Articles

Drug-Resistant *Mycobacterium tuberculosis* in California, 1991 to 1992

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To determine the proportion and distribution of drug-resistant *Mycobacterium tuberculosis* in California, we surveyed all California counties for drug-susceptibility test results for initial isolates from tuberculosis cases counted during the first quarters of 1991 and 1992. Overall, drug-susceptibility test results were not available for 17% of isolates. Among isolates with available test results, the proportion with resistance to isoniazid averaged 8.7%, and the proportion with resistance to at least 2 drugs, multidrug resistance, averaged 5.9% during these two quarters. The proportion of isolates with drug resistance did not change substantially during these time periods. The proportion with combined isoniazid and rifampin resistance remained stable at about 1.1%. Among persons whose isolates were tested for drug resistance, those with a known previous diagnosis of tuberculosis (relative risk [RR] = 2.6; 95% confidence interval [CI], 1.6 to 4.3; $P < .01$) and persons who were foreign born (RR = 1.7; 95% CI, 1.1 to 2.7; $P = .014$) were more likely to have isoniazid-resistant organisms. These statewide data suggest that the initial tuberculosis treatment regimen in California should include 4 antituberculosis drugs, as recommended by the American Thoracic Society and the Centers for Disease Control and Prevention for areas with a prevalence of isoniazid resistance of 4% or greater. The lack of test results for 1 in 6 patients with tuberculosis suggests the need for improved physician and laboratorian education to implement the recommendations that drug susceptibility be tested on all initial isolates.

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During 1975 to 1982, the Centers for Disease Control (now the Centers for Disease Control and Prevention; CDC) conducted surveillance for primary drug resistance among patients with tuberculosis (TB).[1-3] These surveys documented a 6.9% prevalence of resistance to one or more antituberculous drugs among isolates from 20 city and state laboratories across the nation (9.7% and 8.2%, respectively, from Los Angeles and San Francisco, California). From 1982 to 1986, the CDC also counted cases of TB with acquired (secondary) drug resistance.[4] The CDC stopped surveying for drug-resistant *Mycobacterium tuberculosis* in 1986 because of resource limitations and the decreasing trend of primary drug resistance.

In 1991, because of concern over the increasing incidence of TB and the outbreaks of multidrug-resistant TB, the CDC initiated a nationwide retrospective survey of drug susceptibilities of *M tuberculosis* organisms identified in cases counted during the first quarter of that year. Because drug-susceptibility test results were not routinely reported, the only source of statewide information about drug susceptibilities has been the first-quarter survey conducted by the CDC during 1991. We therefore repeated the first-quarter survey for 1992. Until ongoing surveillance is in place, these first-quarter surveys provide information regarding the magnitude of the problem in California that can be used to guide the choice of initial treatment regimens.

Patients and Methods

The study population consisted of all persons with cases of culture-positive tuberculosis counted in California during the first quarters of 1991 and 1992. A case of TB is counted by a county once the diagnosis has been confirmed. We sent each county a list of culture-positive cases counted within their jurisdiction for these two time periods. The information requested included whether drug susceptibility testing was done, when the first isolate was obtained, and drugs to which the isolate was resistant. On the questionnaire, we defined drug resistance as growth on a drug-containing medium (at any concentration tested) that is greater than 1% of that on the control medium.[5] We merged these data with the state Report of Verified Case of TB database to descriptively analyze drug-resistance patterns in California.

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ATS = American Thoracic Society
CDC = Centers for Disease Control and Prevention
TB = tuberculosis

We calculated drug resistance based on the results of drug-susceptibility testing for isolates tested against that drug or a combination of drugs. For example, the denominator for the fraction of organisms resistant to isoniazid and rifampin includes only those tested against both isoniazid and rifampin. We defined multidrug resistance as resistance to two or more drugs.

