Rigaud M, Eduardo R, et al. Latent tuberculosis diagnosis in children by using the QuantiFERON-TB Gold In-Tube test. Pediatrics. 2009; 123:30–37. [PubMed: 19117857]
33. Ling DI, Crépeau CA, Dufresne M, et al. Evaluation of the impact of interferon-gamma release assays on the management of childhood tuberculosis. Pediatr Infect Dis J. 2012; 31:1258–1262. [PubMed: 22828646]
34. Lucas M, Nicol P, McKinnon E, et al. A prospective large-scale study of methods for the detection of latent *Mycobacterium tuberculosis* infection in refugee children. Thorax. 2010; 65:442–448. [PubMed: 20435869]
35. Méndez-Echevarría A, González-Muñoz M, Mellado MJ, et al. Interferon-γ release assay for the diagnosis of tuberculosis in children. Arch Dis Child. 2012; 97:514–516. [PubMed: 21543457]
36. Detjen AK, Keil T, Roll S, et al. Interferon-gamma release assays improve the diagnosis of tuberculosis and nontuberculous mycobacterial disease in children in a country with a low incidence of tuberculosis. Clin Infect Dis. 2007; 45:322–328. [PubMed: 17599309]
37. Moore, M.; Kozik, C.; Tracy, M., et al. Immigrants and refugee children with tuberculosis infection notifications, San Diego County, 2007–2008. Am J Respir Crit Care Med; Poster presentation at the American Thoracic Society International Conference; May 2009; 2009. p. A4104
38. Young J, O'Connor ME. Risk factors associated with latent tuberculosis infection in Mexican American children. Pediatrics. 2005; 115:e647–e653. [PubMed: 15930191]
39. Zwerling A, Behr MA, Verma A, et al. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011; 8:e1001012. [PubMed: 21445325]

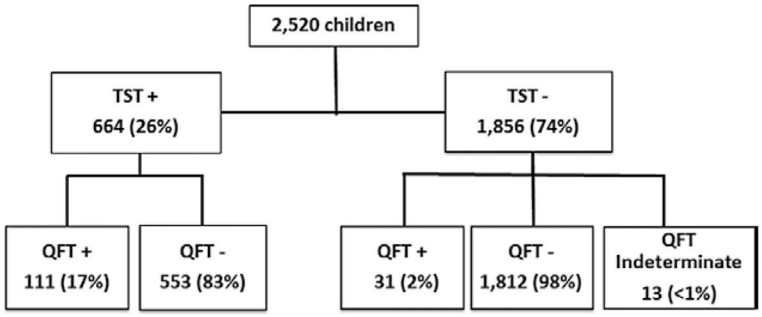

FIGURE 1.
QFT and TST results for all children within the study population.

