

Multidrug-Resistant Tuberculosis Among Patients in Baja California, Mexico, and Hispanic Patients in California

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Tuberculosis (TB) is an important health concern along the 1950-mile international border shared by Mexico and the United States. The neighboring states of Baja California, Mexico, and California, United States, have TB incidence rates that far exceed those of their respective countries. In 2008, the incidence rate for TB in Baja California was 50.9 per 100 000, versus 17.1 per 100 000 nationally in Mexico.¹ In California, the incidence of TB that same year was 7.4 per 100 000, compared with 4.2 cases per 100 000 persons in the United States.²

Multidrug-resistant tuberculosis (MDR-TB) is TB disease associated with *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampin, the 2 most effective TB medications available.³ MDR-TB is found in Mexico and California, and significantly increases treatment and societal costs of TB, with case fatality rates ranging from 12% in HIV-negative to 90% in HIV coinfecting persons.³ Although TB control efforts worldwide are starting to decrease TB incidence and mortality,^{4,5} the emergence of MDR-TB is “threatening to destabilize global TB control,^{6(p261)} and could rapidly turn TB into an untreatable disease, even in high-income countries.⁷

California had an average of 41 MDR-TB cases per year from 1994 to 2003—the highest incidence of MDR-TB in the United States.⁸ More than 85% of the incident MDR-TB cases in California from 1993 to 2006 were among foreign-born individuals, 28% of whom were born in Mexico.⁷ In Mexico, although some studies of MDR-TB prevalence in specific populations have been conducted,^{9–12} there is no routine surveillance data on MDR-TB for comparison.

California and Baja California share a strong migratory dynamic. Translocation and contact between inhabitants of both sides of the border are frequent, and familial and other social relations extend across the border.¹³ This

Objectives. We sought to compare prevalence and determinants of multidrug-resistant tuberculosis (MDR-TB) between tuberculosis patients in Baja California, Mexico, and Hispanic patients in California.

Methods. Using data from Mexico’s National TB Drug Resistance Survey (2008–2009) and California Department of Public Health TB case registry (2004–2009), we assessed differences in MDR-TB prevalence comparing (1) Mexicans in Baja California, (2) Mexico-born Hispanics in California, (3) US-born Hispanics in California, and (4) California Hispanics born elsewhere.

Results. MDR-TB prevalence was 2.1% in Baja California patients, 1.6% in Mexico-born California patients, 0.4% in US-born California patients, and 2.7% in Hispanic California patients born elsewhere. In multivariate analysis, previous antituberculosis treatment was associated with MDR-TB (odds ratio [OR] = 6.57; 95% confidence interval [CI] = 3.34, 12.96); Mexico-born TB patients in California (OR = 5.08; 95% CI = 1.19, 21.75) and those born elsewhere (OR = 7.69; 95% CI = 1.71, 34.67) had greater odds of MDR-TB compared with US-born patients (reference category).

Conclusions. Hispanic patients born outside the US or Mexico were more likely to have MDR-TB than were those born within these countries. Possible explanations include different levels of exposure to resistant strains and inadequate treatment. (*Am J Public Health.* 2013;103:1301–1305. doi:10.2105/AJPH.2012.301039)

condition affects the binational epidemiology of TB and MDR-TB, which is heavily influenced by social networks.¹⁴ The regular contact between residents of Baja California and California involves people of all ethnicities and social groups, but it is most intense for those identified as “Hispanics,” a group that, in California, is composed mainly of persons of Mexican origin.

Susceptibility testing is not routinely conducted in all TB cases in Mexico. However, from 2008 through 2009, as part of a national survey, all newly diagnosed TB cases were tested for drug resistance.¹⁵ Taking advantage of this, we studied differences in the prevalence and determinants of newly diagnosed MDR-TB cases among TB patients in Baja California as compared with Hispanics (a proxy for patients with ties to Mexico) in California, from 2004 through 2009. Although the concepts of ethnicity and race can be questioned when they imply that real genetic differences

exist between different human groups,¹⁶ and the label “Hispanic” has been criticized for its lack of specificity,^{16,17} in the absence of other information, self-reported ethnicity can be used as an indicator of certain social and cultural characteristics.¹⁶ It can also be an index for social inequalities, including discrimination, that reflect inequalities in health.¹⁸ In the study of TB transmission between contiguous states on either side of the US–Mexico border, self-identified ethnicity can be used in this way as a proxy for people who might share social networks, related TB strains, and some social conditions.

