Underuse of Effective Measures to Prevent and Manage Pediatric Tuberculosis in the United States

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Objective: To characterize problems with prevention and management of pediatric tuberculosis (TB) and latent TB infection (LTBI).

Design: A multisite, cross-sectional study using data from medical records and public health logs to categorize and define use of routine prevention practices in managing pediatric TB and LTBI.

Setting: Four areas of the United States.


Main Exposure: Mycobacterium tuberculosis.

Main Outcome Measures: Underuse or nonuse of standard medical and public health interventions.

Results: Almost 40% of children had a TB risk factor related to their country of birth, parental origin, or travel to a country with a high incidence of TB. Children having LTBI were less likely than those having TB to complete treatment (53.7% vs 88.6%, respectively). Almost half (46.3%) of the children with TB came to medical attention late in their course when they already had symptoms. Among 63 adult source patients, 19 (30.2%) previously had LTBI but were not treated, and none of the 40 foreign-born source patients were known to have been evaluated for TB before entry into the United States.

Conclusions: Prevention efforts are unsatisfactory to prevent TB in children. Effective interventions such as treatment of LTBI and TB evaluation of adult immigrants remain less than optimal.

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Tuberculosis (TB) in young children persists as a concerning health problem in the United States despite recent decreases in TB incidence.1 A diagnosis of TB disease or latent tuberculosis infection (LTBI) in a child represents recent transmission of Mycobacterium tuberculosis complex.2 Consequently, trends in TB disease and LTBI in young children are important indicators to assess the effectiveness of TB prevention and control efforts.3

Prompt interventions in the public and private health sectors can prevent a portion of TB cases in children.4,5 For example, investigations of persons having infectious pulmonary TB can avert TB in children who have been infected with M tuberculosis by finding and treating these children before they progress to having TB disease.6,7 Also, children who might benefit from treatment for LTBI can be selected using a standard risk assessment, tested, and, if appropriate, offered treatment.8

Guidelines and best practices for investigating and medically evaluating children exposed to M tuberculosis have been published by the American Academy of Pediatrics and the Centers for Disease Control and Prevention.8-10 This study focused on problems with the underuse of TB prevention and control processes. It is the intent that these findings help public health departments interrupt TB transmission to children or, once the children are infected, prevent progression to disease. Systematic definition of the underuse of prevention measures allows for evaluations specifically designed to improve health outcomes among children at risk for TB and LTBI.11

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radiographic findings that are normal or reveal evidence of healed Guerin immunization, no physical findings of disease, and chest risk factor for LTBI regardless of previous bacilli Calmette-positive TST result based on millimeters of induration with a antituberculosis medications.12 Latent TB infection is defined evidence identifying M tuberculosis complex (including Mycobacterium bovis) or meeting the Centers for Disease Control and Prevention’s clinical case definition specifying that the individual must undergo a complete diagnostic evaluation resulting in a positive tuberculin skin test (TST) result, have signs and symptoms compatible with TB disease (eg, abnormal, worsening, or improving chest radiographic findings or clinical evidence of current disease), and receive treatment with 2 or more antituberculosis medications.11 Latent TB infection is defined as infection with M tuberculosis complex in a person who has a positive TST result based on millimeters of induration with a risk factor for LTBI regardless of previous bacilli Calmette-Guerin immunization, no physical findings of disease, and chest radiographic findings that are normal or reveal evidence of healed disease (eg, calcified granuloma in the lung, hilar lymph nodes, or both).9,10 A source patient is a person having pulmonary TB who presumably transmitted M tuberculosis to a child who later had TB develop or had a positive TST result. A contact investigation consists of epidemiologic and medical evaluations to detect persons who were exposed to infectious TB disease and to ensure that they are tested for LTBI, are evaluated for TB disease, and complete a course of treatment if indicated.7 A source case investigation is initiated when a child with TB has an unknown TB source. The health department attempts to find a previously unidentified person with infectious TB who might be responsible for transmitting TB to the child.

STUDY POPULATION

We collected data on children younger than 5 years who had TB disease or LTBI at 4 study sites: Alameda and San Diego counties in California, New York, New York, and Tarrant County, Texas. The investigators at each site included all of the consecutive cases of TB disease among children and their source patients, if defined by the health department, related to these children. In Alameda County, all of the TB cases were enrolled; in San Diego County, all of the children having TB and receiving care at San Diego County TB Control Clinics were included in the study. In New York, the investigators reviewed all of the cases of TB in children cared for at the chest clinics run by the New York City Department of Health and Mental Hygiene. As an additional measure to capture cases, the computerized TB registry in New York was reviewed for TB cases in children who had been reported but were followed up by other providers. The Tarrant County Public Health Department enrolled all of the consecutive pediatric patients with TB disease living within Tarrant County.

