Clinical Consequences and Transmissibility of Drug-Resistant Tuberculosis in Southern Mexico

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Background: Consequences of drug-resistant tuberculosis (TB) in developing countries using directly observed treatment, short-course (DOTS), are not well defined.

Objective: To determine the impact of drug resistance on clinical outcome and transmission of TB under programmatic conditions.

Patients and Methods: A prospective cohort and molecular epidemiologic study was conducted in southern Mexico. Between March 1995 and February 1998 all patients with persistent cough whose sputa had acid-fast bacilli (AFB) underwent clinical and mycobacteriologic evaluation (species identification, drug susceptibility testing, and IS6110-based genotyping). Treatment was provided in accordance with Mexico’s National Tuberculosis Program. Clinical and microbiologic outcomes and molecular epidemiologically defined transmission were measured.

Results: Mycobacterium tuberculosis was isolated from 238 of the 284 AFB smear–positive persons. The overall rate of resistance was 28.4% (new, 20.7%; retreated, 54.7%), and 10.8% (new, 3.3%; retreated, 35.8%) had multi–drug-resistant TB (ie, resistance to isoniazid and rifampin). After treatment, 75% (new, 81.0%; retreated, 52.8%) were cured, 8% (new, 7.8%; retreated, 7.5%) abandoned therapy, 9% (new, 3.9%; retreated, 28.3%) had treatment failure, and 4% (new, 3.3%; retreated, 7.5%) died. Another 2% of patients relapsed, and 9% died during a median of 24.4 months of follow-up. Drug-resistance was a strong independent risk factor for treatment failure. Being infected with multi–drug-resistant TB was the only factor associated with a decreased likelihood of being in a restriction fragment length polymorphism cluster.

Conclusions: Despite the use of DOTS, patients with drug-resistant TB had a dramatically increased probability of treatment failure and death. Although multi–drug-resistant TB may have a decreased propensity to spread and cause disease, it has a profoundly negative impact on TB control.

Arch Intern Med. 2000;160:630-636

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D IRECTLY OBSERVED treatment, short-course (DOTS), the World Health Organization (WHO) strategy for global tuberculosis (TB) control, has been demonstrated to cure more than 80% of patients and is one of the most significant public health advances of this decade. A crucial component of the strategy is the provision for the administration to all smear-positive cases of a standardized antibiotic regimen that includes rifampin. However, the impact of anti-TB drug resistance on the outcome of standardized antibiotic therapy in developing countries is largely unknown. The importance of this is underscored by a recent global surveillance project that demonstrated that drug-resistant strains of Mycobacterium tuberculosis were globally ubiquitous, and in several countries, so common as to potentially threaten control programs. The Orizaba Health Jurisdiction in southern Mexico has a well-established DOTS-based TB control program, but circumstantial evidence suggested that there were high rates of drug resistance. To better understand the consequences of drug resistance in such settings, we conducted a study of the epidemiology, clinical outcome, and relative transmissibility of drug-resistant TB using conventional and molecular epidemiologic methods.

See also pages 581 and 639

RESULTS

A total of 2525 persons with chronic cough were studied, 284 (11.2%) of whom had microscopically detected AFB and were enrolled in the study. Mycobacterium tuberculosis was isolated from 238 (83.8%) of
the study subjects; the sputa from 31 failed to grow any organisms, 10 were not cultured, 3 were contaminated with other organisms, and 2 grew Mycobacterium fortuitum. Drug susceptibility results were obtained for 232 of these subjects.

To better understand the demographic characteristics of TB in this region, we compared the 232 patients with the general population. As shown in Table 1, patients with TB were more likely to be old and male and to have lower socioeconomic status and urban residence. In comparison with the 52 patients with AFB-positive smears and negative culture results, the 232 patients had a higher frequency of cavitary infiltrates (30% vs 12%; 95% CI, 2.26-4.32; P =.007) and age older than 40 years (OR, 2.26 [95% CI, 1.18-4.32]; P =.01). Persons of indigenous origin were less likely to have drug-resistant TB (OR, 0.26 [95% CI, 0.09-0.80]; P =.02). No correlation was found with sex, socioeconomic level, place of residence, education, year of diagnosis, related illnesses, history of alcohol and drug use, previous hospitalization, imprisonment, selected clinical characteristics, or HIV infection.

From January 1, 1996, to February 28, 1998, 256 cases of AFB-positive pulmonary TB were reported to the TB registry among those persons living in the study area. This study recruited 219 (86%) of these patients during this period.