We evaluated the proportion of isolates without drug-susceptibility test results and possible patient risk factors for not having such testing done, including age, sex, race, ethnicity, country of birth, previous treatment of TB, site of disease (primary or secondary pulmonary disease versus no pulmonary involvement), known diagnosis of the acquired immunodeficiency syndrome (AIDS) (status provided without personal identifiers by the state AIDS office), and vital state at the time of the diagnosis of TB. We examined these same patient risk factors and the possible association with an organism with drug resistance. We also compared the demographic and clinical characteristics of persons with culture-positive TB counted during the first quarters of 1991 and 1992 with those counted during the rest of those years.

We calculated relative risks and 95% Cornfield confidence intervals using Epi Info, version 5, software from the CDC.[6] We used Yates-corrected χ^2 and P values to test for significance.

Results

Of the 1,333 persons with culture-positive tuberculosis during the first quarters of 1991 and 1992, 220 (17%) did not have drug-susceptibility testing done on their initial isolates. Those who had died at the time of being diagnosed with TB were 2.1 times more likely than living patients not to have drug-susceptibility testing done. Women were 1.4 times more likely than men and non-Latinos were 1.3 times more likely than Latinos not to have drug susceptibility testing done on their *M tuberculosis* organisms (Table 1). Drug-susceptibility testing was done with similar frequency across all other racial or ethnic and age groups (data not shown). Being born in the United States, having a previous diagnosis of TB or a known diagnosis of AIDS, or having pulmonary disease did not influence the likelihood of having drug-susceptibility testing.

The proportion of organisms with isoniazid resistance averaged 8.7%, whereas the proportion with multidrug resistance averaged 5.9%. The proportion of organisms with resistance to any single drug, especially to isoniazid, to one or more drugs, to two or more drugs, and to both isoniazid and rifampin did not change significantly in California between the first quarters of 1991 and 1992 (Tables 2 and 3). The proportion of isolates with combined isoniazid and rifampin resistance remained constant at approximately 1.1%. Los Angeles, Orange, and San Francisco counties counted the largest number of cases of *M tuberculosis* isolates with resistance to isoniazid during these time periods, with 43, 14, and 9 cases, respectively, accounting for 9%, 13%, and 6% of isolates tested in those counties, respectively.

The resistance patterns did not change substantially during these two years, nor did the proportion of patients with risk factors for having a resistant organism; therefore, we combined the data from both years. Our analysis of risk factors associated with any drug resistance yielded results similar to those for isoniazid resistance. Given the American Thoracic Society (ATS) and the CDC's emphasis on the prevalence of isoniazid resistance as a basis for decisions regarding initial drug regimens,[7,8] we report comparisons only for isoniazid resistance.

Among persons whose organisms were tested for isoniazid resistance (Table 4), those with a known previous diagnosis of TB were nearly three times more likely to have an isoniazid-resistant organism than were persons with a first-time diagnosis of TB. Those who were foreign born were 1.7 times more likely than persons born in the

TABLE 1.—*Evaluation of Factors Associated With Not Having Drug Susceptibility Testing of* Mycobacterium tuberculosis *(TB) Organisms Performed, First Quarter Surveys, California 1991-1992*

Category	Isolates No.	Isolates No. Not Tested (%)	RR (95% CI)	P Value
Deceased at diagnosis	57	19 (33)	2.1 (1.4-3.1)	<.001
Alive at diagnosis	1,274	200 (16)		
Women	467	92 (20)	1.4 (1.1-1.7)	.03
Men	866	128 (15)		
Non-Latino	876	157 (18)	1.3 (1.0-1.7)	.06
Latino	457	63 (14)		
US born	538	98 (18)	1.2	NS
Foreign born	778	119 (15)		
No previous diagnosis	1,239	205 (17)	1.1	NS
Previous TB diagnosis	91	14 (15)		

CI = confidence interval, NS = not significant, RR = relative risk

TABLE 2.—*Results of Drug-Susceptibility Testing of* Mycobacterium tuberculosis *Isolates for First-Line Drugs, First Quarter Surveys—California, 1991-1992*

Test	Year	M tuberculosis *Isolates* No. Tested	No. Resistant (%)
Isoniazid	1991	602	48 (8.0)
	1992	508	49 (9.6)
Rifampin	1991	599	8 (1.3)
	1992	507	7 (1.4)
Streptomycin	1991	526	41 (7.8)
	1992	450	31 (6.9)
Pyrazinamide	1991	128	5 (3.9)
	1992	120	2 (1.7)
Ethambutol	1991	594	13 (2.2)
	1992	500	8 (1.6)

