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QuantiFERON®-TB Gold In-Tube for the detection of *Mycobacterium tuberculosis* infection in children with household tuberculosis contact

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SUMMARY

SETTING: Improved strategies are needed for detecting *Mycobacterium tuberculosis* infection in children in TB-endemic settings.

OBJECTIVE: To determine the prevalence of *M. tuberculosis* infection by tuberculin skin testing (TST) and by the QuantiFERON®-TB Gold In-Tube (QFT-GIT) test in children with an adult household contact with pulmonary TB in South Africa.

DESIGN: Cross-sectional study.

RESULTS: A total of 167 adult pulmonary TB cases (153/167, 92% human immunodeficiency virus [HIV] infected) and 270 pediatric contacts (median age 6 years, 14/270, 5% HIV-infected) were enrolled. All children completed QFT-GIT testing and 254 (94.1%) completed TST testing. Prevalence of *M. tuberculosis* infection was 28% (71/254, 95%CI 23–34) using TST (5 mm cut-off) and 29% (79/270, 95%CI 24–35) using QFT-GIT ($P = 0.49$). Agreement between TST and QFT-GIT was 81% (kappa 0.58). Nineteen (7%) QFT-GIT results were indeterminate. Children aged <2 years were more likely than older children to have indeterminate QFT-GIT results (aOR 5.7, 95%CI 1.5–22, $P = 0.01$) and discordant QFT-GIT and TST results (aOR 3.5, 95%CI 1.7–7.6, $P = 0.001$).

CONCLUSION: Prevalence of *M. tuberculosis* infection in pediatric contacts was high regardless of the diagnostic method used. TST should not be excluded for the detection of pediatric *M. tuberculosis* infection in this setting, but QFT-GIT may be a feasible alternative in children aged ⩾2 years.

KEY WORDS: tuberculosis; diagnosis; interferon-gamma release assay; latent tuberculosis

CHILDHOOD TUBERCULOSIS (TB) represents a sentinel event within a community, and usually indicates recent transmission from an adult with active pulmonary TB.[1] South Africa is experiencing an explosive human immunodeficiency virus (HIV) epidemic with attendant increases in TB caseloads, including children.[2] In young children, the risk of progression to active disease after *Mycobacterium tuberculosis* infection is high, and they are at risk for severe forms of TB that are associated with high morbidity and mortality. This underlies the need for early detection of *M. tuberculosis* infection in children.[3,4] South African guidelines currently recommend active contact tracing of children who are household contacts of adult TB cases, using tuberculin skin testing (TST) as part of the TB evaluation. Child contacts with a positive TST, as well as all contacts aged <5 years, are currently recommended to receive isoniazid preventive therapy (IPT) in South Africa, once active TB is excluded based on radiography and clinical symptoms.[5–7]

Interferon-gamma (IFN-γ) release assays (IGRAs) for the detection of *M. tuberculosis* infection rely on in vitro stimulation of lymphocytes with TB-specific antigens that are absent from bacille Calmette Guérin (BCG) vaccine and most non-tuberculous mycobacteria.[8] The QuantiFERON®-TB Gold In-Tube (QFT-GIT) test (Cellestis, Carnegie, VIC, Australia) is a commercially available whole blood IGRA. In contrast to TST, IGRAs require only one visit to obtain a result, and can be repeated over time without boosting.

Several issues about the use of IGRAs in children remain unresolved. Phlebotomy is difficult in small children, and may have an impact on the utility of IGRAs in this group of patients. Immunosuppression from malnutrition, HIV and/or young age may also affect responsiveness to antigens and mitogen in IGRA

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assays.[9] We performed a cross-sectional study with limited longitudinal follow-up in children who were household contacts of adults with newly diagnosed pulmonary TB. The primary objective was to determine and compare the prevalence of *M. tuberculosis* infection as assessed by TST and by QFT-GIT. Secondary objectives were to assess agreement between the two test methods and identify factors associated with various patterns of test results.

