Risk Factors for Latent Tuberculosis Infection Among Children in New York City

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ABSTRACT. *Objective.* **Although identification and appropriate treatment of children with latent tuberculosis (TB) infection (LTBI) is considered critical to the control and elimination of TB in the United States, there are limited data on risk factors for LTBI in pediatric populations.**

Methods. **To further improve targeted screening for LTBI, we performed a matched case–control study from September 1996 to December 1998. We actively surveyed 24 primary care clinics serving Northern Manhattan and Harlem twice monthly for case participants 1 to 5 years old with LTBI, defined as a child with a Mantoux tuberculin skin test (TST) ≥10 mm and a normal chest radiograph. Two age- and clinic-matched control participants with TSTs equal to 0 mm were enrolled per case. To determine risk factors for LTBI, a bilingual research worker reviewed the medical records of study participants and administered a questionnaire to the parents of participants.**

Results. **We enrolled 96 cases and 192 controls whom did not differ by age, gender, ethnicity, and race; overall, the mean age of participants was 2.9 years, 51% were male, 80% were Hispanic, and 9% black. Logistic regression analysis demonstrated that contact with an adult with active TB, foreign birth, foreign travel, and a relative with a positive TST were predictive of case status. In contrast, a history of a previous negative TST proved protective and BCG immunization was not an independent risk factor for a positive TST, suggesting that boosting was not important in this population.**

Conclusions. **We identified several risk factors for LTBI in children that can be used to refine targeted surveillance for TB among Hispanic immigrant populations in the United States.** *Pediatrics* **2001;107:999–1003;** ***Mycobacterium tuberculosis, children, latent tuberculosis infection, latent infection, pediatrics.***

ABBREVIATIONS. TB, tuberculosis; LTBI, latent tuberculosis infection; TST, tuberculin skin test; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval; SES, socioeconomic status.

Identification of children with latent tuberculosis (TB) infection (LTBI) and use of appropriate preventive therapy are considered critical to the control and elimination of TB in the United States because such children represent an important reservoir of future cases of active TB.[1–3] The American Thoracic Society, the Centers for Disease Control and Prevention, and public health experts concur that screening for LTBI should focus on high-risk pediatric populations; screening low-risk populations is not cost-effective because a positive tuberculin skin test (TST) has poor positive predictive value.[4,5] High-risk children have been defined as those children who may come in contact with adults with active TB. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that: 1) children who are newly arrived from countries with a high incidence of TB should be screened "immediately"; 2) children with human immunodeficiency virus (HIV)-infected household contacts should have annual TST; and 3) children exposed to adults with other risk factors for active TB, including homelessness, illicit drug use, incarceration, or migrant farm workers should have "less frequent" testing. Children whose parents are foreign-born or whose parents travel to countries where TB is highly prevalent should also be considered for screening.[4,6]

To date, there is limited information derived from systematic studies of risk factors for LTBI in children. Instead, the risk factors for LTBI in children are extrapolated from risk factors observed in adults and children with active TB.[5–9] To validate current recommendations for TST and to refine screening, a multicenter, case–control study was performed to assess risk factors for LTBI in young children in New York City.

METHODS

Study Design

A multicenter, prospective, matched case–control (1:2) study was performed from September 1996 to December 1998. Institutional review board approval was secured from all participating sites including the New York City Department of Health. Informed consent was obtained by the research worker.

Study Participants and Case Definitions

Study participants were asymptomatic children 1 to 5 years old undergoing TST by primary care providers during routine health care. All tests were performed using 5 tuberculin units placed by the Mantoux technique and read in millimeters of induration 48 to 72 hours later by the primary care clinic staff. Children were ineligible for enrollment if they had illness consistent with TB or if they were being evaluated during a contact investigation of an adult with active TB.

Case participants had a TST ≥10 mm and a normal chest radiograph. Control participants had negative TSTs, ie, read as 0 mm. Case and control participants were recruited within 2 months of their TST to avoid recall bias but did not visit the clinic on the

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same day to avoid selecting members of the same family. Two control participants were selected per case and were matched by clinic site and age, ie, within 6 months of case participants <3 years old and within 12 months of case participants 3 to 5 years old. Only 1 child was selected per household. To contact possible study participants for participation, as many as 4 attempts were made by telephone (if the family had a phone) and 1 attempt by mail.

