**A Retrospective Cohort Analysis of Pediatric Tuberculosis in North Carolina, 1994-2002**

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**Abstract**

**Background**: The incidence of pediatric tuberculosis (TB) in North Carolina decreased from the mid 1990s to 2001. In 2002, the number of pediatric TB cases increased from 9 in 2001 to 32 in 2002, representing more than a 250% increase.

**Objective**: To describe the epidemiology and clinical characteristics of pediatric TB in North Carolina and identify factors contributing to the rise in tuberculosis cases among children less than 15 years of age.

**Methods**: Retrospective review of TB surveillance data and local health department records of all reported pediatric TB cases and their source case between the years 1994 and 2002.

**Results**: 180 cases of pediatric TB were reported from 1994-2002. The incidence of pediatric TB increased from 0.53 to 1.85 per 100,000 from 2001 to 2002. TB case rates in 2002 were higher in children less than 5 years of age (3.05 per 100 000) compared to children 5-14 years of age (1.28 per 100 000). TB case rates were 10- to 44-fold higher among minority children compared to non-Hispanic white children. Although there was no significant increase in the incidence of TB in the Hispanic pediatric population, there was a significant increase in the proportion of Hispanic children with tuberculosis (p-value =.04). Children with a foreign association accounted for an increasing proportion of pediatric TB cases over time, however, the increase was not statistically significant (p-value = 0.09). Transmission of TB to children could have been prevented in 6.75% of cases had a source case identified the child as a contact, and in 11.7% of cases had the source case completed prophylaxis for latent TB infection. TB disease may have been prevented in 7.2% of cases had the contact investigation not been delayed, 2.2% of cases had children with latent TB infection completed prophylaxis, and in 4.4% of cases had child contacts <5 years of age with a negative PPD taken or received prophylaxis. Overall, 51/180 cases (28.3%) might have been prevented had appropriate measures been taken.

**Conclusion**: The incidence of pediatric TB increased significantly from 2001 to 2002. TB in the minority population continues to be a problem. TB in children with a foreign-association is increasing. Improvements in contact investigations and completion of prophylaxis for LTBI may reduce the incidence of pediatric TB.

## Introduction

While tuberculosis (TB) continues to be a problem in much of the developing world, the incidence of TB in the United States is declining. Recently, the Centers for Disease Control and Prevention (CDC) reported that the national incidence of TB for the year 2002 was 5.2 per 100,000 population.[1] This represented a 43.5% decline from the 1992 TB case rate and is the lowest recorded TB case rate since the inception of TB surveillance in 1953.

North Carolina has experienced similar trends in its rates of TB. From 1994 to 2001, the total TB case rate decreased 38%, from 7.86 per 100,000 to 4.84 per 100,000. The case rate for pediatric TB also declined during this time from 1.93 to 0.53 per 100,000, or 73%. However, in 2002, this trend towards decreasing TB rates reversed itself as the number of both adult and pediatric TB cases increased. In North Carolina, 32 TB cases in children less than 15 years of age were reported in 2002, an increase of 250% from the previous year. The 32 pediatric TB cases are the most in North Carolina since 1993, when 33 cases were reported in this age group.

While other states in the Southeast region including Alabama, Mississippi, Tennessee, Virginia, have observed increases in the number of pediatric TB cases in 2002 (63.6%, 71.4%, 58.3%, and 50% respectively), none have paralleled the increase observed in North Carolina.[2] Therefore, the substantial increase in cases observed in North Carolina appears to be an isolated occurrence within the Southeast region.

The rise in pediatric tuberculosis is concerning for several reasons. First, most cases of pediatric TB are the result of a primary infection and therefore reflect recent transmission of tuberculosis within the community.[3] Controlling pediatric TB requires rapid identification of all child contacts to adult TB cases and early evaluation and treatment of infection.[4] Current guidelines recommend that children less than 15 years of age who have been exposed to an adult case should be evaluated for TB within one week of being named as a contact.[5] Additionally, exposed children less than 5 years of age with a negative tuberculin skin test on initial evaluation should be placed on prophylactic therapy until they are reexamined in 3 months time.[6] Another cause for concern is that tuberculosis in children is a more severe disease. Young children, especially infants, have higher rates of miliary and meningeal tuberculosis than individuals over 15 years of age.[7,8] Additionally, young children tend to progress from latent infection to active disease much more rapidly than older children and adults.[9,10] Finally, transmission of infection to children will continue to increase the pool of individuals infected with the bacteria and at risk for reactivating and potentially transmitting disease in the future.

Prior epidemiological studies of pediatric tuberculosis in the United States have equated rises in pediatric TB incidence to the increasing number of foreign-born individuals arriving in the United States. These studies found that many children acquired TB infection either outside the United States or within the United States, but from a contact born in a TB endemic region.[11,12] The impact of the foreign community on TB rates in the United States is significant. Previous studies demonstrated that the resurgence of TB observed in the late 1980s and early 1990s was in part due to the rapid influx of immigrants from TB endemic regions.[13] In 2002, foreign-born individuals accounted for the majority of TB cases reported in the United States (51%) and the ratio of foreign-born to US-born cases doubled between 1992 and 2002.[1]

Compared to other states, North Carolina has experienced the greatest percent change in foreign-born population over the past decade. Between 1990 and 2000 North Carolina experienced a 274% increase in the foreign-born population and almost a 400% increase in the Hispanic population.[14] Given these demographic changes and the recent increase observed in the number of pediatric TB cases, we conducted a retrospective cohort analysis of pediatric TB in North Carolina from 1994 to 2002 to test two hypotheses. First, we hypothesized that the increase in the number of pediatric TB cases in 2002 represented a significant increase in the incidence of pediatric TB in North Carolina compared to previous years. Second, we hypothesized that the surge in pediatric tuberculosis is related to the rise in the number of foreign-born individuals, particularly the rise in the Hispanic population. In other words, we hypothesized that there are population specific differences in the rates of pediatric TB with respect to race and ethnicity and to country of origin. Secondary aims of this study were to describe the epidemiology and clinical characteristics of pediatric TB in North Carolina from 1994-2002.