Identification of LTBI among children younger than 5 years varied by site. For children with LTBI, investigators in Alameda used systematic sampling by enrolling every other child with LTBI. Children are generally followed up and reported by Oakland Children’s Hospital, 2 ambulatory care services, and 4 community-based organizations. The Alameda County TB Control Program works closely with these facilities in the management of children with LTBI. In San Diego County, all of the children having LTBI and receiving care at San Diego County TB Control Clinics were included in the study. In New York, children with LTBI cared for at Washington Heights Chest Clinic or Harlem Hospital Chest Clinic were included. In addition, the medical records of pediatric patients with LTBI from 6 pediatric and family medicine clinics that do not consistently refer their patients to the public health chest clinics were reviewed. In Tarrant County, all of the children with LTBI were enrolled. The county health department operates a referral clinic that provides care for most pediatric patients with LTBI in Tarrant County.

DEFINITIONS

For the purpose of this study, a pediatric patient with TB is defined as a child younger than 5 years either with laboratory evidence identifying M tuberculosis complex (including Mycobacterium bovis) or meeting the Centers for Disease Control and Prevention’s clinical case definition specifying that the individual must undergo a complete diagnostic evaluation resulting in a positive tuberculin skin test (TST) result, have signs and symptoms compatible with TB disease (eg, abnormal, worsening, or improving chest radiographic findings or clinical evidence of current disease), and receive treatment with 2 or more antituberculosis medications.11 Latent TB infection is defined as infection with M tuberculosis complex in a person who has a positive TST result based on millimeters of induration with a risk factor for LTBI regardless of previous bacilli Calmette-Guerin immunization, no physical findings of disease, and chest radiographic findings that are normal or reveal evidence of healed disease (eg, calcified granuloma in the lung, hilar lymph nodes, or both).9,10 A source patient is a person having pulmonary TB who presumably transmitted M tuberculosis to a child who later had TB develop or had a positive TST result. A contact investigation consists of epidemiologic and medical evaluations to detect persons who were exposed to infectious TB disease and to ensure that they are tested for LTBI, are evaluated for TB disease, and complete a course of treatment if indicated.7 A source case investigation is initiated when a child with TB has an unknown TB source. The health department attempts to find a previously unidentified person with infectious TB who might be responsible for transmitting TB to the child.

DATA COLLECTION

The institutional review boards at the Centers for Disease Control and Prevention and the respective entities involved in this study at each site approved the study protocol and data collection instruments prior to the start of data collection on children with TB and LTBI and their associated source patients. This cross-sectional study included all of the cases of TB diagnosed in children younger than 5 years from January 1, 2002, to December 31, 2004. Data collection on children with LTBI was for a continuous 12-month period using the data collection start date at each site in early 2003. Study investigators reviewed available medical records for children with TB and LTBI, including those with private health care providers, and abstracted data from source case investigation logs. The investigators also reviewed the available medical records and contact investigation logs of persons with pulmonary TB if the health department determined them to be the child’s presumed source of TB or LTBI. Data collected for the study included demographic information, TB risk factors, clinical information, drugs used and start and stop dates for TB and LTBI treatment, information from contact investigations, and timing of all aforementioned events. Race and ethnicity were classified using the Centers for Disease Control and Prevention surveillance categories. Travel to a country with a high rate of TB was considered a risk factor if the travel length was 7 days or longer. When subspesification for M bovis was available in the laboratory data, this information was collected. Contact and source patient data collection included demographic information, clinical information, and timing and outcomes of investigations conducted by the health department. Information about the course of illness of the adult source patient was used to estimate the period of infectiousness. Data were also collected on reporting and treating source patients with TB.

DATA ANALYSIS

Data analysis was primarily descriptive to determine delayed use or nonuse of recommended TB prevention and control practices. Underuse of prevention measures was categorized as to whether the measures were related to screening, contact and source case investigations, or case management. For defining the timing of events, we considered the date that a child’s evaluation for TB began as the date the first TST was administered or, if a TST was not administered, the date that the first chest radiographic examination was done. Although TB and LTBI are clinically distinct, we aggregated the demographic data from children with TB and LTBI because the epidemiology of children with these conditions is similar within the populations at risk. Why some children progress from LTBI to TB is not fully elucidated, but the change from the dormant state to the disease state relates to the interaction between M tuberculosis and the host immune regulation and to virulence factors specific to the organism.13,14,15 We tested differences in categorical variables using the χ² statistic and the t test for continuous data (eg, age). An α of .05 was considered statistically significant. Associations in risk factors and outcomes were estimated using relative risks and 95% confidence intervals. Statistical analysis was performed using SAS statistical software version 8.0 (SAS Institute, Inc, Cary, North Carolina).


