

# Risk Factors for Central Nervous System Tuberculosis

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## abstract

**OBJECTIVES:** To describe the epidemiology and factors associated with pediatric central nervous system (CNS) tuberculosis (TB) in California from 1993 to 2011.

**METHODS:** We analyzed California TB registry data for persons aged  $\leq 18$  years, comparing CNS TB cases versus non-CNS TB cases reported from 1993 to 2011. Factors associated with CNS TB and TB deaths were identified by using multivariate logistic regression.

**RESULTS:** A total of 200 CNS TB cases were reported. Compared with non-CNS TB case patients, CNS TB case patients were more likely to be aged  $< 5$  years (72.0% vs 43.6%; odds ratio [OR]: 3.8 [95% confidence interval (CI): 2.4–5.9]), US-born (82.0% vs 58.2%; OR: 3.3 [CI: 2.3–4.7]), and Hispanic (75.0% vs 63.2%; OR: 1.7 [CI: 1.3–2.4]). Among US-born CNS TB case patients (during 2010–2011), 76.5% had a foreign-born parent. Tuberculin skin test results were negative in 38.2% of 170 CNS TB cases tested. In multivariate analysis, age  $< 5$  years (adjusted odds ratio [aOR]: 3.3 [CI: 2.0–5.4]), US birth (aOR: 1.8 [CI 1.2–2.7]), and Hispanic ethnicity (aOR: 1.5 [CI: 1.1–2.1]) were associated with an increased risk of developing CNS TB. For deaths, CNS TB (aOR: 3.8 [CI: 1.4–9.9]) and culture positivity (aOR: 6.2 [CI: 2.2–17.3]) were associated with increased risk of death, whereas tuberculin skin test positivity (aOR: 0.1 [CI: 0.04–0.2]) was associated with decreased risk.

**CONCLUSIONS:** Subsets of children are at increased risk for CNS TB in California and may benefit from additional prevention efforts.

**WHAT'S KNOWN ON THIS SUBJECT:** Central nervous system (CNS) tuberculosis has high morbidity and mortality, and it frequently affects children aged  $< 5$  years.

**WHAT THIS STUDY ADDS:** In California, children who were US-born, Hispanic, and aged  $< 5$  years were at increased risk of CNS tuberculosis. Children with CNS tuberculosis were more likely to die. Specific populations of US-born infants might benefit from additional prevention measures.

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Despite advances in the control of tuberculosis (TB) worldwide and in the United States, central nervous system (CNS) TB in children continues to have a high risk of death (~20%) and neurologic sequelae in more than one-half of survivors.<sup>1</sup> In the United States, CNS TB affects ~1% to 3% of all pediatric patients with TB.<sup>2,3</sup> It is most commonly diagnosed in children aged <5 years and may affect the same groups at high risk for pediatric TB in the United States such as immigrants, racial and ethnic minorities, and children who traveled to a country with high prevalence of TB or who had contact with a household visitor from a high-prevalence country.<sup>4-6</sup>

In children, CNS TB is often the result of recently acquired infection after close contact with an infectious TB case in an adult. Risk of dissemination to the CNS after TB exposure is influenced by age and immune status,<sup>7</sup> including BCG vaccination. In most countries outside the United States, BCG vaccination is recommended in early childhood to decrease the risk of disseminated forms of TB such as miliary and CNS TB in children.<sup>8</sup> BCG vaccination has not routinely been used in the United States.<sup>9</sup>

California is the state that reports the most pediatric TB cases<sup>10</sup> and has the largest foreign-born population in the United States.<sup>11</sup> It is therefore an excellent population in which to examine the epidemiology of pediatric CNS TB. To inform ongoing CNS TB prevention activities, our goal was to describe the epidemiology of pediatric CNS TB in California from 1993 to 2011 and to identify factors associated with the development of pediatric CNS TB as well as factors associated with pediatric TB deaths.