United States to have isoniazid-resistant TB. Controlling for birth on foreign soil yielded the same results for persons with a known previous TB diagnosis. Among those without a previous diagnosis of TB, foreign-born persons remained 1.8 times more likely to have an organism resistant to isoniazid ($P = .02$). Sex, ethnicity, patient's status at diagnosis, the site of disease, and having a known diagnosis of AIDS were not associated with isoniazid resistance. An analysis of risk factors for multidrug resistance yielded similar results (data not shown).

Differences in the proportion of isolates with resistance among racial or ethnic groups were not statistically significant. Asians and Pacific Islanders, however, were the racial or ethnic group with the highest proportion of isolates with isoniazid resistance. Of 349 *M tuberculosis* isolates from Asians and Pacific Islanders, 43 (12%) demonstrated resistance to isoniazid; all Asians and Pacific Islanders with resistant organisms were foreign born. Of 170 *M tuberculosis* isolates from African Americans, 16 (9%) were isoniazid-resistant, as were 28 of 393 *M tuberculosis* isolates (7%) from Latinos. Of 189 isolates from non-Latino whites, 10 (5%) were isoniazid-resistant. Only 1 (6%) of the 16 African Americans with isoniazid-resistant isolates was born outside the United States, and of 28 Latinos with isoniazid-resistant isolates, 22 (79%) were born outside this country. Among the foreign born, persons from Mexico, the Philippine Islands, and Vietnam accounted for the largest number of isoniazid-resistant organisms (Table 5). The number of years spent in the United States did not significantly influence the proportion of isolates with isoniazid resistance.

Isoniazid resistance was most prevalent among persons aged 15 to 24 (14/118, 12%) and 25 to 44 years (50/473, 11%). This relationship persisted even after the data were controlled for birth outside the United States or a previous diagnosis of TB. The proportion of isolates with isoniazid resistance was also greater than 4% among persons younger than 4 years, those 45 to 64 years, and those older than 65. None of the six isolates from persons aged 5 to 14 years was resistant to isoniazid.

Of the 12 persons with *M tuberculosis* organisms resistant to both isoniazid and rifampin, 8 (67%) were Asians or Pacific Islanders born outside the United States. Three (25%) were Latino, only one of whom was born outside the United States. Six (50%) had a previous diagnosis of tuberculosis. Of the 12 persons with isoniazid- and rifampin-resistant *M tuberculosis*, 11 (92%) had pulmonary disease, of whom 8 (73%) had both positive sputum smears and cultures, indicating possible infectiousness.

There were no significant differences among persons with culture-positive TB counted as cases during the first quarters of 1991 and 1992 and those counted during the rest of those two years with regard to age, sex, race, ethnicity, birth in the United States, and previous diagnosis of tuberculosis.

Discussion

With the resurgence of tuberculosis and the reported outbreaks of multidrug-resistant TB,[9-12] it is important for clinicians and public health officials to know the prevalence and the distribution of drug-resistant *M tuberculosis*. Multidrug resistance, especially combined isoniazid and rifampin resistance, can render the standard treatment regimen of isoniazid, rifampin, and pyrazinamide ineffective, complicating the choice of therapy. The recently released ATS and CDC guidelines recommend initial four-drug therapy for patients with TB in areas where the prevalence of isoniazid resistance is at least 4%.[7,8] The reasons cited for the recommended initial four-drug regimen include its effectiveness even against isoniazid-resistant organisms, more rapid sputum conversion to negative, an increased ease of administration once the switch is made to directly observed therapy, and an increased chance of cure even if therapy is incomplete. The CDC also recommends obtaining drug-susceptibility results on all initial *M tuberculosis* isolates to guide therapeutic decisions.[7]

Aside from the results of this study, there is little information about drug-susceptibility patterns in California. In one study, drug susceptibility was evaluated among patients admitted to a hospital in Los Angeles

