

# Survey of Drug Resistance of *Mycobacterium tuberculosis* in 3 Mexican States, 1997

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**Background:** Drug resistance threatens global tuberculosis (TB) control efforts. Population-based estimates of drug resistance are needed to develop strategies for controlling drug-resistant TB in Mexico.

**Objective:** To obtain population-based data on *Mycobacterium tuberculosis* drug resistance in Mexico.

**Methods:** To obtain drug resistance data, we conducted a population-based study of TB cases in the states of Baja California, Sinaloa, and Oaxaca, Mexico. We performed cultures and drug susceptibility testing on *M tuberculosis* isolates from patients with newly diagnosed, smear-positive TB from April 1 to October 31, 1997.

**Results:** *Mycobacterium tuberculosis* was isolated from 460 (75%) of the 614 patients. Levels of resistance in new and retreatment TB cases to 1 or more of the 3 current first-line drugs used in Mexico (isoniazid, rifampin, and pyrazinamide) were 12.9% and 50.5%, respectively; the

corresponding levels of multi-drug-resistant TB were 2.4% and 22.4%. Retreatment cases were significantly more likely than new cases to have isolates resistant to 1 or more of the 3 first-line drugs (relative risk [RR], 3.9; 95% confidence interval [CI], 2.8-5.5), to have isoniazid resistance (RR, 3.6; 95% CI, 2.5-5.2), and to have multi-drug-resistant TB (RR, 9.4; 95% CI, 4.3-20.2).

**Conclusions:** This population-based study of *M tuberculosis* demonstrates moderately high levels of drug resistance. Important issues to consider in the national strategy to prevent *M tuberculosis* resistance in Mexico include consideration of the most appropriate initial therapy in patients with TB, the treatment of patients with multiple drug resistance, and surveillance or periodic surveys of resistance among new TB patients to monitor drug resistance trends.

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THE WORLD Health Organization (WHO) has estimated that 90 million cases of tuberculosis (TB) resulting in 30 million deaths occurred in the 1990s.<sup>1</sup> To address this urgent public health need, the WHO has recommended a comprehensive strategy known as directly observed treatment, short-course (DOTS).<sup>2</sup> The DOTS strategy relies on a political commitment to a sustainable national TB program, smear microscopy to detect cases among symptomatic patients seeking health services, the administration of standardized short-course chemotherapy regimens with direct observation of treatment, a regular supply of essential anti-TB drugs, and a standardized recording and reporting system allowing the program to assess outcomes.<sup>2</sup> This strategy has repeatedly demonstrated cure rates of 80% or higher.<sup>2</sup> However, the emergence of *Mycobacterium tuberculosis* strains that are resistant

to anti-TB drugs is a worldwide problem that threatens the efficacy of such TB control efforts.<sup>3</sup>

*See also pages 581 and 630*

*Mycobacterium tuberculosis* drug resistance has serious consequences for both the patient and the TB control program. Drug resistance increases the rate of treatment failure and the costs of TB control.<sup>4</sup> Since cure is often difficult or impossible, community and nosocomial transmission of drug-resistant *M tuberculosis* strains is also a serious potential problem.<sup>5-7</sup> The WHO has also expressed concerns indicating that the treatment of patients with multi-drug-resistant TB diverts resources from basic programmatic priorities such as diagnosing and treating new patients with TB.<sup>8</sup>

Spontaneous mutations leading to drug resistance occur rarely in *M tuberculosis*. Therefore, multidrug therapy can effec-

## METHODS

This survey followed specific guidelines for conducting anti-TB drug surveillance developed by the WHO and the IUATLD and its reference laboratory network partners.<sup>3,8</sup> Because of resource limitations and administrative considerations, the office of the Dirección de Información y Vigilancia Epidemiología opted to include a maximum of 9 randomly selected states. For logistical reasons, states could not be subdivided for sampling purposes. All 31 states and the federal district of Mexico were categorized into 3 strata (low, medium, and high) by reported TB incidence in 1994. Forty-five percent of the cases were in the low-incidence stratum, 20% in the medium stratum, and 35% in the high stratum. Nine of these 32 areas were randomly chosen in proportion to the number of TB cases reported in each stratum in 1994 (4 areas from the low-incidence stratum, 2 from the medium stratum, and 3 from the high stratum). Baja California (40/100 000, high), Sinaloa (36.2/100 000, high), and Oaxaca (27.5/100 000, medium) were then randomly selected as the first 3 of these 9 states to participate in the survey (**Figure**).

