The Role of Chest Radiographs and Tuberculin Skin Tests in Tuberculosis Screening of Internationally Adopted Children

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Background: Internationally adopted children (IAC) are a growing group of US immigrants who often come from countries with high tuberculosis (TB) burdens. There is limited evidence to support current TB screening guidelines in these high-risk children. Therefore, we have prospectively examined the clinical utility of tuberculin skin testing (TST) and subsequent chest radiograph screening for TB disease in recently immigrated, asymptomatic IAC.

Methods: Within 6 months of immigration to the United States, we collected demographic information and assessed the nutritional status of 566 IAC who presented for routine postadoptive care. Children completed standardized clinical examination and TSTs. Chest radiographs were recommended for children with TST induration ≥5 mm. The association between TST induration and clinical outcome was assessed. The clinical utility of chest radiographs was evaluated.

Results: There was no difference in age, birth country, or nutritional status between IAC with TST induration of 0 to <5 mm and those with 5 to <10 mm; IAC with TST ≥10 mm were older, more chronically malnourished, and more likely to emigrate from Guatemala. Among children with TST ≥5 mm (35%), 4 IAC had chest radiographs which were initially interpreted to be abnormal and consistent with TB; ultimately none were diagnosed with TB.

Conclusions: The 5-mm TST cut point did not capture IAC with risk factors for latent TB infection or progression to TB disease, suggesting that this is not a useful screening threshold. In contrast, a 10-mm cut point identified IAC at risk for TB infection and therefore should be a more useful screening threshold. We question the clinical utility of radiographic screening for pulmonary TB in asymptomatic children.

Key Words: tuberculosis, latent tuberculosis, international adoption, tuberculosis screening, pediatrics

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In 2008, 9.4 million people contracted tuberculosis (TB) and 1.3 million people died of the disease worldwide.[1] Epidemiologic data indicate that childhood TB constitutes approximately 5% and 20% of TB cases in low- and high-burden countries, respectively.[2] In the United States, 6% to 7% of TB cases are in children ≤14 years of age.[3]

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Between 1993 and 2004, there was a 5% annual increase in the number of reported cases of TB in foreign-born persons in the United States.[4] In 2007, CDC revised the Tuberculosis Screening and Treatment Technical Instructions for Panel Physicians. In a selection of countries, these guidelines are currently being implemented to ensure that immigrants of all ages complete some level of screening for *Mycobacterium tuberculosis* (*M.tb*) infection and TB disease in their birth country before immigration.[5] In 2008, the TB disease case rate was 10 times higher in foreign-born persons in the United States than in natives.[6] In that same year, over 17,000 internationally adopted children (IAC) joined US families. This growing group of US foreign-born persons is also advised to complete more rigorous screening after immigration, to ensure that we capture children with recent *M.tb* infection or TB disease progression.[7] Screening aids in the early identification of children with latent TB infection (LTBI) and active TB, and enables the delivery of preventative and curative treatment to limit the spread of *M.tb.*

The risk for LTBI increases in children who were foreign born, have visited countries with high TB burdens, or have been in contact with infectious adults.[8,9] Although the risk of LTBI increases with age,[10] the risk for progression from LTBI to active TB is more significant for younger,[11] immunocompromised, malnourished, or chronically diseased children.[12] IAC have a high prevalence of LTBI (0.6%–19%) that increases with age.[13–17] In addition, IAC have significant risk for disease progression due to their young age and typically malnourished states.[16] Therefore, IAC are prime targets for TB screening.

TB diagnosis in children hinges on history of TB exposure, clinical signs and symptoms, tuberculin skin tests (TSTs) or interferon gamma release assays, and radiographic findings.[18] However, clinical history in IAC is often limited and of questionable validity. Therefore, screening for LTBI by TST plays a critical role in this unique at-risk population.

A child's risks for LTBI and progression to TB disease are considered when interpreting TST results.[7] Due to the presence of numerous risk factors, a TST induration ≥10 mm should be considered positive in IAC. Adoption health specialists have questioned whether the use of a 5-mm cut point for a positive TST in IAC is justified, given the uncertainty surrounding IAC's TB exposure and their increased risk of progression to disease if they had been exposed.[19] However, the use of a 5-mm cut point would result in the decreased specificity of the TST because of post-BCG cross reactivity.[16,17] Therefore, our international adoption clinic has elected to obtain chest radiographs to rule out pulmonary TB when TST indurations are ≥5 mm but treat for LTBI when TST indurations are ≥10 mm. Although conservative, this treatment strategy can result in false-positive chest radiographs that may result in unnecessary treatment and additional evaluations.