The TB control programs of Baja California and California are different in terms of resources, mainly in terms of capacity for bacterial culture and sufficiency of staff. Also, completion of treatment is mandated by law in California, which should make it less likely for recently diagnosed cases to have a history of previous treatment.^{19,20} The objective of this

study was to compare the prevalence of risk factors for MDR-TB, including previous treatment and country of birth, among newly diagnosed TB cases (both previously treated and never treated) in Baja California, with those among Hispanics living in California. Recognizing the differences in resources between California and Baja California health systems, we hypothesized that (1) the overall prevalence of MDR-TB would be higher in Baja California than in California, (2) the proportion of TB cases with previous treatment would be higher in Baja California than in California, and (3) the prevalence of MDR-TB would be the same in Baja California and California after adjusting for previous antituberculosis treatment, one of the strongest predictors for MDR-TB globally.

METHODS

Two sources of information were used for this study. Data for Baja California came from Mexico's first National Survey of TB Drug Resistance (ENTB), and data for California came from the California Department of Public Health TB case registry, which conducts continuous TB surveillance in California. ENTB was a representative survey conducted in Mexico from February 2008 through March 2009 to estimate the national prevalence of drug-resistant TB in cases of pulmonary TB, newly diagnosed by sputum smear microscopy.¹⁵ TB cases with ongoing antituberculosis treatment were not included in the ENTB.

The ENTB used a multistage sample design. The first stage selected 9 Mexican states, stratified by their reported TB incidence. The second stage selected clusters of health care units as defined by health jurisdictions within the state, with probability proportional to size. For Baja California, all 4 health jurisdictions in the state were included, so that the final sample represented all known newly diagnosed pulmonary TB cases reported throughout the state during that period. Mexico's National Reference Laboratory, Instituto de Diagnóstico y Referencia Epidemiológicos (InDRE), conducted drug susceptibility testing for 5 "first-line" drugs (isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin) by using BACTEC 460 (Becton Dickinson Diagnostic Instruments, Parks, MD). The Pan American Health Organization has designated the

Mycobacteria Laboratory at INDRÉ as an international reference laboratory. The Pan American Health Organization and the Centers for Disease Control and Prevention's Mycobacteriology and Tuberculosis Laboratory provide quality control rounds to InDRE on an annual and biannual basis, respectively. The Centers for Disease Control and Prevention also conducted quality control of drug susceptibility testing during the ENTB.¹⁵

California data came from the California Department of Public Health, which collates and reports all TB case data by using the US national standardized reporting format called the Report of a Verified Case of Tuberculosis, which includes both culture proven and clinically proven cases. The Report of a Verified Case of Tuberculosis data are considered a census of TB cases in California.⁸ For this study we included all incident (new or previously treated) pulmonary TB cases among patients who self-identified as "Hispanic," reported between 2004 and 2009. California state law²¹ requires that all *M. tuberculosis* isolates be submitted to local public health laboratories for culture and drug susceptibility testing, and that any laboratories without testing facilities submit their isolates to the California Department of Public Health Microbial Diseases Laboratory for drug susceptibility testing. All California isolates identified as MDR-TB were sent to the California Department of Public Health Microbial Diseases Laboratory for archiving. Drug susceptibility testing was completed using BACTEC 460 (Becton Dickinson Diagnostic Instruments), MGIT 960 (Becton Dickinson Diagnostic Instruments), or the agar proportion method.

Variables

The following patient and pathogen variables were extracted from the Baja California and California TB databases: gender, age in years, history of previous TB treatment, and drug susceptibility testing (DST) results. Country of birth was extracted from the California TB database. Other variables that have been related to MDR-TB in previous studies, such as HIV serostatus and reported alcohol or illegal drug use, were not comparable between the Baja California and California databases because of different definitions, and were not included in the analysis. In the ENTB, a case

was considered as having previous TB treatment either by self-report or according to the patient's clinical file.

When discrepancies between self-report and clinical file were found, the case was considered "previously treated" if either source stated so because we felt patients and physicians were less likely to misclassify a "previous treatment" than "no previous treatment." If only 1 source of information was available, that source was used as true value for the "previously treated" variable. In the California database, information on a patient's history of antituberculosis treatment was available from a combination of self-report and clinical records as recorded in the Report of a Verified Case of Tuberculosis variable: "previously treated."

Analysis

Newly diagnosed TB patients were classified as either (1) Mexicans living in Baja California (which included all Baja California patients registered in the ENTB database), (2) Mexico-born Hispanics living in California, (3) US-born Hispanics living in California, or (4) Californian Hispanics born elsewhere. For some analyses, patients were also classified as either Baja California or California. Differences in epidemiological and demographic characteristics of patients and DST results were compared across groups using the χ^2 and rank sum tests for categorical and continuous variables, respectively.