Eligible patients were enrolled from 2 of the 5 major public health care sector institutions, Secretaría de Salud (SSA) and Instituto Mexicano del Seguro Social (IMSS), which together provide health care service to approximately 80% of the population and which diagnose and treat 90% of reported TB cases in Mexico. From January through April 1997, SSA and IMSS physicians, epidemiologists, and laboratory workers in all 3 states received extensive training in conducting the survey. From April 1 to October 31, physicians completed enrollment forms for all patients submitting at least 1 sputum sample for evaluation for symptoms and signs consistent with pulmonary TB.

All acid-fast bacilli (AFB) smear-positive samples were subsequently sent to the respective state laboratories for inoculation onto Lowenstein-Jensen culture medium for 1 to 2 weeks before being forwarded to the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (INDRE) in Mexico City for species identification and drug susceptibility testing. Testing for susceptibility to isoniazid, rifampin, pyrazinamide, streptomycin, and ethambutol was performed using the radiometric (BACTEC) method.<sup>13</sup> The reference institute and the CDC Mycobacteriology

Laboratory, a WHO supranational reference laboratory,<sup>3,8</sup> exchanged and tested a total of 84 *M tuberculosis* isolates for drug susceptibility to isoniazid, rifampin, ethambutol, streptomycin, and pyrazinamide on 3 separate occasions for quality-control monitoring.

A case was defined as a newly diagnosed illness in a patient with AFB smear-positive sputum from which *M tuberculosis* was recovered by culture. Of note, smear microscopy was requested to establish the diagnosis of pulmonary TB in patients who had not been diagnosed or, if previously diagnosed with TB, were not receiving treatment for TB. Resistance in new cases was called *new* for isolates from patients who had never taken anti-TB drugs in the past and *retreatment* for patients reporting previous treatment with anti-TB drugs for at least 30 days. Data on prior TB treatment were unavailable for less than 5% of patients, and these patients were excluded from the analysis. Multi-drug-resistant TB was defined as resistance to at least isoniazid and rifampin.<sup>3</sup>

To examine possible bias introduced by nonenrolled or culture-negative patients, we calculated the range of resistance that would be expected if either 0% or 100% of the patients with missing data (notified but not enrolled and/or enrolled but culture negative) were resistant. Extrapolating from our findings to the 23 575 cases of tuberculosis reported in Mexico in 1997, we calculated the hypothetical proportion of patients with and without a history of anti-TB drug treatment.

Using these estimates, we evaluated several hypothetical models to determine the proportion of new cases with resistance to 2 or more drugs using the current standard 3-drug regimen (isoniazid, rifampin, and pyrazinamide) and the percentage with resistance to 3 drugs if ethambutol were added to the 3-drug regimen. In addition, we determined the proportion of cases of TB with a history of anti-TB drug treatment that would be resistant to 2 or more of the drugs in the standard 3-drug regimen, as well as resistant to 4 or more drugs in the standard 5-drug retreatment regimen recommended by the WHO.<sup>3,11</sup>

Data were analyzed using EpiInfo 6.1 (CDC). The  $\chi^2$  test statistic was used to compare drug resistance between groups. For dichotomous variables, relative risks (RRs) with 95% confidence intervals (CIs) were calculated. The analysis of variance test was used to compare variances of continuous variables between 2 groups.

tively prevent the emergence of drug-resistant strains.<sup>9</sup> The risk factors for the development of drug-resistant TB have been well described.<sup>10</sup> Inappropriate drug regimens that contain too few drugs and nonadherence to therapy are the major causes. Additional risk factors include erratic drug supplies, substandard drug quality, and unrestricted access to anti-TB drugs through over-the-counter sales.<sup>11</sup>