TABLE 3.—*Overall Results of Drug-Susceptibility Testing for Culture-Positive* Mycobacterium tuberculosis, *First Quarter Surveys—California, 1991-1992**

Drug Resistance	Year	M tuberculosis *Isolates* No. Tested	No. Resistant (%)
Resistant to ≥1 drug	1991	604	99 (15)
	1992	509	71 (15)
Resistant to ≥2 drugs	1991	603	33 (5.2)
	1992	507	32 (6.4)
Resistant to both isoniazid and rifampin	1991	599	6 (1.0)
	1992	507	6 (1.2)

*Drugs against which isolates may have been tested include first-line drugs as well as amikacin, ciprofloxacin, capreomycin, cycloserine, ethionamide, kanamycin, ofloxacin, aminosalicylic acid, and rifabutin.

TABLE 4.—*Evaluation of Risk Factors for Isoniazid Resistance, First Quarter Surveys—California, 1991-1992*

Category	Mycobacterium tuberculosis *Isolates* No. Tested	No. Resistant (%)	RR (95% CI)	P Value
Previous TB diagnosis	77	16 (21)	2.6 (1.6-4.3)	<.001
No previous diagnosis	1,031	81 (8)		
Foreign born	657	70 (11)	1.7 (1.1-2.7)	.014
US born	439	27 (6)		
Men	736	60 (8)	.82	NS
Women	374	37 (10)		
Latino	393	28 (7)	.74	NS
Non-Latino	717	69 (10)		
Alive at diagnosis	1,071	97 (9)	*	NS
Deceased at diagnosis	38	0 (0)		

CI = confidence interval, NS = not significant, RR = relative risk, TB = tuberculosis

*Undefined.

County in the mid-1980s, and a prevalence of isoniazid resistance of 10% was found.[13] The most recent population-based study published from California was conducted in Santa Clara County from 1984 to 1986[14]; the authors reported that, among 256 isolates tested, 69 (27%) were resistant to one or more "first-line" drugs (isoniazid, rifampin, streptomycin, or ethambutol). Of these resistant organisms, 59 (86%) were identified in patients born outside the United States; only 44 (24%) of the 187 isolates without drug resistance were identified in foreign-born patients. Of the 256 isolates tested for drug susceptibilities, 31 (12%) were resistant to at least two drugs, and 6 (2.3%) were resistant to both isoniazid and rifampin.

Our study found that the proportion of *M tuberculosis* isolates with resistance to any drug in California, 15%, is comparable with the amount of resistance (14.2%) found during the nationwide first-quarter survey from 1991.[15] These data demonstrated no notable change in the pattern of drug resistance among *M tuberculosis* isolates tested in California between the first quarter of 1991 and that of 1992.

Consistent with the results of other studies, resistance to one or more antituberculosis drugs, especially to isoniazid, was more common among foreign-born persons and among those with a previous diagnosis of TB. These persons belong to population groups already known to be at risk for resistant TB, yet 15% of patients in each of these categories did not have testing for drug susceptibility done on their initial isolates. It is not clear why isoniazid resistance was more prevalent among persons aged 15 to 44 years.

The decreased frequency of susceptibility testing for persons who had died at the time of diagnosis suggests that physicians see less usefulness in doing drug testing for isolates from deceased patients. Drug-resistance information, however, is important for decisions regarding the clinical management of not only patients but also their contacts. Contacts of a person diagnosed with TB at death—that is, of a person who died without receiving antituberculous chemotherapy—are at greater risk of exposure because the health care professional would not have begun treatment of TB while the patient was alive.

