

# Isoniazid-Monoresistant Tuberculosis in the United States, 1993 to 2003

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**Background:** Seven percent of tuberculosis (TB) cases reported to the US National Tuberculosis Surveillance System in 2005 had *Mycobacterium tuberculosis* isolates with resistance to at least isoniazid.

**Methods:** We undertook this study to describe demographic characteristics, risk factor information, and treatment outcomes for persons with isoniazid-monoresistant (resistant to isoniazid and susceptible to rifampin, pyrazinamide, and ethambutol hydrochloride) TB compared with persons with TB susceptible to all first-line anti-TB drugs.

**Results:** The numbers of isoniazid-monoresistant TB cases increased from 303 (4.1%) in 1993 to 351 (4.2%) in 2005. In our multivariate analysis of all TB cases reported from 1993 to 2003, the races/ethnicities of patients with isoniazid-monoresistant TB were significantly more likely to be US-born Asian/Pacific Islander (adjusted odds ratio [aOR], 1.9; 95% confidence interval [CI], 1.4-2.6), foreign-born Asian/

Pacific Islander (1.8; 1.4-2.1), foreign-born black non-Hispanic (1.4; 1.1-1.7), or US-born Hispanic (1.3; 1.1-1.5). Isoniazid monoresistance was also associated with failure to complete therapy within 1 year (aOR, 1.7; 95% CI, 1.5-1.8), a history of TB (1.5; 1.3-1.7), and correctional facility residence (1.5; 1.2-1.7).

**Conclusions:** Isoniazid-monoresistant TB did not decline from January 1, 1993, through December 31, 2005, despite national downward trends observed in overall TB cases and in multidrug-resistant TB cases. Physicians must ensure completion of treatment for patients taking isoniazid as part of their TB or latent TB infection therapy. In addition, physicians should maintain heightened vigilance for isoniazid resistance when evaluating certain at-risk populations for TB and latent TB infection.

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**R**EDUCING THE INCIDENCE OF drug-resistant tuberculosis (TB) has been a consistent priority of TB control in the United States, particularly since multidrug-resistant (MDR) TB (a *Mycobacterium tuberculosis* isolate resistant to at least isoniazid and rifampin) contributed to an increase in TB rates during the 1980s and early 1990s. This national public health effort to reduce MDR TB has included more intensive case management of patients with drug-resistant TB, widespread use of directly observed therapy, and increased education within the medical community.<sup>1</sup> As a result, the percentage of MDR TB cases among persons without a history of TB has declined by 60%, from 2.5% (n=410) of culture-confirmed TB cases in 1993 to 1.0% (n=95) in 2005.<sup>2</sup>

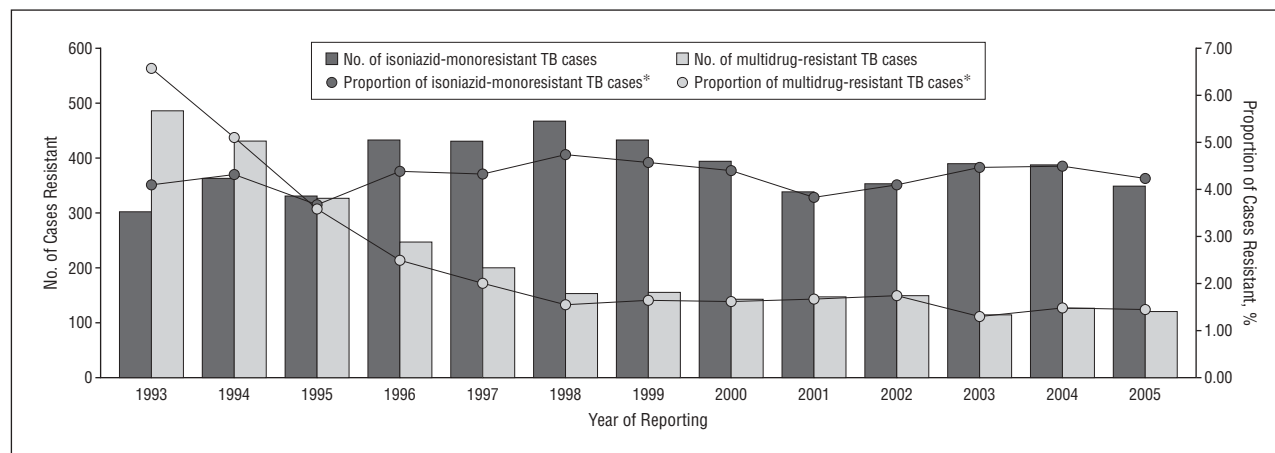
The reduction in MDR TB in the United States suggests success in combating drug resistance, but the percentage of cases with any isoniazid resistance has declined much less during the past 13 years. Primary iso-

niazid resistance dropped only 13% from 1993 to 2005 (from 8.4% of culture-positive cases in 1993 to 7.3% in 2005).<sup>3</sup> Isoniazid is a bactericidal agent used worldwide in first-line treatment regimens for TB disease. In addition, isoniazid monotherapy is the cornerstone of treatment for latent TB infection (LTBI) in the United States.<sup>4,5</sup>

The persistence of isoniazid-resistant TB in the United States, despite downward trends in MDR TB cases, merits further investigation. To maintain the usefulness of this important anti-TB agent, it is necessary to understand the characteristics of patients with isoniazid-monoresistant TB in the United States. This article provides an updated and detailed profile of isoniazid-monoresistance trends from 1993 to 2003 and examines demographic and patient characteristics associated with this type of resistance.