Of the 232 patients, 230 received DOTS, and 2 patients received self-administered treatment. The clinical outcome at the time treatment should have been completed was known for all 232 patients (Table 3). Of these, 173 (75%) were cured (of whom 149 [64%] were bacteriologically confirmed as cured) therapy failed in 22 (9%); 10 (4%) died; the treatment was suspended for 3 (1%) because of adverse drug reactions; and 6 (3%) were transferred to another region. Eighteen patients (8%) abandoned treatment;
Mycobacterial culture, identification, and susceptibility testing were performed on sputa from each enrolled patient. In brief, uncentrifuged sputum was inoculated onto Lowenstein-Jensen media (DIFCO, Mexico City, Mexico) in the local laboratory, and the remaining sputum was frozen at −70°C. The tubes were examined on a weekly basis until growth was detected. Cultures were reported as negative if there was no growth after 8 weeks. Cultures with visible growth were forwarded to the Department of Mycobacteriology at the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos, Mexico City, Mexico (March 1995 to December 1997), or to the Mycobacteriology Laboratory of the Instituto Nacional de la Nutrición, Mexico City, Mexico (January to March 1998), for definitive biochemical identification at the species level. The frozen sputum sample was processed if the first inoculated sample was contaminated or had no growth. Identification and drug susceptibility tests were carried out using the conventional and BACTEC (Becton-Dickinson, Cockeysville, Md) systems.

Mycobacteria isolated from study patients were genotyped at Stanford University, Stanford, Calif, from March 1995 to February 1997, the Instituto Nacional de la Nutrición from March 1997 to February 1998, and the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos from January 1997 to February 1998, using the internationally standardized IS6110-based restriction fragment length polymorphism (RFLP) technique and compared using a computer-assisted visual approach. Patients with identical DNA fingerprints were grouped into clusters, and epidemiological links were investigated using standard methods as previously described.

Patients were observed for a median of 24.4 months after initiation of treatment. Only one patient was lost to follow-up during this time. Twenty-one patients died subsequent to the completion of treatment. Therefore, there were 31 deaths during or after therapy (2 of whom were HIV seropositive), whereas 7 patients (28%) with resistance that did not include isoniazid and rifampin died during follow-up (2 of whom were HIV seropositive), whereas 7 patients (28%) with multi–drug-resistant TB died (none of whom was HIV seropositive).

Categorical variables were compared using χ² test and normally distributed continuous variables with the t test. Sociodemographic data were compared with data from the 1990 census. Data for 1996 were expanded from the 1990 census according to the method recommended by the Instituto Nacional de Estadística, Geografía, e Informática (INEGI). Bivariate and multivariate logistic regression analyses were used to determine factors associated with drug resistance, treatment failure, and clustering; 95% confidence intervals (CIs) were calculated around odds ratio (OR) determinations. Drug resistance was classified as follows: fully susceptible strains, strains resistant to at least 1 drug (including resistance to isoniazid and rifampin), multi–drug-resistant strains (resistant to at least isoniazid and rifampin), and other resistance profiles (strains resistant to any drug or combination of drugs except joint resistance to isoniazid and rifampin). For multivariate analysis, variables were initially included if their respective bivariate analyses yielded P < .2 or if they were considered to be biologically relevant. Pairwise interaction terms were not statistically significant in the multivariate analysis. The goodness of fit of the models was assessed by the χ² goodness-of-fit test. Adequacy of the final model as compared with the initial saturated model was tested with the Hosmer-Lemeshow method. Survival analyses included Kaplan-Meier curves and the Cox proportional hazards model for all-cause mortality. The dBASE IV (NCR Corp, Dayton, Ohio) and STATA 3.0 (Stata Corp, College Station, Tex) programs were used for data analysis.
had an isolate of \textit{M tuberculosis} that had a DNA fingerprint identical to that of at least one other case. Twenty clusters were identified and investigated. The size of each cluster is described in Table 5. Multivariate analysis showed that patients with multi–drug-resistant TB were significantly less likely to be in clusters, whereas clustering was associated with pleural effusion, primary education or less, and cavitary disease (Table 6).

**COMMENT**

It has been amply demonstrated that a well-implemented DOTS-based TB control program is associated with decreased rates of TB and protects against the emergence of drug resistance.\textsuperscript{10-15} However, there are limited data on the outcome of administering a standard regimen containing rifampin to all patients in regions where drug resistance is already problematic. Data are even more limited about the relative propensity of drug-resistant and susceptible strains to spread and cause disease in communities. In this study, we have used conventional and molecular techniques to demonstrate that, in the context of a well-functioning DOTS program, drug-resistant TB has a profoundly adverse impact on treatment outcome, even though multi–drug-resistant strains may have a decreased propensity to spread and cause disease.