Study Sites

The study sites consisted of 24 primary care clinics located in the Washington Heights, Inwood, Harlem, and Morningside Heights sections of Northern Manhattan. Clinics were affiliated with Babies & Children's Hospital of the New York Presbyterian Hospital (5 clinics), Harlem Hospital (13 primary care and school-based clinics), St Luke's/Roosevelt Hospital (1 hospital-based site), and the New York City Health and Hospital Corporation (5 clinics). The sites maintained log books for TSTs and were actively surveyed twice monthly for eligible study participants.

Questionnaire

A questionnaire (piloted by 10 parents of children with negative TSTs from 1 study site whose responses were not used in this study) available in both English and Spanish was administered by 1 bilingual research worker to the primary care takers of the study participants. The questionnaire had a detailed script and inquired about potential risk factors for LTBI, such as demographic characteristics, foreign birth, travel, and socioeconomic factors. Immunizations and chest radiograph results were obtained from the medical record. A circle of contacts diagram was used to identify contacts 15 years of age or older and to elicit risk factors in these contacts, including HIV infection, a history of active TB, illicit drug use, migrant farm work, or incarceration (Fig 1). This strategy of inquiry divides the child's contacts into those adults residing in the household, in day care or school, or from the leisure time environment.[10] Risk factors for contacts were reported by the child's primary care taker.

Statistical Analysis

The questionnaire responses and medical record data were entered into *EpiInfo, Version 6* (Centers for Disease Control and Prevention, Atlanta, GA). Univariate analysis of potential risk factors was performed using a matched analysis in SAS controlling for site and age (SAS Institute, Cary, NC). Mantel-Haenszel odds ratios (OR) and 95% confidence intervals (CIs) were calculated for independent variables. A logistic regression model was constructed for variables found to be significantly associated ($P \leq .05$) with LTBI in the univariate analysis. Socioeconomic status (SES) variables such as crowding, poverty, and parental education were as previously defined.[11]

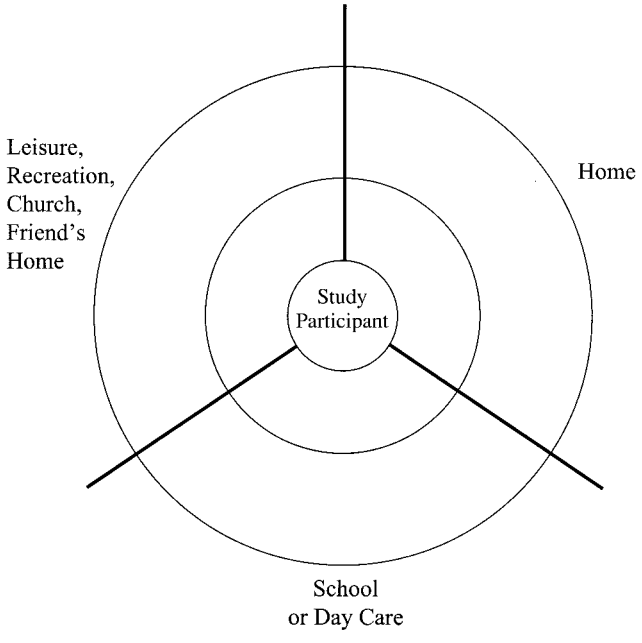

Fig 1. The circle of contacts diagram used to identify the adult contacts (≥15 years old) of the study participants. The research worker inquired about contacts in the child's household, school or day care, and leisure time environment. The research worker then asked about risk factors for TB in each contact.

RESULTS

Study Participant Selection

In all, 288 children participated in this study: 96 cases and 192 age- and clinic- matched controls. Fifty-six triplets (1 case and 2 control participants) were selected from Health and Hospital Corporation clinics, 27 from clinics affiliated with Babies & Children's Hospital, 7 from Harlem Hospital clinics, and 6 from St Luke's/Roosevelt Hospital. Only 4 eligible case participants and 3 control participants refused participation. Surveillance of the logbooks of the sites identified 9 other case participants who were not enrolled; 4 could not be contacted by phone or mail and 5 families without phones did not respond to a mailed request for participation. Four potential control participants without phones did not respond to a mailed request.

