

## Drug-Resistant Pulmonary Tuberculosis in the Baja California-San Diego County Border Population

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A study was conducted to determine the frequency of, and risk factors for, drug-resistant pulmonary tuberculosis (TB) among Baja California (BC) and San Diego County (SDC) residents. Another purpose was to document the amount of contact between pulmonary TB patients and residents of the opposite side of the border. During the period from February 1995 to May 1996, pulmonary TB patients from BC (n = 427) and SDC (n = 331) were evaluated with cultures, drug susceptibility tests, and questionnaires. Drug resistance was found in 41% of the BC Mycobacterium tuberculosis complex (MTB) isolates and 20% of the SDC isolates. Resistance to both isoniazid (INH) and rifampin (RIF) varied from 1% of isolates from SDC patients to 17% of isolates from BC patients. Patients with a history of previous treatment had increased odds of drug-resistant disease. Older BC patients were more likely to have INH- or RIF-resistant TB. Although 42% of Tijuana TB patients reported recent contact with residents from SDC, travel to Mexico and contact with residents from Mexico were not significant risk factors for drug-resistant TB among SDC residents. However, the demonstrated contact between TB patients and residents on opposite sides of the border indicates the importance of coordinating efforts internationally to control TB.

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Although the international boundary divides communities in Southern California and northern BC, these areas are closely linked geographically and economically. Each month there are an average of more than 5 million events of individuals crossing the border northbound between San Diego and Tijuana.<sup>1</sup> The number of individuals traveling southbound is approximately equal to the number traveling northbound.<sup>1</sup> Tuberculosis continues to pose a significant public health problem for communities on both sides of the border.<sup>2</sup> While comprehensive data are available on the incidence of drug-resistant disease among SDC patients through the county's Tuberculosis Control Program, there are only limited data available on drug-resistant TB among BC residents.<sup>2</sup> In addition, there is no published information available on the amount of contact that occurs between TB patients in BC and SDC with residents from the opposite sides of the border.

The purposes of this study were to

- Determine the proportion of drug-resistant disease among patients with pulmonary TB in BC and SDC border communities during a defined time period,
- Determine whether contact occurs between TB patients in BC and SDC and residents from the opposite sides of the border,
- Identify risk factors for drug-resistant TB among pulmonary TB patients in this population.

### Patients and Methods

For purposes of this study, patients were classified as having "pulmonary TB" if they had a sputum culture positive for MTB, which includes *M. tuberculosis* and *M. bovis*.

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Preliminary results from this study were presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 1997 (abstract E-162). This project was approved by the Committee on Protection of Human Subjects, San Diego State University. Informed consent was obtained from all participants.

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**ABBREVIATIONS USED IN TEXT**

BC = Baja California
MTB = <i>Mycobacterium tuberculosis</i> complex
SDC = San Diego County
TB = tuberculosis
ETH = ethambutol hydrochloride
INH = isoniazid
PZA = pyrazinamide
RIF = rifampin
STR = streptomycin sulfate

*Baja California Patients (Descriptive Study)*

During the period between February 1995 and May 1996, physicians based in public health TB clinics, community health centers, and hospitals as well as outreach workers in community settings recruited a convenience sample of patients for participation. Most of these patients (83%) were recruited through Servicios Coordinados de Salud Pública de B.C. and Instituto Mexicano Seguro Social which together serve 87% of the Baja California population.<sup>3</sup> Inclusion criteria consisted of

- Having a TB compatible X-ray film with at least one of the following symptoms: cough, sputum production, hemoptysis, fever of at least two weeks, or weight loss;
- Having a positive acid-fast smear;
- Being a symptomatic household contact of a diagnosed TB case;
- Having at least two of the following symptoms: cough, sputum production, hemoptysis, night sweats, and weight loss.

Patients under treatment for TB also were recruited, if they had received anti-TB medication  $\leq 2$  weeks or if they continued to have positive acid-fast smears four or more weeks after initiation of treatment with anti-TB medication. A total of 3,027 patients were recruited: 1,002 from Ensenada, 965 from Mexicali, and 1,060 from Tijuana. A single sputum specimen was obtained from each patient.

*San Diego County Patients (Population-Based, Prospective Study)*

All 331 TB patients with positive sputum cultures for MTB who were reported to the San Diego County Department of Health Services during the time period from February 1, 1995, to May 31, 1996, were studied.

*Questionnaires and Patient Data*

Survey data was collected from questionnaires used in interviewing patients and from public health case records. Data collected included treatment history, birth date, country and state of birth, place of residence five years ago, number in household, household income, and frequency of transborder travel and contact with residents from the opposite side of the border within the past 30 days. Subjects interviewed included each of the BC patients and 280 (85%) of the 331 reported SDC pulmonary TB patients.