## METHODS

We analyzed data from the National Tuberculosis Surveillance System (NTSS) at the US Cen-



**Figure.** Isoniazid-mono-resistant tuberculosis (TB) and multidrug-resistant TB in the United States, 1993 to 2005. Asterisk indicates among all cases with susceptibility results for isoniazid, rifampin, pyrazinamide, and ethambutol hydrochloride.

ters for Disease Control and Prevention (CDC), which has collected national TB incidence data since 1953.<sup>6</sup> Tuberculosis cases are reported by state health departments to the CDC using the Report of Verified Case of TB (RVCT) standard form. To be included in the national count, a case must satisfy a standardized TB case definition.<sup>2</sup> Our analysis examined data on all TB cases reported from January 1, 1993, through December 31, 2005, during which time drug-susceptibility and risk factor data became available for reported cases. Cases must have been reported from the 50 states or from the District of Columbia, have had culture-positive TB, and have had at least initial drug susceptibility testing (DST) results reported. Drug-susceptible TB cases with MDR TB on final DST results, indicating acquired multidrug resistance during treatment, were excluded. Second DSTs are not uniformly performed for all TB cases. Because this study used routinely collected surveillance data without patient identifiers, institutional review board approval was not required.

We defined an isoniazid-mono-resistant TB case as a culture-confirmed TB case with resistance to isoniazid and with recorded susceptibility to rifampin, pyrazinamide, and ethambutol hydrochloride. In addition, the case could have no recorded resistance to additional anti-TB drugs. Annual numbers and proportions of isoniazid-mono-resistant TB cases were calculated from all TB cases reported from 1993 through 2005. The denominator included all TB cases with susceptibility results for the 4 first-line drugs.

We conducted univariate and multivariate analyses of demographic characteristics, risk factor information, and treatment outcomes associated with isoniazid mono-resistance. The comparison group for odds ratios (ORs), designated as those with drug-susceptible TB, included all TB cases with recorded susceptibility to isoniazid, rifampin, pyrazinamide, and ethambutol and without recorded resistance to additional anti-TB drugs. We limited the univariate and multivariate analyses to those cases reported from 1993 through 2003. This allowed the inclusion of outcome variables such as culture conversion, treatment completion date, reason for stopping treatment, and directly observed therapy information, which can be reported up to 2 years after the initial case reporting date.

We performed univariate analysis using the Cochran Mantel-Haenszel  $\chi^2$  test for ORs. For variables in which interaction was suspected based on literature findings, a Breslow-Day test for homogeneity of ORs was performed. Interaction terms with a significant Breslow-Day value ( $P < .05$ ) were placed in the multivariate model. Any factor significantly associated with isoniazid mono-resistance ( $P < .01$ ) in the univariate analysis was included in the logistic regression model. We performed multivar-

iate analysis using manual backward elimination based on the log likelihood ratio test with 99% confidence. For any variable with more than 10% missing observations, we included a "missing" category in the univariate and multivariate analyses to identify any significant effects of missing values on ORs. All analyses were performed using commercially available statistical software (SAS version 9.1.3; SAS Institute, Inc, Cary, North Carolina).

## RESULTS

The proportion of isoniazid-mono-resistant TB cases increased from 4.1% (303 of 7402) in 1993 to 4.2% (351 of 8262) in 2005, representing a 15.8% increase in the number of isoniazid-mono-resistant TB cases in the United States among all TB cases with reported DST results for the 4 first-line drugs. During those same years, MDR TB cases decreased from 6.6% (486 of 7402) to 1.5% (121 of 8262), representing a 75.1% decrease in the number of MDR TB cases (**Figure**). Therefore, the downward trends seen in the number and proportion of MDR TB cases were not mirrored by a parallel decrease in isoniazid-mono-resistant TB cases in the United States.

From 1993 to 2003, there were 210 940 verified TB cases reported to the NTSS. Of these cases, 41 509 (19.7%) were excluded from this analysis because of the lack of a positive culture, 9425 (4.5%) were excluded because of missing DST results, and 71 601 (33.9%) were excluded because of DST profiles that did not meet case or comparison group criteria; that is, they did not have documented DST results to isoniazid, rifampin, pyrazinamide, and ethambutol treatment. Two hundred nineteen cases (0.1%) found to be MDR TB on the final DST result were also excluded. During this 11-year period, 4247 eligible cases were isoniazid mono-resistant and 83 939 were drug susceptible.

Characteristics of isoniazid-mono-resistant, drug-susceptible, and total eligible TB cases from 1993 to 2003 are given in **Table 1**. The highest proportions of isoniazid-mono-resistant cases (43.0%) and drug-susceptible TB cases (36.9%) occurred in individuals between the ages of 25 and 44 years. Asian/Pacific Islander (Asian/PI) persons represented the highest proportion of isoniazid-mono-resistant cases (33.0%). Black non-Hispanic persons represented the highest proportion of drug-susceptible cases (33.1%). Vari-

