

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

Maria de Lourdes García-García, MD, DrSc; Alfredo Ponce-de-León, MD; Maria Eugenia Jiménez-Corona, MD; Aída Jiménez-Corona, MD, MSc; Manuel Palacios-Martínez, MD; Susana Balandrano-Campos, BA; Leticia Ferreyra-Reyes, MD; Luis Juárez-Sandino, CT; José Sifuentes-Osornio, MD; Hiram Olivera-Díaz, MSc; José Luis Valdespino-Gómez, MD, MPH; Peter M. Small, MD

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

From the Instituto Nacional de Salud Pública, Cuernavaca, Mexico (Drs García-García, M. Jiménez-Corona, A. Jiménez-Corona, Palacios-Martínez, Ferreyra-Reyes, and Valdespino-Gómez and Mr Juárez-Sandino); Stanford University, Stanford, Calif (Dr Small); Instituto Nacional de la Nutrición Salvador Zubirán, (Drs Ponce-de-León and Sifuentes-Osornio), and Instituto Nacional de Diagnóstico y Referencia Epidemiológicos (Ms Balandrano-Campos and Mr Olivera-Díaz), Mexico City, Mexico.

DIRECTLY 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.¹ 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.²

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.^{3,4} 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

PATIENTS AND METHODS

The study area is a predominantly urban region in southern Mexico that includes 134 square kilometers with 278 837 inhabitants.⁴ Tuberculosis control in this region is provided in accordance with the policies of Mexico's National Tuberculosis Program, including passive case finding, acid-fast bacilli (AFB) smear-based diagnosis, and fixed-combination medications provided free of charge under direct observation.⁵ A retrospective review of treatment control cards from 1991 to 1994 demonstrated that 77% of patients successfully completed therapy.³ Since January 1996, all patients diagnosed with TB by the health care system were registered in the TB registry of the local Program of Prevention and Control of Tuberculosis. Previously untreated patients were given isoniazid, rifampin, and pyrazinamide for 2 months, followed by an additional 4 months of isoniazid and rifampin. Patients with TB who had previously been treated for TB (retreatment cases) were also prescribed ethambutol or streptomycin.

From March 1, 1995, to February 28, 1998, all persons identified by the health care system as having cough that persisted for 2 or more weeks were contacted by study personnel. After January 1996, the register of patients with TB was reviewed periodically to identify patients with pulmonary TB who might have been missed by recruiters. Three sputum samples were collected from each person, and unconcentrated Ziehl-Neelsen stains were examined microscopically for the presence of AFB. Patients with sputum that was AFB smear-positive were offered participation in

this study. Those who signed an informed consent form to participate underwent a structured interview, physical examination, human immunodeficiency virus (HIV) testing, and chest radiography. Patients were referred to the appropriate health care organization for therapy. In addition, each person was visited in his or her home to determine the physical characteristics of his or her living quarters and to identify household contacts with persistent cough. This study was approved by the appropriate institutional review boards.

Information on therapeutic response was obtained by a review of treatment control cards at the completion of therapy. Outcomes were coded according to the definitions stipulated by the National Tuberculosis Program and as described previously.³ Briefly, *cure* was defined as the resolution of signs and symptoms at the completion of therapy (the cure was considered bacteriologically confirmed if, concurrently, 2 or more AFB smear or culture results were negative). Patients with positive AFB smear or culture results at the fifth month of treatment were considered to be treatment failures. Patients who died included those whose deaths were the result of any cause during or after therapy. *Relapse* was defined as the reappearance of bacilli in sputa after cure. Data about relapse and death were collected by revisiting patients' homes during the months of June 1997 and June 1998. *Socioeconomic level* was defined based on the characteristics of the household. *Lower socioeconomic level* was defined as having a household with earthen floors and 3 or more persons sleeping in the same room. Information about patients who died was corroborated by review of death certificates.

Continued on next page

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 with complete microbiologic data were more likely to have more than 10 bacilli per oil immersion field (81/232 vs 6/52; $P = .001$), to have cavitory infiltrates (59/202 vs 4/43; $P = .007$), to be of indigenous origin (31/230 vs 15/51; $P = .005$), and to live in homes with earthen floors (41/225 vs 15/49; $P = .05$).

Detailed drug susceptibility results of the 232 subjects for whom data were available are shown in **Table 2**. One hundred sixty-six (71.6%) had TB that was susceptible to all drugs, and 66 (28.4%) were resistant to at least one antimicrobial agent. Of these patients with resistance, 53 (22.8%) had resistance to isoniazid, 29 (12.5%) had resistance to rifampin, and 25 (10.8%) had resistance to at least isoniazid and rifampin (2 had resistance to isoniazid and rifampin, 23 had resistance to isoniazid, rifampin, and other

drugs). The above-mentioned categories of resistance are not exclusive.