## Methods

*Definitions*

We defined a tuberculosis case as any case that met the tuberculosis surveillance-case definition of the Centers for Disease Control and Prevention and that was subsequently reported to the CDC as a verified tuberculosis case.[15] We defined a pediatric tuberculosis case as a tuberculosis case in any child less than 15 years of age. We defined a source case as an individual 15 years of age or greater with smear- or culture- positive pulmonary or laryngeal TB who came into contact with a child diagnosed with tuberculosis. A source case was designated a "household" contact if they lived in the same house or apartment as the pediatric TB case; "close" contact if they did not live in the same household as the pediatric TB case but were either friends or relatives of the child or spent greater than 20 hours a week with the child; and "not close" contact if they were not a relative or friend and spent less than 20 hours a week with the pediatric TB case.

The mode of presentation refers to how the child initially came to the medical attention of clinicians. A child was assigned to the "contact investigation" category if an adult diagnosed with tuberculosis named the child during an investigation conducted by the local health department. Alternatively, the child's parent or guardian could have brought the child in for evaluation and TB skin testing because of knowledge of an ongoing contact investigation and concern about the child's exposure to a known TB case. A child was assigned to the "symptomatic presentation" category if the child presented to a health care provider because of symptoms referable to TB. A child was placed in the "screening association" category if a child came to medical attention because of a positive tuberculin skin test performed solely for screening purposes (ie. school entry, immigration) or if a tuberculin skin test was placed because of another health problem. We designated children as having a 'foreign association" if the child was either foreign-born, had at least one parent who was foreign-born, or a source case that was born outside the United States. "Failure to identify a child" refers to source cases with documented pulmonary or laryngeal TB who did not initially name as a contact a child who subsequently developed TB. An 'initial evaluation' refers to the first assessment conducted to diagnose TB disease in an individual. This assessment consists of a medical history to illicit symptoms referable to TB and risk factors for TB, a tuberculin skin test, and a chest x-ray.

*Data Collection*

North Carolina statutes require all suspected and confirmed cases of *Mycobacteria tuberculosis* to be reported to the local health department. If the local TB control program confirms a suspected case of TB using standard CDC tuberculosis case-definitions, data are then collected on the CDC Report of Verified Case of Tuberculosis (RVCT) forms. The forms are then submitted to the North Carolina Tuberculosis Control program, a branch of the Public Health Division of the North Carolina Department of Health and Human Services. Data recorded on the RVCT forms include demographic, clinical and treatment information, drug susceptibility results, and social risk factors for TB such as HIV status, homelessness, and drug use. Data reported on the RVCT forms are entered into the North Carolina Tuberculosis Information Management System (TIMS) database.

Given that pediatric TB has a more variable presentation than tuberculosis in adults, it is possible that the diagnosis of tuberculosis may not be made initially. Compared to adults, children are less likely to have positive sputum smears or cultures making a definitive diagnosis of tuberculosis difficult. This could result in underreporting of pediatric TB cases. However, if there is a high suspicion that a child may have TB based on history of exposure and symptoms, it is possible they may be treated for TB despite confirmation due to increased risk of TB complications. Since these children are being treated for presumed TB disease, they are reported to the CDC as a case despite definitive evidence. Therefore, it is possible that the annual number of cases reported and counted in the state may actually be an overestimate.

Members of the North Carolina TB Control Program and a volunteer [the author of this paper, K.S.] selected for retrospective review all reported cases of tuberculosis in children less than 15 years of age during the years 1994-2002. Once cases were identified, local and state TB Control Program staff [including volunteer, K.S.] retrospectively reviewed local health department records of each reported pediatric TB case to obtain data not already available using the RVCT database. Data sought from the chart reviews included: prior history of positive tuberculin skin test, prior history of treatment for latent tuberculosis, parents' country of birth, history of recent foreign travel, insurance status, and mode of presentation. For children diagnosed through a contact investigation, additional information with respect to their diagnostic workup and management, their degree of exposure and relationship to the suspected source case, and time elapsed to the commencement of the initial evaluation for TB was collected. For children diagnosed through symptomatic presentation or screening association, health department records were reviewed to determine whether a source case was identified.

For children diagnosed through a screening association, the reason for screening was also recorded.

Local and state TB Control Program staff and volunteer [K.S.] also reviewed the local health department records of any identified source cases. Information sought from the source case records included: the relationship to the identified child, the degree of contact with the child, history of a previous positive tuberculin skin test, history of treatment for latent TB, sputum smear result, quantity of acid-fast bacilli on sputum smear, history of recent foreign travel, how they were diagnosed with TB, history and duration of cough, duration of any other symptoms referable to TB, whether they named the child as a contact, and insurance status. Demographic, clinical and treatment data about source cases, in addition to social risk factors and drug susceptibility results, were also collected using the RVCT database.

Once data was collected and organized, names of all pediatric TB cases and their respective source cases were deleted to create a limited data set. Institutional review board approval was received from both Duke and the University of North Carolina for the analyses, which were then conducted using only the limited data set.

*Statistical Analysis*

Updated intercensal population estimates provided by the U.S. Census Bureau for age, race, and ethnicity using year 2000 census data were not available at the time of the analysis for the state of North Carolina. In an effort to calculate case rates based on age, race, and ethnicity we derived our own population estimates for the intercensal years. Estimates were calculated using the formula

$A=A_0e^{\wedge\lambda t}$ and were based on the assumption that population would grow exponentially over time. Population figures from the 1990 and 2000 U.S. census were used as the base population. All case rates were calculated per 100, 000 persons.