The Mexican TB program currently recommends a 3-drug treatment regimen of isoniazid, rifampin and pyrazinamide for all patients with newly diagnosed TB.<sup>12</sup> Recently collected data from pilot areas implementing a DOTS program in Mexico show cure rates of 87% among newly diagnosed patients. However, population-based data for levels of drug-resistant *M tuberculosis* strains are unavailable for Mexico. In 1994,

the WHO and the International Union Against TB and Lung Disease (IUATLD) proposed a global surveillance project to monitor the prevalence of resistance to 4 of the principal first-line drugs used in TB treatment (isoniazid, rifampin, ethambutol, and streptomycin). To date, 35 countries have completed and published their surveys<sup>3,8</sup>; however, only 7 of these countries were from Latin America. In 1997, the Mexican Ministry of Health, in collaboration with the Centers for Disease Control and Prevention (CDC), initiated a national survey of drug resistance for *M tuberculosis* as part of the WHO global anti-TB surveillance project to assess anti-TB drug resistance. This report describes survey results for 3 Mexican states, Oaxaca, Sinaloa, and Baja California, and represents the first population-based TB drug-resistance data available for Mexico.

## RESULTS

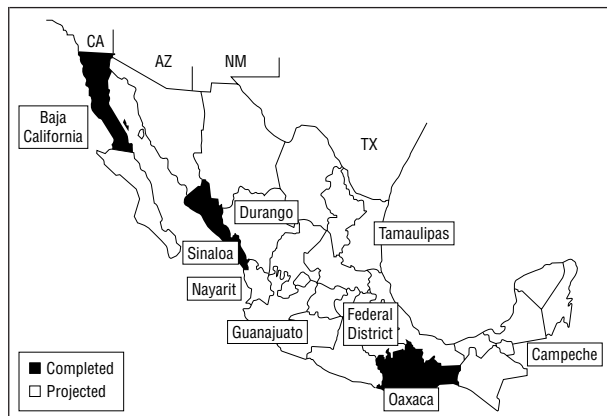
During the study period, 816 cases were reported with AFB smear–positive pulmonary TB; 351 patients from Baja California, 110 from Oaxaca, and 355 from Sinaloa (**Table 1**). Of these, 614 (75%) were enrolled in the study. *Mycobacterium tuberculosis* isolates were available for drug susceptibility testing from 460 (75%) of those enrolled. *Mycobacterium tuberculosis* isolates were not recovered from sputum for the remaining 150 patients (25%); 19% had no growth, 5% were deemed to be contaminated, and 1% had infection with non-tuberculous *Mycobacterium* species. There was no statistically significant difference between culture-positive and culture-negative TB patients by sex or by history of anti-TB drug treatment. Older patients were less likely to be culture-positive ( $P = .02$ ). There was concordance in 400 (95%) of the individual drug susceptibility results among the 84 individual strains exchanged and tested as part of the quality-control monitoring.

The median age of patients was 36 years (range, 10-87 years); 69% were male. Patients with resistance to isoniazid (mean age, 43 years; range, 14-87 years) or to 1 or more of the 3 first-line drugs (mean age, 41 years; range, 14-87 years) were significantly more likely to be older than those with pan-sensitive isolates (mean age, 38 years; range, 10-79 years). There was no difference in the proportion of males among cases that were pan-sensitive (68%), isoniazid resistant (75%), multi-drug resistant (71%), and resistant to 1 or more of the 3 first-line drugs (74%). Although the 3 areas were geographically distinct, there were no significant differences when

compared for resistance to isoniazid, resistance to rifampin, or multiple drug resistance (**Table 2**). Estimation of resistance levels among cases with missing data (notified but not enrolled and/or enrolled but culture negative) yielded a range of resistance values; assuming no resistance among missing cases, the minimum estimate of the percentage of cases with resistance at least to isoniazid, resistance at least to rifampin, and multiple drug resistance in the 3 states ranged from 7.3% to 10.8%, 3.4% to 4.8%, and 2.5% to 4.0%, respectively (Table 2). One hundred seven enrolled patients (24%) had a history of TB treatment.

The aggregate prevalence rates of resistance in new and retreatment cases for all 3 states are shown in **Table 3**. Rates of resistance in new and retreatment cases to 1 or more of the 3 current first-line drugs used in Mexico were 12.9% and 50.5%, respectively (RR, 3.9; 95% CI, 2.8-5.5). Compared with patients with new cases who had drug-resistant isolates, those with retreatment cases were significantly more likely to have *M tuberculosis* strains resistant to 1 or more of the drugs tested, multiple drugs, and 5 drugs.