General Health Status of Study Participants

The immunization and medical records were available and reviewed for 90% of the study participants. The participants were generally in good health; 10% had been previously hospitalized for trauma, infections (eg, pneumonia or bronchitis), asthma, or surgery (eg, tonsillectomy or appendectomy). One control and 2 case participants were receiving oral steroids for asthma at the time of their TST. Overall, 64% of children had received their primary immunization series (defined as 3 diphtheria, pertussis, tetanus and 2 polio vaccines) by 1 year of age, and 52% had received their secondary immunization series (defined as 3 diphtheria, pertussis, tetanus, 3 polio, and 1 measles, mumps, rubella vaccines) by 2 years of age.[12] There was no difference between case and control participants in the rate of timely immunization ($P = .2$).

Univariate Analysis of Risk Factors for LTBI

There were no differences in gender, age, ethnicity or race, or language spoken in the home (Table 1). To determine whether clinic matching lead to similar SES characteristics in case and control participants, several variables were examined including Medicaid eligibility, poverty, parental education, and crowding. There was no difference in the proportion of case and control participants with an annual household income of <$20 000. Case participants were not more likely than were control participants to live in crowded conditions defined as a ratio of persons/room ≥0.71[11] but were more likely to share a bathroom or kitchen with other tenants or live in a single-parent household headed by their mother (Table 1).

Foreign birth, BCG immunization, and foreign travel by both the study participants and their household members were significant risk factors for a positive TST (Table 1). The vast majority (92%) of the

TABLE 1. Univariate Analysis of Demographic Characteristics and SES of Study Participants One to Five Years of Age With and Without Positive TSTs

Characteristic	Cases (n = 96) n (%)	Controls (n = 192) n (%)	OR	95% CI	P Value
Mean age*	2.91	2.84	—	—	.67
Male gender	44 (48)	102 (53)	0.75	0.44, 1.26	.30
Black†	11 (12)	15 (8)	1.7	0.60, 4.42	.40
Hispanic‡	76 (78)	155 (82)	0.89	0.45, 1.84	.87
Spanish-speaking household	46 (48)	72 (38)	1.56	0.91, 2.72	.08
Receiving Medicaid	59 (61)	112 (58)	1.15	0.67, 1.94	.61
Public assistance§	61 (64)	118 (61)	1.04	0.62, 1.75	.03
Income <$20 000	36 (38)	56 (29)	1.52	0.84, 2.67	.19
No adult in household completed high school or obtained graduate equivalency diploma	48 (50)	78 (41)	1.46	0.86, 2.34	.19
Crowding index ≥0.71	91 (96)	170 (90)	2.71	0.85, 10.60	.12
Bathroom or kitchen shared with other tenants	20 (21)	22 (12)	2.0	0.99, 4.30	.034
Single mother household	42 (44)	58 (30)	1.84	1.05, 3.23	.021
Foreign-born visitors	54 (56)	103 (54)	1.15	0.66, 1.87	.38
Foreign travel by household members	40 (42)	60 (31)	1.92	0.92, 2.83	.049
Foreign birth	38 (40)	22 (12)	5.5	2.79, 12.44	<.0001
BCG vaccination	26 (27)	11 (5.7)	7.8	3.03, 22.86	<.0001
Foreign travel	37 (39)	48 (25)	1.8	1.1, 3.4	.013
Contact with TB‖	22 (24)	3 (1.5)	42.0	6.6, 1697	<.0001
Previous negative TST	20 (21)	78 (41)	0.27	0.13, 0.57	<.0001
Ingested unpasteurized milk or cheese	36 (38)	25 (13)	4.6	2.4, 11.1	<.0001
Relative with positive TST	40 (42)	17 (8.9)	8.0	4.1, 25.1	<.0001

* Student's t test.
† Eighty percent of the parents answered the question of race as "no answer" or "other."
‡ Hispanic origins included the Dominican Republic (n = 92), Puerto Rico (n = 56), Equador (n = 18), Mexico (n = 15), or other (n = 50).
§ Public assistance was defined as food stamps, Women, Infant, and Children supplements, Aid to Families With Dependent Children, and/or public housing.
‖ Responses to contact with TB were pooled responses to the following questions: contact with TB in a foreign country, visitor from abroad with active TB, "anyone else with TB?," and anyone with active TB elicited by responses to the circle of contacts diagram.

foreign-born study population was born in Latin America, primarily the Dominican Republic (19% of cases, 5% of controls). Six US-born and 31 foreign-born study participants reported immunization with BCG. Foreign travel was common; 39% of cases and 25% of controls traveled outside the United States and all stayed with family and friends. The most common travel destinations were the Dominican Republic (21% of cases, 17% of controls) and Puerto Rico (6% of cases, 5% of controls) and the remainder traveled to other Latin American countries with high case rates of TB as determined by the World Health Organization.[13] Among those who traveled, there was no difference in the frequency of travel (median: 1.6 times) between case and control participants (P = .3).