Incidence trends in pediatric TB by age, race and ethnicity were analyzed using Poisson regression to model trends over time, with the Pearson chi-square correction for overdispersion. We chose to use Poisson regression because data analysis of the counts of events, in this case the number of pediatric TB cases per 100,000 persons, generally follows the Poisson distribution. Trends in the proportion of TB in foreign-born and foreign-associated children were analyzed in three-year intervals using the chi square test for trends. Trends in the proportion of pediatric to adult TB incidence were analyzed in one-year intervals using the chi square test for trends. Differences in proportions were assessed using the chi-squared test or Fisher's exact test. Continuous variables were compared using the student's t-test, and relative risk and 95% confidence intervals were calculated where appropriate. For all statistical tests, a p-value $< .05$ (two-tailed) was considered significant.

## Results

A search of the North Carolina TIMS database for reported TB cases in persons less than 15 years of age from 1994 to 2002 identified 183 pediatric TB cases. Of the 183 identified cases, 3 were excluded because review of their health department records revealed they were actually adult cases. Therefore, a total of 180 pediatric tuberculosis cases were included in our analysis.

*Trends in Pediatric TB in North Carolina from 1994 to 2002*

The demographic characteristics of the 180 children with tuberculosis are presented in Table 1. The incidence of pediatric TB decreased from 1.93 per 100,000 in 1994 to 0.53 per 100,000 in 2001. This decline represented a significant trend towards decreasing pediatric TB incidence (p-value = .02). In 2002, the incidence of pediatric TB increased to 1.85 per 100,000. This incidence exceeded the upper limit of the 95% confidence interval for pediatric TB incidence in 2002 as predicted by our Poisson regression model had the trend continued (Figure 1).

The majority of pediatric TB cases occurred in children less than 5 years of age. Over the nine- year study period, the incidence of TB in children 0-4 years of age increased from 0.82 per 100,000 in 1994 to 3.05 per 100,000 in 2002. In contrast, the incidence of tuberculosis decreased from 2.49 per 100,000 in 1994 to 1.28 per 100,000 in 2002 in children 5 to 14 years of age (Figure 2). No significant trends in TB incidence were detected in either of these two age groups.

Foreign-born children accounted for 13.9% of pediatric TB cases. Table 2 lists the country of origin for each of the foreign-born cases. Overall, children with a foreign association (see definition in Methods section) accounted for 27.8% of all pediatric TB cases reported during the study period. Trends in the proportion of pediatric TB among children with a foreign association were analyzed in three-year intervals. From 1994 to 1996, children with a foreign association accounted for 18% of pediatric TB cases reported during this time. The percentage increased to 35.6% from 2000 to 2002. Although there was a substantial increase in the proportion of TB cases attributed to children with a foreign association over time, the increase fell short of statistical significance (p-value = .09). Subgroup analysis of foreign association by age group did not reveal any significant trends over time.

Minority children were disproportionately affected with TB (Table 1). Minority children accounted for 88.3% of all pediatric TB cases. Non-Hispanic black children accounted for the majority of pediatric TB cases (63.3%), with Hispanic children having the second highest frequency of TB (18.3%). The case rate in all non-Hispanic children less than 15 years of age fell from 1.78 per 100,000 in 1994 to 0.44 per 100,000 in 2001. Using the Poisson regression model, this decrease represented a significant trend towards declining rates (p-value = 0.002). However, in 2002, the incidence of TB in non-Hispanic children less than 15 years of age increased to 1.39 per 100,000. This incidence exceeded the upper limit of the 95% confidence interval for TB incidence in non-Hispanic children as predicted for 2002 by the Poisson regression model (figure 3).

In 2002, 22 cases of pediatric TB occurred in non-Hispanic children, compared to a total of 7 in 2001. Nineteen of the 22 cases in non-Hispanic children occurred in the non-Hispanic black population. The 19 cases in this population are higher than the number reported in this population in previous years (range 7-14 reported cases in non-Hispanic blacks from 1994-2001). The substantial increase of pediatric TB in non-Hispanic black children in 2002 can be attributed to two microepidemics of TB transmission. In both instances, an adult was symptomatic for more than 4 months before being diagnosed with TB and infected four children. While one adult was a close contact to the children, the other adult was not a close contact (see definitions in Methods section).

With respect to pediatric TB in the Hispanic population, while no significant trend in TB incidence in Hispanic children was observed, the proportion of TB cases in Hispanic children did increase over time. When analyzed in three-year intervals, the proportion of TB cases in Hispanic children increased from 8.2% (1994-1996) to 25.4% (2000-2002). This represented a statistically significant increase in the proportion of TB cases attributed to Hispanic children less than 15 years of age (p-value = .04). Hispanic children also accounted for 91% of all foreign-associated TB cases.

*Mode of Presentation*

Of the 180 pediatric TB cases, 93 children came to the attention of TB clinicians through contact investigations (51.7%), 58 children initially presented symptomatically (32.2%), and 25 children (13.9%) were found through a screening association (figure 4). The mode of presentation for 4 children was unknown (2.2%).

Of the 93 children identified through contact investigations, 64 were determined to have disease upon completion of the initial evaluation (68.8%). Nineteen children (20.4%) identified through contact investigations had no evidence of active disease after the initial evaluation but developed clinical symptoms of TB disease or chest x-ray changes suggestive of active disease before the three-month follow-up visit. An additional 4 children were diagnosed with active disease at the 3-month follow-up visit (4.3%), and the results for the remaining 6 (6.5%) children are unknown (figure 4).