**Table 1. Demographic and Clinical Characteristics of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003**

Characteristic	No. (%)		
	Isoniazid-Monoresistant TB (n=4247)	Drug-Susceptible TB (n=83 939)	Total (N=88 186)
Sex			
Female	1520 (35.8)	30 992 (36.9)	<b>32 512</b> (36.9)
Male	2726 (64.2)	52 943 (63.1)	<b>55 669</b> (63.1)
Missing <sup>a</sup>	1 (0.0)	4 (0.0)	<b>5</b> (0.0)
Age, y			
0-4	36 (0.8)	834 (1.0)	<b>870</b> (1.0)
5-14	25 (0.6)	577 (0.7)	<b>602</b> (0.7)
15-24	446 (10.5)	7325 (8.7)	<b>7771</b> (8.8)
25-44	1827 (43.0)	31 005 (36.9)	<b>32 832</b> (37.2)
45-64	1200 (28.3)	23 411 (27.9)	<b>24 611</b> (27.9)
≥65	712 (16.8)	20 763 (24.7)	<b>21 475</b> (24.4)
Missing	1 (0.0)	24 (0.0)	<b>25</b> (0.0)
Race/ethnicity			
White non-Hispanic	693 (16.3)	19 615 (23.4)	<b>20 308</b> (23.0)
Black non-Hispanic	1193 (28.1)	27 777 (33.1)	<b>28 970</b> (32.9)
Hispanic	919 (21.6)	17 141 (20.4)	<b>18 060</b> (20.5)
Asian/Pacific Islander	1403 (33.0)	17 918 (21.3)	<b>19 321</b> (21.9)
Other or unknown <sup>b</sup>	39 (0.9)	1488 (1.8)	<b>1527</b> (1.7)
Country of origin			
US born	1711 (40.3)	45 809 (54.6)	<b>47 520</b> (53.9)
Foreign born	2512 (59.1)	37 740 (45.0)	<b>40 252</b> (45.6)
Missing	24 (0.6)	390 (0.5)	<b>414</b> (0.5)
Time in United States among foreign-born patients, y			
<1	439 (17.5)	6129 (16.2)	<b>6568</b> (16.3)
1-5	614 (24.4)	8557 (22.7)	<b>9171</b> (22.8)
6-14	544 (21.7)	7165 (19.0)	<b>7709</b> (19.2)
≥15	404 (16.1)	7163 (19.0)	<b>7567</b> (18.8)
Missing	511 (20.3)	8726 (23.1)	<b>9237</b> (22.9)
<b>Total</b>	<b>2512</b> (100)	<b>37 740</b> (100)	<b>40 252</b> (100)
History of TB			
No	3868 (91.1)	79 097 (94.2)	<b>82 965</b> (94.1)
Yes	338 (8.0)	4078 (4.9)	<b>4416</b> (5.0)
Missing	41 (1.0)	764 (0.9)	<b>805</b> (0.9)
Human immunodeficiency virus status			
Negative	1347 (31.7)	27 596 (32.9)	<b>28 943</b> (32.8)
Positive <sup>c</sup>	530 (12.5)	10 527 (12.5)	<b>11 057</b> (12.5)
Missing	2370 (55.8)	45 816 (54.6)	<b>48 186</b> (54.6)
Resident of long-term care facility			
No	4024 (94.7)	78 386 (93.4)	<b>82 410</b> (93.5)
Yes	114 (2.7)	2841 (3.4)	<b>2955</b> (3.4)
Missing	109 (2.6)	2712 (3.2)	<b>2821</b> (3.2)
Resident of correctional facility			
No	4011 (94.4)	80 373 (95.8)	<b>84 384</b> (95.7)
Yes	190 (4.5)	2612 (3.1)	<b>2802</b> (3.2)
Missing	46 (1.1)	954 (1.1)	<b>1000</b> (1.1)
Homeless within the past year			
No	3735 (87.9)	72 856 (86.8)	<b>76 591</b> (86.9)
Yes	254 (6.0)	5591 (6.7)	<b>5845</b> (6.6)
Missing	258 (6.1)	5492 (6.5)	<b>5750</b> (6.5)
Noninjecting drug use			
No	3373 (79.4)	66 491 (79.2)	<b>69 864</b> (79.2)
Yes	289 (6.8)	6035 (7.2)	<b>6324</b> (7.2)
Missing	585 (13.8)	11 413 (13.6)	<b>11 998</b> (13.6)
Alcohol use			
No	3129 (73.7)	60 348 (71.9)	<b>63 477</b> (72.0)
Yes	570 (13.4)	12 640 (15.1)	<b>13 210</b> (15.0)
Missing	548 (12.9)	10 951 (13.0)	<b>11 499</b> (13.0)

(continued)

ables with more than 10% missing observations were alcohol use, injecting drug use, noninjecting drug use, culture conversion, time to culture conversion, sputum smear

status, tuberculin skin test status, directly observed therapy, human immunodeficiency virus (HIV) status, and years in the United States among foreign-born persons. These vari-