In Mexico in 1997, there were 23 575 officially reported TB cases, a rate of 25 per 100 000 population.<sup>15</sup> Assuming that our results are representative of the nation as a whole, 17 917 (76%) of these cases represent patients with no history of TB treatment, and an estimated 2.7% were resistant to 2 or more of the drugs used in the 3-drug regimen (**Table 4**). Therefore, an estimated 484 received therapy with only one effective drug and were at increased risk for treatment failure. In contrast, only an estimated 1.8% of the patients had resistance to 3 or more drugs. If ethambutol had been added



States participating in a survey of *Mycobacterium tuberculosis* drug resistance, Mexico, 1997.

**Table 1. Sputum Smear–Positive Pulmonary Tuberculosis Cases Among Patients Enrolled in Drug Resistance Surveys for Tuberculosis, April 1–October 31, 1997\***

State	Cases Reported, No.	Patients Enrolled in Study, No. (%)	Isolates Recovered,† No. (%)
Baja California	351	295 (84)	215 (73)
Oaxaca‡	110	163 (>100)	110 (67)
Sinaloa	355	156 (44)	135 (87)
<b>Total</b>	<b>816</b>	<b>614 (75)</b>	<b>460 (75)</b>

\*As reported by the Mexican Ministry of Health.

†*Mycobacterium tuberculosis* with drug susceptibility test results.

‡The number of enrolled patients exceeded the number of reported cases because of underreporting and delays in surveillance.

**Table 2. Pulmonary Tuberculosis Cases With Drug-Resistant Isolates by State, Mexico, April 1–October 31, 1997**

Drug	Drug-Resistant Isolates, No. (%) [Range*]			P
	Baja California (n = 215)	Oaxaca (n = 110)	Sinaloa (n = 135)	
Isoniazid	38 (17.7 [10.8-49.6])	24 (21.8 [14.7-47.2])	26 (19.3 [7.3-69.3])	.67
Rifampin	17 (7.9 [4.8-43.6])	14 (12.7 [8.6-41.1])	12 (8.9 [3.4-65.4])	.36
Multiple drugs	14 (6.5 [4.0-42.7])	11 (10.0 [6.7-39.3])	9 (6.7 [2.5-64.5])	.49

\*The ranges were calculated by assuming that either 0% or 100% of all reported cases with missing data (n = 136 for Baja California, n = 53 for Oaxaca, n = 220 for Sinaloa) were resistant.

**Table 3. Sputum Smear–Positive Pulmonary Tuberculosis Cases With Drug-Resistant *Mycobacterium tuberculosis* Isolates by Antituberculosis Treatment History in Three States, Mexico, April 1–October 31, 1997\***

Drug†	No. (%) With Resistance‡			Relative Risk¶ (95% CI)	P
	All Cases (n = 460)	New Cases§ (n = 334)	Retreatment Cases   (n = 107)		
Isoniazid	88 (19.1)	40 (12.0)	46 (43.0)	3.6 (2.5-5.2)	<.001
Rifampin	43 (9.3)	10 (3.0)	31 (29.0)	9.7 (4.9-19.1)	<.001
Ethambutol	29 (6.3)	10 (3.0)	18 (16.8)	5.6 (2.7-11.8)	<.001
Pyrazinamide	25 (5.4)	5 (1.5)	19 (17.8)	11.9 (4.5-31.0)	<.001
Streptomycin	73 (15.9)	40 (12.0)	31 (29.0)	2.4 (1.6-3.7)	<.001
Any first-line drug#	99 (21.5)	43 (12.9)	54 (50.5)	3.9 (2.8-5.5)	<.001
MDR**	34 (7.4)	8 (2.4)	24 (22.4)	9.4 (4.3-20.2)	<.001
5 Drugs	12 (2.6)	3 (0.9)	9 (8.4)	9.4 (2.6-34.0)	<.001

\*CI indicates confidence interval; MDR, multiple drug resistance.

†Resistance to at least the drug indicated.

‡Among culture-positive patients with complete data on treatment history (407/440 [92.5%]).

§No reported history of antituberculosis drug treatment.

||A reported history of previous treatment with antituberculosis drugs.

¶The reference group was new cases.

#Resistance to at least 1 of the 3 first-line drugs (isoniazid, rifampin, pyrazinamide).

\*\*Defined as resistance to at least isoniazid and rifampin.