However, a history of a previous negative TST seemed to be protective. The majority, 16 of 20 cases (80%) and 74 of 78 controls (95%), reported that their previously negative TST was read by a nurse or a physician. No child had a Tine test performed.

Neither visitors from abroad (OR: 1.15; 95% CI: 0.66, 1.87; P = .17) nor foreign travel by other household members including parents (OR: 1.92; 95% CI: 0.92, 2.83; P = 3.23) was associated with an increased risk of a positive TST in case participants.

Univariate Analysis of Risk Factors in Contacts

The circle of contacts diagram elicited a mean of 6 (range: 1–10) contacts 15 years or older in both cases and controls. Several exposures in these contacts were found to be variables predictive of case status: drug abuse, incarceration, homelessness, or active TB (Table 2). However, in this population, migrant farm work was not a risk factor nor was HIV/acquired immunodeficiency syndrome.

TABLE 2. Univariate Analysis of Risk Factors for LTBI in Study Participants One to Five Years of Age as Elicited by Exposures Reported in Adult Contacts

Exposures Reported in Adult Contacts	Cases (n = 96) n (%)	Controls (n = 192) n (%)	OR	95% CI	P Value
Drug abuse	23 (24)	20 (10)	2.80	1.36, 6.23	.002
Incarceration	23 (24)	21 (11)	2.40	1.23, 4.92	.005
Migrant farm worker	33 (34)	56 (29)	1.41	0.72, 2.30	.850
HIV or acquired immunodeficiency syndrome	1 (1)	0 (0)	—	—	—
Sleep in streets or shelter	15 (16)	12 (6)	4.75	1.14, 6.9	.011
Active TB	10 (10)	2 (1)	19.0	2.61, 808	.001
Foreign birth	85 (89)	170 (89)	2.11	0.47, 12.31	.47

Logistic Regression Analysis of Risk Factors

We evaluated the risk factors found to be significant ($P \leq .05$) in the matched univariate analysis (Table 3) by logistic regression and then built a second model using only those factors found to be significant in the first model (Table 4). In the second model, foreign birth, foreign travel, a relative with a positive TST, and contact with someone with active TB remained predictive of LTBI. In addition, a previously negative TST remained protective. BCG immunization and consumption of raw dairy products were not significantly associated with a positive TST, and exposure to a contact with a history of illicit drug use, homelessness, or incarceration did not prove predictive of case status.

DISCUSSION

This is the largest published study of risk factors for LTBI in young children. To date, most studies of TB in children have focused on risk factors for active disease rather than on risk factors for LTBI.[5–9] During the past decade, it has become clear that targeted screening for LTBI in high-risk pediatric populations is desirable[1–5] and that universal school-based screening is not cost-effective.[14] However, the most recent efforts to further refine screening strategies have focused primarily on adults.[1] In contrast, our case–control study in young children could be used to further refine the risk factor profile for tuberculin skin testing of pediatric patients, particularly among Hispanic populations. Targeted tuberculin skin testing of young children is both cost-effective and efficient. Young children are at higher risk of progressing to active TB once infected, are seen frequently by primary providers who are accustomed to performing TST by the Mantoux technique, require smaller dosages of chemoprophylaxis, and experience less toxicity from isoniazid.[15]

Numerous studies have emphasized the importance of providing chemoprophylaxis to children in contact with adults with active TB.[5,6,9] Although being evaluated during a contact investigation for an adult with active TB was an exclusion criteria for enrollment in this study, contact with an adult with TB proved to be the most significant predictor of a positive TST (Table 4). We explored this risk factor in several questions by asking about contact with someone with active TB while in a foreign country, in a visitor, in anyone else, and as elicited by the circle of contacts inquiry. We speculate that in our community the stigma of TB may be overcome by asking specific questions rather than asking about TB exposure in an open-ended question. This suggests that additional consideration should be given to developing culturally sensitive questions to inquire about TB exposure in high-risk populations.