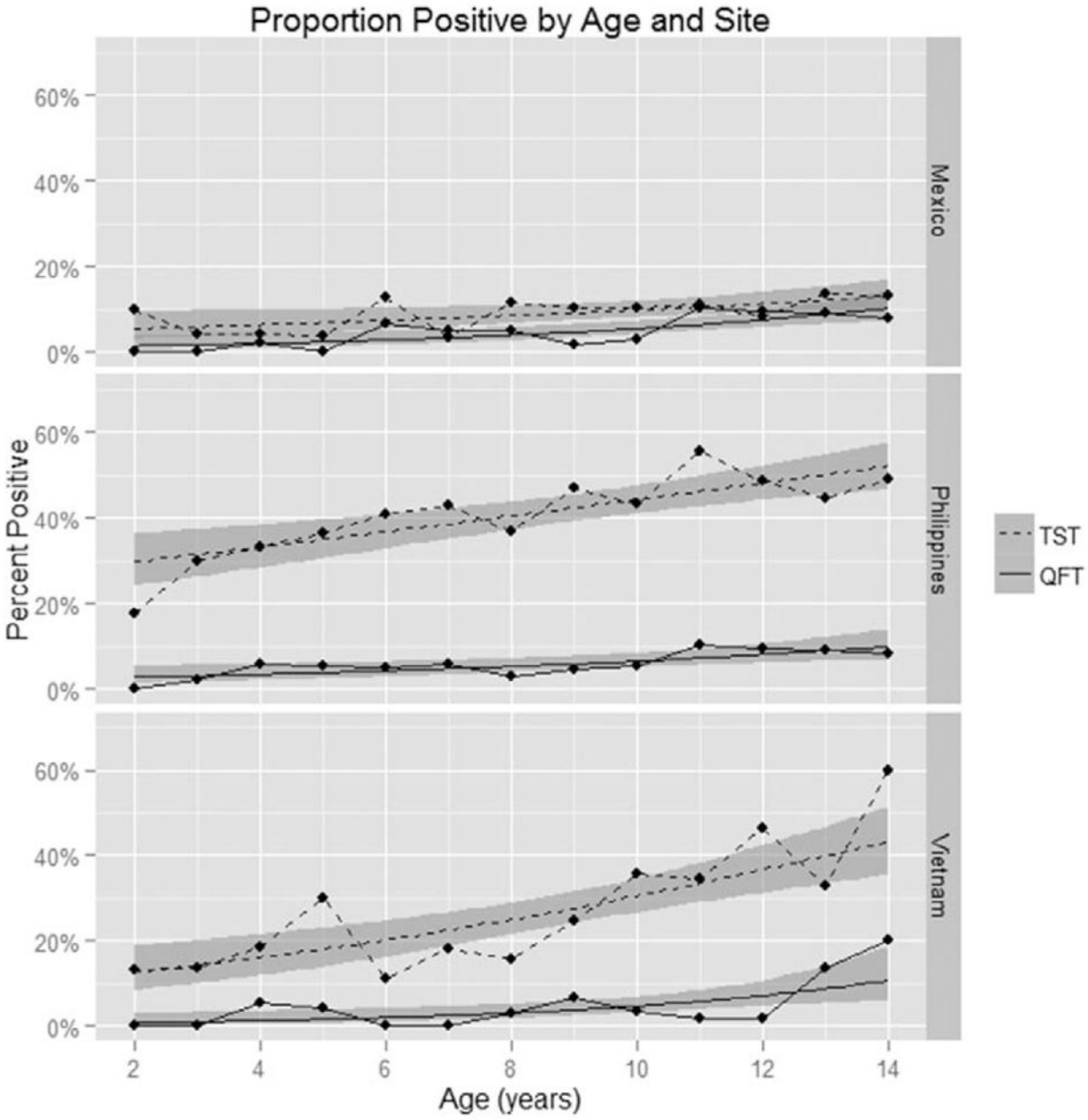

FIGURE 2.

Proportion of children testing positive, by age and country. The proportion who tested positive by age is denoted with a black dot. Dots are connected with a dashed line for TST and a solid line for QFT. Smoother lines (shaded CIs) are shown for each set of points.

TABLE 1

Demographics of Study Population by Country of Examination

Variable	Overall n (%)	Mexico n (%)	Philippines n (%)	Vietnam n (%)
Number of children	2520	970 (38.5%)	952 (37.8%)	598 (23.7%)
Age categories				
2- to 5-years old	512 (20.3)	162 (16.7)	212 (22.3)	138 (23.1)
6- to 9-years old	702 (27.9)	238 (24.5)	276 (29.0)	188 (31.4)
10- to 14-years old	1306 (51.8)	570 (58.8)	464 (48.7)	272 (45.5)
Male sex	1313 (52.1)	506 (52.2)	483 (50.8)	324 (54.2)
TB results in family members				
Family member with culture-confirmed TB	75 (3.0)	2 (0.2)	43 (4.5)	30 (5.0)
Family member was a TB suspect	288 (11.4)	26 (2.7)	182 (19.1)	80 (13.4)
All family members with normal CXR	2157 (85.6)	942 (97.1)	727 (76.4)	488 (81.6)

CXR indicates chest radiograph.

TABLE 2

Percentage of TST+ or QFT+ and Concordance between TST and QFT Results*

		QFT+	QFT−	% TST+	% QFT+	Agreement (%)	κ (95% CI)†
Overall	TST+	111 (4.4)	553 (22.1)	26.5	5.7	76.7	κ = 0.20 (0.16–0.24)
	TST−	31 (1.2)	1812 (72.3)				
Mexico	TST+	36 (3.8)	58 (6.1)	9.8	5.8	91.9	κ = 0.44 (0.34–0.54)
	TST−	20 (2.1)	845 (88.1)				
Philippines	TST+	52 (5.5)	354 (37.2)	42.7	6.3	62.0	κ = 0.13 (0.09–0.17)
	TST−	8 (0.8)	538 (56.5)				
Vietnam	TST+	23 (3.9)	141 (23.7)	27.5	4.4	75.9	κ = 0.18 (0.11–0.25)
	TST−	3 (0.5)	429 (72.0)				

*Excludes 13 children with indeterminate QFT results;

†Kappa statistic (κ) and 95% CIs.

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