STUDY POPULATION AND METHODS

Adult pulmonary TB index cases and their children living in Soweto, South Africa, were enrolled between October 2006 and December 2009. Index cases were recruited from in-patient wards at Chris Hani Baragwanath Hospital and from a nearby referral hospital, as well as from a local community clinic. Eligibility criteria for adult TB index cases were age ⩾18 years, diagnosis of pulmonary TB within the preceding 3 months, presence in the home of at least one age-eligible child for whom the adult was the parent/legal guardian, willingness to have the child undergo study testing and provision of informed consent. For adult index cases, pulmonary TB diagnosis could be based on microbiological tests, histopathology, clinician diagnosis or a combination of these. Performance of diagnostic testing for adult TB suspects was not a component of this study, and diagnoses of pulmonary TB in the adult index cases were made by non-study clinicians. The study team reviewed medical records and interviewed adult index cases to corroborate the diagnosis. A diagnosis of pleural TB without other pulmonary involvement was insufficient for study inclusion. Pediatric contacts (of enrolled adult index cases) were included if they were aged ⩾6 months to ⩽16 years, and were excluded if they had prior diagnosis or treatment of active or latent TB. For the initial study visit, children were assessed at a single study clinic at Baragwanath Hospital; TST was read at this clinic or in the home.

For adult TB index cases, information was obtained through interview and review of medical records. For pediatric contacts, demographic, medical (including BCG vaccination history), and TB exposure information was collected through interview of the enrolled parent/guardian. Index cases were asked questions about the duration of their cough, and duration of daytime/nighttime exposure to pediatric contacts. Nutritional status of children was assessed using anthropometric measures (weight-for-length/height); *Z*-scores for children aged ⩽60 months were calculated using the World Health Organization international child growth reference standards.[10] Children were inspected for a BCG vaccination scar (in South Africa, the BCG policy is to administer one dose at birth). HIV testing was performed; children aged ⩽18 months underwent HIV DNA polymerase chain reaction, and rapid HIV enzyme-linked immunosorbent assay (ELISA) with confirmatory Western blot was used for older children. Treatment for active and/or latent TB was not a component of this study; however, children who met any of the following criteria were referred to local sources of medical care: signs and/or symptoms of active TB, positive TST and/or QFT-GIT, positive HIV test, or age <5 years. For all children, a follow-up visit was attempted at 6 months after enrollment. Information about interval TB diagnosis and treatment for active and latent TB for the child was obtained by interviewing the parent/guardian.

Tuberculin skin testing

TST was performed at enrollment on all pediatric contacts using the Mantoux method. Tuberculin purified protein derivative (PPD) RT-23 (2 units, Statens Serum Institut, Copenhagen, Denmark) was injected subcutaneously into the left forearm and the test was read 48–96 h later. An induration of ⩾5 mm was considered a positive test during the study, as per American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America TB guidelines for TB contacts.[11]

QFT-GIT testing

All children underwent QFT-GIT testing 5–30 min after TST placement. Blood was drawn from the right arm. QFT-GIT testing was performed according to the manufacturer's instructions, and included nil control, mitogen control and TB antigen tubes. Assays were conducted in a single laboratory at the study site by the same trained technician. Average interval between blood collection and initiation of incubation was 8.3 min (median 5, range 2–60, interquartile range 3–10). Following stimulation and centrifugation, harvested plasma specimens were stored at 4°C for up to 28 days prior to ELISA testing. Results were calculated and interpreted by the assay software as positive, negative or indeterminate.

Statistical considerations

The primary objective of the study was to estimate the prevalence of *M. tuberculosis* infection in children with household TB contact. The expected proportion of children with *M. tuberculosis* infection was 0.40. A sample size of 164 children was required to estimate a 95% confidence interval (95%CI) for the prevalence of 40% ± 7.5%. Sample size was increased to account for potential clustering, drop-out, and potential technical problems with TST or QFT-GIT. For study implementation and primary analysis, an induration of ⩾5 mm was considered a positive TST. Secondary analyses used a TST cut-off of 10 mm, as per South African guidelines, induration of respectively ⩾5 mm or ⩾14 mm is considered supportive of TB infection, for HIV-infected and non-HIV-infected children.[7] Data were entered in Microsoft Access by one

investigator (Microsoft, Redmonds, WA, USA), and verified by a second investigator using source documents. Data were analyzed using STATA (version 10.1, StataCorp, College Station, TX, USA). Concordance between QFT-GIT and TST results was assessed using the kappa (κ) statistic. Categorical data were compared using χ^2 and McNemar's tests. Factors associated with QFT-GIT and TST results were assessed using univariate and multivariate logistic regression analysis, with robust variance and clustering on index cases. Covariates for multivariate analysis were based on stepwise selection ($P < 0.3$) or clinical importance. Regression analyses were performed separately for index case factors and pediatric contact factors.

The study was approved by ethics committees at the University of the Witwatersrand and the Johns Hopkins University School of Medicine. Written, witnessed informed consent (and assent for children aged ⩾7 years) was obtained at enrollment in the subjects' preferred language.