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RESULTS

CHILDREN’S CHARACTERISTICS AND TB RISK FACTORS

We assessed underuse of TB prevention and case management interventions in 123 children with TB and 298 children with LTBI in 4 distinct areas of the United States. Demographic characteristics and TB risk factors varied by study site (Table 1). San Diego County had a noteworthy difference compared with other sites in a contributing TB risk factor. Consistent with other studies,11 of the 34 children (32.4%) from San Diego with culture-confirmed TB were infected with M. bovis; 10 of the 11 children had parents who affirmed that the child had ingested unpasteurized milk or milk products.

Child or parent birth in a country other than the United States was common: 137 children (32.5%) were foreign born and 41 parents (33.3%) were foreign born. The most common countries of birth for children were the United States (60.1%) and Mexico (19.5%). Among 103 children with a recorded travel history, 40 (38.8%) reported travel of 7 days or longer outside the United States within the past 12 months. For 27 children with detailed information, 14 had traveled to Mexico and 17 had traveled for 14 days or longer. Overall, 39.4% of children were born, had a parent born, or traveled outside the United States. Children with TB were more likely to be born in the United States than were children with LTBI (relative risk=9.6; 95% confidence interval, 5.5-16.5).

The most common reasons children with TB came to medical attention were owing to symptoms (46.3%) and through TB evaluation during contact investigations (21.1%). In contrast, children having LTBI were likely to be found through routine TB testing activities (47.0%), the most common reason (38.0%) being tested before school entry. Among foreign-born children, 2 of 11 (18.2%) with TB and 5 of 126 (4.0%) with LTBI were screened for TB prior to immigrating to the United States. Most children with TB and LTBI (59.8%; range, 31.3%-90.8%) had a private health care provider at the time of diagnosis.

SOURCE OF TRANSMISSION TO CHILDREN

In this study, 72 source patients were identified. A source patient was more likely to be found for children having TB compared with children having LTBI (42.3% vs 11.4%, respectively; relative risk=3.7; 95% confidence interval, 2.5-5.4). Although the source patient commonly lived in the same home as the child (64.0%), a home visit to assess possible contacts was not conducted for 4 source patients and this information was not recorded for 19 source patients.

Of the 63 source patients for whom complete information was available, 40 (63.5%) were foreign born from 15 different countries and 23 (36.5%) were born in the United States (Table 2). A TB evaluation was not documented for any of the foreign-born source patients prior to immigrating to the United States. Notably, 21 of the 59 US-born children (35.6%) had source patients born outside the United States. Although all of the source patients had at least 1 known TB risk factor (eg, foreign born, homelessness), opportunities to prevent TB in the source patients were missed. Nineteen source patients (30.2%) were previously known to have LTBI but were not treated. Three other source patients were started on treatment for LTBI but did not complete therapy and 1 was nonadherent to treatment.

Three of the 63 source patients had an initial presumptive diagnosis other than TB (2 as community-acquired pneumonia and 1 as upper respiratory tract infection). Nonadherence to treatment was documented for 11 source patients (17.5%). Compared with 6.4% of patients with TB

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1.5% nationally.17 Respiratory specimens were available (4.8%) were started on only 1 or 2 drugs compared with 7.9% missed 3 or more medical appointments. who had information regarding adherence to clinic visits, days and 18 days, respectively. For the 60.1% of children rifampin to the start of treatment for TB and LTBI were 4.5

treatment (receiving treatment). The median times from chest radiography to the start of treatment for TB and LTBI were 4.5
days and 18 days, respectively. For the 60.1% of children who had information regarding adherence to clinic visits, 7.9% missed 3 or more medical appointments.

**CASE MANAGEMENT**

*Mycobacterium tuberculosis* was cultivated from 83 children with TB (67.5%). Seven children (5.7%) were started on 2 or fewer drugs. Treatment by directly observed therapy was used extensively for children with TB (89.4%) and treatment completion was high (88.6%). In contrast, treatment by directly observed therapy was less frequent in children having LTBI (4.7%) and treatment completion was lower (53.7%) completed treatment and 11.4% were still receiving treatment). The median times from chest radiography to the start of treatment for TB and LTBI were 4.5 days and 18 days, respectively. For the 60.1% of children who had information regarding adherence to clinic visits, 7.9% missed 3 or more medical appointments.