## METHODS

### Study Population and Data Sources

Cases of TB in pediatric patients (aged ≤18 years old) reported in California from 1993 to 2011 were

analyzed. TB is reportable by law in California (California Code of Regulations Title 17§2500). Each local health jurisdiction in California reports TB cases to the California Department of Public Health Tuberculosis Registry according to case definitions of the Centers for Disease Control and Prevention.<sup>12</sup> Registry data undergo routine quality control procedures during and after data collection and have been found to be reliable.<sup>13</sup> The registry includes information about demographic and clinical characteristics, directly observed therapy, treatment, and outcomes. Data on parents' country of origin for children aged <15 years, interferon- $\gamma$  release assays (IGRA), nucleic acid amplification tests (NAAT), diabetes mellitus, end-stage renal disease, non-HIV immunosuppression, tumor necrosis factor- $\alpha$  therapy, postorgan transplantation, and being a contact to a case have been collected since 2010. California TB and HIV registries were matched to identify TB/HIV co-infected patients. BCG vaccination history is not collected in the TB registry. To infer BCG vaccination status, information regarding current BCG policies was abstracted from the BCG World Atlas<sup>14,15</sup> (<http://www.bcgatlas.org/>) for each country in which a California pediatric TB case patient was born. Data on the annual number of persons aged 0 to 18 years during 1993 to 2011 were obtained from the California Department of Finance.<sup>16</sup> These data were used to calculate case rates (expressed as cases per 100 000 population).

This analysis was conducted as part of the California Department of Public Health's mandate to routinely collect and analyze surveillance data for public health purposes.

### Definitions

A CNS TB case was defined as a case of TB reported to the TB registry that either: (1) was reported as involving the meninges, spinal cord, or brain; or (2) had *Mycobacterium tuberculosis*

complex isolated from a culture specimen collected from the meninges, brain, spinal cord, or cerebrospinal fluid (CSF). Non-CNS TB cases were defined as all other TB cases. Because pyrazinamide (PZA) resistance testing was not universal in the early time period, pansusceptible TB was defined as documented susceptibility to isoniazid and rifampin, with results for PZA being either susceptible or not tested. Multidrug-resistant TB was defined as resistance to both rifampin and isoniazid.

### Statistical Analysis

The Cochran-Armitage trend test was used to assess trends of the proportion of pediatric TB cases that were CNS TB and the proportion of CNS TB cases that had culture-positive results. Categorical data for comparisons between CNS and non-CNS TB cases were analyzed by using the  $\chi^2$  test or Fisher's exact test. Odds ratios (ORs), adjusted odds ratios (aORs), and 95% confidence intervals (CIs) were calculated with bivariate and multivariate logistic regression to identify factors associated with the development of CNS TB in all pediatric patients with TB. Age, gender, and variables significantly associated with CNS TB in bivariate analysis ( $P < .05$ ) were entered into the model. Culture positivity and treatment outcome were not included in the model because they were deemed to be a consequence of CNS TB, not a risk factor for development of CNS disease. Variables for which data were only available during 2010 and 2011 were not included in the multivariable model.

A multivariate logistic regression model was also developed to identify factors independently associated with death in all pediatric patients in California from 1993 to 2011. Site of disease (CNS or non-CNS), age, gender, and variables significantly associated with death ( $P < .05$ ) were entered into the model. The Hosmer-Lemeshow test was used to assess goodness of fit

for both models. SAS Enterprise 9.3 software (SAS Institute, Inc, Cary, NC) was used for data analysis.

## RESULTS

From 1993 to 2011, a total of 6193 cases of TB in children aged  $\leq 18$  years were reported in California. Of those, 200 (3.2%) were CNS TB and 5993 were non-CNS TB. Pediatric case rates decreased for CNS TB (from 0.21 to 0.14 per 100 000) and for non-CNS TB (from 6.83 to 1.66 per 100 000), but there was an increasing trend in the proportion of pediatric TB cases in California involving the CNS ( $P$  for trend = .0047) (Fig 1). During this period, the proportion of CNS TB cases that had culture-positive results remained stable ( $P$  for trend = .53). CNS TB cases occurred in 23 of 46 jurisdictions that reported TB during the analysis period. The majority (63.5%) of CNS TB cases were reported by 3 counties in southern California (Los Angeles, San Diego, and Orange), which accounted for 46.6% of all TB cases among persons aged  $\leq 18$  years from 1993 to 2011.

