ORIGINAL ARTICLES

Resistant *Mycobacterium tuberculosis* Strains From Immigrants in the Community of Madrid: Current Assessment

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OBJECTIVE: Immigration to Spain from countries with high rates of tuberculosis infection is increasing. The aim of this study was to describe and analyze resistance to antituberculosis drugs in strains isolated from foreign-born patients in the Community of Madrid.

PATIENTS AND METHODS: A cohort of immigrants was identified at 14 hospitals in the Community of Madrid. To assess the sensitivity of isolated strains, we used the MGIT 960 system and/or the proportion method of Canetti. Clinical and sociodemographic information was recorded for each patient. We compiled descriptive statistics and performed univariate analysis, followed by multiple logistic regression analysis.

RESULTS: From a total of 312 cases, 268 strains were isolated. Sensitivity was tested in 221 strains. The proportion of immigrants with no health care coverage was 19.9%. Thirty-one strains (14.0%) were resistant; 24 (12.6%) were in newly diagnosed cases and 6 (27.3%) were in patients who had been treated previously. Ten strains (4.5%) were multidrug resistant. Resistance to isoniazid was detected in 18 strains (9.5%). Multidrug resistance was associated with a history of prior antituberculosis treatment (odds ratio, 5.94; 95% confidence interval, 1.46-24.18).

CONCLUSIONS: Barriers to health care faced by immigrants with tuberculosis should be removed. Treatment should begin with 4 drugs while the results of sensitivity tests are pending. A history of prior antituberculosis treatment should raise a suspicion of multidrug resistance.

Key words: *Immigration. Tuberculosis. Resistance. Community of Madrid.*

Situación actual de las resistencias de Mycobacterium tuberculosis en la población inmigrante de la Comunidad de Madrid

OBJETIVO: Actualmente en España se está produciendo un incremento de la población de inmigrantes que proceden de países con altas tasas de incidencia de enfermedad tuberculosa. El objetivo de este trabajo ha sido describir y analizar las resistencias a fármacos antituberculosos entre la población inmigrante de la Comunidad de Madrid.

PACIENTES Y MÉTODOS: La cohorte de inmigrantes fue identificada a través de 14 hospitales de la Comunidad de Madrid. Para evaluar la susceptibilidad de las cepas aisladas se utilizó el sistema MGIT 960 y/o el método de las proporciones de Canetti. De cada paciente se recogió información clínica y sociodemográfica. En primer lugar se realizó un estudio descriptivo y, posteriormente, un análisis univariante y multivariante por medio de regresiones logísticas.

RESULTADOS: Se identificaron 312 casos, en los que se aislaron 268 cepas. Se obtuvo información de sensibilidad de 221 cepas. El 19,9% de la muestra no tenía cobertura sanitaria. Fueron resistentes 31 cepas (14,0%), de las que 24 (12,6%) correspondían a casos nuevos y 6 (27,3%) a casos previamente tratados. Diez cepas (4,5%) fueron multirresistentes. La resistencia a isoniacida en casos nuevos fue del 9,5% (18 cepas). La multirresistencia se asoció a historia previa de tratamiento antituberculoso (*odds ratio* = 5,94; intervalo de confianza del 95%, 1,46-24,18).

CONCLUSIONES: Es necesario eliminar los problemas de acceso al sistema sanitario entre los inmigrantes afectados de tuberculosis. Las pautas de tratamiento deberían comenzar con 4 fármacos hasta conocer los resultados de sensibilidad. La historia previa de tratamiento antituberculoso debe incrementar la sospecha de multirresistencia.

Palabras clave: *Inmigración. Tuberculosis. Resistencias. Comunidad de Madrid.*

Introduction

Tuberculosis is one of the oldest diseases known. We understand how to treat it and prevent transmission, yet it remains a public health challenge. Although mainly poor countries are affected, recent decades have seen the resurgence of tuberculosis in industrialized societies because of human immunodeficiency virus (HIV) infection, lack of support for surveillance programs, and the rise of economic immigration.[1] The 1980s and beginning of the

This study was partially funded by a grant from the Instituto de Salud Carlos III (project SBPY 1254/02-02).

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Manuscript received July 4, 2006. Accepted for publication October 9, 2006.

1990s brought international concern after several nosocomial outbreaks due to virulent, multidrug-resistant strains occurring mainly in HIV-infected patients.[2-4] At first an HIV-related pandemic was feared,[5] but the incidence of resistant tuberculosis has not increased with the passage of time. Like other countries, Spain saw a change in the epidemiology of tuberculosis after 1995, as new patterns emerged in relation to both the use of antiretroviral drugs and the rising population of economic immigrants.[6] In the Community of Madrid foreign birth became the main risk factor for tuberculosis after 2000, outranking HIV seropositivity.[7] The rise in economic immigration along with the increase in multidrug-resistant strains of *Mycobacterium tuberculosis* in Eastern European countries has once again created a certain unease about controlling this disease.[8] Resistant strains present a great challenge because their treatment is both complicated and costly.