Both the strengths and weaknesses of this study arise from having collected data in only a single health jurisdiction where TB is managed according to the policy of Mexico’s National Tuberculosis Control Program. The intensity of scrutiny possible in such a small area permits a detailed description of the realities of implementing these policies in this jurisdiction; however, the results may not be generalizable to other regions. Even with such scrutiny, it is difficult to precisely define the cause of death; thus, we analyzed risk factors associated with all-cause mortality (as has been recommended by the WHO).\textsuperscript{20} In addition, we only treated patients whose sputum was AFB smear positive, and thus the study is biased toward patients with a greater concentration of bacilli in their sputum and with more advanced disease. All 5 HIV-infected individuals died during follow-up, probably in part as a result of their HIV infection. However, the overall impact of HIV on the results of this study is likely to be small, since the rate of HIV infection in this region remains relatively low. Finally, treatment was initiated for most previously untreated patients with only 3 drugs, and outcome results may have been better with the addition of a fourth agent, as is currently recommended in other developing countries.

The high rates of drug-resistant TB detected by this prospective population-based surveillance project are comparable with the findings of other community-based studies conducted in Mexico.\textsuperscript{17-19} Our finding that nearly 1 in 3 patients in this region, which has a relatively good TB control program, harbors strains of \textit{M tuberculosis} resistance to at least one drug is a cause for significant concern. Our observation that prior anti-TB therapy was the strongest risk factor for having drug-resistant TB supports the contention that the highest public health priority is administering DOTS to drug-susceptible patients. However, taken together these studies suggest that drug resistance must be specifically addressed by TB control policies.

Our evaluation of the magnitude of drug resistance in this area may be biased, since we only studied smear-positive patients. The important role of patients with smear-negative TB in the transmission of the disease has been proven.\textsuperscript{20} In one study conducted in Mexico,\textsuperscript{21} paucibacillary cases had a significantly greater rate of isoniazid resistance than smear-positive cases (20% vs 6%; \( P = .02 \)); thus, AFB–smear-based detection would grossly underestimate the actual rates of drug resistance.

The most disturbing results of the study are the poor clinical outcomes of persons with \textit{Mycobacterium tuberculosis} compared with the general population (Table 6).

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Variable} & \textbf{Study Population} (\( N = 232 \)) & \textbf{AFB-Positive Smears and Negative Culture Results} (\( N = 52 \)) & \textbf{1996 Population} (\( N = 296,037 \)) \\
\hline
Age, y & 42.7 (17.7) & 40.2 (17) & 39.1 (16.4) \\
Male & 139/232 (59.9) & 28/52 (54) & 145,058 (49.0)
Lower socioeconomic status & 208/226 (92.0) & 48/50 (96) & 20,273 (6.8)
Rural residence & 13/231 (5.6) & 4/52 (8) & 32,564 (11.0)
Primary school or less education & 161/230 (70.0) & 29/51 (57) & . . .
House with dirt floor & 41/225 (18.2) & 15/49 (31) & . . .
Indigenous & 31/231 (13.5) & 15/51 (29) & . . .
Alcohol usage & 115/231 (49.8) & 21/51 (41) & . . .
Drug usage & 18/231 (6.9) & 2/51 (4) & . . .
BCG scar & 94/230 (40.9) & 21/49 (43) & . . .
Cavitary disease & 59/229 (25.9) & 4/43 (9) & . . .
HIV infection & 5/221 (2.3) & 1/45 (2) & . . .
Previous TB treatment & 48/231 (20.8) & 10/51 (20) & . . .
More than 10 bacilli per oil immersion field & 81/232 (34.9) & 6/52 (12) & . . .
\hline
\end{tabular}
\caption{Selected Sociodemographic and Clinical Characteristics of Patients With \textit{Mycobacterium tuberculosis} Compared With the General Population*}
\end{table}

*AFB indicates acid-fast bacilli; BCG, bacille Calmette-Guérin; HIV, human immunodeficiency virus; and TB, tuberculosis. Ellipses indicate data not available.

†Denominator indicates the number of patients for whom data were available.

‡Values are mean (SD).

§P < .05, with study population as the comparison group.
independently associated with these poor outcomes in multivariate analysis.