US-born children were more likely than foreign-born children to be identified through a contact investigation (OR=5.25, 95%CI 2.85, 47.75). When compared to non-Hispanic white children, non-Hispanic black children were more likely to be identified through a contact investigation (OR=2.04, 95%CI 0.81, 5.16), while Asian children were less likely to be identified through a contact investigation (OR=0.27, 95%CI 0.05, 1.44).

Of the 25 children identified through a screening association, 8 children were screened during well child visits, 5 children were screened for immigration or refugee purposes, and 3 were screened because of an abnormal finding during evaluations for an unrelated health problem. The reasons for TB screening in the remaining 9 children are unknown.

*Source Case Characteristics*

A total of 82 source cases were identified. Because a number of children had the same source case, a source case was found for a total of 113 of the 180 pediatric TB cases (62.8%). Non-Hispanic black children (OR = 2.6, 95% CI

1.87, 3.64) and children born in the United States (OR = 8.64, 95%CI 3.42, 21.84) were significantly more likely to have a source case identified. Hispanic children were less likely to have a source case identified (OR = 0.45, 95% CI 0.21, 0.98).

The source case was a parent, guardian, or relative of the child contact in 78.8% (89/113) of children for whom a source case was identified. Source cases were household contacts to 60 children (53.1%). An additional 42 children (37.2%) were close contacts to the source case, while 5 children (4.4%) were not close contacts to the source case. The contact status of 6 children (5.3%) was unknown.

Some demographic and clinical characteristics of the source cases are presented in Table 3. Of the 82 source cases, 16 (19.5%) were foreign-born, with Mexico being the most common country of origin. The sputum smear was AFB positive in 87.8% of the source cases (72/82) of which 68.1% (49/72) were markedly smear-positive, with 3+ AFB on the smear. When compared to the cohort of all adult TB cases, source cases were significantly more likely to be female, have a cavitary lesion on chest x-ray, and have a positive sputum smear.

*Missed Opportunities to prevent TB transmission or disease*

We identified several missed opportunities to decrease the probability of disease progression in children. Focusing on the 93 children identified through contact investigations, 51 (54.8%) were brought in for evaluation within one week of being named as a contact, and 66 (71.0%) were brought in for evaluation within two weeks. Initial evaluations were delayed by more than 2 weeks for 13 children, representing 7.2% of all pediatric TB cases. In addition, there were 8 children (4.4% of all TB cases) less than 5 years of age exposed to TB who had a negative PPD on initial evaluation but either failed to take prophylaxis or were not prescribed prophylactic therapy as recommended by the CDC and the North Carolina TB Control Program. Finally, 4 children with a prior positive tuberculin skin test failed to complete a full course of prophylaxis for latent TB infection.

Opportunities to prevent disease transmission were also identified. Twelve children who were contacts to an adult TB case were never named as contacts during the contact investigation. These 12 children represented 6.8% of all pediatric TB cases. Furthermore, disease transmission might have been prevented in 21 children (11.7% of all pediatric TB cases) had 16 of the 24 source cases with a prior positive tuberculin skin test completed a full course of prophylaxis. Had appropriate measures been taken, a total of 51 (28.3%) pediatric TB cases may have been prevented from 1994-2002.

## Discussion

We hypothesized that the increase in the number of pediatric tuberculosis cases in 2002 represented a statistically significant increase in pediatric TB incidence. Our results support this hypothesis. We found that the incidence of pediatric TB in North Carolina in 2002 was significantly higher than expected using a Poisson regression analysis to model trends over time. Although other statistical tests for trends did not find a significant increase in incidence, we believe these tests are inappropriate to model incidence over time.

The incidence of pediatric TB in North Carolina for 2002 was higher than the national pediatric TB case rate of 1.5 per 100,000, which is unchanged from the 2001 case rate. North Carolina is the only state in the Southeast region with this significant of an increase in pediatric TB. In fact, nationally, only Oklahoma experienced a greater absolute increase in pediatric TB cases than North Carolina.[2] Whether the increase in pediatric TB incidence in North Carolina is an isolated occurrence or is the beginning of a new trend is unclear. Continued surveillance of pediatric TB incidence over the next several years will be necessary in order to make this determination.

The incidence of TB in children less than 5 years of age was found to be higher than those in the older age group (5-14 years of age) from 1997 to 2002. Prior studies have also demonstrated higher case rates in this younger population.[16,17,18] The higher incidence in the younger age group may reflect increased susceptibility to disease or increased exposure to adult TB cases.

In order to ascertain the impact of the foreign community on the increase in pediatric TB incidence, we elected to analyze trends using foreign association in lieu of foreign-birth. We feel foreign association is a better reflection of the impact of the immigrant community on pediatric TB rates. Many immigrants from TB endemic countries have already been infected with *Mycobacterium tuberculosis* prior to immigrating to the U.S. and roughly half will progress to active disease within 5 years of arriving.[13,19] Therefore, TB disease in U.S.-born children of these immigrants likely reflects the global burden of TB. Classifying these cases as US-born cases minimizes the impact of the immigrant community on pediatric TB rates. Though we observed an increase in the proportion of children with TB and a foreign association over time, this increase was not statistically significant (p-value = .09). Given that North Carolina had the largest percent increase in its foreign-born population (274%) of any state, we would have expected a greater impact. However, foreign-born persons only make up 5% of the total North Carolina population. Thus, the small absolute numbers of foreign-born individuals in the state may explain why trends in foreign association were not significant.

Minority children were disproportionately affected with TB having rates anywhere from 10 to 44-fold times higher than those observed in non-Hispanic white children. While the case rates for minority children in North Carolina decreased since the last published report of pediatric TB in the state[20], the disparity continues to be striking. Potential causes for the higher rates of TB in minority children might include higher incidence of tuberculosis in adult minorities, decreased access to health care, poorer living conditions, and more frequent exposure to adults at increased risk for TB. Additionally, minority children are more likely to have a foreign association thereby increasing their risk for exposure to TB.