We estimated the prevalence of MDR-TB as the proportion of TB patients in each subgroup with drug resistance to at least isoniazid and rifampicin. We calculated crude odds ratios (ORs) of MDR-TB comparing patients by group, age, gender, and history of previous treatment. A multivariate logistic regression model was used to investigate the association of MDR-TB with classification group and previous treatment, adjusting by age and gender. Analyses were conducted with Stata version 11 (Stata-Corp LP, College Station, TX).

RESULTS

The study population comprised 633 Mexican TB patients living in Baja California and 2952 Hispanic TB patients living in California (1878 Mexico-born, 549 US-born, and 525 Hispanics born elsewhere). Patients in

California born in countries other than Mexico and the United States included 163 from Guatemala, 122 from El Salvador, 74 from Peru, and 166 from other countries. Mexico-born Hispanics reported being in the United States for a median of 13.3 years (interquartile range [IQR] = 3.5–26.2), whereas those born elsewhere reported being in the United States for a median of 7.3 years (IQR = 2.5–18.5; $P < .001$).

The US-born group was slightly younger than the other 3 groups ($P < .001$; Table 1). The percentage of female patients also differed between groups ($P < .001$), with the higher percentage observed in the US-born group. Among Mexican patients, 83 of 488 patients with information on previous treatment (17.0%) had received antituberculosis treatment on at least 1 previous occasion, compared with 130 of 2920 California patients (4.5%; $P < .001$).

In Baja California, 521 (82.3%) patients had DST results available for all 5 first-line drugs. In California, 2952 (99%) patients had DST results available, but the actual drugs tested varied (Table 1). Of the California patients, 1802 (61%) were tested for all 5 first-line drugs (isoniazid, rifampicin, pirazinamide,

ethambutol, streptomycin), with 1150 (39%) tested for diverse combinations of drugs (data not shown). Among the *M. tuberculosis* strains tested for all 5 first-line drugs, 437 (83.9%) were pansensitive in Baja California, and 1418 (78.7%) were pansensitive in California. The proportion pansensitive was lower for those living in California and born in Mexico, compared with the other 3 groups (Table 1). In Baja California, 57 (10.9%) patients were resistant to at least 1 drug (monoresistant), and in California, 273 (15.2%) patients were resistant to at least 1 drug.

Eleven of the 521 TB patients with drug susceptibility testing data available in Baja California had MDR-TB (prevalence = 2.1%), and 46 of the 2928 Hispanic TB patients with drug susceptibility testing data available in California had MDR-TB (prevalence = 1.6%; $P = .361$). MDR-TB prevalence was highest in Hispanics born in other countries (2.7%), followed by the Baja California group (2.1%) and the Mexico-born California group (1.6%), with the US-born Hispanics having the lowest prevalence of MDR-TB (0.4%). Of the Baja California MDR-TB cases, 3 were previously treated, 3 were not previously treated, and 5

had no information on previous treatment. Of the California MDR-TB cases, 10 were previously treated, 35 were not previously treated, and 1 had no information on previous treatment.

On univariate analysis, the odds of MDR-TB in Baja California patients versus all 3 groups of California Hispanics combined was 1.4 (95% confidence interval [CI] = 0.70, 2.66). In the univariate model, which compared the 4 different subgroups, the US-born individuals had significantly lower odds of MDR-TB compared with the Baja California patients, Mexico-born California Hispanics, or those born elsewhere outside of the United States (Table 2).

After adjusting for age, gender, and comparison group, previous antituberculosis treatment was significantly associated with MDR-TB (OR = 6.57; 95% CI = 3.34, 12.96). Additionally, Mexico-born California TB patients and those born outside of the United States were more than 5 times as likely to have MDR-TB compared with Hispanic TB patients born in the United States, but the difference between US-born California Hispanics and Baja California patients was no longer significant (Table 2).