RESULTS

A total of 167 adult index TB cases and 270 pediatric contacts were enrolled (Figure 1). The median and mean number of enrolled pediatric contacts per adult index case were respectively 2 and 2.0 (range 1–5). The majority of adult index cases were HIV-infected women (Table 1). Approximately half of the index cases had microbiologically confirmed TB (sputum smear- and/or culture-positive), with the remainder diagnosed based on clinical and radiologic findings. Among pediatric contacts, 52% were female, the median age was 6 years (range 6 months–16 years), 42% were aged <5 years, and most (95%) were BCG-vaccinated. Few children (14/270, 5%) tested positive for HIV infection. Only 2/270 children (0.7%) reported having weight loss, and none reported fever lasting >2 weeks, cough lasting >2 weeks or pneumonia in the preceding 6 months. None were referred by study staff for active TB based on signs and/or symptoms. Ninety-four children were referred for further evaluation for a positive TST and/or QFT-GIT test, 14 were referred for a positive HIV test, and an additional 74 were referred for age <5 years but no positive test. A 6-month follow-up visit was completed for 196/270 (72.5%) children, and the remainder were lost to follow-up. At the time of follow-up, 37/196 (19%) were receiving treatment for active TB and 19/196 (10%) were receiving treatment for latent TB infection, as reported by the parent/guardian.

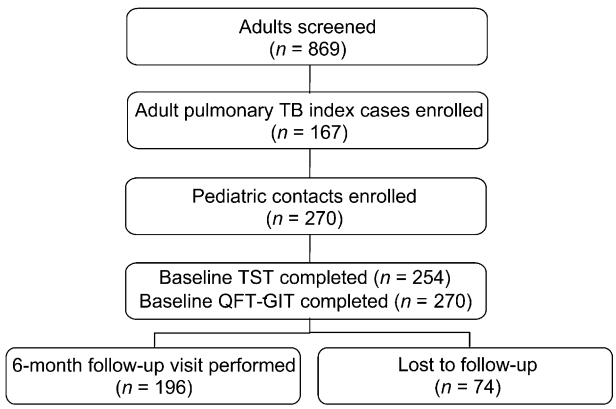

Figure 1 Flow diagram for study participants. TB = tuberculosis; TST = tuberculin skin test; QFT-GIT = QuantiFERON®-TB Gold In-Tube.

Table 1 Characteristics of study participants at enrollment

Characteristic	Adult index cases (*n* =167) *n* (%)	Pediatric contacts (*n* =270) *n* (%)
Sex		
Female	117 (70)	141 (52)
Male	50 (30)	129 (48)
Age, years		
Median [IQR]	34 [30–40]	6 [3–9]
<2	NA	51 (19)
2–5	NA	76 (28)
6–10	NA	91 (34)
>10	NA	52 (19)
Ethnicity		Not obtained
African/Black	160 (96)	
Colored/mixed race	5 (3)	
Unspecified or other	2 (1)	
HIV		
Infected	153 (92)	14 (5)
Non-infected	4 (2)	251 (93)
Unknown	10 (6)	5 (2)
TB diagnosis category		NA
Smear-positive TB (positive sputum AFB smear)	68 (41)	
Smear-negative TB (positive sputum culture, negative smear)	19 (11)	
Clinical TB (culture- and smear-negative)	80 (48)	
Median weight-for-age *Z* score [IQR]*	NA	0.13 [–0.86–0.97]
Median weight-for-height *Z* score [IQR]*	NA	1.3 [–0.05–2.14]
Median height-for-age *Z* score [IQR]*	NA	–1.44 [–2.8––0.5]
BCG vaccinated per report of parent/guardian	NA	257 (95)

*For children aged ⩽60 months.
HIV = human immunodeficiency virus; TB = tuberculosis; IQR = interquartile ratio; NA = not available; BCG = bacille Calmette-Guérin.