### Epidemiology and Characteristics of CNS TB Cases

Among the 200 CNS TB cases, 144 (72.0%) were in children aged  $< 5$

years, with 46 (23.0%) cases in children aged  $\leq 12$  months; 150 (75.0%) patients were Hispanic, and 164 (82.0%) were US-born (Table 1). Overall, 63.0% of cases occurred in US-born Hispanic children. Among US-born patients with CNS TB reported during 2010 and 2011, 76.5% had at least 1 foreign-born parent. Approximately 60% ( $n = 118$ ) of the CNS TB cases had a positive culture result for *M tuberculosis*, with 78.0% ( $n = 92$ ) of the isolates from a CNS site. Of the positive culture results from a non-CNS site, 69.2% ( $n = 18$ ) were gastric aspirates. Among the 10 patients tested with IGRA, 6 (60.0%) had a positive culture result. Eleven patients had an NAAT performed, 6 (54.5%) from CSF. Among the 4 patients with a positive culture result from the CSF who also had an NAAT performed on CSF, the NAAT was positive for 1, negative for 2, and indeterminate for 1. Both of the remaining patients with CSF NAAT performed had negative CSF culture results and negative NAAT results. The tuberculin skin test (TST) was negative ( $< 5$ mm) in 38.2% ( $n = 65$ ) of the 170 patients who were tested. One patient (0.5%) had HIV infection. No patients had other medical risk factors for TB such as non-HIV immunosuppression, anti-tumor necrosis factor- $\alpha$  therapy, postorgan

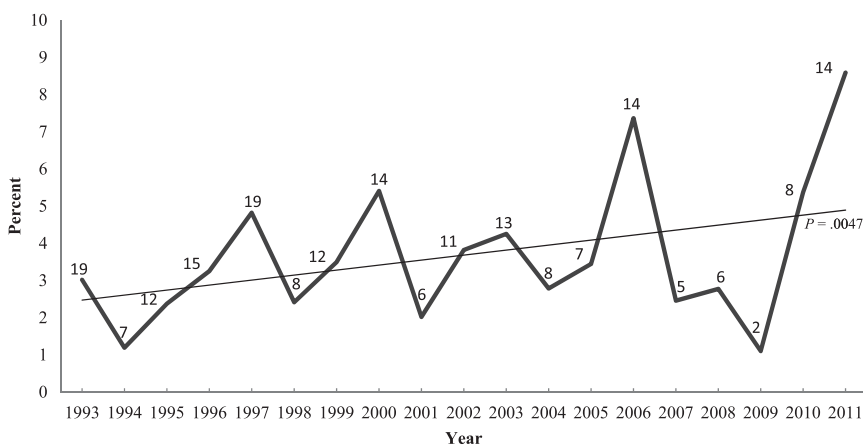
transplantation, diabetes mellitus, or end-stage renal disease.

Among the 118 culture-positive cases, 114 (96.6%) had susceptibility information available, with 93 (81.6%) of isolates pansusceptible; 16 (14.0%) with resistance to isoniazid, rifampin, or PZA; and 5 (4.4%) with multidrug-resistant TB. PZA monoresistance (consistent with *Mycobacterium bovis*) was the most common resistance pattern, found in 11 (12.0% [all of whom were Hispanic]) of 92 cases that were tested. Overall, 4.5% of children with CNS TB died, and all died after initiation of TB treatment.

