Mycobacterium bovis as a Significant Cause of Tuberculosis in Children Residing Along the United States–Mexico Border in the Baja California Region

Wayne M. Dankner, MD*, and Charles E. Davis, MD‡§

ABSTRACT. Objective. To determine the role of Mycobacterium bovis in active pediatric tuberculosis (TB) in a United States–Mexico border region.

Method. We reviewed all new cases of pediatric (<15 years old) TB presenting to San Diego hospitals and clinics from 1980 to 1997. Patients were categorized by age, ethnicity, country of origin, culture results, and disease manifestations. Case definitions were similar to those used by the Centers for Disease Control and Prevention. M bovis was distinguished from Mycobacterium tuberculosis by standard biochemical tests.

Results. The median age of the 563 identified patients was 4.1 years old. The yearly incidence began rising in 1989 and peaked in the mid-1990s. Hispanics constituted 78.9% of the patients, but they were less likely to be foreign-born (21.6%) than were black children and Asian/Pacific Islanders. Overall, M bovis caused 10.8% of all TB during this period. Of the 180 patients with positive culture results, however, M bovis accounted for 33.9% and M tuberculosis 66.1%. This high percentage of M bovis infections was largely attributable to its contribution to extrapulmonary TB (55.2% of all culture-positive specimens). M bovis patients were also even more likely to be Hispanic (90.2%), to present with extrapulmonary disease (95.1%), and to be older than 12 months (96.8%).

Conclusion. These data demonstrate the dramatic impact of this underappreciated cause of zoonotic TB on US children at the Mexican border and underscore the need for cross-collaboration to enforce existing Mexican pasteurization laws. Pediatrics 2000;105(6). URL: http://www.pediatrics.org/cgi/content/full/105/6/e79; pediatric tuberculosis, Mycobacterium bovis, Mycobacterium tuberculosis, zoonotic tuberculosis, extrapulmonary tuberculosis, United States–Mexico border area.

ABBREVIATIONS. HIV, human immunodeficiency virus; TB, tuberculosis; CDC, Centers for Disease Control and Prevention; PPD, purified protein derivative; INH, isoniazid; AFB, acid-fast bacillus.

Beginning in the mid-1980s, a sharp increase in the incidence and prevalence of tuberculous disease in the United States reversed the steady decline of the last several decades. This increase, which persisted through the early- to mid-1990s, was fueled by the human immunodeficiency virus (HIV) epidemic and by an increasing proportion of active disease in foreign-born individuals. Although most of the attention was directed toward the significant rise of disease in adults, there was an alarming increase in the pediatric-aged population as well. Much of the pediatric disease was identified in minority populations, especially in children from large cities, mirroring the increasing epidemic in adults. Traditional teaching has stressed that children with tuberculous disease are sentinel events for active adult disease and that preadolescents usually acquire disease from close contact with a family member or other adult household contact. Because aerosols are the route of transmission to these pediatric patients, Mycobacterium tuberculosis is usually the primary organism considered to be responsible for infection and disease in this age group. As we reported previously, however, Mycobacterium bovis causes tuberculous disease in both adults and children in the San Diego/Baja California region. Because the infections in children likely represented recent acquisition, we sought to determine the actual contribution of this mycobacterial species to the current prevalence of pediatric tuberculous disease in this unique crossborder region.

METHODS

New cases of tuberculous disease in children <15 years of age for the years 1980–1997 were identified through investigation of multiple sources. These included medical chart review of both inpatient and outpatient records using the International Classification of Diseases, Ninth Revision codes 010-018 inclusive and review of tuberculosis (TB) culture logs at the 2 primary pediatric medical facilities in San Diego (University of California, San Diego Medical Center and Children's Hospital of San Diego). In addition, we reviewed yearly reports of pediatric TB cases reported to the Department of Health Services and the San Diego County Public Health Laboratory to identify unique cases seen at other facilities in San Diego. Patients were included regardless of whether they resided in San Diego County. The majority of patients who resided outside San Diego County came from neighboring counties (Imperial County, Orange County, and Los Angeles County) and Tijuana, Mexico. The inclusion of patients from outside the San Diego County area precluded performing population-based incidence rates.

Case definitions were similar to those used by the Centers for Disease Control and Prevention (CDC) except that we considered children who presented with isolated hilar adenopathy (intrathoracic lymph nodes) on chest radiograph to have pulmonary TB instead of lymphatic TB. Children were considered foreign-born if their country of origin was outside of the 50 states, District of Columbia, Puerto Rico, or any of the US territories. For purposes of categorizing patients as to the source of their tuberculous infection, we counted patients with a well-documented history of
contact to a source case (with an identified *M tuberculosis* isolate) to be in the *M tuberculosis* category and not to have disease caused by *M bovis*.