Multivariate analysis revealed an independent association between drug resistance and previous treatment (OR, 7.25 [95% CI, 3.51-15.0]; $P < .001$) 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, unconcentrated 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.⁶ 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.^{7,8} Patients with identical DNA fingerprints were grouped into clusters, and epidemiological links were investigated using standard methods as previously described.⁴

Categorical variables were compared using χ^2 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).⁹ 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 χ^2 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 5.0 (Stata Corp, College Station, Tex) programs were used for data analysis.

the median duration of treatment for these patients was 96.8 days (SD, 78.3). Failure occurred in 3 (2%) of 166 patients with fully susceptible strains, 5 (12%) of 41 patients with drug-resistant strains that did not include resistance to isoniazid and rifampin, and 14 (56%) of 25 patients with multi-drug-resistant TB. Outcomes were more favorable for new cases than for retreated cases. Unadjusted analysis showed that retreated cases had a higher probability of therapy failure than new cases (OR, 11.1 [95% CI, 4.1-29.7]; $P < .001$).

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 treatment during the study period (31/231 [13.4%]). Four patients were diagnosed with relapsed TB after being cured at the end of treatment. Cultures were obtained at the time of relapse from 2 patients and showed fully susceptible TB.

Variables analyzed for their association with failure or death included those previously described, as well as duration of symptoms prior to diagnosis, time elapsed between diagnosis and initiation of treatment, time elapsed between diagnosis and sputum-smear conversion, radiographic extent of disease, symptoms and signs (cough, hemoptysis, fever, sweats, weight loss,

general malaise), associated diseases, weight and height, number of bacilli visualized microscopically, compliance with treatment, and clustering. The variables found to be independently associated with treatment failure were resistance to isoniazid and rifampin, other resistance, primary education or less, hemoptysis, and time elapsed for sputum conversion (**Table 4**).

Mortality during or after therapy was significantly greater for patients with drug-resistant TB. Death occurred in 17 patients (10%) with fully susceptible TB (3 of whom were HIV seropositive). Seven patients (17%) 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).

Cox adjusted relative risks showed that multidrug resistance ranked third after HIV infection and radiologic findings as an independent predictor of mortality (Table 4). The estimated survival of HIV-negative patients according to drug resistance is shown in the **Figure**. Patients with multi-drug-resistant TB had a significantly poorer prognosis than patients with fully susceptible strains or with other resistant strains ($P = .03$).

Restriction fragment length polymorphism analysis was carried out on isolates from 188 (81%) of 232 culture-confirmed patients. Sixty-eight patients (36%)

had an isolate of *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 cavitory 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.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).¹⁶ 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.¹⁷⁻¹⁹ Our finding that nearly 1 in 3 patients in this region, which has a relatively good TB control program, harbors strains of *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 hav-

Table 1. Selected Sociodemographic and Clinical Characteristics of Patients With *Mycobacterium tuberculosis* Compared With the General Population*

Variable	No. of Patients (%) [†]		
	Study Population (N = 232)	AFB-Positive Smears and Negative Culture Results (n = 52)	1996 Population (N = 296 037)
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	31/230 (13.5)	15/51 (29§)	...
Alcohol usage	115/231 (49.8)	21/51 (41)	...
Drug usage	16/231 (6.9)	2/51 (4)	...
BCG scar	94/230 (40.9)	21/49 (43)	...
Cavitory disease	59/202 (29.2)	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§)	...

*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.

ing 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.²⁰ In one study conducted in Mexico,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 drug-resistant TB who were treated with standardized therapy. Patients who were infected with a strain of *M tuberculosis* that was susceptible to all drugs had only a 2% chance of treatment failure. However, this rate increased to 29% if their isolate was resistant to any drug and to 56% if the resistance included both isoniazid and rifampin. Similarly, mortality increased dramatically in these same groups (10%, 21%, and 28%, respectively). Furthermore, drug resistance was