With more than a decade of clinical experience with this population, we question the appropriate TST induration size that should trigger chest radiographic screening in asymptomatic IAC and the general clinical utility of such chest radiographs. In light of recently revised CDC guidelines which place great emphasis on

screening through TST and chest radiographs, these questions are highly relevant. Therefore, we completed a cross-sectional study to evaluate the clinical usefulness of using a 5-mm TST cut point as the threshold beyond which further chest radiographic screening for TB disease is done in asymptomatic IAC. The study also assessed the relationship between documented chest radiograph readings and TST indurations in the same population.

METHODS

Study Design and Population

We completed a prospective cross-sectional study of TB screening in immigrant children at the Adoption Health Services (AHS) of Rainbow Babies and Children Hospital in Cleveland, Ohio. The AHS is a multispecialty clinic which provides services for children involved in domestic and international adoptions. The majority of patients seek care independent of referral from a primary care physician. All IAC who presented to the AHS (between August 2000 and June 2009) for postadoptive care within 6 months of arrival in the United States and had a TST placed by AHS clinic staff were eligible for inclusion in the study. The study was approved by the Institutional Review Board of University Hospitals Case Medical Center.

Measures

At the time of each child's TST placement, we recorded their gender, birth country, and age; conducted a physical examination; and measured their weight, stature, or length, and head circumference. The recumbent length was measured for children <24 months and the stature was measured for children ≥24 months.[20] Weight-for-height (WHZ) and height-for-age Z (HAZ) scores were calculated using the 2000 CDC growth chart reference population. WHZ scores were used to assess wasting (acute malnutrition) and HAZ scores were used to assess stunting (chronic malnutrition).[21] Z score indicators of nutritional status are valid in children who are ≤10 years old.[21] A Z score <-2 but >-3 signifies moderate malnutrition and a Z score <-3 signifies severe malnutrition.[22]

Using the Mantoux method, 5 tuberculin units of Purified Protein Derivative (Tubersol [5 TU/0.1 mL], Connaught, Swiftwater, PA) were placed intradermally on the left forearm of each IAC. The transverse diameter of induration was then measured in millimeters using the "ball-point" technique within 48 to 72 hours.[23] Intraobserver validation studies were completed among clinic staff throughout the study to limit reader bias. IAC with initial TST <5 mm within 3 months of arrival in the United States were advised to receive a repeat TST in 6 months to minimize the likelihood of false negatives due to malnutrition on arrival. All IAC with TST ≥5 mm on initial TB screening were advised to complete a chest radiograph as part of routine clinical care. For analytic purposes, chest radiographs that had no signs of pathology or active TB disease were categorized as "Normal." Chest radiographs that had signs of pulmonary TB disease such as mediastinal and hilar lymphadenopathy,[24] parenchymal disease, and pleural effusions[9] were categorized as "Abnormal, consistent with TB." Chest radiographs that had lung pathology that is not associated with pulmonary TB disease (such as perihilar and peribronchial thickening without focal consolidation) were categorized as "Abnormal, not TB." All abnormal chest radiographs were reviewed by an AHS pediatrician in consultation with a pediatric radiologist in a nonblinded fashion, as is customary in routine clinical care.

Statistical Analysis

Data were summarized using frequency and percentages for categorical variables, and mean, standard deviation, and range for continuous variables. Comparison between TST induration groups (0 mm ≤TST <5 mm, 5 mm ≤TST <10 mm, and TST ≥10 mm) was performed using the Pearson χ^2 statistic and analysis of variance (ANOVA). Multiple logistic regression was used to investigate the relationship between TST induration and demographic and birth characteristics. Due to the potential differences in LTBI and TB disease risk factors between children with 5 mm ≤TST <10 mm and TST ≥10 mm, separate logistic regression models were fit for TST ≥5 and ≥10 mm. Results are presented as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). $P \leq 0.05$ were regarded as statistically significant. All analyses were completed on coded anonymous data using SAS version 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Age, Gender, and Birth Country

The study population comprised all 566 IAC who had presented to the AHS between August 2000 and June 2009. Of these, 22 children (3.9%) were excluded from analysis due to incomplete documentation. Descriptive statistics for the remainder of the sample (N = 544) are shown in Table 1, stratified by induration groups. The birth countries of the IAC were Russia (N = 186), China (N = 105), Guatemala (N = 105), Korea (N = 35), Kazakhstan (N = 25), Ukraine (N = 20), Vietnam (N = 9), Bulgaria (N = 5), Philippines (N = 4), India (N = 3), Romania (N = 1), Thailand (N = 1), and others (N = 45). IAC with birth countries other than Russia, Guatemala, and China were grouped into the category "Other Countries" to create more balanced groups for statistical analysis.