In this Hispanic, primarily Dominican pediatric population, foreign birth and foreign travel also proved to be significant risk factors for LTBI. In New York City, TB case rates among the foreign-born have not decreased during the past decade, despite much progress in reducing the overall number of cases.[16] Similarly, foreign birth continues to be the most important risk factor for TB in the United States.[17] Furthermore, our study participants traveled to the Dominican Republic and other countries in Latin America with high case rates of TB.[13] This finding confirms the recommendation for "immediate" testing of children newly arrived from a country with high rates of TB and supports targeting surveillance efforts for LTBI in immigrant communities.[1–5] In addition, this study may have broader implications for the United States during the next decade. The US Census Bureau estimates that the Hispanic population will grow to comprise 14.6% of the US population by 2010 and 33.5% of that population will be foreign-born.[18]

We found that a history of a positive TST in a relative was also predictive of case status. Soren et al[19] performed TST on the household contacts of children with LTBI in our community and found that 32% of contacts had a TST ≥10 mm. Although no cases of active TB were found among these household contacts, the findings by this previous study and by our current study suggest that testing contacts of children with LTBI could further enhance surveillance for LTBI.

Crowding, poverty, and lower SES variables were found among a high proportion of our study population. Although these factors are well known to be

TABLE 3. Risk Factors for LTBI as Determined by Logistic Regression Analysis Using All Risk Variables Found to Be Significant in Univariate Analysis

Variable	Parameter Estimate	Standard Error	Risk Ratio	*P* Value
Bathroom or kitchen shared with other tenants	0.207	0.561	1.230	.712
Single mother household	0.472	0.470	1.603	.315
Foreign birth	1.648	0.715	5.195	.021
BCG immunization	1.435	0.903	4.201	.112
Foreign travel	1.711	0.603	5.537	.005
Foreign travel by household member	−0.428	0.689	0.652	.534
Contact with active TB	3.609	1.160	36.94	.0019
Previous negative TST	−2.573	0.679	0.076	.0001
Ingestion of unpasteurized milk or cheese	0.016	0.658	1.016	.981
Relative with positive TST	2.697	0.654	14.83	<.0001
Contact with illicit drug use	1.229	0.744	3.419	.098
Contact with history of incarceration	−0.199	0.671	0.819	.766
Contact with history of sleeping in shelter or streets	−0.024	0.683	0.976	.972

TABLE 4. Risk Factors for LTBI as Determined by Logistic Regression Using the Significant Variables in the Above Model

Variable	Parameter Estimate	Standard Error	Risk Ratio	*P* Value
Foreign birth	2.219	0.515	9.201	<.0001
Foreign travel	2.015	0.540	7.504	.0002
Contact with active TB	4.121	1.167	61.616	.0004
Previous negative TST	−2.657	0.646	0.070	<.0001
Relative with positive TST	2.757	0.621	15.745	<.0001

associated with communities with high rates of active TB,[6–9,11] they could not be assessed as risk factors for LTBI in our study because of the clinic-matching study design used.

Several additional previously described risk factors for LTBI were not confirmed by our study. In our model, immunization with BCG was not an independent risk factor for a positive TST. Most likely, BCG immunization was confounded by foreign birth. However, previously administered TSTs proved protective rather than predictive of a positive TST in case participants. These 2 observations suggest that boosting was not an important phenomenon in our study population.[20] Risk factors for TB in adult contacts such as a history of incarceration, illicit drug use, or HIV/acquired immunodeficiency syndrome did not predict LTBI in case participants. Finally, there was no association between a positive TST and consumption of unpasteurized dairy products as was found in children in San Diego using a similar study design.[21] This suggests that different immigrant communities may have unique risk factors for LTBI.

There were some limitations to this study. Most of the clinics were affiliated with academic centers. Other children in this same catchment area are served by private physicians and it is possible that such children have additional risk factors for LTBI. A history of BCG immunization could not always be confirmed independently by immunization records. Finally, risk variables in contacts may have been underreported; these factors are socially undesirable and were reported by the primary care takers of the study participants rather than by the contacts themselves. Furthermore, we could not validate these risk factors by comparison with other databases, such as drug rehabilitation programs or health care records.

CONCLUSION

Several important risk factors for LTBI in young children were elicited. These included: contact with an adult with active TB, foreign birth, foreign travel, and a relative with a positive TST. A history of a previous negative TST proved protective and suggested that boosting was not an important phenomenon in this population. Targeted screening efforts for LTBI should continue to focus on immigrant communities derived from countries with high rates of TB. Future surveillance efforts for LTBI could be further refined by using a simple screening questionnaire assessing risk factors in young children in primary care settings.

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