Although Hispanic children accounted for a significantly greater proportion of pediatric TB cases over time, no trend towards increasing incidence of TB in Hispanic children was observed. In contrast, a trend towards declining TB rates in the non-Hispanic children was observed from 1994 to 2001. In 2002, the incidence of TB in non-Hispanic children exceeded the predicted incidence as determined by the Poisson regression analysis. We found that the increase in the non-Hispanic population could be attributed to two microepidemics of childhood cases in separate North Carolina counties. In both these instances, the adult source case did not seek health care despite having symptoms of active TB for greater than 4 months. The reasons why care was not sought could not be determined in this retrospective study. Possible reasons include lack of health insurance (or other barriers to care), lack of education or insight as to the severity of their illness, or competing priorities such as alcohol or drug abuse. Future prospective studies are needed to more definitively identify reasons for prolonged infectiousness, which can then help direct future interventions.

Pediatric TB cases came to medical attention in one of two major ways: by virtue of a contact investigation or the development of symptoms of TB disease. The majority of pediatric TB cases, 51.7%, were detected through contact investigations. Although this is lower than the 80% detection rate previously reported in North Carolina,[20] it is similar to the proportion diagnosed through contact investigations in a study of pediatric TB in Houston, Texas.[21] It is commonly believed that because young children have fewer contacts and because most cases of TB in children reflect recent transmission, a source case should be identified more frequently. However, as we found in our study, children with TB are increasingly more likely to have a foreign association. Since these children may be infected outside the United States (if foreign-born) or by short-term visitors from TB endemic regions, it may be difficult to identify these children through a contact investigation. Therefore, the lower percentage of children identified through contact investigations in our study, compared to Nolan's,[20] can be partly attributed to the increasing number of children with a foreign association in North Carolina over time.

Another one-third of children were evaluated because of symptoms or signs referable to TB (58/180). Of these, a source case was retrospectively identified in 15/58 children who presented symptomatically. The percentage of children evaluated because of symptoms or signs of TB is similar to what has been reported elsewhere[21,22] and highlights a systematic failure to identify latent infection and implement therapy to prevent disease progression.

A source case was eventually identified in almost two-thirds of pediatric TB cases. Non-Hispanic black children and children born in the United States were significantly more likely to have a source case identified, while Hispanic children were significantly less likely. Reasons for this are similar to those mentioned earlier with regards to detection through contact investigations.

Source cases were more frequently primary caregivers or household contacts, both of which are known risk factors for TB infection in child contacts.[23] Additionally, when compared to the cohort of all adult TB cases, source cases were significantly more likely to have a positive sputum smear or a cavitary lesion on chest x-ray. This finding supports the conclusions of other investigators that positive sputum smear and cavitary lesions on chest film in a source case are predictive of TB disease in child contacts.[24] Interestingly, we also found that source cases were significantly more likely to be female. Historically, there is almost a 2:1 male to female ratio in adult TB cases. The higher frequency of female source cases is not surprising since they tend to be more involved in child care and therefore are in closer contact with children than their male counterparts.

Since childhood tuberculosis usually results from recent transmission of TB within the community, each case is considered evidence of ongoing community transmission of disease and is a failure on the part of the public health system to prevent disease. We identified several missed opportunities to prevent either transmission or progression of disease in children. A little over one-fourth of pediatric TB cases (51/180, 28.3%) may have been averted had these opportunities for prevention not been missed. This is consistent with data reported from Alabama, Houston, and a previous study from North Carolina.[20, 25, 26] Failure of adult source cases to take previously prescribed prophylaxis for latent TB infection with subsequent development of active disease and transmission to children accounted for the majority of preventable cases (11.7%). Achieving higher rates of completion of prophylaxis for latent TB infection would help to reduce the TB burden in children. Directly observed preventive therapy (DOPT) for adults is offered in only some counties in North Carolina. In contrast, DOPT is provided for children with latent TB infection who were contacts to a case of TB. Providing DOPT to infected adults, while ideal, would place a significant strain on health department resources. Furthermore, while treatment of active TB is required by law, treatment of latent TB (TB prevention) is an option individuals may choose or decline. Educating individuals about the benefits of prophylactic therapy probably remains the most feasible method to increase compliance with prophylactic therapy.

TB transmission may also have been prevented in 6.8% of cases had child contacts been named by adult source cases during the contact investigation. The inability to elicit these names could be considered interview failures. In a recent study conducted by the CDC, 13% of TB patients did not have any contacts identified. Since most people interact with at least a few other individuals, nearly every case of TB should have at least one contact identified. Thus, the inability to elicit contacts may reflect either interviewer skill, interviewer understanding of the patient's social environment, or the patient's desire to keep personal interactions and relationships private.[27] Improved and continued training of TB field staff is warranted increase the numbers of contacts named.

Delayed contact investigations also resulted in several missed opportunities to prevent disease in children. Child contacts to adult cases are supposed to be evaluated within one week of being identified.[5] We found that in approximately 7% of our pediatric TB cases, initial evaluations were delayed by more than 2 weeks. Reasons for these delays were not identified in this retrospective analysis. Possible causes may include transportation difficulties, language barriers, work-related problems, or indifference. Program deficiencies may include inadequate staffing precluding repeated home visits, competing priorities, or lack of skill in eliciting names of contacts.