San Diego County patients previously diagnosed with TB were classified as previously treated.

*Laboratory Testing*

Sputum specimens from BC and most SDC patients were processed using the NaOH-NALC method, examined for acid-fast bacilli using the fluorochrome stain, and cultured on Lowenstein-Jensen slants, Middlebrook 7H10 agar plates, and Bactec 12B media using standard methods<sup>4,5</sup> at San Diego County and Imperial County Public Health Laboratories. Some specimens from SDC patients were cultured in clinical laboratories. Isolates of mycobacteria were identified using a combination of DNA probes (Gen-Probe, San Diego, CA), biochemical tests,<sup>4</sup> and in some cases, high performance liquid chromatography.<sup>6</sup>

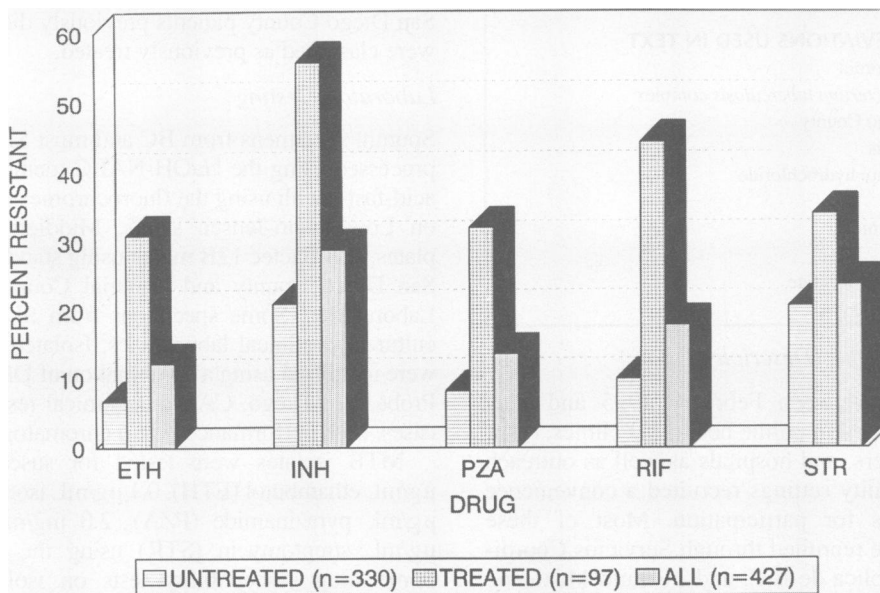
MTB isolates were tested for susceptibility to 2.5  $\mu\text{g/mL}$  ethambutol (ETH), 0.1  $\mu\text{g/mL}$  isoniazid (INH), 100  $\mu\text{g/mL}$  pyrazinamide (PZA); 2.0 mg/mL RIF, and 2.0  $\mu\text{g/mL}$  streptomycin (STR) using the Bactec system.<sup>5</sup> Some drug susceptibility tests on isolates from SDC patients were performed in other laboratories using the proportional method<sup>7</sup> and comparable concentrations of drugs.

*Statistical Analyses*

Analyses were conducted using SPSS 7.0 software. The Pearson's Chi-square and the Fisher exact tests were used to identify various independent variables from the questionnaire responses that were significantly associated with drug resistance to individual or multiple drugs (dependent variables). Two tests were used to eliminate independent variables strongly associated with each other: tolerance of independent variables, and multicollinearity via a correlation matrix. The backward stepwise logistic regression model was used; that is, all independent variables were included initially, then variables not significantly related to the outcome were removed one at a time. The Hosmer and Lemeshow goodness-of-fit test was used to determine the reliability of odds ratios.

**Results**

MTB was isolated from a total of 427 BC patients. Of the 427 isolates from these patients, 419 were identified as *M. tuberculosis* and the remaining 8 as probable *M. bovis*. Drug susceptibility testing was completed on all 427 isolates. The 331 isolates from SDC patients were identified as follows: 205 *M. tuberculosis*, 4 *M. bovis*, and 122 MTB. Isolates from the group of 122 MTB isolates could not be further identified as *M. tuberculosis* or *M. bovis* because equivocal results were obtained with biochemical tests, the cultures became non-viable during storage, or the clinical laboratories that performed the cultures had discarded the isolates. There was no significant difference in drug resistance of isolates from SDC patients interviewed and drug resistance of isolates from patients unavailable for interviews (data not shown). Data on drug susceptibility of isolates to ETH, INH, and RIF were available for all SDC patients. Susceptibility results for PZA and STR were available on 89% of SDC isolates.