The history of previous treatment is important to the evaluation of tuberculosis resistance. Such resistance among new cases—in patients who have never received antituberculosis treatment or who have been treated for less than a month—must be distinguished from resistance among cases that have been treated for a month or more.[9,10] Rates of new-case resistance offer information on how well preventive measures are succeeding, as they reflect either the transmission of resistant strains from smear-positive patients or spontaneous mutations of the bacillus. Calculating new-case resistance rates for population groups and specific geographic areas allows treatment protocols to be tailored to meet local needs. Rates of resistance among treated cases, on the other hand, provide information on how well control programs are working, as they reflect the adequacy of and compliance with treatment plans.

Information about the prevalence of resistant strains among the immigrant population is scarce in Spain and limited to very specific geographic areas. The aim of this study was to describe the distribution of resistant *M tuberculosis* strains isolated from foreign-born persons in the Community of Madrid and to identify the variables associated with such resistance.

Patients and Methods

Design

This was a cross-sectional cohort study in which the following 14 public hospitals in the Community of Madrid participated: Hospital Carlos III, Hospital Clínico, Hospital 12 de Octubre, Fundación Hospital Alcorcón, Fundación Jiménez Díaz, Hospital de Getafe, Hospital Gregorio Marañón, Hospital de Móstoles, Hospital Príncipe de Asturias, Hospital de La Princesa, Hospital Ramón y Cajal, Hospital Severo Ochoa, Hospital Cantoblanco, and Hospital de la Fuenfría. The last 2 hospitals were long-term care facilities with wards specifically reserved for tuberculosis patients. Both receive referrals from any hospital in the Community of Madrid. The listed hospitals represent 77.7% (14/18) of the public facilities in the area. Data were gathered by the microbiology departments in 11 hospitals, the internal medicine and infectious disease departments in 9, the respiratory medicine departments in 8, and the tuberculosis inpatient care units in 2. The study was coordinated by the Spanish Center for Tropical Medicine of the Carlos III Institute of Health.

Definitions

– Resistance among new cases: resistant *M tuberculosis* strains isolated from patients who have never received antituberculosis treatment or who have been treated for less than 1 month. To calculate the frequency of this type, the number of new cases with resistant strains is divided by the total number of new cases found[9,10]

– Resistance among previously treated cases: resistant *M tuberculosis* strains isolated from patients who were previously treated with antituberculosis drugs for at least 1 month. To calculate the frequency of this type, the number of previously treated cases with resistant strains is divided by the total number of previously treated cases found[9,10]

– Overall resistance, or all resistant cases: the sum of new and previously treated cases with resistant strains

– Single-drug resistance: strains resistant to 1 antituberculosis drug

– Polydrug resistance: strains resistant to more than 1 antituberculosis drug

– Multidrug resistance: strains resistant at least to isoniazid and rifampicin

– At-risk drinker: a man who consumes more than 28 units of alcohol per week or a woman who consumes over 16 units[11]

– Diagnostic delay: time elapsing between the onset of symptoms and diagnosis of the disease. This information was reported by the patient

Inclusion Criteria and Data Collection

All cases met the following criteria: *a)* immigrant status (all persons who did not have Spanish citizenship were so-considered for the purposes of this study); *b)* diagnosis of tuberculosis based on a positive culture in 2003 (from January 1 to December 31); *c)* age over 15 years; and *d)* not incarcerated.

Information was gathered with a questionnaire developed specifically for the study and previously piloted with 30 subjects. Two study coordinators from the Spanish Center for Tropical Medicine gathered data in all but 2 hospitals, where doctors were assigned to collect information. Clinical information was obtained by reviewing the medical records, and personal information was recorded during an interview in hospital or at the first visit of an outpatient to a primary care clinic. The history of antituberculosis treatment was also checked in those interviews. Interpreters were used when necessary. All patients received information about the study and gave their written consent.

Microbiological Tests

The strains were cultured on solid media (Löwenstein–Jensen, Coletsos, or both; Biomérieux, Marcy l'Etoile, France) and/or in liquid media (MGIT, Becton Dickinson, Sparks, Maryland, USA; BacT/ALERT, Biomérieux). The first strains isolated from a patient were submitted to the laboratory for sensitivity studies. Antibiograms to first-line drugs were performed by the microbiology departments of the participating hospitals (MGIT liquid media system) and/or by the Spanish national reference laboratory for mycobacteria (National Center of Microbiology in Majadahonda, Madrid), where the method of proportions of Canetti[12] was used for all drugs except pyrazinamide. In this method, before Löwenstein–Jensen media had solidified, the following drugs were added at the stated concentrations: isoniazid at 0.2, 0.5, and 1 µg/mL; rifampicin at 20 and 40 µg/mL; ethambutol at 1.5 and 2 µg/mL; and streptomycin at 4 and 8 µg/mL. To test pyrazinamide with the method of proportions, the BACTEC radiometric system (Becton Dickinson) was used with Middlebrook medium at a pH of 5.5 and a drug concentration of 100 µg/mL. Strains were considered resistant when the number

of colony-forming units was equal to or greater than the cutoff established by Canetti. Sensitivity to second-line drugs was tested in resistant strains.