### CNS TB Compared With Non-CNS TB

Patients with CNS TB were more likely to be 0 to 4 years old (72.0% vs 43.6%; OR: 3.8 [95% CI: 2.4–5.9]), US-born (82.0% vs 58.2%; OR: 3.3 [95% CI: 2.3–4.7]), and Hispanic (75.0% vs 63.2%; OR: 1.7 [95% CI: 1.3–2.4]) (Table 1). TST positivity ( $\geq 5$  mm) was lower in CNS TB patients who had known results (61.8% vs 94.1%; OR: 0.1 [95% CI: 0.1–0.2]), with TST results not reported (not done or unknown) for 15.0% of CNS TB cases and 5.6% of non-CNS TB cases. Among foreign-born children with TB in California during the study period, the majority (58.0%) were from Latin America. Nearly all foreign-born patients in both groups (97.2% CNS TB vs 99.1% non-CNS TB;  $P = .25$ ) were born in a country in which BCG vaccination is recommended at birth. Among patients who were tested, a larger proportion of non-CNS TB patients had positive IGRA (84.0% of 69 vs 60.0% of 10;  $P = .31$ ) and positive NAAT results (53.2% of 77 vs 45.5% of 11;  $P = .22$ ), although the differences were not statistically significant.

Patients with CNS TB were more likely to have a positive culture result (59.0% vs 33.0%; OR: 2.9 [95% CI: 2.2–3.9]) and were more likely to die (4.5% vs 0.4%; OR: 12.7 [95% CI:



**FIGURE 1**

Proportion of pediatric (aged 0–18 years) TB cases that involve the CNS according to year in California, 1993 to 2011. <sup>a</sup>Trend assessed by using the Cochran-Armitage trend test. Numerical labels indicate the number of pediatric CNS TB cases.

**TABLE 1** Epidemiology and Factors Associated With Pediatric (Aged 0–18 Years) CNS TB Versus Non-CNS TB Cases in California, 1993 to 2011

Characteristic	CNS TB (N = 200)	Non-CNS TB (N = 5993)	Bivariate	Multivariate (N = 6177)
	N (%)	N (%)	OR (95% CI)	aOR (95% CI)
Demographics (CNS n; non-CNS n, if different from overall total)				
Age, y <sup>a</sup>				
0–4	144 (72.0)	2615 (43.6)	3.8 (2.4–5.9)	3.3 (2.0–5.4)
5–14	34 (17.0)	1873 (31.3)	1.2 (0.7–2.1)	1.3 (0.8–2.3)
15–18	22 (11.0)	1505 (25.1)	Ref	Ref
Female gender <sup>a</sup>	99 (49.5)	2961 (49.4)	1.0 (0.7–1.3)	1.0 (0.7–1.3)
Race/ethnicity <sup>a</sup>				
Hispanic	150 (75.0)	3787 (63.2)	1.7 (1.3–2.4)	1.5 (1.1–2.1)
Not Hispanic	50 (25.0)	2202 (36.8)	Ref	Ref
Unknown	0	4	UND	
Not-Hispanic (n = 50; 2206 <sup>b</sup> )				
Not-Hispanic white	5 (10.0)	303 (13.7)	Ref	
Not-Hispanic black	9 (18.0)	521 (23.6)	1.0 (0.3–3.1)	
Not-Hispanic Asian	35 (70.0)	1324 (60.0)	1.6 (0.6–4.1)	
Not-Hispanic other/unknown	1 (2.0)	58 (2.6)	1.0 (0.1–9.1)	
Origin <sup>a</sup> (n = 200; 5982)				
Foreign-born	36 (18.0)	2500 (41.8)	Ref	Ref
US-born	164 (82.0)	3482 (58.2)	3.3 (2.3–4.7)	1.8 (1.2–2.7)
Clinical characteristics				
Culture specimen positive for <i>M tuberculosis</i> complex	118 (59.0)	1978 (33.0)	2.9 (2.2–3.9)	
Site of positive culture specimen (n = 118)				
CNS site	92 (78.0)	NA		
Non-CNS site only	26 (22.0)	NA		
TST <sup>a</sup>				
Positive (≥5 mm)	105 (52.5)	5322 (88.8)	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Negative	65 (32.5)	336 (5.6)	Ref <sup>c</sup>	Ref <sup>c</sup>
Not done/unknown	30 (15.0)	335 (5.6)		
HIV infection (n = 200; 5992)				
Yes	1 (0.5)	22 (0.4)	1.4 (0.2–10.2)	
No	199 (99.5)	5970 (99.6)	Ref	
Susceptibility results (n = 114; 1977)				
Pansusceptible <sup>d</sup>	93 (78.8)	1527 (77.2)	Ref	
INH resistance (non-MDR)	5 (4.2)	167 (8.5)	0.5 (0.2–1.2)	
RIF resistance (non-MDR)	0	5 (0.2)	UND	
MDR	5 (4.2)	37 (1.9)	2.2 (0.9–5.8)	
PZA mono-resistance	11 (9.3)	189 (9.6)	1.0 (0.5–1.8)	
Reason for TB evaluation <sup>e</sup> (n = 22; 313)				
TB symptoms	18 (81.8)	127 (40.6)	6.7 (2.2–20.1)	
Contact investigation	1 (4.6)	80 (25.6)	0.1 (0.02–1.05)	
Other	3 (13.6)	108 (34.5)	0.3 (0.1–1.04)	
DOT (n = 187; 5828)				
Yes	134 (71.7)	3996 (68.6)	1.1 (0.8–1.6)	
Outcomes at end of treatment (n = 190; 5896)				
Completed treatment	175 (92.1)	5590 (94.8)	0.6 (0.4–1.1)	
Died	9 (4.5)	23 (0.4)	12.7 (5.8–27.8)	
Moved/lost	6 (3.2)	255 (4.3)	0.7 (0.3–1.6)	
Other	0	28 (0.5)	UND	