Results of baseline testing

Among 270 enrolled pediatric contacts, all (100%) completed QFT-GIT testing, while only 254 (94.1%) completed TST testing ($P < 0.001$). The estimated prevalence of *M. tuberculosis* infection was 28% (71/254, 95%CI 23–34) using TST with a 5 mm cut-off for positivity, and 29% (79/270, 95%CI 24–35) using QFT-GIT ($P = 0.49$). Overall, 35% of children were positive by either the QFT-GIT or the TST test

Table 2 Baseline TST and QFT-GIT test results for pediatric contacts

	TST-positive *n* (%)	TST-negative *n* (%)	Total *n* (%)
5 mm cut-off for TST positivity			
QFT-GIT-positive	56 (22)	19 (8)	75 (30)
QFT-GIT-negative	12 (5)	149 (59)	161 (63)
QFT-GIT-indeterminate	3 (1)	15 (6)	18 (7)
Total*	71 (28)	183 (72)	254
10 mm cut-off for TST positivity			
QFT-GIT-positive	48 (19)	27 (11)	75 (30)
QFT-GIT-negative	7 (3)	154 (61)	161 (63)
QFT-GIT-indeterminate	2 (1)	16 (6)	18 (7)
Total*	57 (22)	197 (78)	254

*TST testing was not completed for 16 children. Of these 16, four were QFT-GIT-positive, 11 were QFT-GIT-negative and 1 was QFT-GIT-indeterminate.
TST = tuberculin skin test; QFT-GIT = QuantiFERON®-TB Gold In-Tube.

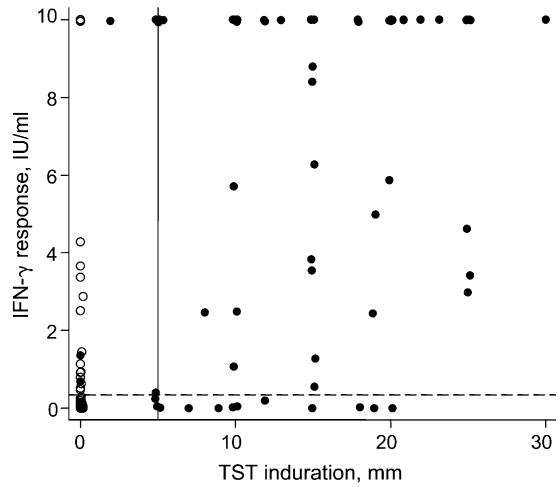

Figure 2 QFT-GIT vs. TST results. Quantitative TST and QFT-GIT baseline results for individual pediatric study participants for whom results for both tests were available. The solid line represents the cut-off (5 mm) for a positive TST, and the dashed line represents the cut-off for a positive QFT-GIT. QFT-GIT responses > 10 IU/ml are shown as 10 IU/ml to preserve the scale. IFN-γ = interferon-gamma; IU = international unit; TST = tuberculin skin test; QFT-GIT = QuantiFERON®-TB Gold In-Tube.

(94/270, 95%CI 29–41). Baseline results for TST and QFT-GIT are shown in Table 2. There was 'moderate agreement' of 81% between TST (5 mm cut-off) and QFT-GIT results (κ 0.58). Among the 49 children with discordant TST (5 mm cut-off) and QFT-GIT results, 19 (39%) were QFT-GIT positive/TST-negative, 12 (25%) were QFT-GIT-negative/TST-positive, 15 (30%) were QFT-GIT indeterminate/TST-negative and 3 (6%) were QFT-GIT indeterminate/TST-positive (Table 2). Among the 14 HIV-infected children, 6/14 (43%) were positive by QFT-GIT vs. 4/14 (29%) by TST using 5 mm cut-off for positivity ($P = 0.5$). Among 37 children being treated for active TB at follow-up, baseline QFT-GIT positivity was 29/37 (78%) and TST positivity (5 mm cut-off) was 27/36 (75%). As shown in Figure 2, among individuals with discordant results by QFT-GIT and TST, the quantitative values for both tests were evenly distributed over a wide range, with little clustering near the respective cut-offs for test positivity.

When a TST induration of ⩾10 mm was considered positive, the estimated *M. tuberculosis* prevalence was 22% (57/254, 95%CI 0.17–0.28). Using this higher TST threshold, there was a significant difference in estimated *M. tuberculosis* infection prevalence between TST and QFT-GIT (22% vs. 29%, respectively, $P = 0.002$), with agreement of 79% and κ of 0.54. Among 52 children with discordant TST (10 mm cut-off) and QFT-GIT results, 27 (52%) were QFT-GIT-positive/TST-negative, 7 (13%) were QFT-GIT negative/TST-positive, 16 (31%) were QFT-GIT-indeterminate/TST-negative, and two (4%) were QFT-GIT-indeterminate/TST-positive. Of note, among the 14 HIV-infected children, 10 had a TST induration of 0 mm; the remaining four children had a TST induration >15 mm and were therefore included in the analysis that used a cut-off threshold of 10 mm induration.