**Table 1. Demographic and Clinical Characteristics of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003 (cont)**

Characteristic	No. (%)		
	Isoniazid-Monoresistant TB (n=4247)	Drug-Susceptible TB (n=83 939)	Total (N=88 186)
Vital status			
Alive	4169 (98.2)	81 211 (96.8)	85 380 (96.8)
Deceased	75 (1.8)	2678 (3.2)	2753 (3.1)
Missing	3 (0.1)	50 (0.1)	53 (0.1)
Disease site			
Pulmonary	3331 (78.4)	62 141 (74.0)	65 472 (74.2)
Extrapulmonary	634 (14.9)	14 693 (17.5)	15 327 (17.4)
Both	282 (6.6)	7092 (8.4)	7374 (8.4)
Missing	0	13 (0.0)	13 (0.0)
Sputum smear			
Negative	1510 (35.6)	29 421 (35.1)	30 931 (35.1)
Positive	2023 (47.6)	36 673 (43.7)	38 696 (43.9)
Missing	714 (16.8)	17 845 (21.3)	18 559 (21.0)
Tuberculin skin test			
Negative	467 (11.0)	12 115 (14.4)	12 582 (14.3)
Positive	2477 (58.3)	43 973 (52.4)	46 450 (52.7)
Missing	1303 (30.7)	27 851 (33.2)	29 154 (33.1)
Chest radiograph diagnosis			
Normal	479 (11.3)	10 361 (12.3)	10 840 (12.3)
Abnormal	3648 (85.9)	71 130 (84.7)	74 778 (84.8)
Missing	120 (2.8)	2448 (2.9)	2568 (2.9)
Abnormal chest radiographs			
Noncavitary not consistent with TB	118 (3.2)	3035 (4.3)	3153 (4.2)
Noncavitary consistent with TB	2434 (66.7)	49 136 (69.1)	51 570 (69.0)
Cavitary	1039 (28.5)	18 068 (25.4)	19 107 (25.6)
Missing	57 (1.6)	891 (1.3)	948 (1.3)
<b>Total</b>	<b>3648 (100)</b>	<b>71 130 (100)</b>	<b>74 778 (100)</b>
Received initial isoniazid			
No	297 (7.0)	3872 (4.6)	4169 (4.7)
Yes	3937 (92.7)	79 657 (94.9)	83 594 (94.8)
Missing	13 (0.3)	410 (0.5)	423 (0.5)
DOT			
Total DOT	1698 (40.0)	33 846 (40.3)	35 544 (40.3)
Self only	1154 (27.2)	25 565 (30.5)	26 719 (30.3)
Both DOT and self	1206 (28.4)	20 163 (24.0)	21 369 (24.2)
Missing	189 (4.5)	4365 (5.2)	4554 (5.2)
Culture conversion			
Yes	2500 (58.9)	43 360 (51.7)	45 860 (52.0)
No	645 (15.2)	13 835 (16.5)	14 480 (16.4)
Missing	1102 (25.9)	26 744 (31.9)	27 846 (31.6)
Time to conversion, mo			
<2	1356 (31.9)	24 019 (28.6)	25 375 (28.8)
≥2	1129 (26.6)	19 050 (22.7)	20 179 (22.9)
Did not convert	645 (15.2)	13 835 (16.5)	14 480 (16.4)
Missing	1117 (26.3)	27 035 (32.2)	28 152 (31.9)

(continued)

ables had a missing category included in the univariate and multivariate analyses to identify any significant effects of missing data.

Among all cases included in the analysis, 59.1% of isoniazid-monoresistant TB cases occurred in persons born outside of the United States, while 54.6% of drug-susceptible cases occurred in US-born persons (Table 1). Foreign-born patients with isoniazid-monoresistant TB were most commonly from the Philippines (520 cases [20.7%]), Mexico (377 cases [15.0%]), Vietnam (245 cases [9.8%]), Haiti (162 cases [6.4%]), India (152 cases [6.1%]), and China (143 cases [5.7%]).

Results of univariate and multivariate analyses for the demographic characteristics are given in **Table 2**. A test for colinearity of variables was performed using condition indexes and variance decomposition proportion, and no variables were found to be collinear with each other. Demographic characteristics significantly associated with isoniazid monoresistance were age, race/ethnicity, and country of origin. However, results of the Breslow-Day test revealed interaction between race/ethnicity and country of origin. Therefore, they were included as stratified terms in the multivariate analysis. After stratification, patients with isoniazid-monoresistant TB were more likely to be US-born

**Table 1. Demographic and Clinical Characteristics of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003 (cont)**

Characteristic	No. (%)		
	Isoniazid-Monoresistant TB (n= 4247)	Drug-Susceptible TB (n=83 939)	Total (N=88 186)
Completed therapy within 1 y <sup>d</sup>			
Yes	2385 (56.2)	55 082 (65.6)	57 467 (65.2)
No	1379 (32.5)	16 126 (19.2)	17 505 (19.9)
Not eligible	368 (8.7)	9261 (11.0)	9629 (10.9)
Missing	115 (2.7)	3470 (4.1)	3585 (4.1)
Provider type			
Health department	2085 (49.1)	37 014 (44.1)	39 099 (44.3)
Private or other	1051 (24.7)	22 997 (27.4)	24 048 (27.3)
Both	1031 (24.3)	22 056 (26.3)	23 087 (26.2)
Missing	80 (1.9)	1872 (2.2)	1952 (2.2)
Year of reporting			
1993-1998	2333 (54.9)	46 130 (55.0)	48 463 (55.0)
1999-2003	1914 (45.1)	37 809 (45.0)	39 723 (45.0)
Missing	0	0	0

Abbreviation: DOT, directly observed therapy.

<sup>a</sup>For any variable with missing values for more than 10% of the sample, a "missing" category was included in the univariate and multivariate analyses.

<sup>b</sup>Because of small numbers among persons of American Indian and Alaskan Native race/ethnicity, they were grouped with missing and unknown into a single category of "other or unknown."

<sup>c</sup>For California, only human immunodeficiency virus–positive TB cases are reported from 1993 to 2003.