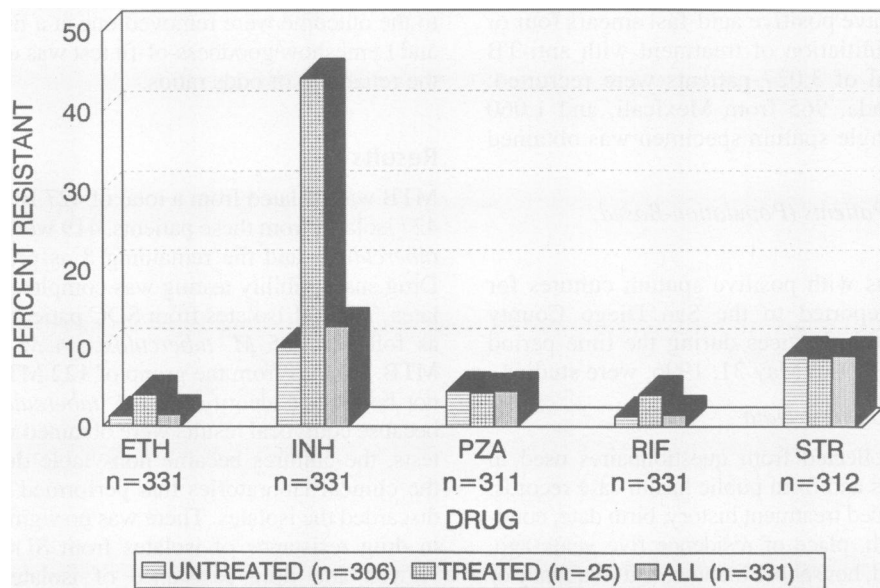
**Figure 1.**—Percentage of resistance among the individual *M. tuberculosis* complex isolates from 427 Baja California patients to each of the individual drugs is shown by patient treatment history. ETH = ethambutol hydrochloride, INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, STR = streptomycin sulfate

*Drug Resistance*

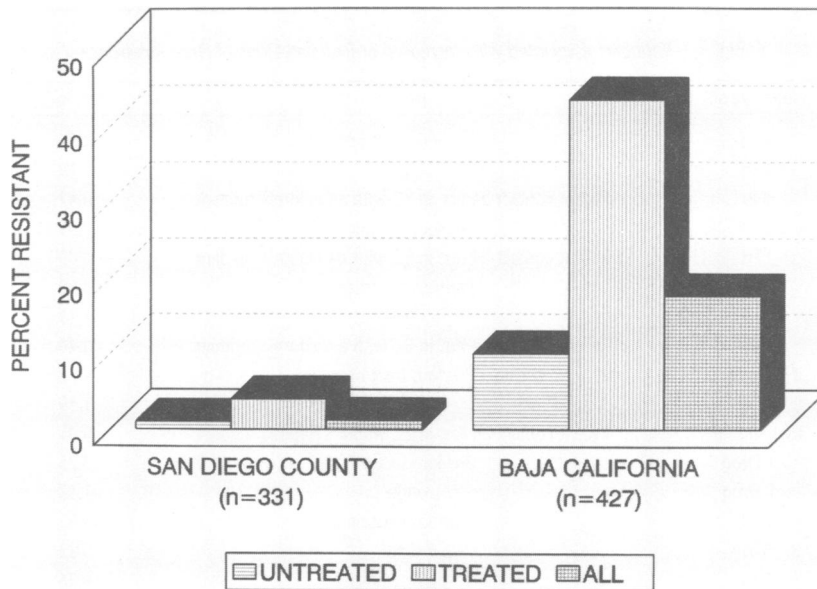
Resistance of isolates from BC patients to the individual drugs by treatment history is shown in Figure 1. Overall resistance varied from 12.2% (52 of 427) to ETH to 28.8% (123 of 427) to INH. The percentages of patients with strains showing drug resistance to the individual

drugs ETH, INH, PZA, and RIF were more than twice as high among patients with a history of previous treatment than those from patients with no prior treatment.

Overall resistance of isolates from the SDC patients varied from 1.5% (5 of 331) for ETH and RIF to 12.7% (42 of 331) for INH. As shown in figure 2, the proportion of isolates resistant to INH was 4-fold higher among



**Figure 2.**—Percentage of resistance among the *M. tuberculosis* complex isolates from San Diego County patients to each of the individual drugs is shown by patient treatment history. ETH = ethambutol hydrochloride, INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, STR = streptomycin sulfate



**Figure 3.**—Percentage of combined resistance to both isoniazid (INH) and rifampin (RIF) among the *M. tuberculosis* complex (MTB) isolates from Baja California and San Diego County patients are shown by patient treatment history.

those from patients with a history of previous treatment as compared to those from untreated patients.