Nineteen (7%) children had an indeterminate QFT-GIT result. Among these 4/19 (21%) were aged <2 years, 10/19 (53%) were aged 2–5 years, 4/19 (21%) were aged 6–10 years, and 1/19 (5%) were >10 years.

An exploration of factors associated with a positive TST or QFT-GIT was undertaken. There was a significant association between adult index case smear status (including degree of smear positivity) and positive TST (5 mm cut-off) and positive QFT-GIT (Table 3). Index case age, sex, duration of cough, daytime duration of exposure, and nighttime exposure to pediatric contacts were not associated with a positive QFT-GIT or TST result. Of pediatric factors assessed, only age > 10 years was significantly associated with a positive QFT-GIT (aOR 3.3, 95%CI 1.2–8.6, $P = 0.018$); no pediatric factors were associated with a positive TST (Table 4). There were no associations between anthropometric *Z*-scores and either QFT-GIT or TST results. The associations found in regression analysis between index and pediatric factors and TST positivity did not change when using a higher threshold of 10 mm for TST positivity.

Factors listed in Tables 3 and 4 were also assessed for association with discordance between TST and QFT-GIT results, and for association with indeterminate QFT-GIT results. Using a 5 mm cut-off for TST positivity, children aged <2 years were more likely than older children to have discordant QFT-GIT and TST results (aOR 3.5, 95%CI 1.7–7.6, $P = 0.001$), but there were no other significant associations. Among children aged <2 years with discordant results, there was an even distribution in the direction of discordance; 5/14 (36%) were QFT-GIT-positive/TST-negative, 5/14 (36%) were QFT-GIT-negative/TST-positive, and 4/14 (29%) were QFT-GIT-indeterminate/

Table 3 Adult index case factors associated with a baseline positive QFT-GIT or TST*

	QFT-GIT			TST (5 mm cut-off for positivity)		
	n positive/ *N* (%)	OR (95%CI)	aOR (95%CI)	*n* positive/ *N* (%)	OR (95%CI)	aOR (95%CI)
Adult index case age, years						
18–25	9/23 (39)	Reference	Reference	8/22 (36)	Reference	Reference
26–35	36/130 (28)	0.59 (0.25–1.4)	0.91 (0.30–2.8)	33/126 (26)	0.62 (0.21–1.8)	0.83 (0.20–3.5)
36–45	24/90 (27)	0.57 (0.23–1.4)	0.84 (0.25–2.9)	24/82 (29)	0.72(0.24–2.2)	1.6 (0.36–7.4)
>45	10/27 (37)	0.91 (0.29–2.9)	2.0 (0.42–9.2)	6/24 (25)	0.58 (0.13–2.6)	1.4 (0.20–9.7)
Adult index case sex						
Male	21/73 (29)	Reference	Reference	22/68 (32)	Reference	Reference
Female	58/197 (29)	1.0 (0.5–1.9)	1.8 (0.81–3.8)	49/186 (26)	0.75 (0.37–1.5)	1.2 (0.50–2.7)
Adult index case HIV status						
Infected	70/249 (28)	0.29 (0.05–1.7)	0.24 (0.02–2.9)	61/233 (26)	0.26 (0.05–1.5)	0.23 (0.03–1.9)
Non-infected	4/7 (57)	Reference	Reference	4/7(57)	Reference	Reference
Adult index case type of TB diagnosis						
Smear-positive TB	39/113 (34)	Reference	Reference	41/105 (39)	Reference	Reference
Smear-negative, culture-positive TB	3/34 (9)	0.18 (0.05–0.7)†	0.84 (0.09–7.8)	3/31 (10)	0.17 (0.05–0.6)†	2.7 (0.56–13)
Clinical TB	37/123 (30)	0.81 (0.45–1.5)	3.9 (0.67–23.5)	27/118 (23)	0.46 (0.24–0.89)	—
Adult index case smear grade						
Negative	27/115 (42)	Reference	Reference	21/108 (19)	Reference	Reference
Scanty	1/12 (8)	0.3 (0.05–1.6)	—	0/11 (0)	—	—
1+	16/50 (32)	1.5 (0.7–3.6)	5.5 (0.89–34.7)‡	19/47 (40)	2.81 (1.2–6.7)§	7.9 (1.5–41)¶
2+	6/19 (32)	1.5 (0.5–4.9)	8.7 (1.2–62)‡	7/17 (41)	2.9 (0.8–10.6)	15.7 (2.6–92)¶
3+	16/32 (50)	3.2 (1.4–7.4)#	11.4 (1.8–72)‡	15/30 (50)	4.1 (1.5–11.1)§	11.7 (2.2–62)¶
Exposure to index case during the day						
Minority of day (< 6 h)	32/113 (28)	Reference	Reference	29/110 (26)	Reference	Reference
Majority of day (> 7 h)	46/154 (30)	1.1 (0.63–1.8)	1.3 (0.69–2.3)	42/141 (30)	1.2 (0.67–2.1)	1.1 (0.58-2.1)