The relative ability of drug-susceptible and drug-resistant strains to spread and cause disease has been the subject of intense debate and speculation. Although animal studies suggest that certain drug-resistant strains have a diminished capacity to cause disease, epidemiologic studies in human populations have shown that rates of infection and disease are comparable among contacts with both susceptible and drug-resistant TB. The acceptance of clustering as a proxy for the transmission and rapid progression of TB provides a new opportunity to examine this issue.

Our molecular epidemiologic data suggest that drug-resistant strains of *M tuberculosis* may have a diminished capacity to spread and cause disease. However, alternate interpretations must be excluded before this presumption can be stated with certainty.

Acceptable cure rates for drug-resistant TB are achievable in developed and developing countries with individualized antibiotic regimens tailored to the patient's mycobacterial antibiotic susceptibility results. This approach requires specialized laboratory, clinical, and pharmaceutical resources, which are unavailable in most developing countries. Consequently, the majority of the world's drug-resistant TB cases are treated with standardized regimens. In this study we demonstrate that even when a standardized regimen was administered under direct observation by a well-functioning control program, therapy failed in 29% of patients with drug-resistant TB and 21% died. If confirmed in other settings, this implies that although the widespread implementation of DOTS is likely to be essential for TB control, in regions with high rates of drug resistance, it may not be sufficient.

### Table 2. Results of Drug Susceptibility Testing of Patients Isolates According to Previous Tuberculosis Treatment

<table>
<thead>
<tr>
<th>Resistance</th>
<th>New Cases (n = 179)</th>
<th>Retreated Cases (n = 53)</th>
<th>All Cases (n = 232)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One Drug</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>15 (8.4)</td>
<td>2 (3.8)</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>1 (0.6)</td>
<td>3 (5.7)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>5 (2.8)</td>
<td>1 (1.9)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22 (12.3)</td>
<td>6 (11.3)</td>
<td>28 (12.1)</td>
</tr>
<tr>
<td><strong>Two drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid and streptomycin</td>
<td>3 (1.7)</td>
<td>0 (0)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Isoniazid and rifampin</td>
<td>2 (1.1)</td>
<td>4 (7.5)</td>
<td>6 (2.6)</td>
</tr>
<tr>
<td>Isoniazid and ethambutol</td>
<td>1 (0.6)</td>
<td>2 (3.8)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Ethambutol and streptomycin</td>
<td>2 (1.1)</td>
<td>0 (0)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Isoniazid and pyrazinamide</td>
<td>2 (1.1)</td>
<td>1 (1.9)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>10 (5.6)</td>
<td>7 (13.2)</td>
<td>17 (7.3)</td>
</tr>
<tr>
<td><strong>Three Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, rifampin, and streptomycin</td>
<td>2 (1.1)</td>
<td>2 (3.8)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>Isoniazid, rifampin, and ethambutol</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Isoniazid, streptomycin, and ethambutol</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Isoniazid, rifampin, and pyrazinamide</td>
<td>0 (0)</td>
<td>8 (15.1)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Isoniazid, ethambutol, and pyrazinamide</td>
<td>0 (0)</td>
<td>1 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4 (2.2)</td>
<td>11 (20.8)</td>
<td>15 (6.5)</td>
</tr>
<tr>
<td><strong>Four Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, rifampin, streptomycin, and ethambutol</td>
<td>1 (0.6)</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Isoniazid, rifampin, streptomycin, and pyrazinamide</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Isoniazid, rifampin, ethambutol, and pyrazinamide</td>
<td>0 (0)</td>
<td>2 (3.8)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1 (0.6)</td>
<td>4 (7.5)</td>
<td>5 (2.2)</td>
</tr>
<tr>
<td><strong>Five Drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide</td>
<td>0 (0)</td>
<td>1 (1.9)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td><strong>Total Any Drug</strong></td>
<td>37 (20.7)</td>
<td>29 (54.7)</td>
<td>66 (28.4)</td>
</tr>
<tr>
<td><strong>Total multi-drug-resistant tuberculosis</strong></td>
<td>6 (3.3)</td>
<td>19 (35.8)</td>
<td>25 (10.8)</td>
</tr>
</tbody>
</table>

*Reference group.