DOT, directly observed therapy; FB, foreign-born; INH, isoniazid; MDR, multidrug-resistant; RIF, rifampin; UND, undefined/unable to calculate.

<sup>a</sup> Variables included in multivariate logistic regression model.

<sup>b</sup> Includes 4 patients with unknown Hispanic ethnicity but known race.

<sup>c</sup> Includes negative, not done, and unknown TST as the reference group in the multivariate logistic regression model.

<sup>d</sup> Susceptible to INH and RIF, and susceptible to PZA if tested.

<sup>e</sup> Information available for 2010 and 2011.

5.8–27.8]) than patients with non-CNS TB. Culture positivity was similar among CNS TB and non-CNS TB case patients who died (78.3% vs 77.8%;  $P = .976$ ). Compared with no deaths

before treatment among patients with CNS TB, 14 (0.2%) patients in the non-CNS TB group died before treatment was started. CNS TB cases were less likely to be diagnosed

through a contact investigation than non-CNS TB cases (4.6% vs 25.6%; OR: 0.1 [95% CI: 0.02–1.05]), but this information only reflects data from 2010 and 2011. Twenty-two (0.4%)

patients were HIV-positive in the non-CNS TB group compared with 1 (0.5%) patient of the CNS TB group ( $P = .53$ ). Other medical risk factors for non-CNS TB patients included tumor necrosis factor- $\alpha$  antagonist therapy ( $n = 1$ ), diabetes mellitus ( $n = 2$ ), end-stage renal disease ( $n = 6$ ), and other non-HIV immunosuppression ( $n = 24$ ). There were no significant differences in susceptibility patterns between CNS and non-CNS TB cases.

In multivariate analysis ( $n = 6177$ ), we found that age <5 years compared with age 15 to 18 years (aOR: 3.3 [95% CI: 2.0–5.4]), US birth (aOR: 1.8 [95% CI: 1.2–2.7]), and Hispanic ethnicity (aOR: 1.5 [95% CI: 1.1–2.1]) were independently associated with CNS TB. TST positivity (versus TST negative/not done/unknown; aOR: 0.1 [95% CI: 0.1–0.2]) was associated with decreased risk for CNS TB. The association between TST positivity and CNS TB did not vary according to how missing TST data were handled (excluded, considered positive, or considered negative).