*TST: 5 mm induration defined as a positive test. Other factors considered in the univariate analysis that were not statistically significant and not shown in the tables included nighttime exposure to index case, number of bedrooms in house, number of adults living in the household, and duration of cough for the adult.
†$P = 0.008$ (QFT-GIT), $P = 0.006$ (TST).
‡$P = 0.067$, 0.030, <0.0001, respectively, for 1+, 2+, and 3+; 'scanty' dropped from the regression.
§$P = 0.02$, 0.005 for 1+ and 3+, respectively; 'scanty' dropped from the regression.
¶$P = 0.013$, 0.002, 0.004 for 1+, 2+, and 3+, respectively; 'scanty' dropped from the regression.
#$P = 0.005$.
QFT-GIT = QuantiFERON®-TB Gold In-Tube; TST = tuberculin skin test; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; TB = tuberculosis.

Table 4 Pediatric factors associated with a baseline positive QFT-GIT or TST*

	QFT-GIT			TST (5 mm cut-off)		
	n positive/ total (%)	OR (95%CI)	aOR (95%CI)	*n* positive/ total (%)	OR (95%CI)	aOR (95%CI)
Pediatric contact: age, years						
<2	10/51 (20)	Reference	Reference	9/46 (20)	Reference	Reference
2–5	24/76 (32)	1.9 (0.82–4.4)	2.0 (0.84–5.1)	23/73 (32)	1.9 (0.78–4.6)	1.5 (0.61–3.9)
6–10	24/91 (26)	1.5 (0.65–3.3)	1.6 (0.68–3.7)	21/87 (24)	1.3 (0.56–3.1)	1.2 (0.50–2.9)
>10	21/52 (38)	2.8 (1.1–7.3)†	3.3 (1.2–8.6)‡	18/48 (38)	2.5 (0.92–6.6)	2.4 (0.85–6.6)
Pediatric contact: sex						
Male	41/129 (32)	Reference	Reference	32/121 (26)	Reference	Reference
Female	38/141 (27)	0.79 (0.44–1.4)	0.77 (0.42–1.5)	39/133 (29)	1.2 (0.63–2.1)	1.1 (0.57–2.0)
Pediatric contact: HIV status						
Infected	6/14 (43)	1.8 (0.63–5.5)	2.4 (0.65–8.7)	4/14 (29)	1.0 (0.3–3.5)	1.1 (0.30–4.4)
Non-infected	72/251 (29)	Reference	Reference	65/235 (28)	Reference	Reference
Pediatric contact: BCG vaccination status						
Vaccinated	75/257 (29)	Reference	Reference	68/243 (28)	Reference	Reference
Not vaccinated	2/5 (40)	1.6 (0.21–12.5)	1.2 (0.12–12)	2/4 (50)	2.6 (0.35–19)	1.9 (0.25–15.1)
Pediatric contact: weight for height Z score			—			—
$Z < -2$	1/3 (33)	1.3 (0.11–15)		0/2 (0)	—	
$-2 > Z < 2$	20/71 (29)	Reference		19/69 (28)	Reference	
$Z > 2$	6/29 (21)	0.67 (0.24–1.9)		8/27 (30)	1.1 (0.4–2.9)	

*A TST induration of 5 mm was used as the cut-off point for test positivity. Other factors considered in the univariate analysis that were not statistically significant and not shown in the tables included height for age *Z* score and weight for age *Z* score.
†$P = 0.038$ for age > 10 years.
‡$P = 0.018$.
QFT-GIT = QuantiFERON®-TB Gold In-Tube; TST = tuberculin skin test; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; HIV = human immunodeficiency virus; BCG = bacille Calmette-Guérin.