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

Resistance	No. (%)		
	New Cases (n = 179)	Retreated Cases (n = 53)	All Cases (n = 232)
One Drug			
Isoniazid	15 (8.4)	2 (3.8)	17 (7.3)
Rifampin	1 (0.6)	3 (5.7)	4 (1.7)
Ethambutol	1 (0.6)	0 (0)	1 (0.4)
Streptomycin	5 (2.8)	1 (1.9)	6 (2.6)
Pyrazinamide	0 (0)	0 (0)	0 (0)
Total	22 (12.3)	6 (11.3)	28 (12.1)
Two drugs			
Isoniazid and streptomycin	3 (1.7)	0 (0)	3 (1.3)
Isoniazid and rifampin	2 (1.1)	4 (7.5)	6 (2.6)
Isoniazid and ethambutol	1 (0.6)	2 (3.8)	3 (1.3)
Ethambutol and streptomycin	2 (1.1)	0 (0)	2 (0.9)
Isoniazid and pyrazinamide	2 (1.1)	1 (1.9)	3 (1.3)
Total	10 (5.6)	7 (13.2)	17 (7.3)
Three Drugs			
Isoniazid, rifampin, and streptomycin	2 (1.1)	2 (3.8)	4 (1.7)
Isoniazid, rifampin, and ethambutol	1 (0.6)	0 (0)	1 (0.4)
Isoniazid, streptomycin, and ethambutol	1 (0.6)	0 (0)	1 (0.4)
Isoniazid, rifampin, and pyrazinamide	0 (0)	8 (15.1)	8 (3.4)
Isoniazid, ethambutol, and pyrazinamide	0 (0)	1 (1.9)	1 (0.4)
Total	4 (2.2)	11 (20.8)	15 (6.5)
Four Drugs			
Isoniazid, rifampin, streptomycin, and ethambutol	1 (0.6)	0 (0)	1 (0.4)
Isoniazid, rifampin, streptomycin, and pyrazinamide	0 (0)	2 (3.8)	2 (0.9)
Isoniazid, rifampin, ethambutol, and pyrazinamide	0 (0)	2 (3.8)	2 (0.9)
Total	1 (0.6)	4 (7.5)	5 (2.2)
Five Drugs			
Isoniazid, rifampin, streptomycin, ethambutol, and pyrazinamide	0 (0)	1 (1.9)	1 (0.4)
Total Any Drug	37 (20.7)	29 (54.7)	66 (28.4)
Total multi-drug-resistant tuberculosis	6 (3.3)	19 (35.8)	25 (10.8)

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

Outcome	No. (%)			Odds Ratio (95% Confidence Interval)	P
	New Cases (n = 179)	Retreated Cases (n = 53)	All Cases (n = 232)		
Cure*	145 (81.0)	28 (53)	173 (74.5)	1.0	...
Abandon	14 (7.8)	4 (8)	18 (7.8)	1.50 (0.4-4.8)	.50
Failure	7 (3.9)	15 (28)	22 (9.5)	11.1 (4.1-29.7)	<.001
Death	6 (3.4)	4 (8)	10 (4.3)	3.5 (0.9-13.0)	.07
Others	7 (3.9)	2 (4)	9 (3.9)	1.5 (0.3-7.5)	.60

*Reference 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.^{22,23} 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.^{24,25} 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.

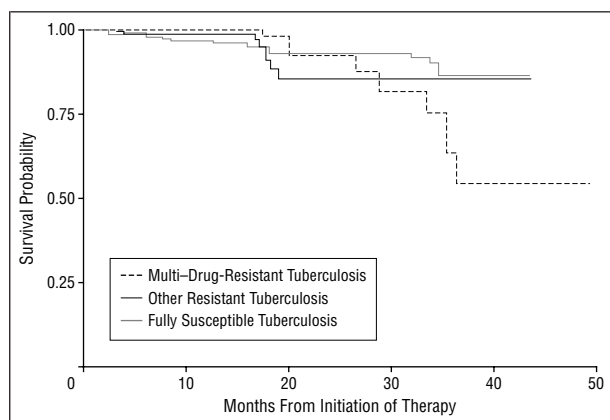
Table 4. Risk Factors Associated With Treatment Failure or Death*

	Failure†		Death‡	
	Odds Ratio (95% Confidence Interval)	P	Hazard Ratio (95% Confidence Interval)	P
Resistance to isoniazid and rifampin	394.9 (30.7-5084.9)	<.001	3.1 (1.2-8.4)	.02
Other resistance	11.4 (1.4-90.8)	.02	1.4 (0.5-4.2)	.50
Primary school or less education	9.17 (1.3-62.5)	.02
Time to AFB conversion (>3 mo)	8.4 (1.4-50.4)	.02
Interstitial infiltrate	4.6 (1.6-13.2)	.005
HIV infection	36.1 (8.5-152.2)	<.001
Hemoptysis	7.3 (1.0-52.1)	.05

*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

Cluster Size, No. of Patients	No. of Clusters	Total, No. of Patients
2	9	18
3	5	15
4	4	16
6	1	6
13	1	13
All	20	68

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

Table 6. Multivariate Risk Factors Associated With Clustering

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

*Compared with fully susceptible strains.