Four cases of TB (2.2%) occurred in children with known latent tuberculosis infection. These children developed disease after failing to comply with prophylactic therapy. Of even greater concern is the development of disease in 8 children (4.4%) less than 5 years of age exposed to TB, with a negative PPD upon initial evaluation, and who subsequently did not take or were not prescribed prophylaxis while awaiting their 3-month evaluation. The CDC, American Academy of Pediatrics, and American Thoracic Society jointly recommend that exposed children less than 5 years of age should be placed on prophylactic therapy until a 3- month follow-up evaluation has been completed and infection has been ruled out.[6] This recommendation stems from the fact that the tuberculin skin test can take up to 12 weeks post-exposure to convert, that young children can quickly progress to disease, and that in young children more severe forms of tuberculosis can occur within the first few months of exposure. Our finding of 4.4% of cases resulting from this missed opportunity is significantly lower than that previously reported for North Carolina[20] and lower than data reported out of Houston.[26] Furthermore, no such cases occurred in 2002 as a result of this omission indicating that these recommendations are being followed more closely and highlighting the importance of DOPT in exposed children.

Our study has several limitations. First, several different individuals were involved in collecting data from health department records. Thus, there may have been some variability in the interpretation and recording of data. Second, firm population figures for age, race, and ethnicity census were not available at the time of this study. As such, we calculated our own population estimates in an effort to determine case rates based on the assumption that population would grow exponentially over time. This methodology may have either over- or underestimated incidence in some subgroups. Additionally, because the absolute number of pediatric TB cases in North Carolina is relatively low, many of our statistical analyses were run using a small sample size. This may have influenced our p-values and therefore these should be interpreted cautiously. One could even argue that p-values in this setting are inappropriate given that the sample consists of the entire population of pediatric TB cases in North Carolina and not just a subset of pediatric TB cases.

North Carolina experienced a significant increase in its incidence of pediatric tuberculosis in 2002. However, it is too early to tell whether this is an isolated increase or the beginning of a trend. Two microepidemics that occurred in separate counties, both in populations with low socioeconomic status, may be partly responsible for the increase in pediatric TB observed in North Carolina in 2002. Unfortunately, it is difficult to predict where and when these clusters of cases will occur. Prompt evaluation and treatment of cases and contacts is the only way to prevent such miniepidemics from occurring. We did not see any significant increase in TB incidence in our Hispanic children or children with a foreign association. However, the proportion of cases attributed to these two subgroups did rise over time indicating that the immigrant community has impacted the rates of pediatric TB in North Carolina. As the immigrant population continues to increase, surveillance of high-risk children with a foreign association may be necessary to help control pediatric TB within our state. Finally, we found that roughly one-fourth of our pediatric TB cases may have been prevented had appropriate measures been taken. Improving contact investigations and compliance with prophylactic therapy for latent TB infection in both adults and children may help to reduce the incidence of pediatric TB.

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## Appendix

| TABLE 1: Demographic characteristics of children <15 years with TB | |
|---|---|
| **Characteristic** | **Children 0-14yr**<br>**N=180 (%)** |
| **Gender** | |
| Male | 96 (53.3%) |
| Female | 84 (46.7%) |
| **Age** | |
| Children less than 5 yrs of age | 97 (53.9%) |
| Children between 5 and 14 years of age | 83 (46.1%) |
| **Race/Ethnicity** | |
| non-Hispanic white | 21 (11.7%) |
| non-Hispanic African American | 114 (63.3%) |
| non-Hispanic Asian/Pacific Islander | 12 (6.7%) |
| Hispanic | 33 (18.3%) |
| Total non-white minority | 159 (88.3%) |
| **Country of origin** | |
| US-born | 155 (86.1%) |
| Foreign-born | 25 (13.9%) |