Because *M bovis* and *M tuberculosis* are both homologous to the nucleic acid probes used to identify species of the *M tuberculosis* complex, *M bovis* was distinguished from *M tuberculosis* by standard biochemical tests, including negative niacin and nitratase results; sensitivity to thiophene-2-carboxylic acid hydrazide; and in the first 14 years of surveillance, by a positive pyrazinamidase test result; and within the last 3 years, by pyrazinamidine resistance in the Bactec system (Johnston Laboratories Inc, Towson, MD). All cultures were either performed or confirmed at University of California, San Diego Medical Center microbiology laboratory or the County Public Health Laboratory. *M bovis*–BCG strains were identified by phage typing or by high-performance liquid chromatography and patients infected with these isolates were subsequently eliminated from the data analysis.

**Statistical Analysis**

Differences between demographic groups and clinical manifestations of TB caused by *M bovis* and *M tuberculosis* were compared by the χ² test or Fisher’s exact test, where appropriate using Winks statistical program (TexasSoft, Cedar Hill, TX). Statistical significance was set at *P* < .05.

**RESULTS**

**Demographic Information**

During the 18 study-years, 563 children were diagnosed with TB. The median age was 4.1 years old with a range of 1 month to 14.8 years of age (Fig 1). The number of children with tuberculous disease first began to rise in 1989 and peaked between 1991 and 1994 before beginning a gradual decline (Fig 2). The ethnic distribution revealed 444 (78.9%) Hispanic children, 56 (9.9%) Asian/Pacific Islanders, 41 (7.3%) black non-Hispanics, 15 (2.7%) whites, and 7 (1.2%) Native Americans. Although there were no age differences among these ethnic groups, black children and Asian/Pacific Islanders were more likely to be foreign-born (63.4% and 78.2%, respectively) than children of Hispanic origin (21.6%; *P* < .001; Fig 3). The vast majority of the foreign-born Hispanic children (95.8%) were from Mexico with the remainder coming from Central American countries. Only 7 children had conditions that could have predisposed them to develop tuberculous disease, including 4 with malignancies (3 with leukemia and 1 with neuroblastoma), 1 older child with systemic lupus erythematosus on steroid therapy, a child with trisomy 21, and a neonate who was diagnosed with congenital TB. However, 30 children had evidence of prior or recent tuberculous infection or disease. Eighteen had a history of purified protein derivative (PPD) reactivity, 9 had a history of tuberculous disease, and 3 were reportedly receiving isoniazid (INH) preventive therapy for reactive PPD tests at the time that they were diagnosed with active TB. Twenty-three children with active tuberculous disease had close adult contacts that were *M tuberculosis* culture-positive and believed to be the source cases for these children.

Overall, 325 (57.7%) patients were diagnosed with pulmonary or pleural-based disease and 238 (42.3%) with extrapulmonary disease (Table 1). Of those with extrapulmonary disease, 201 had only extrapulmonary disease and 373 had evidence of concomitant pulmonary disease (abnormal chest radiographs). The most common extrapulmonary site was lymphatic (excluding intrathoracic lymph node involvement as described in “Methods”), followed by the central nervous system and abdominal foci. Only 3 patients with lymph node involvement had disease outside of the cervical or submandibular regions (2 had disease in an axillary node and 1 had disease in an inguinal node). Excluding patients with *M bovis* infection (which contributed significantly to extrapulmonary manifestations and also was heavily represented in children of Hispanic origin), Hispanic patients were still more likely to have extrapulmonary disease than the other ethnic groups (40.6% vs 19.5%; *P* < .001).

Only 74 (22.8%) of the 325 patients with primary pulmonary or pleural-based disease had a positive acid-fast bacillus (AFB) culture result or were an intimate contact of a culture-positive source case. The majority of the patients with pulmonary disease were diagnosed by clinical criteria, ie, positive PPD, abnormal chest radiograph on presentation, and decision to treat with antituberculous therapy by the primary or consulting physician. In contrast, 105 (44.1%) of the 238 patients with extrapulmonary disease had positive AFB culture results. The diagnosis was established on most, 106 (79.7%), of the others by histopathologic identification of granulomas with or without a positive AFB smear, by abnormal CSF findings and radiologic findings consistent with central nervous system tuberculous, or by radiograph appearance consistent with extrapulmonary tuberculous disease in conjunction with a positive PPD.