†Compared with other radiographic appearances.

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 Diagnóstico y Referencia Epidemiológicos, Mexico City, Mexico; by the Human Retrovirus Unit, Universidad Nacional Autónoma de México/Instituto Nacional de Diagnóstico y Referencia Epidemiológicos, Mexico City, which processed samples for HIV tests; and by Manuel Tielve, MD, and his group at the Instituto Nacional de la Nutrición Salvador Zubirán, Mexico City, for providing radiographic interpretation.

Corresponding author: Maria de Lourdes García-García, Secretaria Académica, Instituto Nacional de Salud Pública, Avenida Universidad No. 655, Colegio Santa María Ahuacatlán, Cuernavaca, México, 62508 (e-mail: garcigar@insp3.insp.mx).

REFERENCES

- Kochi A. Tuberculosis control: is DOTS the health breakthrough of the 1990s? *World Health Forum*. 1997;18:225-232.
- Pablos-Mendez A, Raviglione MC, Laszlo A, et al, for the World Health Organization–International Union Against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. Global surveillance for antituberculosis-drug resistance, 1994–1997 [published correction appears in *N Engl J Med*. 1998;339:139]. *N Engl J Med*. 1998;338:1641-1649.
- García-García ML, Small PM, García SC, et al. Tuberculosis epidemiology and control in Veracruz, Mexico. *Int J Epidemiol*. 1999;28:135-140.
- García-García ML, Palacios Martínez M, Ponce-de-León A, et al. The role of core groups in transmitting *M tuberculosis* in a high prevalence community in Southern Mexico. *Int J Tuberc Lung Dis*. 1999;4:1-6.
- Secretaría de Salud. Norma oficial para el control y prevención de la tuberculosis en la atención primaria a la salud. *Diario Oficial*. 1995;496:20-29. Norma No. NOM-006-SAA2-1993.
- Nolte FS, Mechock B. Mycobacterium. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH, eds. *Manual of Clinical Microbiology*. 6th ed. Washington, DC: ASM Press; 1995:400-437.
- van Embden JDA, Cave MD, Crawford JT, et al. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: recommendations for a standardized methodology. *J Clin Microbiol*. 1993;31:406-409.
- Woelfler BF, Bradford WZ, Paz A, Small PM. A computer assisted molecular epidemiologic approach for confronting the re-emergence of tuberculosis. *Am J Med Sci*. 1995;311:17-22.
- Instituto Nacional de Estadística, Geografía, e Informática. *Anuario Estadístico del Estado de Veracruz, México*. Aguascalientes, México: Talleres Graficos del Instituto Nacional de Estadística, Geografía, e Informática; 1995:125-446.
- Kin SJ, Bai GH, Hong YP. Drug resistant tuberculosis in Korea, 1994. *Int J Tuberc Lung Dis*. 1997;1:302-308.
- Styblo K, Dankova D, Drapela J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia: report for the first four