**Figure 1: Poisson regression model of trends in pediatric TB incidence from 1994 to 2002**

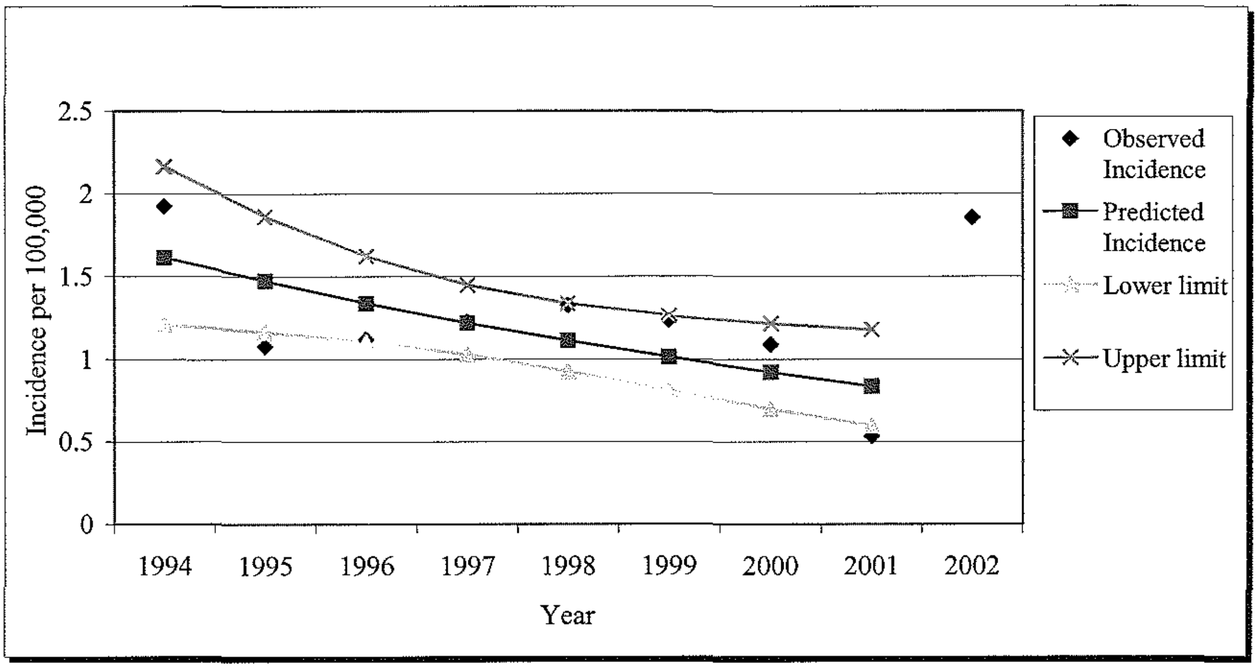
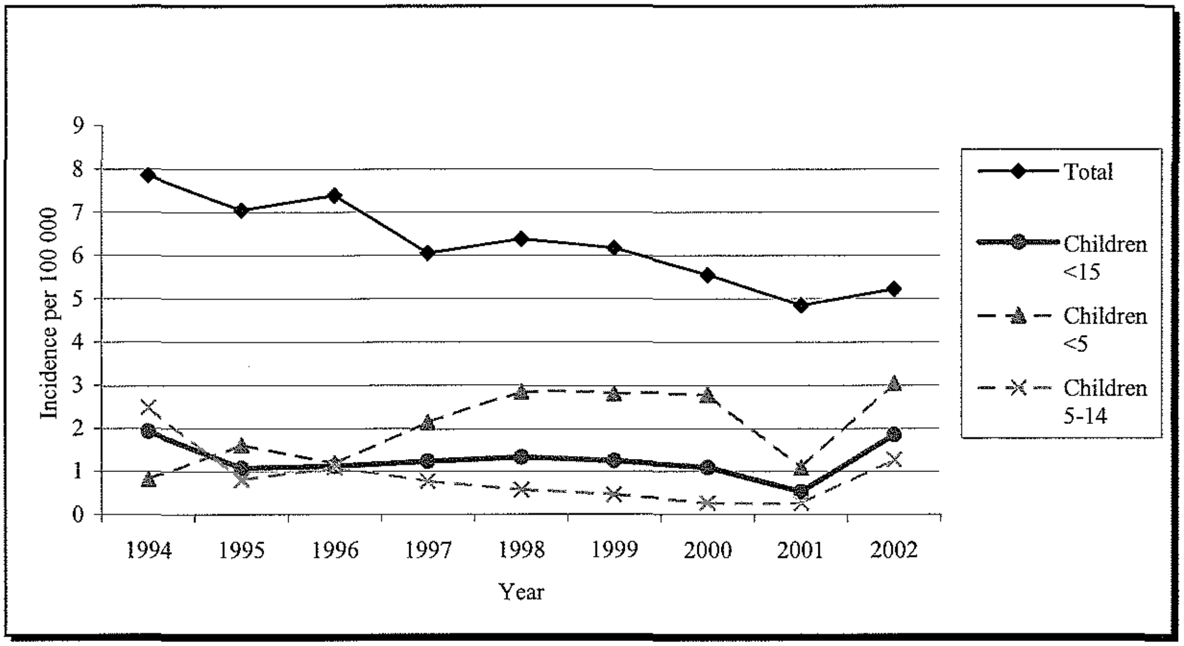


**Figure 2: Incidence of tuberculosis by age group**



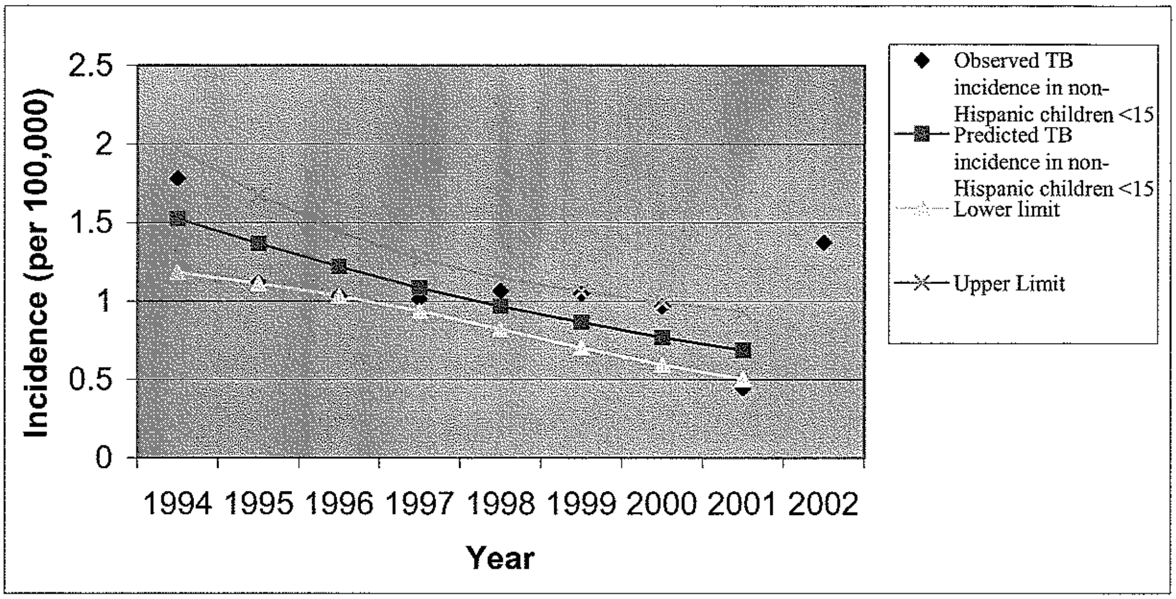
| Table 2: Country of Origin for foreign born children | |
|---|---|
| Country | Number of Children N (%) |
| Mexico | 10 (40%) |
| Asia | |
| Vietnam | 3 (12%) |
| Philippines | 1 (4%) |
| Other Asia* | 2 (8%) |
| Africa§ | 5 (20%) |
| Central America (less Mexico)¶ | 3 (12%) |
| South America | 0 |
| Europe/Former USSR | 0 |
| Carribean | 1 (4%) |