### Table 3. Treatment Outcome of Study Patients According to New or Retreatment Cases

<table>
<thead>
<tr>
<th>Outcome</th>
<th>New Cases (n = 179)</th>
<th>Retreated Cases (n = 53)</th>
<th>All Cases (n = 232)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure*</td>
<td>145 (81.0)</td>
<td>28 (53)</td>
<td>173 (74.5)</td>
<td>1.0</td>
<td>. . .</td>
</tr>
<tr>
<td>Abandon</td>
<td>14 (7.8)</td>
<td>4 (8)</td>
<td>18 (7.8)</td>
<td>1.50 (0.4-4.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Failure</td>
<td>7 (3.9)</td>
<td>15 (28)</td>
<td>22 (9.5)</td>
<td>11.1 (4.1-29.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>6 (3.4)</td>
<td>4 (8)</td>
<td>10 (4.3)</td>
<td>3.5 (0.9-13.0)</td>
<td>.07</td>
</tr>
<tr>
<td>Others</td>
<td>7 (3.9)</td>
<td>2 (4)</td>
<td>9 (3.9)</td>
<td>1.5 (0.3-7.5)</td>
<td>.60</td>
</tr>
</tbody>
</table>

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Table 4. Risk Factors Associated With Treatment Failure or Death

<table>
<thead>
<tr>
<th>Failure†</th>
<th>Death‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds Ratio (95% Confidence Interval)</td>
<td>Hazard Ratio (95% Confidence Interval)</td>
</tr>
<tr>
<td>Resistance to isoniazid and rifampin*</td>
<td>394.9 (30.7-5084.9) &lt; .001</td>
</tr>
<tr>
<td>Other resistance</td>
<td>11.4 (1.4-90.8) .02</td>
</tr>
<tr>
<td>Primary school or less education</td>
<td>9.17 (1.3-62.5) .02</td>
</tr>
<tr>
<td>Time to AFB conversion (&gt;3 mo)</td>
<td>8.4 (1.4-50.4) .02</td>
</tr>
<tr>
<td>Interstitial infiltrate</td>
<td>... ...</td>
</tr>
<tr>
<td>HIV infection</td>
<td>... ...</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>7.3 (1.0-52.1) .05</td>
</tr>
</tbody>
</table>

*AFB indicates acid-fast bacilli; HIV, human immunodeficiency virus.
† Logistic regression.
‡ Cox proportional hazard model.

The estimated survival of human immunodeficiency virus-negative patients according to drug resistance (P < .01).

Table 5. Cluster Size and the Number of Clusters Among 188 Patients With Tuberculosis From Orizaba, Mexico

<table>
<thead>
<tr>
<th>Cluster Size, No. of Patients</th>
<th>No. of Clusters</th>
<th>Total, No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>All</td>
<td>20</td>
<td>68</td>
</tr>
</tbody>
</table>

Table 6. Multivariate Risk Factors Associated With Clustering

<table>
<thead>
<tr>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance to isoniazid and rifampin*</td>
<td>0.16 (0.4-0.6) .008</td>
</tr>
<tr>
<td>Other resistance*</td>
<td>1.14 (0.5-2.7) .80</td>
</tr>
<tr>
<td>Pleural effusion†</td>
<td>15.28 (1.6-147.9) .02</td>
</tr>
<tr>
<td>Primary school or less education</td>
<td>3.41 (1.6-7.4) .002</td>
</tr>
<tr>
<td>Cavitary disease†</td>
<td>2.18 (1.0-4.6) .04</td>
</tr>
</tbody>
</table>

*Compared with fully susceptible strains.
†Compared with other radiographic appearances.

Accepted for publication October 20, 1999.

This study was supported by grant AI35969 from the National Institutes of Health, Bethesda, Md.

The authors acknowledge the support provided by the state and local TB control program, particularly by

Edit Rodriguez, MD, MPH, Yolanda Jaramillo, MD, MAHS, Sadoc Jimenez, MD, MPH, and Guadalupe Canales, MD, MPH; by the considerable efforts of the participating interviewers, nurses, and physicians; by the HIV and Other STDs Laboratory, Instituto Nacional de Diagnostico y Referencia Epidemiologicos, Mexico City, Mexico; by the Human Retrovirus Unit, Universidad Nacional Autonoma de Mexico/Instituto Nacional de Diagnostico y Referencia Epidemiologicos, Mexico City, which processed samples for HIV tests; and by Manuel Tielve, MD, and his group at the Instituto Nacional de la Nutricion Salvador Zubiran, Mexico City, for providing radiographic interpretation.

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Error in Table. In the Original Investigation titled “Clinical Consequences and Transmissibility of Drug-Resistant Tuberculosis in Southern Mexico,” published in the March 13 issue of the ARCHIVES (2000;160:630-636), the confidence interval for the odds ratio for resistance to isoniazid and rifampin was incorrectly reported in Table 6 as “(0.4-0.6).” It should have been “(0.04-0.6).”