<sup>d</sup>To complete therapy within 1 year, patients must meet standard criteria. Factors that make a patient ineligible for completion of therapy within 1 year include rifampin resistance, meningial TB disease, and miliary TB disease in individuals younger than 6 years.<sup>6</sup>

Asian/PI or US-born Hispanic than US-born white. In addition, they were more likely to be foreign-born Asian/PI or foreign-born black non-Hispanic than foreign-born white.

Patient characteristics found to be significantly associated with isoniazid-monoresistant TB in univariate and multivariate analysis are given in **Table 3**. Isoniazid monoresistance was significantly associated with a history of TB and with residence in a correctional facility. Notably, there was no significant association between isoniazid monoresistance and positive HIV status, although 54.6% of cases had missing or unknown HIV data. Our analysis also showed that injection drug use was negatively associated with isoniazid monoresistance.

**Table 4** lists the associations among isoniazid monoresistance, TB clinical characteristics, and treatment outcomes. Patients with isoniazid-monoresistant TB were significantly more likely to have pulmonary TB disease rather than extrapulmonary involvement only or combined pulmonary and extrapulmonary TB. Regarding treatment differences, patients with isoniazid-monoresistant TB were less likely to have isoniazid included in their initial treatment regimen. These patients had a significantly longer mean duration of therapy (10.0 months) compared with patients with drug-susceptible TB (8.3 months) and were less likely to complete therapy within 1 year if eligible. Duration of therapy was analyzed as a continuous variable, and the adjusted OR was 1.0 (95% confidence interval, 1.0-1.1).

Because of our knowledge that pyrazinamide-susceptibility testing is performed less frequently than susceptibility testing for other first-line drugs, we investigated the effect of removing the requirement for a

pyrazinamide-susceptibility result on the adjusted ORs in the multivariate analysis. There were 141 262 cases (83.4% of all culture-positive cases) used for the model in which no pyrazinamide testing was required, and 83 763 cases (49.4% of all culture-positive cases) were used for the model in which pyrazinamide testing was required. After repeating the analysis without the criteria for pyrazinamide-susceptibility results, we found that there was minimal effect on the direction and significance of the ORs for variables associated with isoniazid resistance.

## COMMENT

In contrast to the national decline in MDR TB cases, there has been little change in the number of isoniazid-monoresistant TB cases during the 13-year period. A recent study<sup>7</sup> estimated that 291 000 to 433 000 persons per year start treatment for LTBI in the United States. If our finding that 4.8% of US cases have isoniazid monoresistance is applied to these data, we estimate that, at a minimum, 13 968 to 20 784 patients are treated with a drug to which their infection is resistant (this estimate does not include cases resistant to isoniazid plus other drugs). Because isoniazid continues to have a prominent role in treatment regimens for TB disease and for LTBI, it is essential to understand what factors may be contributing to isoniazid monoresistance so that physicians can make more informed treatment decisions when evaluating these patients.

Few studies have examined characteristics of isoniazid monoresistance in the United States. An analysis of drug-resistant TB trends during the mid 1990s identified several risk factors associated with

**Table 2. Odds Ratios for Demographic Characteristics of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003<sup>a</sup>**

Characteristic	No. (%)		Odds Ratio (99% Confidence Interval)	
	Isoniazid-Monoresistant TB (n=4247)	Drug-Susceptible TB (n=83 939)	Unadjusted	Adjusted <sup>b</sup>
Sex				
Female	1520 (35.8)	30 992 (36.9)	1 [Reference]	1 [Reference]
Male	2726 (64.2)	52 943 (63.1)	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Age, y				
0-4	36 (0.8)	834 (1.0)	1.3 (0.9-1.8)	1.5 (1.0-2.1)
5-14	25 (0.6)	577 (0.7)	1.3 (0.8-1.9)	1.2 (0.8-1.8)
15-24	446 (10.5)	7325 (8.7)	1.8 (1.6-2.0)	1.5 (1.3-1.7)
25-44	1827 (43.0)	31 005 (36.9)	1.7 (1.6-1.9)	1.5 (1.4-1.7)
45-64	1200 (28.3)	23 411 (27.9)	1.5 (1.4-1.6)	1.4 (1.3-1.5)
≥65	712 (16.8)	20 763 (24.7)	1 [Reference]	1 [Reference]
Race/ethnicity				
White non-Hispanic	693 (16.3)	19 615 (23.4)	1 [Reference]	...
Black non-Hispanic	1193 (28.1)	27 777 (33.1)	1.2 (1.1-1.3)	...
Hispanic	919 (21.6)	17 141 (20.4)	1.5 (1.4-1.7)	...
Asian/Pacific Islander	1403 (33.0)	17 918 (21.3)	2.2 (2.0-2.4)	...
Other or unknown <sup>c</sup>	39 (0.9)	1488 (1.8)	0.7 (0.5-1.0)	...
Country of origin				
US born	1711 (40.3)	45 809 (54.6)	1 [Reference]	...
Foreign born	2512 (59.1)	37 740 (45.0)	1.8 (1.7-1.9)	...
Time in United States among foreign-born patients, y				
<1	439 (17.5)	6129 (16.2)	1 [Reference]	NA
1-5	614 (24.4)	8557 (22.7)	1.0 (0.9-1.1)	NA
6-14	544 (21.7)	7165 (19.0)	0.9 (0.8-1.1)	NA
≥15	404 (16.1)	7163 (19.0)	0.8 (0.7-0.9)	NA
Missing	511 (20.3)	8726 (23.1)	0.8 (0.7-0.9)	NA
<b>Total</b>	<b>2512 (100.0)</b>	<b>37 740 (100.0)</b>	...	...
Origin stratified by race/ethnicity				
White non-Hispanic				
US born	571 (13.4)	16 666 (19.9)	1 [Reference]	1 [Reference]
Foreign born	120 (2.8)	2871 (3.4)	1 [Reference]	1 [Reference]
Black non-Hispanic				
US born	847 (19.9)	22 534 (26.8)	1.1 (1.0-1.2)	1.0 (0.9-1.1)
Foreign born	342 (8.1)	5170 (6.2)	1.6 (1.3-2.0)	1.4 (1.1-1.7)
Hispanic				
US born	212 (5.0)	4427 (5.3)	1.4 (1.2-1.6)	1.3 (1.1-1.5)
Foreign born	699 (16.5)	12 575 (15.0)	1.3 (1.1-1.6)	1.1 (0.9-1.4)
Asian/Pacific Islander				
US born	47 (1.1)	810 (1.0)	1.7 (1.2-2.3)	1.9 (1.4-2.6)
Foreign born	1348 (31.7)	17 042 (20.3)	1.9 (1.6-2.3)	1.8 (1.4-2.1)
Other or unknown <sup>b</sup>				
US born	34 (0.8)	1372 (1.6)	0.7 (0.5-1.0)	0.7 (0.5-1.1)
Foreign born	3 (0.1)	82 (0.1)	0.9 (0.3-2.8)	0.9 (0.3-3.1)
Injecting drug use				
No	3615 (85.1)	70 671 (84.2)	<b>74 286 (84.2)</b>	
Yes	83 (2.0)	2554 (3.0)	<b>2637 (3.0)</b>	
Missing	549 (12.9)	10 714 (12.8)	<b>11 263 (12.8)</b>	