Statistical Analysis

A double-entry database was designed with SPSS version 13.0 software for analysis. Descriptive statistics were compiled for resistance among new and previously treated cases as well as for all resistant cases overall, expressed as frequencies for categorical variables and means (SD) for quantitative ones.

New-case resistance was analyzed in relation to all resistant cases. The small number of resistant strains in previously treated cases (6) prevented further statistical analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated by logistic regression, first with univariate and then multivariate models. The dependent variable was the presence or absence of resistance. The univariate analysis considered the following independent variables: sex (male/female); origin (place of birth: Latin America, North Africa, Sub-Saharan Africa, Europe, Asia); age (years, as a continuous variable); diagnostic delay (days, as a continuous variable); new case (yes/no); HIV (seronegative/seropositive); at-risk drinking (yes/no); public health care coverage (yes/no); and legal immigration status (documented/undocumented). Independent variables that were significantly related to resistance in the univariate analysis ($P<.05$) were entered into the multivariate models. Variables identified in the literature as potentially associated with the presence of resistance were also entered. Information on the variables used was available for 90% of the patients.

Given the small number of strains resistant to streptomycin and their distribution, and the low frequency of multidrug-resistant strains, it was not possible to analyze them by region of origin.

Results

Three hundred twelve cases of disease caused by *M tuberculosis* were identified by the participating hospitals in 2003. A total of 268 strains of the bacillus were isolated. Information about sensitivity was available for 221 strains (82.5% of the isolates). Sensitivity was not studied for 18 strains (6.7%) and the results were unavailable for 29 (10.8%).

Sample

No significant differences in patient characteristics were found between cases for which information regarding sensitivity could or could not be obtained. Men (66.5%) outnumbered women and the population was young, with a mean age of 32.9 (11.5) years. All patients were economic immigrants, meaning they were born in countries with low per capita income levels. Most came from Latin America (46.2%, n=102). The next-largest group came from Europe, entirely made up of immigrants from Eastern Europe (15.8% of the total) and Portugal (2.7%). North African immigrants made up 17.6% (n = 39) of the sample; all came from Morocco. Regarding their legal immigration status, undocumented immigrants numbered 124 (57.4%) and 44 patients in that category (34.8%) lacked public health care coverage. The median time elapsing between the patient's arrival in Spain and the tuberculosis diagnosis was less than 30 months (interquartile range [IQR], 10-48 months). The median diagnostic delay was 42 days (IQR, 16-94 days). Induction treatment started with 3 drugs in 70 patients (32.2%).

Overall Resistance

The overall rate of resistance was 14%. Analysis of resistance by drugs gave the following results: 24 strains (10.9%) were resistant to isoniazid, 12 (5.4%) to streptomycin, 10 (4.5%) to rifampicin, 5 (2.3%) to pyrazinamide, 5 (2.3%) to rifabutin, 2 (0.9% to ethambutol, and 1 each (0.5%) to ethionamide, ofloxacin, para-aminosalicylic acid, and thiacetazone.

The distribution of resistance is shown in Table 1. The rate of single-drug resistance was found to be 7.6% and, importantly, isoniazid resistance was detected in 4.5% of all isolated strains. No strain was found to be resistant to rifampicin alone and therefore all cases of resistance to that drug occurred in multidrug-resistant strains. Polydrug resistance was found in 6.3% of the strains and multidrug resistance in 4.5%.

Table 2 shows the rates of resistance to antituberculosis drugs overall and by drug, according to the sociodemographic variables studied. All at-risk drinkers were men. The univariate analysis (Table 3) indicated that persons at greater risk of multidrug-resistant tuberculosis were those who had been previously treated (OR, 6.81; 95% CI, 1.76-26.41) and, for men, those who were at-risk drinkers (OR, 3.91; 95% CI, 1.04-14.70). After multivariate analysis (Table 4) the only variable that remained a risk factor for harboring a multidrug-resistant strain was previous antituberculosis treatment (OR, 5.94; 95% CI, 1.46-24.18).

Resistance in New Cases

Of the 190 strains of *M tuberculosis* isolated in new cases, 24 (12.6%) were resistant. The rates of resistance to specific drugs in new cases were as follows: isoniazid, 18 (9.5%); streptomycin, 9 (4.7%); rifampicin, 6 (3.2%); pyrazinamide, 3 (1.6%); ethambutol, 2 (1.1%); rifabutin, 2 (1.1%); para-aminosalicylic acid and thiacetazone, 1 each (0.5%). Multidrug resistance was found in 6 cases (3.2%). The profile of resistance in new cases is shown in Table 1. Single-drug resistance was found in 7.4% and polydrug resistance in 6.3%.