Figure 3 shows frequency of drug resistance to both INH and RIF. Overall frequency of resistance to both drugs among SDC patients was 1.2%. However for the isolates from BC patients, resistance varied from 10% (33 of 330) of those without previous treatment to 43.3% (42 of 97) of those with a history of previous treatment.

Frequency of resistance to one or more drugs is shown in Table 1. Isolates from 59% of the BC patients and 80% of the SDC patients were susceptible to all primary drugs.

*Transborder Contacts*

As shown in Table 2, 42.2% (68 of 161) of culture proven TB patients from Tijuana reported having ≥4 hours of contact with one or more residents from the U.S. within the past 30 days. Of these 68 patients, 78% had positive acid-fast smears. Most of the contact occurred with U.S. residents who traveled to Tijuana. Less than 19% (47 of 257) of the patients surveyed from

Ensenada and Mexicali reported contact with U.S. residents. Among SDC TB patients, 16% reported having contact with residents from Mexico. Eighteen of 57 (31.6%) SDC patients born in Mexico indicated that they had visited Mexico within the past 30 days.

*Risk Factors for Drug-Resistant Tuberculosis Among TB Patients*

Independent variables directly or indirectly associated with drug resistance and showing a good fit with the models are shown in Table 3. History of previous treatment was the only variable associated with increased odds of drug-resistant TB among residents on both sides of the border.

**Discussion:**

The data reveals substantially higher frequencies of drug-resistant pulmonary TB in BC than in SDC. The data on

Resistant to	Patients from	
	Baja California (n = 427)	San Diego County (n = 293)
0 Drugs	59.4%	79.6%
1 Drug	17.1%	15.0%
2 Drugs	7.5%	3.4%
3 Drugs	4.9%	1.0%
4 Drugs	5.9%	0.3%
5 Drugs	5.2%	0.7%

Patients from	Any Transborder Contact	On the Same Side of the Border	On the Opposite Side of the Border
Ensenada, Baja California (n = 81)	16.0%	14.8%	2.3%
Mexicali, Baja California (n = 176)	19.3%	14.2%	6.8%
Tijuana, Baja California (n = 160)	42.2%	39.1%	16.1%
San Diego County (n = 234)	15.8%	12.0%	10.3%

TABLE 3.—Variables Associated with Increased or Reduced Odds of Drug Resistance

Isolates of Patients from	Resistance to	Variable	Odds Ratio	95% Confidence Interval
Baja, California	INH	Previous treatment	3.30	2.01 - 5.44
	INH	Age	1.19	1.03 - 1.38
	INH	Recent contact $\geq$ 4 hrs. in BC with a California resident	0.47	0.26 - 0.86
	ETH	Previous treatment	2.99	1.59 - 5.64
	ETH	Recent contact $\geq$ 4 hrs. in BC with a California resident	0.49	0.21 - 1.16
	RIF	Previous treatment	4.58	2.60 - 8.04
	RIF	Age	1.19	1.00 - 1.41
	RIF	Recent contact $\geq$ 4 hrs. in BC with a California resident	0.40	0.19 - 0.86
	INH and RIF	Previous treatment	4.72	2.68 - 8.32
	INH and RIF	Age	1.19	1.00 - 1.41
	INH and RIF	Recent contact $\geq$ 4 hrs. in BC with a California resident	0.41	0.19 - 0.88
	> 1 Drug	Previous treatment	2.25	1.42 - 3.57
	> 1 Drug	Age	1.13	1.00 - 1.29
San Diego County	INH	Previous treatment	5.95	1.87 - 18.92
	INH	Age	0.83	0.68 - 1.02
	PZA	Hispanic ethnicity	4.86	1.45 - 16.24
	STR	Age	0.80	0.63 - 1.02
	> 1 Drug	Previous treatment	3.21	1.06 - 9.73
	> 1 Drug	Age	0.80	0.67 - 0.94

BC = Baja California; ETH = ethambutol hydrochloride; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; STR = streptomycin sulfate

frequency of drug resistance among the two populations, however, cannot be directly compared because the study of the BC patients was not a population-based study. Nevertheless, the magnitude of INH and RIF multidrug resistant TB (75 of 427) cases appears substantial compared to the few (4 of 331) cases in SDC. Data from the Pan American Health Organization collected in 1994 also has indicated substantially higher drug resistance rates among TB patients residing in Mexican border communities than in their nearby U.S. sister cities.<sup>2</sup> The Pan American Health Association statistics recorded 29% of TB cases as drug resistant in San Luis Rio Colorado, Sonora, compared to 4% in nearby Yuma, Arizona; 30% in Tijuana, BC, but 20% in San Diego, California; and 56% in Nuevo Laredo, Tamaulipas, with 16% in Webb County, Texas. While these data were not determined using population-based studies, they do suggest that a relatively high proportion of TB patients residing in BC Mexican border communities are infected with drug resistant MTB.