**Table 4. Estimated Monotherapy Among Patients With New and Previously Treated Tuberculosis (TB), by Drug Regimen, Mexico, 1997\***

Regimen	No. (%) Receiving Monotherapy	
	No. History of TB (n = 17 917)	History of TB (n = 5658)
3-Drug regimen, resistant to $\geq 2$ drugs	484 (2.7)	1358 (24.0)
4-Drug regimen, resistant to $\geq 3$ drugs	323 (1.8)	...
5-Drug retreatment regimen, resistant to $\geq 4$ drugs	...	741 (13.1)

\*There were 23 575 cases of tuberculosis reported in Mexico in 1997. These estimates were derived by extrapolating resistance data from the 3 states collected between April 1 and October 31, 1997. Monotherapy indicates that patients were receiving multidrug therapy with only one effective drug.

to the initial 3-drug regimen, the number of patients receiving therapy with only one effective drug (based on susceptibility testing) would be 323, a 33% reduction. Among the previously treated patients, an estimated 1358 (24%) received therapy with only one effective drug. With a 5-drug retreatment regimen, the number of patients receiving therapy with only one effective drug would have been 741, a 45% reduction compared with a 3-drug regimen.

## COMMENT

This is the first population-based study of anti-TB drug resistance from 3 states in Mexico. Among new and retreatment cases, we found elevated levels of resistance to isoniazid (12.0% and 43.0%, respectively) and multiple drug resistance (2.4% and 22.4%, respectively). Previous studies of the prevalence of drug-resistant TB in Mexico have suggested a wide range of resistance lev-

els.<sup>14,16-18</sup> A survey of 10 Latin American countries conducted between 1986 and 1990 by the Pan-American Health Organization and the WHO found 19.1% primary drug resistance in Mexico.<sup>17</sup> Between 1989 and 1993, the INDRE evaluated 1811 *M tuberculosis* isolates from a variety of states and found an average primary resistance of 8.3%.<sup>19</sup> More recently, Peter et al<sup>18</sup> found that 17% of 427 isolates collected in Baja California were multi-drug resistant. However, previous studies were not population based, relying instead on convenience samples or special populations (eg, chronically ill or hospital-based patients), and are not representative of the general population of TB patients.

When compared with results from 35 countries participating in the WHO/IUATLD global anti-TB drug resistance surveillance from 1994 through 1997, Mexico would have ranked ninth highest for primary resistance to at least 1 of 4 drugs (isoniazid, rifampin, ethambutol, streptomycin), at 18.3%.<sup>3,8</sup> When we compared resistance levels among patients who had received prior anti-TB drug treatment, Mexico would have ranked sixth out of 35 countries, at 52.3%. Of particular concern, we found a history of anti-TB drug treatment to be a strong risk factor for resistance to single drugs as well as to all combinations of drugs. Clearly, prevention strategies to thwart the development of further drug resistance among TB patients in Mexico are warranted.

Previous studies examining community and nosocomial transmission of *M tuberculosis* have implicated immunosuppression, in particular, human immunodeficiency virus (HIV) disease, as an important risk factor for drug-resistant TB.<sup>6,7,20</sup> We do not have HIV seroprevalence data and are unable to ascertain the specific contribution of HIV.

Our survey has some important limitations. First, although we sought to obtain a representative sample of 3 Mexican states, they constitute less than 10% of the 32 Mexican states (31 states and the federal district). Although the 3 states are geographically dispersed, we can



not ascertain with accuracy the representativeness of these states for the nation as a whole. However, the demographic characteristics of our study patients are similar to characteristics found among reported TB cases from the remaining areas of Mexico.<sup>15</sup> Second, the incomplete enrollment of patients with reported TB cases in Sinaloa (44%) limits inferences on the representativeness of this study population. In contrast, the fact that the number of enrolled patients exceeded the number of reported cases in Oaxaca is likely influenced by underreporting and reporting delays in surveillance. Overall, we enrolled 75% of the AFB smear-positive patients and we were unable to successfully culture 25% of the samples submitted. However, there were no statistically significant differences between culture-positive and culture-negative TB patients by sex or treatment history. The potential effects of our finding that older patients were less likely to be culture positive include the possibility that streptomycin resistance could actually be higher than what is reported in our study. Despite limitations we identified, levels of drug resistance in this study (isoniazid among new cases, 12.0%; multiple drug resistance, 2.4%) are consistent with those among Mexican-born persons diagnosed with TB while visiting or residing in the United States (isoniazid among new cases, 9.1%; multiple drug resistance, 1.7%).<sup>21</sup>