TABLE 1—Characteristics and DST Results of Reported Tuberculosis Cases Among Patients in Baja California, Mexico (2008–2009), and Hispanic Patients in California (2004–2009)

| | TB Cases Reported in Baja California (n = 633), Median (IQR), %, or No. (%) | Hispanic TB Cases Reported in California | | |
|---------------------------------------|---|--|--|--|
| | | Mexico-Born (n = 1878), Median (IQR), %, or No. (%) | US-Born (n = 49), Median (IQR), %, or No. (%) | Born Elsewhere (n = 525), Median (IQR), %, or No. (%) |
| Age, ^{***} y | 33 (25–45) | 43 (30–58) | 28 (19–51) | 37 (27–55) |
| Female ^{***} | 23.4 | 29.8 | 42.1 | 41.9 |
| Previous treatment ^{***} | 17.0 | 4.7 | 3.7 | 4.6 |
| Cases with DST ^{a,***} | 521 (82.3) | 1864 (99.3) | 543 (98.9) | 524 (99.8) |
| DST results ^b | | | | |
| Pansensitive ^{**} | 437/521 (83.9) | 852/1118 (76.2) | 228/276 (82.6) | 327/397 (82.4) |
| MDR-TB [*] | 11/521 (2.1) | 30/1861 (1.6) | 2/543 (0.4) | 14/524 (2.7) |
| Isoniazide resistant ^{**} | 36/521 (6.9) | 166/1863 (8.9) | 25/543 (4.6) | 51/524 (9.7) |
| Rifampin resistant | 12/521 (2.3) | 33/1862 (1.8) | 5/543 (0.9) | 15/524 (2.9) |
| Ethambutol resistant | 7/521 (1.3) | 18/1862 (1.0) | 6/543 (1.1) | 8/523 (1.5) |
| Streptomycin resistant [*] | 52/521 (10.0) | 96/1137 (8.4) | 15/283 (5.3) | 46/399 (11.5) |
| Pirazinamide resistant ^{***} | 22/521 (4.2) | 223/1845 (12.1) | 69/534 (12.9) | 11/521 (2.1) |

Note. DST = drug susceptibility test; IQR = interquartile range; MDR-TB = multidrug-resistant tuberculosis.

Source. Data for Baja California are from the National Survey of TB Drug Resistance, México. Data for California are from the California Department of Health Services Registry of Reports of Verified Cases of TB.

^aIncluded DST for at least 1 drug.

^bCategories are not mutually exclusive; percentages do not always total 100%.

* $P < .05$; ** $P < .01$; *** $P < .001$.

TABLE 2—Logistic Regression Model of Multidrug-Resistant Tuberculosis in Reported Tuberculosis Cases Among Patients in Baja California, Mexico (2008–2009), and Hispanic Patients in California (2004–2009)

| Variable | Univariate Model, OR (95% CI) | Final Multivariate Model, ^a OR (95% CI) |
|--|-------------------------------|--|
| Age, y | 0.99 (0.98,1.01) | 0.98 (0.97,1.00) |
| Gender | | |
| Male (Ref) | 1.00 | 1.00 |
| Female | 1.05 (0.60,1.83) | 0.90 (0.48,1.66) |
| Previous antituberculosis treatment | 5.75 (3.01,10.98) | 6.57 (3.34,12.96) |
| National origin group | | |
| US-born, living in California (Ref) | 1.00 | 1.00 |
| Mexican, living in Baja California | 5.83 (1.29,26.45) | 2.82 (0.55,14.48) |
| Mexico-born, living in California | 4.43 (1.06,18.60) | 5.08 (1.19,21.75) |
| Hispanic, born elsewhere, living in California | 7.43 (1.68,32.83) | 7.69 (1.71,34.67) |

Note. CI = confidence interval; OR = odds ratio.

Source. National Survey of TB Drug Resistance, México. California Department of Public Health.

^aAge, gender, and ethnic group classifications were included as covariates in a linear logistic model.

DISCUSSION

In this study we estimated the prevalence of MDR-TB and identified associated factors in a US–Mexico cross-national population. Using Hispanic ethnicity as an indicator of possible relationships to Mexico, we sought to compare MDR-TB prevalence in TB patients in Baja California and California. Even though similar TB strains might be shared between Baja California and California, we expected that patients in Mexico would be more likely to develop acquired MDR-TB because of differences in resources available to TB control programs on each side of the border, such as those required to perform culture and drug sensitivity testing and understaffing.^{19,20} Those differences put TB patients in Mexico at increased risk for inadequate or incomplete treatment, the main risk factor for MDR-TB.³ We hypothesized that MDR-TB prevalence would be higher in Baja California than in California, and also that, after adjusting by previous treatment (the primary risk factor for MDR-TB), this difference would be negligible.

However, according to our results, MDR-TB prevalence in Baja California (2.1%) was not significantly higher than that in Hispanics in California (1.6%) as a whole, but there were significant differences in the odds of MDR-TB between the different subpopulations of Hispanics in California, stratified by their country of origin. US-born Hispanics had a significantly

lower prevalence of MDR-TB compared with the other Hispanic groups in California. This difference could not be accounted for by differences in history of previous treatment because when this was controlled for in the multiple logistic regression models, US-born Hispanic patients still had lower adjusted odds of MDR-TB compared with the foreign-born California cases.