Children with a TST induration ≥10 mm were older than children with 0 mm ≤TST <5 mm and those with 5 mm ≤TST <10 mm. There was no difference in age between children with 0 mm ≤TST <5 mm and those with 5 mm ≤TST <10 mm. There was no association between induration groups and gender or birth country.

Nutritional Status

Nutritional characteristics of the induration groups are shown in Table 1. Children with TST induration ≥10 mm were more stunted (chronically malnourished) than those with 0 mm ≤TST <5 mm and 5 mm ≤TST <10 mm. There was no difference in the degree of wasting (acute malnourishment) among the 3 induration groups.

Chest Radiograph Results

Of the study population, 35% (193 of 544) had TST induration ≥5 mm and were advised to receive a chest radiograph, to ensure that there was no pulmonary TB. Of that group, 103 children (53.4%) had 5 mm ≤TST <10 mm and 90 children (46.6%) had TST ≥10 mm. In both induration groups, the majority of children had normal chest radiographs (71.8% and 78.9%, respectively). One percent (1 of 103) of the group with 5 mm ≤TST <10 mm had chest radiographs that were "Abnormal, Consistent with TB" compared with 3.3% (3 of 90) of those with TST ≥10 mm. Both groups had 6 children each, with chest radiographs that were "Abnormal, not TB." Overall, there were 29 children (21 children with 5 mm ≤TST <10 mm and 8 with TST ≥10 mm) who had chest radiographs done at an outside facility with no documented results. There is no record that a chest radiograph was ever done by 1 child with 5 mm ≤TST <10 mm and 2 children with TST ≥10 mm.

There were no differences in mean age, degree of wasting, or stunting between IAC with normal chest radiographs and those with radiographic abnormalities (consistent with and not consistent

TABLE 1. Descriptive Statistics for Study Population

Characteristic	TST Induration Groups			*P*
	0 mm ≤TST <5 mm N = 351	5 mm ≤TST <10 mm N = 103	TST ≥10 mm N = 90	
Mean age ± SD (age range) (yr)	1.69 ± 1.74 (0.10 to 15.28)	1.46 ± 1.13 (0.45 to 7.00)	2.77 ± 3.00 (0.55 to 15.58)	<0.0001*
Gender				
No. female (%)	233 (66.4)	56 (54.4)	54 (60.0)	0.068
Country of origin				0.1092
Russia (%)	110 (31.3)	35 (34.0)	41 (45.6)	
China (%)	77 (21.9)	17 (16.5)	11 (12.2)	
Guatemala (%)	64 (18.2)	24 (23.3)	18 (20.0)	
Other countries (%)	100 (28.5)	27 (26.2)	20 (22.2)	
Wasting†	n = 339	n = 103	n = 83	
WHZ, mean ± SD (range)	−0.26 ± 1.12 (−4.73 to 2.03)	−0.07 ± 1.00 (−2.85 to 2.52)	−0.24 ± 1.19 (−3.13 to 2.28)	0.3205
Stunting‡	n = 342	n = 103	n = 85	
HAZ, mean ± SD (range)	−0.89 ± 1.16 (−4.63 to 3.08)	−0.78 ± 0.97 (−2.99 to 1.62)	−1.19 ± 1.24 (−5.06 to 1.30)	0.0402§

*TST ≥10 mm differed from 0 mm ≤TST <5mm and 5 mm ≤TST <10 mm.

†Ten children were excluded from analysis because they were >10 years old. Unable to calculate WHZ scores for an additional 9 children so WHZ statistics is based on 525 children.

‡Ten children were excluded from analysis because they were >10 years old. Unable to calculate HAZ scores for 4 children so HAZ statistics are based on 530 children.

§TST ≥10 mm differed from 0 mm ≤TST <5 mm and 5 mm ≤TST <10 mm.

TST indicates tuberculin skin test; WHZ, weight-for-height Z score; HAZ, height-for-age Z score; SD, standard deviation.

TABLE 2. Multivariate Regression of TST Outcomes and Variables of Interest

Characteristic	TST Induration Groups					
	TST ≥5 mm (N = 193)			TST ≥10 mm (N = 90)		
	OR	95% CI	*P*	OR	95% CI	*P*
Age (yr)	1.11	1.01–1.22	0.0251	1.28	1.15–1.42	<0.0001
Country of origin			0.0697			0.0228
Other countries	Ref	—	—	Ref	—	—
Guatemala	1.78	1.02–3.10		2.44	1.12–5.34	
Russia	1.57	0.99–2.50		2.31	1.22–4.38	
China	1.00	0.55–1.81		1.13	0.48–2.68	
Male gender	1.33	0.90–1.96	0.1475	0.95	0.58–1.57	0.8527
HAZ scores	0.98	0.85–1.12	0.7380	0.88	0.72–1.07	0.2044

TST indicates tuberculin skin test; OR, odds ratio; CI, confidence interval; HAZ, height-for-age Z score.

with TB disease). There were insufficient counts to assess the association between radiographic results and TST induration groups, gender, or birth country.