* China, Pakistan

§ Ethiopia, Somalia, Sudan

¶ Nicaragua, Honduras, Guatemala

**Figure 3: Poisson regression analysis of TB incidence in non-Hispanic children < 15 years of age**



# Figure 4: Reasons for assessing children with TB

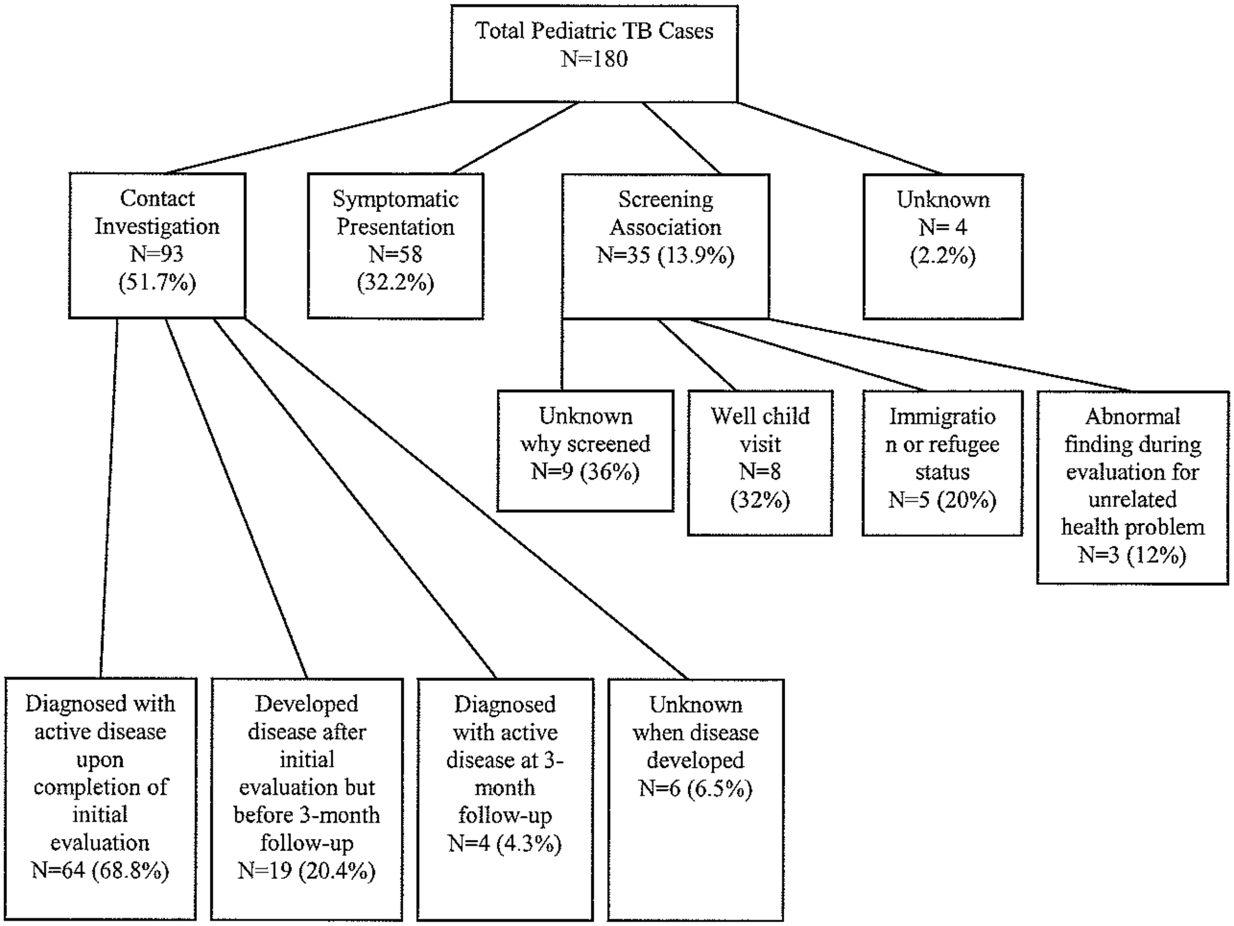


**Table 3: Characteristics of Source Cases compared to Total Adult Population**

| Characteristic | Source Case Number (%) | Tot. Adult Pop Number (%) | Odds Ratio |
|---|---|---|---|
| Male | 44 (53.7%) | 2333 (70.3%) | |
| Female | 38 (46.3%) | 984 (29.7%) | 2.05 (p< .001) |
| Race/Ethnicity | | | |
| non-Hispanic White | 15 (18.3%) | 918 (27.7%) | |
| non-Hispanic Black | 54 (65.9%) | 1861 (56.1%) | |
| non-Hispanic Asian/Pacific Islander | 3 (3.6%) | 158 (4.8%) | |
| Hispanic | 10 (12.2%) | 350 (10.6%) | |
| US Born | 66 (80.5%) | 2745 (87.8%) | |
| Foreign Born | 16 (19.5%) | 569 (17.2%) | |
| Postive Sputum Smear | 72 (87.8%) | 1708 (51.5%) | 6.78 (p< .001) |
| Many (3+) | 49 (68.1%) | | |
| Cavitary lesion on X-Ray | 41 (50%) | 972 (29.3%) | 2.41 (p < .001) |
| HIV Positive | 4 (4.9%) | 351 (10.6%) | |
| IV or other illicity Drug Use | 14 (17.1%) | 345 (10.4%) | |
| Alcohol Use | 28 (34.1%) | 967 (29.2%) | |