### Factors Associated With Pediatric TB Deaths

In the multivariate model of death among pediatric TB cases ( $n = 6009$ ), we found that CNS TB (aOR: 3.8 [95% CI: 1.4–9.9]) and culture positivity (aOR: 6.2 [95% CI: 2.2–17.3]) were independently associated with increased risk of death. TST positivity (aOR: 0.1 [95% CI: 0.04–0.2]) was associated with lower risk (Table 2).

### DISCUSSION

In this population-based analysis, we observed a decline in the overall incidence of pediatric CNS TB cases during an 18-year period but an increase in the proportion of pediatric TB cases that involved the CNS. Even after adjusting for age, ethnicity, and TST positivity, being US-born conferred a doubling of the odds of CNS TB. In addition, after

adjusting for multiple factors, children with CNS TB were nearly 4 times more likely to die, an unsurprising but significant finding. Last, our finding that CNS TB cases were less likely to have a positive TST or IGRA (less than two-thirds of CNS TB cases tested had a positive test result) serves as an important reminder that negative TST or IGRA results should not be used to rule out CNS TB. This finding could be explained by the possible contribution of lack of false-positive TST results due to BCG cross-reactivity among US-born children or by anergy from overwhelming infection.<sup>17,18</sup> Anergy could also explain the association we found between deaths and TST negativity.

Our findings on the characteristics of CNS TB patients are broadly similar to those found in other studies. The young age at diagnosis has been well documented<sup>2,3,19</sup> and highlights how susceptible these youngest children are to developing CNS TB. The Hispanic predominance was consistent with other California studies<sup>3,6</sup> but was higher than in the United States overall (39% to 66%).<sup>2,20,21</sup> The predominance of US birth has been noted, albeit to a lesser extent, in other US and California studies. However, a higher percentage of US-born children in our cohort had a foreign-born parent compared with other pediatric TB studies in the United States (64% to 68%),<sup>6,20,21</sup> possibly reflecting an increase in the foreign-born population in California since those studies were conducted.

The dominant demographic pattern among children with CNS TB (very young, US-born Hispanic children living in southern California) may reflect immigration and residency patterns among persons coming from Latin America to California. Immigrants from Latin America who have children in California are more likely to live in the south.<sup>11</sup> In addition, foreign-born immigrants with TB disease are less likely to seek

medical care due to language, socioeconomic, and other barriers to accessing care,<sup>22</sup> and thus transmission of TB within the United States might be greater within these populations (including to children).

Other factors may contribute to the apparent risk of US birth. First, most foreign-born children do not enter the United States immediately after birth, and thus there is a larger population of US-born children in the youngest age groups that are most at risk for CNS TB. These young children may progress rapidly to CNS TB after exposure in the United States or after brief foreign travel. In contrast, foreign-born children who may be more likely to have been exposed in their country of birth may have passed the window during which they would have developed CNS TB before coming to the United States. Another contributing factor could be lack of BCG vaccination among US-born children.

The finding that few CNS TB cases were identified during contact investigation of an adult source case is worth additional discussion. This finding could be the result of lack of timely or complete contact investigations that missed children with active TB disease before it spread to the CNS. Alternatively, progression to CNS TB could occur so rapidly in these children that even timely and complete contact investigations do not prevent these cases. Additional investigation is needed to determine whether improved contact investigation can reduce CNS TB in young children.

Similar to other studies of pediatric CNS TB,<sup>18,23</sup> we found that slightly more than one-half of our patients had a positive culture result, with >20% coming from non-CNS sites. This finding highlights the importance of obtaining multiple culture specimens from multiple sites in children with suspected CNS TB to increase the yield of culturing.<sup>24</sup>