None of the 4 children with chest radiographs initially interpreted to be "Abnormal, consistent with TB," ultimately received the diagnosis of TB. One of the children was a 2-year-old boy from Liberia with a TST induration of 14.5 mm. His chest radiograph had shown "possible lymphadenopathy." A follow-up CT scan was unremarkable and the child was further treated for LTBI. Consistent with routine clinical practice in the AHS, chest radiographs of the other 3 children were reviewed by an AHS pediatrician in consultation with a pediatric radiologist or TB specialist. All 3 chest radiograph readings were revised and final interpretations were not associated with TB. All 3 children subsequently completed LTBI treatment. None of these children developed active TB in the subsequent 2 years (Table, Supplemental Digital Content 1, http://links.lww.com/INF/A676 has descriptions of these 3 scenarios).

Logistic Regression Analysis

Unadjusted logistic regression models showed that the odds of IAC having TST ≥5 mm increased 10% for every 1-year increase in age (OR, 1.10; 95% CI, 1.01–1.20; $P = 0.0364$). Results also showed that the odds of IAC having TST ≥10 mm increased 24% for every 1-year increase in age (OR, 1.24; 95% CI, 1.13–1.37; $P < 0.0001$) and 19% for every unit decrease in HAZ score (OR, 0.81; 95% CI, 0.67–0.99; $P = 0.0375$).

Adjusted models (Table 2) showed that when simultaneously controlling for birth country, sex, and stunting (chronic malnourishment), the odds that an IAC had a TST ≥5 mm increased by 11% for every 1-year increase in age (OR, 1.11; 95% CI, 1.01–1.22; $P = 0.0251$), whereas the odds that an IAC had TST ≥10 mm increased by 28% for every 1 year of age (OR, 1.28; 95% CI, 1.15–1.42; $P < 0.0001$). Overall, birth country was not significantly associated with TST ≥5 mm ($P = 0.0697$); however, it was associated with TST ≥10 mm ($P = 0.0228$).

IAC from Guatemala (OR, 2.44; 95% CI, 1.12–5.34) and Russia (OR, 2.31; 95% CI, 1.22–4.38) were more than twice as likely to have a TST ≥10 mm as children from other countries.

DISCUSSION

This study assessed the clinical utility of considering 5 mm ≤TST <10 mm to be an indication for TB screening in asymptomatic children who recently immigrated to the United States. We hypothesized that a 5-mm TST cut point is clinically useless because asymptomatic IAC with 5 mm ≤TST <10 mm would be no different than asymptomatic IAC with TST <5 mm. We also proposed that a higher TST cut point of 10 mm would be more

sensitive and specific for capturing IAC at risk for LTBI and TB disease.

Identification of a TST cut point that maximizes both TST specificity and sensitivity in IAC has been a well-recognized clinical challenge in this unique population. A lower TST cut point raises sensitivity,[9] as it captures even those children who are unable to mount a robust immune response due to malnutrition or psychosocial stress. However, a lower threshold compromises specificity as it is less able to distinguish a true-positive TST due to *M.tb* infection from a false-positive TST due to non-TB mycobacterium infection or post-BCG cross reactivity.[9,17,25,26] This could result in expensive, unnecessary follow-up tests and treatment for presumed infection.[8] In theory, a higher TST cut point raises the specificity of the test,[9] because a positive result is more likely due to true *M.tb* infection but sensitivity is compromised as immunosuppressed children are more likely to be wrongly detected (false negatives).[11,27]