Table 5 shows the distribution of new-case resistance by sociodemographic variables. The univariate analysis (Table 6) showed that at-risk drinking was associated with greater risk of a man's harboring a multidrug-resistant strain (OR, 14.18; 95% CI, 2.45-82.03). The multivariate analysis (Table 7) found no significant risk factors for isoniazid resistance in this group.

Resistance in Previously Treated Cases

Six (19.4%) of the 22 strains isolated in previously treated patients were found to be resistant. Resistances by drug were as follows: isoniazid, 5 (22.7%); rifampicin, 4 (18.2%); pyrazinamide, 2 (9.1%);

TABLE 1
Patterns of Resistance in *Mycobacterium tuberculosis* Strains Isolated From Immigrants Diagnosed in the Community of Madrid in 2003*

	Type of Resistance					
	Total, n=221		New Cases, n=190		Previously Treated Cases, n=22	
	No.	%	No.	%	No.	%
Single-drug resistance						
I	10	4.5	8	4.2	1	4.5
S	5	2.3	4	2.1	1	4.5
Z	1	0.4	1	0.5	–	–
E	1	0.4	1	0.5	–	–
Polydrug resistance						
I + S + E	1	0.4	1	0.5	–	–
I + P + S	1	0.4	1	0.5	–	–
I + S	1	0.4	1	0.5	–	–
I + S + PAS	1	0.4	1	0.5	–	–
I + R	2	0.8	2	2.1	–	–
I + R + ETO + RB	1	0.4	–	–	1	4.5
I + R + Z + RB	2	0.8	1	0.5	1	4.5
I + R + Z + RB + S + OFX	1	0.4	–	–	1	4.5
I + R + RB	1	0.4	1	0.5	–	–
I + R + S	2	0.8	1	0.5	1	4.5
I + R + TH	1	0.4	1	0.5	–	–
Total	31	14.0	24	12.6	6	27.3

*E indicates ethambutol; ETO, ethionamide; I, isoniazid; OFX, ofloxacin; PAS, para-aminosalicylic acid; R, rifampicin; RB, rifabutin; S, streptomycin; TH, thiacetazone; Z, pyrazinamide.

TABLE 2
Resistant Strains of *Mycobacterium tuberculosis* Isolated From Immigrants Diagnosed With Tuberculosis in the Community of Madrid in 2003, Distributed by Drug and Sociodemographic Variables*

	Resistant Strains					
Variables	Total	Isoniazid	Pyrazinamide	Streptomycin	Ethambutol	Multidrug Resistance
Sex, n=221						
Male, n=147	22 (15%)	17 (11.6%)	2 (1.4%)	9 (6.1%)	2 (1.4%)	8 (5.4%)
Female, n=74	9 (12.2%)	7 (9.4%)	3 (4%)	3 (4%)	–	2 (2.7%)
Origin, n=221						
Latin America, n=102	15 (14.7%)	12 (11.7%)	4 (3.9%)	4 (3.9%)	–	5 (4.9%)
North Africa, n=39	6 (15.4%)	4 (10.2%)	1 (2.6%)	3 (7.7%)	1 (2.6%)	2 (5.1%)
Sub-Saharan Africa, n=32	5 (15.6%)	5 (15.6%)	1 (3.1%)	3 (9.4%)	–	3 (9.4%)
Europe, n=41	4 (9.7%)	2 (4.9%)	–	3 (7.3%)	–	–
Asia, n=7	1 (14.3%)	1 (14.3%)	–	–	–	–
Age, n = 219, y	28 (25-36)	27.5 (24.2-35.7)	32.0 (27-47)	32 (27.2-42.5)	27 (27-27)	28 (25.7-36.2)
Diagnostic delay, n=211, d	31 (14-96.5)	30.5 (14.5-142.5)	45.5 (9.25-105.0)	38 (16.7-81.2)	90 (90-90)	20 (11-90)
New cases, n=212						
Yes, n=190	24 (12.6%)	18 (9.5%)	3 (1.6%)	9 (4.7%)	2 (1.1%)	6 (3.2%)
No, n=22	6 (27.3%)	5 (22.7%)	2 (9.1%)	3 (13.6%)	–	4 (18.2%)
HIV, n=165						
Positive, n=13	3 (23.1%)	3 (23.1%)	–	1 (7.7%)	–	2 (15.4%)
Negative, n=152	23 (15.1%)	19 (12.5%)	4 (2.6%)	8 (5.3%)	2 (1.3%)	7 (4.6%)
At-risk drinking, n=209						
Yes, n=33	5 (15.2%)	4 (12.1%)	–	1 (3%)	–	4 (12.1%)
No, n=176	26 (14.8%)	20 (11.4%)	5 (2.8%)	11 (6.2%)	2 (1.1%)	6 (3.4%)
Public health care system coverage, n=221						
Yes, n=177	24 (13.6%)	18 (10.2%)	5 (2.8%)	10 (5.6%)	2 (1.1%)	6 (3.4%)
No, n=44	7 (15.9%)	6 (13.6%)	–	2 (4.5%)	–	4 (9.1%)
Legal immigration status, n=216						
Documented, n=92	11 (12%)	6 (6.5%)	2 (2.2%)	7 (7.6%)	1 (1.1%)	2 (2.2%)
Undocumented, n=124	20 (16.1%)	18 (14.5%)	3 (2.4%)	5 (4.0%)	1 (0.8%)	8 (6.5%)
Total	31	24	5	12	2	10