Thus, within the entire study population, 179 pa-

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**Fig 1.** Age distribution of children with tuberculous disease. The Neg category includes patients with negative culture results. The ND category includes those who did not have cultures performed. The *M tuberculosis* complex category includes all patients with culture-proven *M tuberculosis*, the 2 patients infected with *M africanum*, the 1 patient whose isolate could not be specified further than the stage of *M tuberculosis* complex, and the intimate contacts of documented *M tuberculosis* adult source cases. Ages depicted are inclusive of a 12-month span, eg, 1 = 0 to 12 months; 2 = 12.1 to 24 months; 3 = 24.1 to 36 months, etc. The total number of infections is indicated by the height of the bars. The number of infections by *M tuberculosis*, *M bovis*, and those that were either culture-negative or were not cultured for mycobacteria are depicted by the differences in shading, as indicated in the figure.
patients (31.8%) were culture-positive for M tuberculosis complex strains, including the 23 intimate contacts of M tuberculosis culture-positive adults. Of these 179 patients, 115 (64.2%) were positive for M tuberculosis, 61 (34.1%) for M bovis, and 2 (1.1%) for M africanum. One other isolate was identified as M tuberculosis complex by DNA probe but could not be speciated further because of contamination. Seven children had isolates identified as M bovis-BCG; and as stated in “Methods,” these patients were eliminated from the study population and data analysis.

All 61 M bovis strains were sensitive to the first line antituberculous drugs, excluding pyrazinamide to which M bovis is innately resistant. Of the M tuberculosis strains, full sensitivity profiles were available for 108, including 19 from the close adult contacts. Of the M tuberculosis strains, 16.7% were resistant to 1 or more antituberculous drugs and the INH resistance rate was 8.3%. The INH-resistant strains included 5 (5.2%) resistant to INH alone; 2 (2.1%) resistant to streptomycin and INH; 1 (1.0%) resistant to INH, streptomycin, and ethambutol; and only 1 (1.0%) resistant to both INH and rifampin. There were no differences in the sensitivity results from the strains isolated from the infected close adult contacts, compared...
with the strains isolated directly from the infected children.

*M. bovis*‐Related Disease

As noted above, there were 61 children (25 of whom had been described previously) with culture proven *M. bovis* tuberculous disease identified during this 18‐year period. The median age of these children (3.7 years old) was not statistically different from those who were not culture‐positive for this mycobacterial species. However, more *M. bovis*‐infected children were greater than 12 months of age at the time of their diagnosis than children with *M. tuberculosis*‐proven disease (96.8% vs 76.1%; *P* < .001). In addition, there were other statistically significant differences in the ethnic distribution and disease manifestations between those with and without documented *M. bovis*‐related disease (Fig 3). Children with *M. bovis* disease were more likely to be of Hispanic origin than were those without documentation of this bacterium (90.2% vs 77.5%; *P* = .022), but, somewhat unexpectedly, less likely to be foreign‐born (7.6% vs 20.7%; *P* = .006). Additionally, children with *M. bovis* proven extrapulmonary disease seemed no less likely to have a positive chest radiograph than children with *M. tuberculosis*‐proven extrapulmonary disease (9.3% vs 18.7%; *P* = .10). This difference becomes statistically significant if the children with miliary disease, who by definition invariably have abnormal chest radiographs, are eliminated from the comparison (2.0% vs 13.7%; *P* = .019).

Children with *M. bovis*‐proven infection were also more likely to present with extrapulmonary disease than their counterparts without *M. bovis* isolated from culture (95.1% vs 35.8%; *P* < .001), thus *M. bovis* proven disease accounted for 24.4% of all extrapulmonary manifestations seen over the 18‐year period of surveillance. Furthermore, as demonstrated in Table 1, when only culture‐proven cases are considered, *M. bovis* contributed even more significantly (55.2%) to the overall prevalence of extrapulmonary TB and individually for 92.3% of abdominal infections, 72.1% of lymphadenitis, 55.6% of bone/joint infections, 35.7% of miliary infections, and 15.8% of central nervous system infections.

**DISCUSSION**

The alarming rise in tuberculous disease in the adult US population between the mid- to late‐1980s and the early‐ to mid‐1990s has now begun to decline. A recent study from the CDC demonstrates a similar trend in the pediatric population, lagging in time slightly behind the adult experience in both the increase and the subsequent decrease. This phenomenon was predictable by virtue of the expected route of transmission from adults to children and the predilection of young children to manifest TB as active disease. The increasing influx of foreign‐born individuals from TB endemic regions and the coepidemic of HIV infection with its risk for a higher rate of TB reactivation in the previously infected adult population have contributed to this resurgence. At first glance, our data would seem to mirror that described in the CDC report, with an increase in pediatric TB cases starting in 1989, continuing without a definite decline until 1995, and decreasing more significantly in the last 2 years. Additionally, foreign‐born children contributed significantly in our series to the prevalence of TB in this area and our rate of 29.3% was similar to that of 19% to 23% reported by the CDC for the overall national experience. Although minorities also figured prominently in the prevalence of tuberculosis disease at the national level (80%–86%) and in our own region (97.3%), there were significant differences between our series and the CDC report. Some of these differences could influence the nature of TB control measures and resource allocation.