TST-negative. When indeterminate QFT-GIT results were excluded, age < 2 years continued to be the only significant risk factor for discordant results (aOR 3.22, 95%CI 1.3–7.7, $P = 0.007$). Age remained the only covariate significantly associated with discordance using a higher TST threshold for positivity of 10 mm (aOR 2.34, 95%CI 1.07–5.1, $P = 0.03$). The HIV status of the child was not associated with discordant results regardless of threshold for TST positivity (aOR 1.2, 95%CI 0.34–4.6 and aOR 1.02, 95%CI 0.26–4.0) for 5 mm and 10 mm TST cut-offs, respectively). In multivariate analysis, only pediatric contacts aged <2 years were found to have increased odds of having an indeterminate QFT-GIT result (aOR 5.7, 95%CI 1.5–22.0, $P = 0.01$). No index case factors or other pediatric factors were associated with an indeterminate QFT-GIT result.

DISCUSSION

The prevalence of *M. tuberculosis* infection among pediatric contacts of adult TB cases was similar as assessed by QFT-GIT or TST (5 mm induration cut-off). However, significantly more children would be identified with *M. tuberculosis* infection by QFT-GIT compared to TST if a higher threshold of 10 mm was used to define TST positivity, as is currently recommended in some settings, including South Africa. At the individual level, there was reasonable agreement between TST and QFT-GIT in our pediatric cohort, consistent with other studies.[12–15] Despite concerns about the challenges of phlebotomy in children, all children were able to provide specimens adequate for QFT-GIT testing. It should be noted, however, that children aged <6 months—perhaps the most challenging age group in which to successfully draw blood—were not included in this study, which was performed by a trained, well-equipped, study-dedicated research staff; these factors likely contributed to the success of phlebotomy. Unlike other studies using QFT-GIT in children, we did not have a high proportion of indeterminate tests.[16–18] Importantly, approximately 30% of the pediatric contacts of adult index TB cases had a positive QFT-GIT test, underscoring the potentially high prevalence of TB infection in this population.[19–22]

An extensive evaluation was conducted to examine the potential association between index case and pediatric factors, and positive QFT-GIT and TST results in pediatric contacts. Interestingly, index case sputum smear status was the only index case factor associated with positive TST and QFT-GIT results in pediatric contacts, consistent with the hypothesis of increased TB transmission resulting from higher degrees of smear-positive disease. We did not find an association between malnutrition and QFT-GIT results, as has been demonstrated elsewhere with IGRAs, but our analysis was limited by the small number of undernourished children in our study.[9] Age > 10 years appeared to be associated with a positive QFT-GIT result among pediatric contacts, and may represent either improved test performance in this age group, or potentially a greater propensity for TB infection with increased age, both due to and independently of household contact.

Interpretation of discordance between the tests remains challenging. While some have suggested that discordance occurs more frequently in those who have IFN-γ or TST values around their respective cut-off points for test positivity, we did not find this to be the case.[19] It was notable, however, that children aged <2 years were more likely to have discordant TST and QFT-GIT results in our study, and that there was a substantial reduction in discordance with increasing age. The reasons for these findings are unclear, but may be related to effects of BCG vaccination in young infants, indeterminate QFT-GIT results in the youngest children, immune functional status, or the nature of pediatric TB infection. Interestingly, there was an even distribution in the direction of discordance between TST and QFT-GIT tests, suggesting that both TST and QFT-GIT tests should be interpreted with caution in very young children. While the overall proportion of children with an indeterminate result by QFT-GIT testing was low (7%) in our study, we found that the youngest children were significantly more likely than older children to have an indeterminate result. This age-related association has been reported in TB-endemic and non-endemic settings as well as in healthy and immunocompromised children.[16,23–25] While the relatively few HIV-infected children included in this study precluded our drawing definitive conclusions, we note that there was a greater proportion of HIV-infected children positive by QFT-GIT compared to TST, although the difference was not statistically significant.

Our study had several limitations. First, we were unable to obtain information on a microbiologic diagnosis of TB for every adult index case, and almost half had been diagnosed with TB based on clinical and radiographic findings. This situation is not uncommon in resource-limited settings. Second, 74 pediatric contacts (27% of the initial enrolled cohort) did not return for a follow-up study visit at 6 months and therefore we were not able to ascertain whether treatment for active or latent TB in these contacts had been administered. Third, our study was not designed to assess test sensitivity for active TB in the pediatric contacts, and methods used to determine active TB status after medical referrals were unknown.