*Data are expressed as number (%) of patients or as median (interquartile range). HIV indicates human immunodeficiency virus.

TABLE 3
Univariate Analysis: Study of Variables Associated With Drug-Resistant *Mycobacterium tuberculosis* Strains Isolated from Immigrants Diagnosed With Tuberculosis in the Community of Madrid in 2003*

Variables	All Resistant Strains		Resistance to Isoniazid		Resistance to Streptomycin†		Multidrug Resistance†	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex								
Male	1.27 (0.55-2.92)	.57	1.25 (0.49-3.17)	.64	1.54 (0.40-5.88)	0.52	2.07 (0.43-10.01)	.36
Female	1		1		1		1	
Origin								
Latin America	1		1		NA	NA		
North Africa	1.05 (0.38-2.95)	.92	0.86 (0.26-2.84)	.80				
Sub-Saharan Africa	1.07 (0.36-3.23)	.90	1.39 (0.45-4.29)	.57				
Europe	0.63 (0.19-2.02)	.98	0.38 (0.08-1.80)	.22				
Asia	0.97 (0.11-8.61)	.43	1.25 (0.14-11.29)	.84				
Age, y	0.98 (0.95-1.02)	.38	0.98 (0.94-1.02)	.34	1.10 (0.97-1.06)	.60	1.00 (0.95-1.06)	.89
New cases								
Yes	1		1		1		1	
No	2.59 (0.92-7.27)	.07	2.81 (0.93-8.52)	.07	3.17 (0.79-12.74)	.10	6.81 (1.76-26.41)	.005
HIV								
Positive	1		1		1		1	
Negative	0.59 (0.15-2.33)	.45	0.48 (0.12-1.89)	.29	0.67 (0.08-5.78)	.71	0.27 (0.05-1.43)	.12
At-risk drinking								
Yes	1		1		1		1	
No	0.97 (0.34-2.74)	.95	1.07 (0.34-3.38)	.90	0.47 (0.06-3.76)	.48	0.26 (0.07-0.96)	.04
Diagnostic delay, d	1.001 (0.99-1.002)	.30	1.01 (1.00-1.01)	.15	1.01 (1.00-1.03)	.11	1.00 (0.99-1.01)	.45
Public health care coverage								
Yes	1		1		1		1	
No	1.21 (0.48-3.01)	.69	1.39 (0.52-3.75)	.51	0.79 (0.17-3.76)	.77	2.85 (0.77-10.57)	.12
Legal immigration status								
Documented	1		1		1		1	
Undocumented	1.42 (0.64-3.12)	.39	2.43 (0.93-6.40)	0.07	.51 (0.16-1.66)	.26	3.10 (0.64-14.97)	.16

*CI indicates confidence interval; NA, not analyzable; OR, odds ratio; HIV, human immunodeficiency virus. OR, 95% CI, and *P* values were calculated by logistic regression.
†The low number of strains isolated meant that streptomycin and multidrug resistance could not be analyzed in relation to country of origin.

TABLE 4
Multivariate Analysis of Factors Associated with Resistant *Mycobacterium tuberculosis* Strains Isolated in the Immigrant Population of the Community of Madrid in 2003*

Variables	RAll Resistant Strains		Isoniazid-Resistant Strains		Streptomycin-Resistant Strains†		Multidrug-Resistant Strains†	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex								
Male	1.38 (0.53-3.63)	.50	1.45 (0.48-4.32)	.50	1.54 (0.38-6.16)	.54	1.10 (0.19-6.48)	.92
Female	1		1		1		1	
Origin								
Latin America	1	1			NA	NA		
North Africa	1.17 (0.39-3.49)	.77	0.95 (0.27-3.36)	.93				
Sub-Saharan Africa	1.27 (0.39-4.08)	.68	1.67 (0.50-5.53)	.40				
Europe	0.56 (0.15-2.12)	.39	0.23 (0.03-1.85)	.16				
Asia	1.04 (0.10-10.40)	.97	1.35 (0.13-13.88)	.80				
Age, y	0.98 (0.94-1.02)	.30	0.98 (0.94-1.02)	.29	1.01 (0.96-1.06)	.78	1.00 (0.94-1.06)	.92
New case								
Yes	1				1		1	
No	2.67 (0.90-7.89)	.08	2.70 (0.83-8.77)	.10	3.41 (0.81-14.28)	.09	5.94 (1.46-24.18)	.01
At-risk drinking								
Yes	1				1		1	
No	1.15 (0.35-3.55)	.80	1.15 (0.33-4.05)	.82	2.92 (0.34-25.07)	.33	0.32 (0.07-1.44)	.14

*OR indicates odds ratio; CI, confidence interval; NA, not analyzed. OR, 95% CI, and *P* values were calculated by logistic regression.
†The low number of strains isolated meant that streptomycin and multidrug resistance could not be analyzed in relation to country of origin.