The first and most important difference that impacts both the prevalence and presentation of pediatric tuberculous disease in our region is the predominance of children of Hispanic origin. They accounted for 78.9% of all the pediatric TB infections identified in this series, although Hispanics presently make up only ~25% of the population in San Diego County. Although we included children in our series that resided outside the county, the San Diego County statistics are a reasonable reflection of the ethnic distribution in the surrounding counties. Only 21.6% are foreign‐born, with the vast majority coming from Mexico, but this figure may be misleading in terms of how and where the US‐born Hispanic children were exposed to TB. As pointed out in the CDC report, these young children may be exposed to recently immigrated parents from TB endemic regions, such as Mexico. Exposure to extended families, friends, and others with TB during frequent travel across the border is equally important. However, our data also identify a unique epidemiologic situation associated with this crossborder phenomenon, namely exposure to a zoonotic source of TB. This is supported not only by the data presented in this report, but also by 2 recent studies performed by Besser et al. in San Diego County, which explored the potential source cases for children with either tuberculous infection or tuberculous disease. In these studies, the only risk factor for TB in approximately one third of the children was ingestion of dairy products, likely derived from raw, unpasteurized milk. Very few were exposed to adults with TB. The role of unpasteurized milk products is also strongly suggested in our series by the near absence of culture proven *M. bovis* infections in the age group <12 months of age, in stark contrast to the number of culture‐proven infections with *M. tuberculosis*. As shown in Fig 1, there were only 2 patients in this age group with cultures positive for *M. bovis*, compared with 34 with *M. tuberculosis*. This disproportionate ratio did not occur at any other age. These data strongly implicate unpasteurized milk products in the transmission of *M. bovis* because it correlates perfectly with the practice of breastfeeding and the use of commercial infant formulas, which delay exposure to bovine dairy products until 6 to 12 months of age. Additionally, the uncommon isolation of *M. bovis* in children with primary pulmonary disease in contrast to those with culture‐proven *M. tuberculosis* and the fact that *M. bovis* only accounts for <3% of cul-
ture-proven pulmonary disease in adults in San Diego County (unpublished data) argues against respiratory transmission of this organism to the pediatric population.

Another important difference between the experience in San Diego and that described for the remainder of the United States is the rate of extrapulmonary disease in our population of children with TB. Previously, we reported the unusually high number of children with abdominal TB in our region and described the manifestations and management of this form of TB. In the present report, we analyzed all forms of extrapulmonary disease to determine the contribution of *M. bovis* to the unusually high rate of extrapulmonary TB in children along the border of California with Baja. First, we found that the rate of extrapulmonary disease among non-Hispanic children was similar to that recently reported by the CDC, but significantly greater in Hispanic children, the group with the greatest risk for exposure to unpasteurized dairy products from Mexico. We then compared the isolation rates of *M. bovis* to *M tuberculosis* for each category of extrapulmonary disease and found that *M. bovis* was contributing heavily to the burden of disease in our region. It is also possible that we underestimated the burden of disease caused by *M. bovis* because its dysgonic growth characteristics and the absence of pyruvic acid supplements in many primary media may be disadvantageous in terms of primary isolation from culture material. Nevertheless, *M. bovis* still accounted for 55.2% of all culture-positive patients with extrapulmonary disease. The strong predominance for gastrointestinal related organs without any associated pulmonary foci observed on chest radiograph, cervical lymphadenopathy, and abdominal disease highlights the oral route of transmission for this pathogen. These figures are reminiscent of the experience with this species as a cause of childhood TB in the early 1900s. In our earlier review of the historical significance of this organism, *M. bovis* was heavily associated with extrapulmonary disease in children <14 years of age. These similarities between the historical documentation of *M. bovis* disease in previous endemic regions of the world, the virtual eradication of this pathogen from the milk supply in the United States for the last several decades, and the data reported here demonstrate the continued presence of this organism in unpasteurized dairy products from the Baja region of northern Mexico. Its impact on the expression of tuberculous disease in the pediatric population of the San Diego region has been substantial.

Although we did not formally evaluate health care costs associated with *M. bovis*-related disease, the predominance of extrapulmonary disease would be expected to have a major impact on the use of health care resources, including hospitalizations, surgical services, treatment, and potential long-term morbidity. Although history has taught us that many factors must be considered in the elimination of *M. bovis* as a zoonotic disease in children, public health education efforts directed at high-risk populations and cross-border collaborative efforts to enhance the adherence to pasteurization laws already in effect in Mexico would be a major step toward the eradication of this pathogen from the pediatric population along the San Diego–Mexico border.

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