**TABLE 2** Factors Associated With Death Among Children (Aged 0–18 Years) With TB in California, 1993 to 2011

Characteristic	Died (N = 32)	Did Not Die (N = 6142)	Bivariate	Multivariate (N = 6009)
	N (%)	N (%)	OR (95% CI)	aOR (95% CI)
Demographics (died n; did not die n, if different from overall total)				
Age, y <sup>a</sup>				
0–4	14 (43.7)	2739 (44.6)	0.8 (0.3–1.7)	1.5 (0.6–4.2)
5–14	8 (25)	1896 (30.9)	0.6 (0.2–1.6)	1.5 (0.5–4.4)
15–18	10 (31.3)	1507 (24.5)	Ref	Ref
Female gender <sup>a</sup> (n = 32; 6141)	16 (50)	3033 (49.4)	1.0 (0.5–3.2)	1.1 (0.5–2.4)
Ethnicity (n = 32; 6138)				
Hispanic	23 (71.9)	3903 (63.6)	1.5 (0.7–3.2)	
Not Hispanic	9 (28.1)	2235 (36.4)	Ref	
Origin (n = 32; 6133)				
US-born	17 (53.1)	3622 (59.1)	0.8 (0.4–1.6)	
Foreign-born	15 (46.9)	2511 (40.9)	Ref	
Clinical characteristics				
Site of disease <sup>a</sup> (n = 32; 6141)				
CNS TB	9 (28.1)	191 (3.1)	12.7 (5.8–27.8)	3.8 (1.4–9.9)
Non-CNS TB	23 (71.9)	5950 (96.9)	Ref	Ref
Culture specimen positive for <i>M tuberculosis</i> complex <sup>a</sup>	25 (78.1)	2056 (33.5)	7.1 (3.1–16.4)	6.2 (2.2–17.3)
TST <sup>a</sup>				
Positive (≥5 mm)	8 (25)	5418 (88.2)	0.1 (0.02–0.1)	0.1 (0.04–0.2)
Not positive	24 (75)	724 (11.8)	Ref <sup>b</sup>	Ref <sup>b</sup>
HIV infection <sup>a</sup> (n = 32; 6141)				
Yes	1 (3.1)	22 (0.4)	8.9 (1.2–68.6)	4.1 (0.5–34.8)
No	31 (96.9)	6119 (99.6)	Ref	Ref
Susceptibility results (n = 25; 2022)				
Pansusceptible <sup>c</sup>	18 (72)	1593 (79.6)	0.7 (0.3–1.8)	
INH resistance (non-MDR)	2 (8)	168 (8.4)	1.0 (0.2–4.2)	
RIF resistance (non-MDR)	0	5 (0.2)	UND	
MDR	1 (4)	41 (2.1)	2.0 (0.3–15.5)	
PZA mono-resistance	4 (16)	195 (9.7)	1.8 (0.6–5.3)	
DOT <sup>a</sup> (n = 29; 5983)				
Yes	25 (6.2)	4104 (68.6)	2.8 (1.09–8.2)	2.1 (0.7–6.3)

DOT, directly observed therapy; INH, isoniazid; MDR, multidrug-resistant; RIF, rifampin; UND, undefined/unable to calculate.

<sup>a</sup> Variables included in multivariate logistic regression model.

<sup>b</sup> Includes negative, not done, and unknown TST as the reference group in the multivariate logistic regression model.

<sup>c</sup> Susceptible to INH and RIF, and susceptible to PZA if tested.

More than 20% of our cases had some form of drug resistance, highlighting the importance of using molecular assays to detect drug resistance quickly. A recent study in California from 2004 to 2011<sup>25</sup> found that the prevalence of PZA mono-resistance was 22.0% of all pediatric (aged <15 years) TB cases and that PZA mono-resistant case patients were more likely to be Hispanic and US-born and have extrapulmonary disease. They also found that PZA mono-resistance likely indicates *M bovis* disease (96% positive predictive value for *M bovis* in Hispanic persons). This prevalence of *M bovis* disease may have important implications for prevention if the route of infection

is through consumption of unpasteurized dairy products.