TABLE 5
Resistant Strains of *Mycobacterium tuberculosis* Isolated From New Cases Among Immigrants Diagnosed in the Community of Madrid in 2003, Distributed by Drug and Sociodemographic Variables*

Variables	Resistant Strains					
	Total	Isoniazid	Pyrazinamide	Streptomycin	Ethambutol	Multidrug
Sex, n=190						
Male, n=125	16 (12.8%)	12 (9.6%)	–	6 (4.8%)	2 (1.6%)	4 (3.2%)
Female, n=65	8 (12.3%)	6 (9.2%)	3 (4.6%)	3 (4.6%)	–	2 (3.1%)
Origin, n=190						
Latin America, n=90	12 (13.3%)	9 (10%)	2 (2.2%)	3 (3.3%)		–3 (3.3%)
Morocco, n=35	6 (17.1%)	4 (11.4%)	1 (2.9%)	2 (5.7%)	1 (2.9%)	(5.7%)
Sub-Saharan Africa, n=25	3 (12.0%)	3 (12.0%)	–	2 (8.0%)	–	1 (4.0%)
Europe, n=35	2 (5.7%)	1 (2.9%)	–	2 (5.7%)	1 (2.9%)	–
Asia, n=5	1 (20.0%)	1 (20.0%)	–	–	–	–
Age, n=190, y	27.5 (24.2-32.0)	27.0 (23.7-32.7)	32.0 (28.0-32.0)	32.0 (27.5-38.0)	27.0 (27.0-27.0)	27.5 (24.5-28.5)
HIV, n=145						
Positive, n=13	3 (21.3%)	3 (23.1%)	–	1 (7.7%)	–	2 (15.4%)
Negative, n=132	18 (13.6%)	14 (10.6%)	2 (1.5%)	7 (5.3%)	2 (1.5%)4 (3.0%)	
At-risk drinkers, n=184						
Yes, n=26	5 (19.2%)	3 (23.1%)	–	1 (3.8%)	–	4 (15.4%)
No, n=158	19 (12.0%)	14 (10.6%)	3 (1.9%)	8 (5.1%)	2 (1.3%)	2 (3.1%)
Diagnostic delay, n=185, d	45 (15-120)	31 (16-217.5)	31 (2-120)	38 (14.2-95.7)	90 (90-90)	24.5 (11.5-142.5)
Public health care coverage, n=190						
Yes, n=157	21 (13.4%)	15 (9.6%)	–	–	–	4 (2.5%)
No, n=33	3 (9.1%)	3 (9.1%)	3 (1.9%)	9 (5.7%)	2 (1.3%)	2 (6.1%)
Legal immigration status, n=188						
Documented, n=84	11 (13.1%)	6 (7.1%)	1 (1.0%)	7 (8.3%)	1 (1.2%)	2 (2.4%)
Undocumented, n=104	13 (12.5%)	12 (11.5%)	2 (2.4%)	2 (1.9%)	1 (1.0%)	4 (3.8%)
Total	24	18	3	9	2	6

*Data are expressed as number (%) of patients or as median (interquartile range). HIV indicates human immunodeficiency virus.

streptomycin and rifabutin, 3 (13.6%); and ofloxacin and ethionamide, 1 (4.5%). Multidrug resistance was identified in 4 (18.4%). The distribution of resistance for previously treated cases is shown in Table 1. The types of resistance distributed by drugs and sociodemographic variables are shown in Table 8. All resistant strains in previously treated cases were in men over 25 years of age who were neither HIV-infected nor at-risk drinkers. No resistant strain was isolated in previously treated patients from Morocco or from Asia. The low number of cases of resistance among previously treated cases and the distribution of sociodemographic variables among them made further statistical analysis meaningless.

Discussion

The findings from this study give us a clearer picture of the pattern of drug-resistance in *M tuberculosis* strains in foreign-born persons in the Community of Madrid, although the subjects included represented only a portion of the population because the strains were collected at only 14 participating centers (77.7% of all public hospitals) and because of the established inclusion criteria. Incarcerated individuals were not included owing to administrative problems, so the rate of resistance may have been underestimated given the risk factors sometimes found in that subpopulation. However, as both sociodemographic and clinical data were collected, and as the population sample came from all parts of the Community of Madrid, our study provides valuable information about resistance to antituberculosis drugs in the defined area, especially considering the small number of studies carried out in the immigrant population.