- years of the study (1961-1964). *Bull World Health Organ.* 1967;37:819-874.
12. Boulahbal F, Khaled S, Tazir M. The interest of follow-up of resistance of the tubercle bacillus in the evaluation of a programme. *Bull Int Union Tuberc Lung Dis.* September 1989;64:23-25.
 13. Chaulk CP, Moore-Rice K, Rizzo R, Chaisson RE. Eleven years of community-based directly observed therapy for tuberculosis. *JAMA.* 1995;274:945-951.
 14. Fujiwara PI, Larkin C, Frieden TR. Directly observed therapy in New York City: history, implementation, results, and challenges. *Clin Chest Med.* 1997;18:135-148.
 15. Weis SE, Slocum PC, Blais FX, et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *N Engl J Med.* 1994;330:1179-1184.
 16. Chaulet P, Zidouni N. Evaluation of applied strategies of tuberculosis control in the developing world. In: Reichman L, Hershfield E, eds. *Tuberculosis.* New York, NY: Marcel Dekker Inc; 1992:601-627.
 17. Lazslo A, De Kantor IN. A random sample survey of initial drug resistance among tuberculosis cases in Latin America. *Bull World Health Organ.* 1994;72:603-610.
 18. Centers for Disease Control and Prevention. Population-based survey for drug resistance of tuberculosis—Mexico, 1997. *MMWR Morb Mortal Wkly Rep.* 1998;47:371-375.
 19. Sifuentes-Osornio J, Ponce-de-León A, Bobadilla-del-Valle M, et al. Drug resistance in *Mycobacterium tuberculosis*: a survey in the central area of Mexico [abstract]. *Clin Infect Dis.* 1996;23:886.
 20. Behr MA, Warren SA, Salamon H, et al. Transmission of *Mycobacterium tuberculosis* from AFB smear-negative patients. *Lancet.* 1999;353:444-449.
 21. Kato-Maeda M, Sifuentes-Osornio J, Bobadilla del Valle M, Ruiz-Palacios GM, Ponce-de-León A. Drug resistance among acid-fast bacilli smear negative tuberculosis patients in the Sierra Madre of Mexico [letter]. *Lancet.* 1999;353:1709.
 22. Cohn ML, Kovitz C, Oda U, Middlebrook G. Studies on isoniazid and tubercle bacilli: the growth requirements, catalase activities, and pathogenic properties of isoniazid-resistant mutants. *Am Rev Tuberc.* 1954;70:641-664.
 23. Snider DE Jr, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *Am Rev Respir Dis.* 1985;132:125-132.
 24. Park MM, Davis AL, Schlunger NW, Cohen H, Rom WN. Outcome of MDR-TB patients, 1983-1991: prolonged survival with appropriate therapy. *Am J Respir Crit Care Med.* 1996;153:317-324.
 25. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *Int J Tuberc Lung Dis.* 1998;2:877-884.

- Nonsteroidal antiinflammatory drugs are associated with both upper and lower gastrointestinal bleeding. *Dig Dis Sci*. 1997;42:990-997.
21. García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L. Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. *Arch Intern Med*. 1998;158:33-39.
 22. García Rodríguez LA, Walker AM, Pérez Gutthann S. Nonsteroidal antiinflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. *Epidemiology*. 1992;3:337-342.
 23. Smalley WE, Ray WA, Daugherty JR, Griffin MR. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly persons. *Am J Epidemiol*. 1995;141:539-545.
 24. Cullen DJ, Hawkey GM, Greenwood DC, et al. Peptic ulcer bleeding in the elderly: relative roles of *Helicobacter pylori* and non-steroidal anti-inflammatory drugs. *Gut*. 1997;41:459-462.
 25. Matikainen M, Kangas E. Is there a relationship between the use of analgesics and non-steroidal anti-inflammatory drugs and acute upper gastrointestinal bleeding? a Finnish case-control prospective study. *Scand J Gastroenterol*. 1996;31:912-916.
 26. Jick H, Vessey MP. Case-control studies in the evaluation of drug-induced illness. *Am J Epidemiol*. 1978;107:1-7.
 27. Chan T, Critchley J, Lau J, Sung J, Chung S, Anderson D. The relationship between upper gastrointestinal hemorrhage and drug use: a case control study. *Int J Clin Pharmacol Ther*. 1996;34:304-308.
 28. Takkouche B, Cadarso-Suárez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol*. 1999;150:206-215.
 29. Poole C, Greenland S. Random-effects meta-analyses are not always conservative. *Am J Epidemiol*. 1999;150:469-475.
 30. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
 31. Walker AM. *Observation and Inference: An Introduction to the Methods of Epidemiology*. Newton Lower Falls, Mass: Epidemiology Resources Inc; 1991.
 32. Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol*. 1994;140:290-296.
 33. Cooper H, Hedges LV. *The Handbook of Research Synthesis*. New York, NY: Russell Sage Foundation; 1994.
 34. Olivero J, Graham D. Gastric adaptation to nonsteroidal anti-inflammatory drugs in man. *Scand J Gastroenterol Suppl*. 1992;193:53-58.
 35. Yola M, Lucien A. Evidence of the depletion of susceptibles effect in non-experimental pharmacoeconomic research. *J Clin Epidemiol*. 1994;47:731-737.
 36. Robins JM. Causal inference from complex longitudinal data. In: Berkane M, ed. *Lecture Notes in Statistics*. New York: Springer-Verlag NY Inc; 1997:69-117.
 37. Shapiro S. Meta-analysis/shmeta-analysis. *Am J Epidemiol*. 1994;140:771-778.
 38. Greenland S. Can meta-analysis be salvaged? *Am J Epidemiol*. 1994;140:783-787.
 39. Rothman KJ, Greenland S. *Modern Epidemiology*. Philadelphia, Pa: Lippincott-Raven Publishers; 1998.
 40. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med*. 1999;340:1888-1899.

Correction

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)."