Abbreviations: NA, variable was not included in regression modeling; ellipsis, variable was stratified in the final model.

<sup>a</sup>The variables in Tables 2, 3, and 4 were included in a single logistic regression model. Individual totals may not add up to column totals because missing totals for those variables with less than 10% missing observations were not included in univariate and multivariate analyses. Odds ratios are not reported for nonstratified variables.

<sup>b</sup>The Hosmer-Lemeshow goodness-of-fit test was used to assess the final model.

<sup>c</sup>Because of small numbers among persons of American Indian and Alaskan Native race/ethnicity, they were grouped with missing and unknown into the single category of "other or unknown."

isoniazid-resistant TB, including foreign birth, a history of TB, Asian/PI race/ethnicity, and age younger than 65 years.<sup>8</sup> A study<sup>9</sup> conducted among patients with isoniazid-resistant TB in Germany also identified younger age and a history of TB treatment as risk factors for isoniazid resistance. The present analysis

examines a broader scope of isoniazid monoresistance by using national surveillance data during an extended period and by including more detailed clinical and treatment information.

Of particular note in our analysis are the differences among racial/ethnic groups when stratified by country

**Table 3. Odds Ratios for Characteristics of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003**

Characteristic	No. (%)		Odds Ratio (99% Confidence Interval)	
	Isoniazid-Monoresistant TB (n=4247)	Drug-Susceptible TB (n=83 939)	Unadjusted	Adjusted <sup>a</sup>
History of TB				
No	3868 (91.1)	79 097 (94.2)	1 [Reference]	1 [Reference]
Yes	338 (8.0)	4078 (4.9)	1.7 (1.5-1.9)	1.5 (1.3-1.7)
Human immunodeficiency virus status				
Negative	1347 (31.7)	27 596 (32.9)	1 [Reference]	...
Positive <sup>b</sup>	530 (12.5)	10 527 (12.5)	1.0 (0.9-1.1)	...
Missing	2370 (55.8)	45 816 (54.6)	1.1 (1.0-1.1)	...
Resident of long-term care facility				
No	4024 (94.7)	78 386 (93.4)	1 [Reference]	1 [Reference]
Yes	114 (2.7)	2841 (3.4)	0.8 (0.6-0.9)	1.1 (0.9-1.4)
Resident of correctional facility				
No	4011 (94.4)	80 373 (95.8)	1 [Reference]	1 [Reference]
Yes	190 (4.5)	2612 (3.1)	1.5 (1.3-1.7)	1.5 (1.2-1.7)
Homeless within the past year				
No	3735 (87.9)	72 856 (86.8)	1 [Reference]	...
Yes	254 (6.0)	5591 (6.7)	0.9 (0.8-1.0)	...
Injecting drug use				
No	3615 (85.1)	70 671 (84.2)	1 [Reference]	1 [Reference]
Yes	83 (2.0)	2554 (3.0)	0.6 (0.5-0.8)	0.6 (0.5-0.8)
Missing	549 (12.9)	10 714 (12.8)	1.0 (0.9-1.1)	0.9 (0.8-1.0)
Noninjecting drug use				
No	3373 (79.4)	66 491 (79.2)	1 [Reference]	...
Yes	289 (6.8)	6035 (7.2)	0.9 (0.8-1.1)	...
Missing	585 (13.8)	11 413 (13.6)	1.0 (0.9-1.1)	...
Alcohol use				
No	3129 (73.7)	60 348 (71.9)	1 [Reference]	...
Yes	570 (13.4)	12 640 (15.1)	0.9 (0.8-1.0)	...
Missing	548 (12.9)	10 951 (13.0)	1.0 (0.9-1.1)	...