**OBSTACLES TO IMPLEMENTING PREVENTION OPPORTUNITIES**

During most contact investigations (70.0%), public health investigators encountered 1 or more substantial barriers that nationallу.16 10 source patients (15.9%) were started on a 3-drug regimen rather than a 4-drug regimen; 3 patients (4.8%) were started on only 1 or 2 drugs compared with 1.5% nationally.17 Respiratory specimens were available for 61 source patients, of whom 51 (83.6%) had positive sputum smear results for acid-fast bacilli and 57 (93.4%) had positive culture results for *M. tuberculosis* complex. Eight source patients (13.1%) had resistance to at least 1 first-line antituberculosis drug, including 2 source patients who had multidrug-resistant TB.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age, median, y</td>
<td>31.5</td>
</tr>
<tr>
<td>Child's relationship to source, No. (%) (n=86)</td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>29 (33.7)</td>
</tr>
<tr>
<td>Other relative</td>
<td>28 (32.6)</td>
</tr>
<tr>
<td>Nonrelative</td>
<td>15 (17.4)</td>
</tr>
<tr>
<td>Not documented</td>
<td>14 (16.3)</td>
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<tr>
<td>Country of birth, No. (%)</td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>23 (36.5)</td>
</tr>
<tr>
<td>Mexico</td>
<td>19 (30.2)</td>
</tr>
<tr>
<td>Other</td>
<td>21 (33.3)</td>
</tr>
<tr>
<td>Time in United States to start of TB therapy, y (n=31)</td>
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</tr>
<tr>
<td>Median (median range for sites)</td>
<td>5.1 (1.3-13.8)</td>
</tr>
<tr>
<td>Mean</td>
<td>10.6</td>
</tr>
<tr>
<td>Duration of symptoms, wk (n=39)</td>
<td></td>
</tr>
<tr>
<td>Median (median range for sites)</td>
<td>6.5 (0.7-36.0)</td>
</tr>
<tr>
<td>Mean</td>
<td>8.3</td>
</tr>
<tr>
<td>Delay from report to child's visit, d</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>14.3</td>
</tr>
<tr>
<td>Mean</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Abbreviation: TB, tuberculosis.

a Nine additional source patients (resulting in 5 children with TB and 4 children with latent TB infection) were reported without sufficient data for further analysis.

b Restricted to foreign-born source patients.

potentially threatened the effectiveness of the investigation (Table 3). The most common difficulties were related to language differences, logistical barriers associated with the inability to find or identify contacts, or contacts who refused evaluation.

Before TB was diagnosed, 37 children (30.1%) had prior testing with a negative TST result (Table 4); 27 of these children had a TST conversion to a positive result within 2 years. In addition, LTBI was previously diagnosed in 10 children; however, only 6 of the children started treatment. Among the 298 children with LTBI, 42 (14.1%) had a previously documented nega-

<table>
<thead>
<tr>
<th>Problem</th>
<th>No./Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language barrier</td>
<td>12/48 (25.0)</td>
</tr>
<tr>
<td>Incomplete information</td>
<td>15/60 (25.0)</td>
</tr>
<tr>
<td>Translator needed but not used</td>
<td>8/44 (18.2)</td>
</tr>
<tr>
<td>Unable to find contacts</td>
<td>7/48 (14.6)</td>
</tr>
<tr>
<td>Contacts refused evaluation</td>
<td>7/48 (14.6)</td>
</tr>
<tr>
<td>Missed appointments</td>
<td>6/48 (12.5)</td>
</tr>
<tr>
<td>Unwilling to name contacts</td>
<td>4/48 (8.3)</td>
</tr>
<tr>
<td>Home visit not done</td>
<td>3/44 (6.8)</td>
</tr>
<tr>
<td>Investigation not done</td>
<td>1/60 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: LTBI, latent tuberculosis infection; NA, not applicable; TB, tuberculosis; TST, tuberculin skin test.

a For came to medical attention to reported to health department, the median was 12 days, the mean was 33.3 days, and the range was 0 to 190 days (n=114). b Twenty-seven children with TB and 42 children with LTBI were removed from the analysis because they were found through a contact or source case investigation.