The lack of a significant difference in MDR-TB prevalence between US-born Hispanics and Baja California patients, after previous TB treatment was accounted for, could indicate that previous TB treatment is the primary risk factor associated with the development of MDR-TB in this population regardless of the patients' state of residence.

However, the persistence of a differential risk for MDR-TB between the 3 California groups, after previous treatment was accounted for, raises a number of questions. One possible reason for a higher prevalence in California Hispanics born outside the United States, compared with the US-born, might be their exposure to resistant TB strains in their place of origin. This might be the case for those born in Peru, where MDR-TB prevalence among new patients is one of the highest in Latin America, at 5.3%.³ Such exposure would have increased their likelihood of primary resistance, which in turn would decrease the relevance of previous treatment as a risk factor. Another explanation could be that non-US-born patients had

received previous treatment outside of the United States.²² If, in those countries, the drug course received was incomplete or delivered with suboptimal drug choices, that could promote the selection of resistant bacteria in those patients.³ Measurement error of the treatment history may lead to residual confounding of the estimated adjusted association between birthplace and prevalence of MDR-TB. Finally, accuracy of reporting previous treatment may differ across groups. Recent immigrants may underreport a previous TB diagnosis if they believe this could compromise their situation in the United States, in which case secondary MDR-TB might be misclassified as primary.

Among the limitations of our study was the difference in diagnostic methods routinely used by the TB control programs in Mexico and the United States. In Mexico, pulmonary TB cases are diagnosed mainly by sputum smear, whereas in the second country cases are routinely cultured. Although this could cause a difference between Baja California and California in the proportion of suspect cases correctly diagnosed, there is no evidence that sputum smear negative cases are different from positives in their probability of being MDR, so no bias should result.

Another limitation was the low MDR-TB prevalence, which resulted in wide confidence intervals. This could have been addressed if more years of data were available for Baja California. The lack of data on cases treated in the private sector in Baja California also limited the number of cases studied. The lack of information on other comorbid diseases, such as diabetes and HIV coinfection, limited further stratification of the MDR-TB population into different risk groups.²³ Some of our variables were imperfect indicators, as in the classification by previous treatment on the basis of self report for some cases in Baja California.

Also imperfect is the race/ethnicity indicator, "Hispanic," which includes people of diverse national and ethnical origins. Although most of the Hispanics in the California sample were of Mexican origin, many of them came from other countries. Even among those of Mexican origin, the ethnic composition might differ, as some of those classified as "Hispanic" in California could be members of indigenous groups from Mexico or Central America. Indigenous populations in Mexico have been

shown to be at higher risk for MDR-TB compared with the nonindigenous population,¹² so this could be a confounder that should be accounted for in future studies.

All of the limitations mentioned should be addressed in future studies. More comparable data, and studies on molecular epidemiology, should provide a better picture of the similarities and dissimilarities in MDR-TB across the border region.

In conclusion, our results indicate that individuals who might share sociocultural characteristics and social networks through which TB can be transmitted can have varying prevalences of MDR-TB. Access to care and the characteristics of national public health programs, including the resources available to TB control programs, may explain these differences. Additionally, the high frequency of previous TB treatment among Baja California patients (17%) shows the difficulties faced by TB control programs in low-resourced settings.

A new TB episode in a patient with a history of previous treatment can result from relapse, treatment abandonment, or new primary infection. The first 2 situations reflect inadequate treatment, such as inappropriate selection of drugs, suboptimal dosage, or the barriers to access that patients experience, all of which are considered in the Directly Observed Therapy–Short Course strategy.³ Public health programs must address these issues. If the emergence of MDR-TB and other forms of drug resistance is to be controlled, governments and civil society must find innovative ways to face the challenges of financing, program organization, laboratory capacity, and political commitment,²⁴ or these disparities in MDR-TB prevalence will likely worsen over time. ■

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Contributors

I. Bojorquez-Chapela conceptualized and designed the study, conducted analyses, and wrote the article. R. F. W. Barnes conducted analyses and helped write the article. J. Flood, H. López-Gatell, R. S. Garfein, J. M. Vinetz, A. Catanzaro, and M. Kato-Maeda helped design the study, interpret the data, and write the article. C. E. Bäcker and C. Alpuche helped interpret the data and write the article. T. C. Rodwell conceptualized and designed the study and analyses, and wrote the article.

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Human Participant Protection

This study was approved by the institutional review boards of University of California, San Diego and California Department of Public Health in the United States, and the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* in Mexico.

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