Abbreviation: Ellipsis, factor was dropped during regression modeling.

<sup>a</sup>The Hosmer-Lemeshow goodness-of-fit test was used to assess the final model.

<sup>b</sup>For California, only human immunodeficiency virus-positive TB cases are reported from 1993 to 2003.

of origin. Two US-born racial/ethnic groups had an increased likelihood of isoniazid monoresistance, Asian/Pis and Hispanics, while 2 foreign-born groups, black non-Hispanics and Asian/Pis, were more likely to have isoniazid-monoresistant TB than their US-born counterparts. This finding suggests that US-born persons are not uniformly more likely to have isoniazid-monoresistant TB, despite the widespread use of isoniazid in the United States for decades. It is unclear whether increased isoniazid monoresistance among some foreign-born populations is a result of suboptimal therapy for TB disease, misdiagnosed LTBI in a patient with TB disease, or a higher prevalence of isoniazid-monoresistant strains among countries outside the United States. The increased likelihood among US-born Asian/Pis and Hispanics may be the result of increased family or social contact with foreign-born persons of similar race/ethnicity.

As expected, a history of TB was associated with isoniazid monoresistance, presumably because patients were exposed to isoniazid during their previous TB episode. This suggests the need for more detailed examination of persons who have undergone prior treatment for TB. Because the RVCT lacks patient-specific details regarding a previous episode of TB, a follow-up study to examine specific characteristics of previous TB treatment associ-

ated with isoniazid monoresistance could further explain this relationship.

The lack of association between isoniazid monoresistance and HIV status is a departure from previous findings<sup>8</sup> but is not entirely surprising. Although rifampin resistance may result from inadequate TB treatment due to drug interactions between certain antiretroviral drugs and rifampin, the same mechanism of interaction does not occur with isoniazid.<sup>4</sup> Nevertheless, the large amount of missing data regarding HIV status in our study might be clouding a true association between isoniazid-monoresistant TB and HIV status.

The increased likelihood of residence in a correctional facility among patients with isoniazid-monoresistant TB is a valuable finding and could enhance TB control measures within certain correctional institutions, particularly in those regions that have identified an increased proportion of isoniazid-monoresistant cases. In 2006, the CDC issued updated recommendations for the control of TB in correctional facilities.<sup>10</sup> This document includes guidelines regarding proper laboratory practice within correctional facilities and stresses the importance of performing DSTs on all initial isolates. While DST panels should be performed for all patients with TB in the United States, it

**Table 4. Odds Ratios for Clinical Characteristics and Treatment Outcomes of Patients With Isoniazid-Monoresistant Tuberculosis (TB) and Drug-Susceptible TB, United States, 1993 to 2003**

Characteristic	No. (%)		Odds Ratio (99% Confidence Interval)	
	Isoniazid-Monoresistant TB (n=4247)	Drug-Susceptible TB (n=83 939)	Unadjusted	Adjusted <sup>a</sup>
Vital status				
Alive	4169 (98.2)	81 211 (96.8)	1 [Reference]	...
Deceased	75 (1.8)	2678 (3.2)	1.8 (1.5-2.3)	...
Disease site				
Pulmonary	3331 (78.4)	62 141 (74.0)	1 [Reference]	1 [Reference]
Extrapulmonary	634 (14.9)	14 693 (17.5)	0.8 (0.7-0.9)	0.8 (0.7-0.9)
Both	282 (6.6)	7092 (8.4)	0.7 (0.7-0.8)	0.7 (0.6-0.7)
Sputum smear				
Negative	1510 (35.6)	29 421 (35.1)	1 [Reference]	...
Positive	2023 (47.6)	36 673 (43.7)	1.1 (1.0-1.2)	...
Missing	714 (16.8)	17 845 (21.3)	0.8 (0.7-0.9)	...
Tuberculin skin test				
Negative	467 (11.0)	12 115 (14.4)	1 [Reference]	1 [Reference]
Positive	2477 (58.3)	43 973 (52.4)	1.5 (1.3-1.6)	1.2 (1.1-1.4)
Missing	1303 (30.7)	27 851 (33.2)	1.2 (1.1-1.4)	1.1 (1.0-1.3)
Chest radiograph diagnosis				
Normal	479 (11.3)	10 361 (12.3)	1 [Reference]	...
Abnormal	3648 (85.9)	71 130 (84.7)	1.1 (1.0-1.2)	...
Noncavitary not consistent with TB	118 (3.3)	3035 (4.3)	1 [Reference]	NA
Noncavitary consistent with TB	2434 (67.8)	49 136 (70.0)	1.3 (1.1-1.5)	NA
Cavitary	1039 (28.9)	18 068 (25.7)	1.5 (1.2-1.8)	NA
Received initial isoniazid				
No	297 (7.0)	3872 (4.6)	1 [Reference]	1 [Reference]
Yes	3937 (92.7)	79 657 (94.9)	0.6 (0.6-0.7)	0.2 (0.2-0.3)
DOT				
Total DOT	1698 (40.0)	33 846 (40.3)	1 [Reference]	...
Self only	1154 (27.2)	25 565 (30.5)	0.9 (0.8-1.0)	...
Both DOT and self	1206 (28.4)	20 163 (24.0)	1.2 (1.1-1.3)	...
Missing	189 (4.5)	4365 (5.2)	0.9 (0.7-1.0)	...
Culture conversion				
Yes	2500 (58.9)	43 360 (51.7)	1 [Reference]	1 [Reference]
No	645 (15.2)	13 835 (16.5)	0.8 (0.7-0.9)	0.9 (0.8-1.0)
Missing	1102 (25.9)	26 744 (31.9)	0.7 (0.7-0.8)	0.8 (0.7-0.9)
Time to conversion, mo				
<2	1356 (31.9)	24 019 (28.6)	1 [Reference]	NA
≥2	1129 (26.6)	19 050 (22.7)	1.0 (1.0-1.1)	NA
Did not convert	645 (15.2)	13 835 (16.5)	0.8 (0.8-0.9)	NA
Missing	1117 (26.3)	27 035 (32.2)	0.7 (0.7-0.8)	NA
Completed therapy within 1 y <sup>b</sup>				
Yes	2385 (56.2)	55 082 (65.6)	1 [Reference]	1 [Reference]
No	1379 (32.5)	16 126 (19.2)	2.0 (1.8-2.1)	1.7 (1.5-1.8)
Not eligible	368 (8.7)	9261 (11.0)	0.9 (0.8-1.0)	1.6 (1.4-1.8)
Provider type				
Health department	2085 (49.1)	37 014 (44.1)	1 [Reference]	1 [Reference]
Private or other	1051 (24.7)	22 997 (27.4)	0.8 (0.8-0.9)	0.9 (0.8-1.0)
Both	1031 (24.3)	22 056 (26.3)	0.8 (0.8-0.9)	0.9 (0.8-0.9)
Years of reporting				
1993-1998	2333 (54.9)	46 130 (55.0)	1 [Reference]	...
1999-2003	1914 (45.1)	37 809 (45.0)	1.0 (0.9-1.1)	...