CONCLUSIONS

The estimated prevalence of latent TB infection in pediatric contacts of adult TB cases in Soweto was high, regardless of the method used for diagnosis. QFT-GIT was feasible in this setting, although our

results suggest that TST need not be excluded as a tool for detection of pediatric TB infection despite a high rate of BCG vaccination. Caution should be used, however, in interpreting QFT-GIT and TST results in children aged <2 years.

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RÉSUMÉ

CONTEXTE : Dans les contextes où la tuberculose (TB) est endémique, une amélioration des stratégies s'impose pour la détection de l'infection par *Mycobacterium tuberculosis* chez les enfants.

OBJECTIF : En Afrique du Sud, détermination de la prévalence de l'infection *M. tuberculosis* par le test cutané tuberculinique (TST) et par le test QuantiFERON®-TB Gold In-Tube (QFT-GIT) chez les enfants en contact dans le ménage avec un sujet adulte souffrant de TB.

SCHÉMA : Etude transversale.

RÉSULTATS : On a enrôlé dans l'étude 167 cas de TB pulmonaire chez l'adulte (153/167 ; 92% infectés par le VIH) ainsi que 270 sujets-contact pédiatriques (âge médian 6 ans ; 14/270 ; 5% infectés par le VIH). L'ensemble des enfants ont bénéficié du test QFT-GIT et 254 (94,1%) ont eu un test TST complet. La prévalence de l'infection *M. tuberculosis* a été de 28% par le TST (71/254 ; IC95% 23–34) et de 29% par le QFT-GIT (79/270 ; IC95% 24–35) ($P = 0,49$). Le degré de concordance entre TST et QFT-GIT a été de 81% (kappa 0,58). Il y a eu 19 résultats indéterminés du QFT-GIT (7%). Les enfants âgés de <2 ans sont plus susceptibles que les enfants plus âgés d'avoir des résultats indéterminés du QFT-GIT (aOR 5,7 ; IC95% 1,5–22 ; $P = 0,01$) ainsi que des discordances entre les résultats du QFT-GIT et du TST (aOR 3,5 ; IC95% 1,7–7,6 ; $P = 0,001$).

CONCLUSION : Chez les sujets-contact pédiatriques, la prévalence de l'infection *M. tuberculosis* est élevée, quelle que soit la méthode de diagnostic utilisée. Il ne faut pas rejeter le TST pour la détection de l'infection d'infection *M. tuberculosis* pédiatrique dans ce contexte, mais le QFT-GIT peut être une alternative acceptable chez les enfants âgés de ⩾2 ans.

RESUMEN

MARCO DE REFERENCIA: Se precisan mejores estrategias de detección de la infección por *Mycobacterium tuberculosis* en los niños de entornos donde la tuberculosis (TB) es endémica.

OBJETIVO: Determinar la prevalencia de infección tuberculosa mediante la prueba cutánea de la tuberculina (TST) y la prueba del QuantiFERON®-TB Gold en tubo (QFT) en los niños de hogares con un contacto de TB pulmonar en Sudáfrica.

MÉTODO: Fue este un estudio transversal.

RESULTADOS: Participaron en el estudio 167 adultos con TB pulmonar (153 de ellos, [92%] infectados por el virus de la inmunodeficiencia humana [VIH]) y 270 contactos pediátricos (mediana de la edad 6 años y 14 de ellos [5%] infectados por el VIH). En todos los niños se practicó la prueba del QFT y 254 (94,1%) completaron la prueba tuberculínica. La prevalencia de infección tuberculosa fue 28% (71 de 254; IC95% 23–34) con base en la reacción a la tuberculina (valor discriminatorio 5 mm) y 29% (79 de 270; IC95% 24–35) según la prueba del QFT ($P = 0,49$). La concordancia entre las pruebas fue de 81% (índice kappa 0,58). Diecinueve (7%) resultados de la prueba QFT no fueron concluyentes. Los niños de <2 años de edad exhibieron mayor probabilidad de obtener resultados no concluyentes en la prueba QFT que los niños mayores (OR ajustado 5,7; IC95% 1,5–22; $P = 0,01$) y presentaron también mayor probabilidad de obtener resultados discordantes entre ambas pruebas (ORa 3,5; IC95% 1,7–7,6; $P = 0,001$).

CONCLUSIÓN: La prevalencia de infección tuberculosa en los contactos pediátricos fue alta, independientemente del método diagnóstico utilizado. En estos entornos, no se debe excluir la prueba TST de la detección de la infección tuberculosa en los niños, pero la prueba del QFT podría constituir una opción viable en los niños a partir de los 2 años de edad.