In support of our hypotheses, univariate analysis showed that there was no statistical difference between IAC with 5 mm $\leq$TST $<$10 mm and those with TST $<$5 mm with respect to risk factors for LTBI (age, birth country) or risk factors for progression to TB disease (age, nutritional status). Hence, a 5-mm TST cut point seems to lack specificity in identifying an at-risk population of asymptomatic IAC and may not be a useful clinical indicator for additional TB screening. Furthermore, both univariate and bivariate analyses illustrated that a 10-mm TST cut point did identify IAC who were older. This finding suggests that there is utility in using the recommended 10-mm TST cut point to guide additional TB screening,[7] as this cut point seems to capture a subgroup of children with an increased risk for LTBI. Similar analysis showed that a 10-mm TST cut point identified IAC who were more stunted (chronically malnourished) than IAC identified by a 5-mm TST cut point. It may seem counterintuitive that the more malnourished children were able to mount a greater immune response (signified by a larger TST induration) because literature has described on numerous occasions the associations between malnourished children, anergy, and false-negative TSTs.[16,26,27] However, these associations have especially been described for severely malnourished children. In our study, only 6.7% (6 of 90) of IAC with TST $\geq$10 mm were severely stunted (that is, HAZ <-3).[28–30] Thus, IAC in our study were still likely to be sufficiently nourished to mount an immune response.

Because birth country, age, and HAZ are all associated, multivariate analysis was completed to fully understand the relationship among these covariates and the dependent variable (TST). Comparison of the multivariate models also illustrated that a TST cut point of 10 mm is more effective at capturing children at risk for TB infection as compared with a TST cut point of 5 mm. This is evident by the greater age-related odds of TST positivity for a 10-mm cut point as compared with a 5-mm cut point. Additionally, only the 10-mm cut point is able to capture children with a greater risk of infection due to variations in birth country risk. IAC from Guatemala and Russia were more than twice as likely to have a TST $\geq$10 mm as IAC from other countries. This may be due to the fact that a large proportion of IAC in our study population were from Russia and Guatemala. However, we feel that these results are still valid because the demographics of the IAC in our study reflect the nationwide demographics of IAC in the United States during the study period.[31] The association between TST induration size and birth country may also be explained by the use of BCG vaccinations with different counts of viable bacteria per unit of BCG[32,33] or by the use of different strains of the vaccine in the different countries.[33]

Both age and birth country were significantly associated with HAZ in our sample, suggesting the presence of confounding factors. However, the change in the OR was minimal and after controlling for the confounding effects, HAZ was not significant in the model.

In addition to evaluating TST cut points, we also analyzed the usefulness of chest radiographs to screen for pulmonary TB. Radiographic results were not associated with the age or nutritional status of IAC. Although we had limited power to complete analysis of radiographic outcomes, our limited descriptive results do raise questions about the usefulness of chest radiographs in asymptomatic IAC. There was some variation in the interpretations of chest radiographs originally thought to be abnormal and consistent with TB. The subjectivity that is inherent in radiographic interpretations makes us question the clinical value and cost effectiveness of chest radiographic screening for pulmonary TB in asymptomatic IAC. Our study illustrates that there is no indication to complete chest radiographs in IAC with 5 mm $\leq$TST $<$10 mm as this TST induration range does not identify a group of children with increased risk for LTBI or progression to TB. Although none of the IAC with TST $\geq$10 mm ultimately received the diagnosis of TB disease, we still feel that a 10-mm TST cut point is a clinically useful indicator for TB disease screening in asymptomatic IAC because it at least identifies those children at greater risk of acquiring the disease. From a public health standpoint, this is valuable because it will help limit the potential spread of TB disease. Our findings further support the 2007 revised CDC Tuberculosis Screening and Treatment Technical Instructions for Panel Physicians that guide preimmigration screening. These guidelines recommend chest radiographs to be completed in 2- to 14-year-old children from countries with a World Health Organization-estimated TB incidence rate of $\geq$20 cases per 100,000 who have a TST $\geq$10 mm, show symptoms of TB, or are HIV positive. Furthermore, the guidelines state that TST screening should only be completed in children $<$2 years of age (from similar countries) if they have symptoms suggestive of TB.[5] Children who are $<$15 years old and are from countries with lower TB burden are only required to complete TST screening if they show signs and symptoms of TB or if they are HIV positive.[5]

A main clinical goal of TB screening is to evaluate population with a high probability of having LTBI or progression to TB following infection.[34] Our study has shown that even though a cut point of 5 mm is considered to be more sensitive, it fails to identify a group of asymptomatic IAC with increased risks for LTBI or TB progression, and thus is a poor screening cut point. In contrast, our study indicates that a 10-mm threshold is more effective at identifying children with a greater risk of LTBI and guides more efficient use of subsequent screening tools. In IAC, a group of children whose clinical history may have limited validity, completion of a chest radiograph to rule out TB before the initiation of LTBI treatment is indicated to ensure that isoniazid monotherapy is not erroneously commenced. Nevertheless, we question the usefulness of a chest radiograph to rule out TB in asymptomatic IAC with TST $<$10 mm, especially if this group of children has consistent clinical monitoring as is frequently the case.

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