As in other studies, the population in this study was young and comprised mainly men.[14] The birthplaces of the patients we studied clearly reflected the foreign-born population in this community.[15]

It is important to note that 44 patients (34.8% of the undocumented population) did not have public health care coverage. Other studies have found that this group has difficulty accessing the health care system,[16] a situation of concern because it could make tuberculosis treatment difficult and therefore represent an obstacle to controlling the disease.[17] International organizations have called for a lowering of barriers to health care access for immigrants with tuberculosis.[17,18]

The literature on overall drug resistance of *M tuberculosis* strains is disparate. Reported rates of resistance in the general population vary widely, from 2.8%[19] to 21.3%[20] of strains isolated. Differences may be mainly related to the geographic scope or timing of studies. The distribution of resistant *M tuberculosis* strains among foreign-born persons in Spain has been studied little, but findings here have also been heterogeneous. The overall rates of resistant

TABLE 6
Univariate Analysis of Factors Associated with Resistant *Mycobacterium tuberculosis* Strains Isolated in New Cases Among the Immigrant Population of the Community of Madrid in 2003*

Variables	All Resistant Strains		Isoniazid-Resistant Strains		Multidrug Resistant Strains†	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex						
Male	1.05 (0.42-2.59)	.92	1.04 (0.37-2.92)	.93	1.04 (0.19-5.84)	.96
Female	1		1		1	
Origin						
Latin America	1		1		NA	
North Africa	1.34 (0.46-3.92)	.59	1.16 (0.33-4.05)	.81		
Sub-Saharan Africa	0.89 (0.23-3.42)	.86	1.23 (0.30-4.92)	.77		
Europe	0.39 (0.08-1.86)	.24	0.26 (0.03-2.17)	.22		
Asia	1.62 (0.17-15.79)	.68	2.25 (0.23-23.37)	.49		
Age, y	0.96 (0.92-1.01)	.07	0.95 (0.90-1.00)	.08	0.94 (0.85-1.04)	.22
At-risk drinking						
Yes	1.74 (0.59-5.16)	.32	1.87 (0.56-6.20)	.31	14.18 (2.45-82.03)	.003
No	1		1		1	
HIV						
Positive	1		1		1	
Negative	0.53 (0.13-2.10)	.36	.39 (0.1-1.61)	.19	0.17 (0.03-1.05)	.06
Diagnostic delay, d	1.001 (1.000-1.002)	.18	1.00 (1.00-1.03)	.07	0.99 (0.99-1.01)	.65
Public health care coverage						
Yes	1		1		1	
No	0.65 (0.18-2.31)	.50	0.95 (0.26-3.48)	.94	2.47 (0.43-14.07)	.31
Legal immigration status						
Documented	1		1		1	
Undocumented	0.95 (0.40-2.24)	.91	1.70 (0.61-4.73)	.31	1.67 (0.29-9.18)	.57

*OR indicates odds ratio; NA, not analyzed. OR, 95% CI, and *P* values were calculated by logistic regression.
†The low number of strains isolated meant that streptomycin and multidrug resistance could not be analyzed in relation to country of origin.

tuberculosis reported for the immigrant population of the Community of Madrid have ranged from 3.6%[21] to 30.1%.[20] As a result, besides considering the differences in geographic scope and time span of studies, it is important to remember that the composition of an immigrant population can vary within a community, and that changes have occurred quickly in recent years.

The overall rate of resistance in our study (14%) may be an underestimate, given that the regional registry of tuberculosis cases for Madrid has reported an overall resistance rate of 21.5% for the general population.[14] The difference may be due to the inclusion criteria applied in our study and to the smaller geographic area covered, but not to the completeness of information collected given that the number of isolates for which we constructed antibiograms in this study (221) was greater than the number in the registry (209).

TABLE 7
Multivariate Analysis of Factors Associated with Resistant *Mycobacterium tuberculosis* Strains Isolated in New Cases Among the Immigrant Population of the Community of Madrid in 2003*

Variables	All Resistant Strains		Isoniazid-Resistant Strains	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex				
Male	0.92 (0.32-2.59)	.85	0.88 (0.27-2.91)	.83
Female	1		1	
Origin				
Latin America	1		1	
North Africa	1.46 (0.46-4.64)	.46	1.27 (0.33-4.89)	.73
Sub-Saharan Africa	1.07 (0.26-4.37)	.99	1.52 (0.35-6.54)	.58
Europe	0.43 (0.09-2.08)	.26	0.29 (0.03-2.45)	.26
Asia	2.28 (0.21-24.95)	.52	3.49 (0.30-41.11)	.32
Age, y	0.95 (0.91-1.001)	.05	0.94 (0.89-1.001)	.05
At-risk drinking				
Yes	2.05 (0.62-6.85)	.24	2.32 (0.60-8.93)	.22
No	1		1	

*OR indicates odds ratio; CI, confidence interval. OR, 95% CI, and *P* values were calculated by logistic regression.