The results of the present analysis provide the basis for focusing interventions on children most at risk for CNS TB in California. Specifically, because the majority of cases occurred among US-born, Hispanic children, who are also likely to have a parent born outside the United States, this group might benefit from focused interventions. In addition, because a greater number of cases occurred in the youngest age group, interventions would have to start early in life to have the most impact. Potential strategies include intensified testing and treatment of latent TB

infection (LTBI) among parents and caregivers of children in populations at risk for TB, intensified testing among infants to identify and treat infection before CNS TB can develop, and the limited use of BCG vaccination among US-born children in communities with higher rates of TB. Despite not being used in the United States, BCG vaccination may be an attractive intervention because it could be incorporated into existing vaccination programs and has a protective efficacy against miliary and CNS TB in neonates and infants of 86% to 90% in randomized controlled trials.<sup>26,27</sup> It has a relatively low rate of adverse

effects<sup>28–33</sup> and has been used widely across the globe. In developed countries, such as the United Kingdom and Australia, BCG vaccination is only used in high-risk groups (eg, children with a caregiver from a country with a high incidence of TB, children who live in areas with high incidence of TB).<sup>27,34</sup> In the United States, BCG vaccination has never been used routinely even in high-risk populations, although recommendations exist for its use in very limited situations.<sup>9,35</sup> A CNS TB prevention strategy using BCG vaccination would need to consider that the absolute number of pediatric CNS TB cases is small (2–14 cases per year during 2007–2011), protection provided by BCG vaccination is not complete, and vaccination could complicate contact investigations involving BCG-vaccinated children aged <2 years in whom IGRA use is not recommended.<sup>36</sup>

More aggressive use of screening and treatment of TB infection among foreign-born adult caregivers of the youngest children or among young children is another strategy. This procedure is more consistent with the current TB prevention practices in the United States, and the use of IGRAs as well as shorter treatment regimens<sup>37</sup> may improve the efficacy of LTBI testing and treatment programs. Early identification of LTBI in very young (eg, those aged <24 months) US-born children with foreign-born parents or who travel at a young age would require ongoing education of primary care providers and families. Currently, selective testing and treatment of LTBI in children based on risk factors are recommended,<sup>36</sup> but the frequency of this screening is not known. One drawback is that TST is less sensitive in younger children (eg, those aged <12 months),<sup>38,39</sup> and screening and treatment at 12 months of age would not prevent the one-quarter of the cases occurring in younger children.

The limitations of our study include lack of information from 1993 to 2009 for variables collected only since 2010 (eg, parent's country of birth, being identified during a contact investigation). Our analysis included data from a single state, potentially limiting the generalizability of our findings. In addition, the small number of cases limited the ability to adjust for confounding, and there could have been opportunity for residual confounding on the variables chosen for the multivariate analysis (eg, age). Last, as is common in pediatric TB, not all TB cases were confirmed by positive culture results, and we had limited additional data with which to confirm culture-negative CNS TB cases, raising the possibility that some children diagnosed with TB (both CNS and non-CNS TB) may not have had TB at all. However, analyzing all reported cases allowed examination of cases across the spectrum of clinical severity. In addition, in the analysis of death, we adjusted for culture positivity, and CNS TB remained significantly associated with death. Despite these limitations, to our knowledge, this is the largest observational, population-based study of pediatric CNS TB in a low-incidence country.<sup>18,40–44</sup>

## CONCLUSIONS

Children who are aged <5 years, Hispanic, and US-born are at increased risk of developing CNS TB in California and may benefit from additional prevention efforts. These efforts could include aggressive TB infection screening and treatment among very young children, their parents, and adult caregivers. The limited use of BCG vaccination could also be considered. These strategies could focus on infants in the United States, born to families with TB risk factors such as those with foreign-born parents or who travel to areas with high TB rates.

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## ABBREVIATIONS

aOR: adjusted odds ratio  
CI: confidence interval  
CNS: central nervous system  
CSF: cerebrospinal fluid  
IGRA: interferon- $\gamma$  release assays  
LTBI: latent tuberculosis infection  
NAAT: nucleic acid amplification tests  
OR: odds ratio  
PZA: pyrazinamide  
TB: tuberculosis  
TST: tuberculin skin test

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