**I**N MEXICO, the initiation of anti-TB drug treatment for a patient with newly diagnosed pulmonary TB is based on AFB-positive sputum smears; sputum cultures are not routinely available.<sup>12</sup> A fundamental principle of TB therapy is to initiate treatment with at least 2 fully effective drugs to avoid the selection of drug-resistant strains. Although no international standard exists, resistance to isoniazid in isolates from patients with new cases in all 3 states exceeded 4%, the level at which the CDC and the American Thoracic Society recommend beginning empiric anti-TB treatment with a 4-drug regimen containing isoniazid, rifampin, ethambutol, and streptomycin or pyrazinamide.<sup>22</sup> We used our survey data to model the potential impact of changing from the current 3-drug initiation of anti-TB treatment to the 4-drug initial treatment regimen and the 5-drug retreatment regimen recommended by the WHO.<sup>11</sup> We found that the number of patients with new and previously treated TB receiving therapy with less than 2 fully effective drugs would be reduced by nearly half, from 2.7% and 24.0% of new and previously treated patients to 1.8% and 13.1%, respectively. Current Mexican Ministry of Health policy recommends that patients requiring retreatment should be treated by a specialist.<sup>12</sup> These results stress the importance of accurately determining a patient's treatment history to administer the appropriate anti-TB drug regimen and thus improve the likelihood of cure.

Several considerations are likely to influence discussions regarding the adequacy of the current 3-drug regimen. First, although the data are not immediately generalizable, the survey provides the most representative and population-based drug resistance data available to date; performing surveys in additional states will be necessary and will take time. Second, the costs and antici-

pated benefits of moving from a 3- to 4-drug regimen will have to be carefully weighed. The current 3-drug regimen costs approximately \$120 per complete treatment course (not including indirect costs); adding ethambutol would increase this cost by approximately 30% per patient. Programmatic issues, such as the ability to meet the goal of curing 85% of TB patients, will also need to be considered. Currently, the national Mexican TB program is expanding DOTS coverage to the entire country. Our model suggests that changing to a 4-drug initial regimen could contribute to improved cure rates and to the reduction of the further development of resistance in newly diagnosed patients. However, the model assumes the ability to correctly classify TB patients as never having had previous therapy, distinguishing them from those who completed therapy, preferably under a DOTS program. Additional retreatment failures could be prevented through the institution of a 5-drug retreatment regimen for patients with a history of TB.

Completion of therapy for patients with TB is a complex process involving patients, health care providers, and programmatic factors. A well-functioning TB control program, in particular a program based on DOTS, has been shown to have a temporal relationship with falling rates of multi-drug-resistant TB.<sup>3,23-25</sup> In resource-poor developing countries, efforts to institute individualized management of drug-resistant TB cases have been resisted because they are perceived to constitute a diversion of resources away from activities to identify and treat the larger number of persons with drug-susceptible TB. Concern has been voiced that the treatment of drug-resistant TB is not "cost-effective" in resource-poor countries, while others have emphasized that it is ethically inappropriate to deny access to adequate therapy.<sup>26,27</sup> Although the adequacy of the current initial regimen is being considered by Mexican authorities, another important unmet need is the continued expansion of current efforts to closely supervise and monitor TB treatment through the expansion of the DOTS program to the entire country. Clearly, a rational, evidence-based strategy must be developed to address the growing problem posed by multi-drug-resistant TB.

A secondary benefit of this survey includes the consequent improvement in TB surveillance and the laboratory network in the study states of Baja California, Oaxaca, and Sinaloa. All 3 state laboratories now have the capacity to perform *M tuberculosis* cultures. The newly developed culture capacity in these 3 states will be useful for ongoing surveillance efforts and for the management of cases not responding to routinely recommended regimens. Our survey also provides important baseline population-based data for assessing the impact of the many programmatic changes within the TB program currently under way throughout Mexico.

In summary, our results reveal substantial levels of drug resistance in the 3 states studied. Expanding the DOTS program to the entire country, considering the adoption of a 4-drug treatment regimen for patients with no history of treatment, and the development of a national strategy to treat patients with multi-drug-resistant TB are important actions to limit drug resistance. As changes are made in the TB program to combat the problem of drug resistance in Mexico, it will be im-

portant to monitor trends in *M tuberculosis* drug resistance, either by implementing ongoing surveillance or by performing periodic surveys.

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