A study by Sifuentes-Osornio and co-workers<sup>8</sup> of MTB isolates from 84 patients, mostly from the Mexico City region, reported a similar proportion of isolates resistant to individual primary drugs as we found among BC patients: ETH, 10%; INH, 24%; RIF, 19%; STR, 12%; and combined resistance to INH and RIF, 20%. They found that 70% of isolates, a higher proportion than our figure of 59%, were susceptible to all drugs evaluated. However, they did not test for PZA susceptibility. Another notably higher proportion of drug-resistant isolates, 70%, was reported by Alvarez-Gordillo et al. among 18 patients in the Mexican state of Chiapas.<sup>9</sup> Possible reasons for differing proportions of patients with drug resistant TB among

different regions of Mexico are non-random sampling of patients and varying resources for detection of cases and ensuring completion of treatment. A population-based study being conducted by the U.S. Centers for Disease Control and Prevention and the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos of Mexico in several Mexican states may provide a more comprehensive picture of the prevalence of drug resistant TB in Mexico (R. Granich, MD, U.S. Centers for Disease Control and Prevention, personal communication, December 1997).

Within the U.S. there is also variation in the percentage of drug resistant TB cases reported by individual states, although the variation is not as pronounced as reported within Mexico. The percentage of SDC pulmonary TB patients infected with INH resistant strains, 12.7%, is higher than the 1996 figures for all reported TB patients in California (9.8%), Arizona (5.9%), Texas (5.4%), and nationally (8.0%).<sup>10</sup>

Our data, demonstrating that 32% of Mexican born SDC TB patients surveyed had visited Mexico within the past 30 days, is consistent with a previous study conducted by the U.S. Centers for Disease Control and Prevention. They demonstrated that 35% of foreign-born Hispanic TB patients residing in U.S. border communities visit their country of origin, primarily Mexico, at least monthly.<sup>11</sup> Our report is the first that documents transborder contact between Mexican residents with TB and persons residing in the U.S. The reported contact of 68 smear-positive Tijuana patients with residents from the U.S. indicates a potential for international transmission. The notable finding that 15.8% (37 of 234) SDC TB patients reported contact with BC residents estab-

lishes that TB transmission across the border is likely to be bidirectional, south to north as well as north to south. However, the extent of such transmission is difficult to demonstrate without availability of longitudinal DNA fingerprinting data and epidemiological investigation of isolates with matching fingerprints.

The relationship between previous treatment and both drug resistant and multiple drug resistant TB has been well documented by others.<sup>12-14</sup> The tendency for BC patients to have an increased risk of TB resistant to >1 drug with increasing age could be related to an increased chance of exposure to someone with drug-resistant TB over time. In addition, some patients may have undertaken unreported, self prescribed, ineffective TB treatment. Arevalo et al. noted that patients over age 45 in Spain had an increased risk of drug-resistant TB.<sup>14</sup> The higher risk of younger SDC patients for TB resistant to ≥1 drug may reflect more recent infection during a time when drug resistant TB is more prevalent worldwide. The connection of Hispanic ethnicity to PZA resistance among SDC patients may stem from the fact that *M. bovis*, which is inherently resistant to this drug, is most commonly associated with the Hispanic population in SDC.<sup>15</sup>

Others have linked drug-resistant TB with additional risk factors, including cavitary lung disease,<sup>17,18</sup> HIV infection,<sup>16,19</sup> hepatic cirrhosis,<sup>14</sup> and homelessness.<sup>19</sup> However, our study did not attempt to evaluate these factors because of difficulty in obtaining the information. Although foreign-born individuals have been reported to have increased rates of drug-resistant TB,<sup>16,18</sup> foreign birth was not implicated as an independent risk factor in the SDC patient population, possibly because of sample size, the large proportion (78%) of the SDC patients who were foreign born, or the commonness of other risk factors among foreign-born patients.

Although this study was not designed to document transborder transmission of TB, 42% of Tijuana patients and 16% of SDC patients had recent contact lasting ≥4 hours with residents from the opposite side of the border. Further studies are needed to determine the amount of transmission caused by this type of contact, but our findings suggest that coordinated binational efforts may be important for TB control in this border region.

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