Women and non-Latinos were less likely to have drug-susceptibility tests done on their *M tuberculosis* isolates. This finding suggests that physicians may be more aware of the risk of drug-resistant organisms among Latinos, although it is not clear why women would be less likely than men to have such testing done. Physicians should be reminded to obtain drug-susceptibility tests on initial *M tuberculosis* isolates from all patients, as recommended by the CDC.[7]

A possible limitation of the representativeness of these data is the year-to-year and quarter-to-quarter variation in case-counting practices; no uniform mechanism yet exists for ensuring systematic methods of case counting. The cases counted during the first quarters of 1991 and 1992 represent only 15% to 18% of the total number of cases reported to the state during these years. Two of the six counties reporting the largest number of TB cases during the first quarter of 1991, San Diego and Santa Clara counties, counted no cases during the first

TABLE 5.—*Proportion of* Mycobacterium tuberculosis *Isolates Resistant to Isoniazid, by Country of Origin for Foreign-Born Patients, First Quarter Surveys—California, 1991-1992*

Country of Origin	M tuberculosis *Organisms* No. Tested	No. Resistant	(%)
Latin America			
Mexico	221	18	(8)
El Salvador	21	1	(5)
Guatemala	17	1	(6)
Other countries	35	2	(6)
Asia			
Philippines	107	10	(9)
Vietnam	80	15	(19)
China	55	9	(16)
South Korea	29	7	(17)
Laos	20	3	(15)
Other countries	43	2	(5)
Other countries or unknown	29	4	(14)

quarter of 1992, even though persons were diagnosed with TB during that period. The consistency of the results from each quarter imply that these data for drug-resistance patterns in California are reasonable preliminary estimates. Because information regarding only the first isolate was requested, these data give limited information about the incidence of acquired (secondary) drug resistance. The strong association between drug resistance and a previous diagnosis of TB suggests acquired drug resistance.

Another possible limitation of this study is that standard medical practice has not always included routine testing for drug susceptibilities. Our analysis was based only on those isolates tested, for which drug-susceptibility results were available. It is unclear what role clinicians' index of suspicion and the availability of testing or test results—including such issues as quality, timeliness, technologic advancement, and cost—may have played in causing an overestimate or an underestimate of the problem of drug resistance.

Despite accounting for a fifth of the nation's cases of TB (source: California Tuberculosis Control Branch) and despite reporting a proportion of foreign-born persons among patients with TB more than twice that of the rest of the country (60% versus 25%[15]), California seems to have a relatively low rate of multidrug-resistant TB, especially isoniazid- and rifampin-resistant TB, compared with the magnitude reported in New York[15,16] and possibly Florida.[9,10] There was a slight but not significant increase in the proportion of isoniazid-resistant isolates in California from 1991 to 1992, however. No racial or ethnic, age, or sex group had a proportion of isolates with isoniazid resistance of less than 4%, with the exception of those aged 5 to 14 years and American Indians (with fewer than 10 isolates tested from each group). Even among US-born patients and those without a previous diagnosis of TB, the proportion of isolates with isoniazid resistance was greater than 4%.

The results of this statewide analysis, therefore, suggest that all patients diagnosed with TB in California should be treated initially with the four-drug regimen as recommended by the ATS and the CDC,[7,8] unless local data define specific subgroups with a prevalence of isoniazid resistance of less than 4%. The four-drug regimen of isoniazid, rifampin, pyrazinamide, and ethambutol is preferred in California to the other recommended regimen of isoniazid, rifampin, pyrazinamide, and streptomycin because resistance to ethambutol was lower than that to streptomycin in this study. In addition, ethambutol is more readily available and can be taken orally, whereas streptomycin cannot. It should also be noted that resistance to both isoniazid and rifampin was only 1% during 1991 and 1992, suggesting that 99% of patients were susceptible to at least two of the drugs isoniazid, rifampin, and ethambutol and that the four-drug regimen that includes these drugs should be adequate for 99% of patients in California. The lack of drug-susceptibility testing for 17% of isolates shows the need for improved compliance with the CDC recommendation that drug-susceptibility testing be done on all initial isolates. Only then can the drug regimen be appropriately altered, if necessary.

The use of the expanded Report of Verified Case of TB, which began in January 1993, will allow state and local tuberculosis control programs and the CDC to monitor systematically both primary and acquired drug resistance among all new cases of TB. Health departments will also monitor the extent of physician compliance with the recommendations to do drug-susceptibility tests on all initial isolates and to first start with a four-drug regimen. These data, as well as information on the completion of therapy by patients, will allow a better definition of the causes of drug resistance and its trends so that control measures can be effectively directed.

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