Table 2. Characteristics of 63 Adult Source Patients Linked to 52 Children With Tuberculosis and 34 Children With Latent Tuberculosis Infectiona

Table 3. Problems Encountered During 60 Contact Investigations of Source Patients Linked to Children Younger Than 5 Years With Tuberculosis or Latent Tuberculosis Infectiona

Table 4. Missed Interventions to Prevent and Manage Tuberculosis and Latent Tuberculosis Infection in Children Younger Than 5 Yearsa
Preventing *M tuberculosis* transmission and TB disease in young children is an essential public health activity. Our study demonstrates weaknesses in current private and public prevention practices as they pertain to TB screening for foreign-born persons entering the United States, TB investigations, and treatment for LTBI. For example, we found that slightly more than half of children with LTBI completed treatment, a finding consistent with another national study.21,22 The underuse of directly observed therapy for LTBI results in low completion rates, putting children who do not complete treatment at risk for subsequent TB disease.

The influence of global TB is evident in this study population. Almost 40% of children had a risk factor related to country of birth, parental origin, or travel to a country with a high incidence of TB. Yet, despite high rates of TB among children shortly after entering the United States,23,24 only 2 children were known to have TB screening before entry; both children had TB on entry. Other diagnostic delays may have resulted from foreign-born adults entering the United States with no TB evaluation because they are nonimmigrant visitors exempt from screening or had an evaluation using the limited current TB screening practices.21,22 Our data support the importance of health departments focusing on nontraditional risks such as US-born children who may have immigrant parents and who may travel to their parent’s country of origin or ingest unpasteurized milk or milk products.23,24

In our study, we documented adult source patients with diagnostic delays.5,23,26 Twelve of 63 source patients (19.0%) were mothers of the children. A possible missed opportunity for prevention was the failure to complete the TB evaluation and treatment after pregnancy. In a recent study27 from New York, only 9.3% of non-US-born women completed postpartum treatment for LTBI.

The proportions of children having TB and LTBI who did not have a source case investigation done, 14.6% and 28.1%, respectively, suggest that these investigations might be an underused strategy to target children at risk and should be a routine TB control activity where resources permit.7,28,29

We identified limitations in carrying out contact and source case investigations, essential methods for identifying children at risk for TB and LTBI. Barriers encountered were related to language differences, disagreement in beliefs about the value of medical treatment, and legal issues and perceptions around naming contacts.30 These issues adversely affect the ability of health department staff to effectively obtain information on contacts and locations of potential transmission. Perhaps the most striking missed opportunity is that despite known risk factors for TB, many source patients were not tested for LTBI or, if known to have LTBI, either were not treated or had an inadequate course of treatment. We found that children were not always named as contacts and delays in evaluation occurred even when children were linked to a known source patient.4,5,31,32 Another underused intervention was having home visits conducted for source patients, although home visits are known to increase the yield of high-risk contacts, especially children.33 We also found documentation of delays in the diagnosis and treatment of adults with pulmonary TB, delays that have been associated with TB transmission20 and the development of TB disease in children.4,5

This study is limited in that it relies on medical records and events reported to the health department. Databases of medical records and public health logs might lack essential information for fully assessing the timing and extent of use of prevention interventions. For example, health care providers did not routinely ask questions assessing risk factors such as travel to another country. An additional limitation is that in those sites using clinic-based enrollment, their study population might not be representative of all children with LTBI. However, the population of children with LTBI has not been entirely defined and their demographic characteristics differ from locality to locality.34 Nevertheless, we believe that many findings from this study are applicable to other areas of the country.

In summary, we assessed current practices for preventing pediatric TB disease and LTBI. The children in this study were predominantly from minority groups, reflecting the health disparity in this country. In agreement with a recent study showing that black and Hispanic children are less likely to receive counseling for preventive care,35 we report on failures to test children for LTBI and, surprisingly, have found that children with TB were more likely to be born in the United States. One explanation is that children in the United States are more likely to be recently infected, especially those identified through a contact investigation, and disease tends to occur relatively rapidly in children. The children who were born outside the United States may have had more longstanding infection and thus may be at lower risk for disease.

In light of the multiple underuses of TB prevention measures found in this study, health departments should evaluate each child with TB to determine why interventions were not brought to bear in time to prevent TB infection and stop progression to disease. Ultimately, to accelerate the decline of TB in the United States, health departments must adopt a policy of zero tolerance for pediatric TB.

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Author Contributions: Dr Lobato had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Lobato, Sun, Saiman, and Reichard. Acquisition of data: Lobato, Sun, Moonan, Weis, Saiman, Reichard, and Feja. Analysis and interpretation of data: Lobato, Sun, Weis, and Saiman. Drafting of the manuscript: Lobato and Sun. Critical revision of the manuscript for important intellectual content: Lobato, Sun, Moonan, Weis, Saiman, and Reichard. Study supervision: Lobato, Weis, and Saiman.

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