Abbreviations: DOT, directly observed therapy; NA, factor was not included in regression modeling; ellipsis, factor was dropped during regression modeling.

<sup>a</sup>The Hosmer-Lemeshow goodness-of-fit test was used to assess the final model.

<sup>b</sup>To complete therapy within 1 year, patients must meet standard criteria. Factors that make a patient ineligible for completion of therapy within 1 year include rifampin resistance, meningial TB disease, and miliary TB disease in individuals younger than 16 years.<sup>6</sup>

may be particularly important to emphasize this practice within correctional facilities.

Isoniazid-monoresistant TB cases demonstrated a longer mean treatment duration and a decreased likelihood of completion of therapy within 1 year. These findings not only may reflect a delayed response to treat-

ment among this patient population but also may indicate that some physicians deliberately extend treatment for their patients with isoniazid-monoresistant TB. This treatment practice is supported by a previous retrospective cohort study<sup>11</sup> of patients with isoniazid-monoresistant TB that demonstrated an association between shorter treat-

ment duration and greater likelihood of relapse, suggesting the benefit of an extended duration of therapy within this population. In addition, a recommended regimen for isoniazid-monoresistant TB is 12 months of rifampin and ethambutol, which may make a patient unlikely to complete therapy within 1 year.<sup>4</sup>

We included a large number of variables in the univariate and multivariate analyses in an attempt to create a preliminary profile of patients with isoniazid-monoresistant TB and to generate new hypotheses for more defined studies. However, this broad approach may have produced some associations that, although statistically significant, are neither clinically important nor biologically plausible. An example is the modest association between isoniazid monoresistance and a positive TST result, for which there is no clear clinical explanation. To reduce the number of spurious associations, we used a more rigorous cutoff of  $P < .01$  in univariate and multivariate analyses.

The incomplete drug-susceptibility data on almost 40% of all TB cases poses limitations on our analysis of isoniazid-monoresistance trends in the United States. However, the minimal effect on the ORs of removing the pyrazinamide-susceptibility criteria and the lack of significance of the year of reporting suggest that the missing susceptibility data do not strongly affect our conclusions. The high percentage of missing values for several other RVCT variables, particularly HIV status, also limits interpretation of the results. In addition, NTSS data exclude prior DST patterns for patients with TB having a history of TB, so we are unable to comment on the specific types of resistance (ie, primary vs acquired) among patients with isoniazid-monoresistant TB.

Information collected on the RVCT provides only a snapshot of each patient, so valuable information such as previous treatment regimens or TB genotype characteristics is not captured. In addition to a detailed examination of a cohort of patients with isoniazid-monoresistant TB, pairing National Tuberculosis Genotyping Service data with drug-resistance results from the NTSS might provide an opportunity to explore the molecular epidemiological findings of isoniazid monoresistance and to begin to estimate the incidence of advancement to MDR TB among patients with isoniazid-monoresistant TB. Furthermore, an examination of treatment practices for patients with isoniazid-monoresistant TB among different TB control programs might identify the most effective management of these patients and estimate the frequency of acquired multidrug resistance among patients with isoniazid-monoresistant TB.

As cited in *Ending Neglect*,<sup>12</sup> the study by the Institute of Medicine on strategies for elimination of TB in the United States, TB treatment should occur in the context of patient-centered programs that are based on individual patient characteristics. With better characterization of patients with isoniazid-monoresistant TB and with heightened physician vigilance for isoniazid monoresistance in their communities, we can apply the successful principles of MDR TB reduction to this popula-

tion. Focused efforts to prevent the development and transmission of all types of drug-resistant TB are essential to continued progress toward TB elimination.

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