TABLE 8
Resistant Strains of *Mycobacterium tuberculosis* Isolated From Previously Treated Cases Diagnosed Among Immigrants in the Community of Madrid in 2003, Distributed by Drug and Sociodemographic Variables*

Variables	Previously Treated Cases With Resistant Strains		
	All Resistant Strains	Isoniazid-Resistant Strains	Multidrug Resistant Strains
Sex, n=22			
Male, n=18	6 (33.3%)	5 (27.8%)	4 (22.2%)
Female, n=4	–	–	–
Origin, n=22			
Latin America, n=12	3 (25.0%)	3 (25.0%)	2 (16.7%)
North Africa, n=2	–	–	–
Sub-Saharan Africa, n=4	2 (50.0%)	2 (50.0%)	2 (50%)
Europe, n=3	1 (33.3%)	–	–
Asia, n=1	–	–	–
Age, n=22			
15-25 y, n=3	–	–	–
26-35 y, n=10	2 (20.0%)	2 (20.0%)	2 (20%)
36-45 y, n=6	2 (33.3%)	1 (16.7%)	–
> 45 y, n=3	2 (66.7%)	2 (66.7%)	2 (66.7%)
HIV, n=17			
Positive, n=0	–	–	–
Negative, n=17	4 (28.6%)	4 (28.6%)	3 (21.7%)
At-risk drinking, n=21			
Yes, n=6	–	–	–
No, n=15	6 (40.0%)	5 (33.3%)	4 (26.7%)
Diagnostic delay, n=20, d			
median (IQR)	30 (13.5-60)	25 (10.2-52.5)	20 (7-60)
Total	6	5	4

*IQR indicates interquartile range; HIV, human immunodeficiency virus.

The multivariate analysis of overall resistance indicated that only prior antituberculosis treatment was associated with multidrug-resistant strains (OR, 5.94; 95% CI, 1.46-24.18). This association is well documented in the literature[19,22,23] and may be related to incorrectly prescribed prior treatment regimens or regimens in which compliance was poor. A rigorous treatment history should be taken during patient interviews as the suspicion of possible multidrug resistance in a previously treated patient would be higher and, therefore, appropriate control measures would need to be taken.

The 12.6% rate of resistance (24 strains) in new cases was similar to rates reported for immigrant populations in Barcelona[24] and Castellón.[25] In the Community of Madrid, the new-case rate has not been studied in immigrants until now, although the incidence in the general population has been found to be 7.4%,[2] a figure that is clearly lower than the rates we calculated for the immigrant population in our study. Greater vulnerability to resistant strains among previously untreated immigrants might be related to the high incidence of tuberculosis infection in their countries or to their socioeconomic conditions in Spain, which evidently can favor transmission. Living conditions, in which a large number of individuals share quarters and maintain close social relationships with others in their group, mean that they will have greater contact with *M tuberculosis* strains, some of which will be resistant. Other authors have pointed out that stress and problems related to the migratory experience may lead to greater immunosuppression, facilitating transmission of the disease.[26] One of the most important findings of our study was that the rate of resistance to isoniazid among new cases was 9.5%, a figure that should be borne in mind given that 32.3% of the patients in our population sample started treatment with 3 drugs. Our data suggest that treatment should be started with 4 drugs, in keeping with the guidelines of international organizations,[27] and that such treatment should be maintained until sensitivity has been ascertained. The fourth drug of choice would be ethambutol, for the low rate of resistance to that antibiotic.

In this study place of birth was unrelated to new-case resistance, although it could not be introduced in all logistic regression models because of low statistical power. It is important to note, however, that no multidrug-resistant strain was isolated in the European or Asian populations.

There are no studies to date on resistance in previously treated foreign-born cases with which to compare our data, and the number of such cases we identified was too low to draw conclusions. It is important to point out, however, that the resistance rate we observed for previously-treated cases (19.4%) was similar to the rates reported for the general populations of Barcelona[24] and Madrid.[2] This information stands out because at first we might expect that the rates of resistance among previously treated foreign-born cases would be higher than in the

general population, given the difficulties of both diagnosis and access to medication that might be assumed for these immigrants' countries of origin. However, the energetic implementation of directly-observed treatment programs in those countries of origin, as well as the widespread use of medications combined in a single tablet, might explain the relatively low rates of resistance in this group.[28]

Finally, given that HIV serology was available for only 74.7% of the cases from whom strains were isolated, it was not possible to introduce this variable into the multivariate analysis. Although resistant tuberculosis in the context of HIV infection is disputed,[29] some studies suggest that resistant strains are more prevalent in HIV-infected patients.[4] Therefore, although the univariate analysis indicated that this factor was far from significant, it would have been instructive to be able to include it in a multivariate analysis.

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