Drug Resistance Among Tuberculosis Patients, New York City, 1991 and 1992

CYNTHIA R. DRIVER, RN, MPH
THOMAS R. FRIEDEN, MD, MPH
ALAN B. BLOCH, MD, MPH
IDA M. ONORATO, MD

All the authors are with the Division of Tuberculosis Elimination, National Center for Prevention Services, Centers for Disease Control and Prevention (CDC). Ms. Driver is an Epidemic Intelligence Service Officer in the Surveillance and Epidemiologic Investigations Branch, and Dr. Onorato is Chief of the Branch. Dr. Frieden is Medical Officer in the Program Services Branch and Director of the Bureau of Tuberculosis Control, New York City Department of Health. Dr. Bloch is a Medical Epidemiologist, Program Services Branch.

Mr. Ken Dansbury, Computer and Statistical Service Activity, Division of Tuberculosis Elimination, CDC, and Mr. Michael Williams and Ms. Yelena Schuster, Bureau of Tuberculosis Control, New York City Department of Health, assisted in computer programming and data collection.

Tearsheet requests to Cynthia R. Driver, RN, MPH, Centers for Disease Control and Prevention, National Center for Prevention Services, Division of Tuberculosis Elimination, Surveillance and Epidemiologic Investigations Branch, 1600 Clifton Road, NE, Mailstop E-10, Atlanta, GA 30333, telephone 404-639-8117.

Synopsis

The authors assessed drug susceptibility patterns among tuberculosis patients reported to the New York City Department of Health in the first quarters of 1991 and 1992. Resistance to one or more drugs was seen in 26 percent (137 ÷ 520) in 1991 and 24 percent (122 ÷ 517) in 1992. Resistance to isoniazid was seen in 22 percent and 19 percent of patients in 1991 and 1992, respectively; resistance to rifampin in 15 percent and 14 percent; and to both isoniazid and rifampin in 15 percent and 14 percent.

Combined resistance to four first line drugs (isoniazid, rifampin, streptomycin, and ethambutol) was seen in 6 percent (1991) and 8 percent (1992). Patients with organisms resistant to both isoniazid and rifampin were as likely among U.S. born as among foreign born, and younger patients were more likely than older patients to have isoniazid and rifampin resistant organisms. These findings underscore the importance of obtaining susceptibility testing in all patients who have cultures positive for Mycobacterium tuberculosis.

SINCE 1990, the Centers for Disease Control and Prevention (CDC) and the New York City Department of Health (NYC DOH) have investigated nosocomial outbreaks of multidrug resistant tuberculosis (TB) in six hospitals in NYC, involving more than 230 patients (*1–4* and unpublished data, NYC DOH). In these isolates, 94 percent had resistance to both isoniazid (INH) and rifampin (RIF), and 46 percent of isolates were resistant to six or more anti-TB medications (unpublished data, CDC). A survey of all New York City patients with positive mycobacterial cultures in April 1991 showed that 30 percent of patients with prior anti-TB therapy and 7 percent of patients without prior treatment had resistance to both INH and RIF (*5*).

Although rates of drug-resistant TB have generally been low in the past in the nation as a whole, several areas have had increased rates. For 1975 to 1982, a nationwide study of 20 city and State laboratories found overall resistance to one or more anti-TB drugs in 6.9 percent of never treated (primary) cases. However, the border region of south Texas had a rate of 11.3 percent (*6*). In a 1976 study of all hospitalized TB patients in a large southern California hospital 35.5 percent had resistance to one or more drugs, and 19.6 percent had resistance to two or more drugs (*7*).

In this paper, we report the results of surveys of drug resistance among reported TB cases in the first quarters of 1991 and 1992 in New York City and describe the characteristics of patients with isolates resistant to INH and RIF.

Since 1985, the CDC has received individual case reports without personal identifiers on all TB cases reported in the United States. The variables collected include demographic factors such as sex, age, race, ethnicity, and country of origin, as well as clinical factors such as whether the disease is recurrent versus new and the disease site. However, until January 1993, drug susceptibility test results were not collected as part of routine national surveillance.

Nationwide surveys were conducted to assess drug resistance in TB cases reported to CDC in the first quarters of 1991 and 1992. In New York City in 1992, more than 90 percent of TB cases were culture

confirmed. Reporting of results of drug susceptibility became mandatory in New York City in mid-1991.

Methods

We analyzed susceptibility results for culture-positive TB cases reported to the NYC DOH during these periods. Susceptibility results were collected for the initial isolate of each culture-positive patient. Susceptibility results not available in health department records were obtained through searches of records of 51 hospitals and 5 private laboratories.

Susceptibility testing methods varied by laboratory. Organisms were considered resistant to a given drug by the proportion method if the number of organisms on the drug-containing plates was 1 percent or more of the growth observed on the control plates. Using the radiometric method, drug resistance was defined as equivalent or greater growth in the drug containing vial as compared with the control vial. For each drug, a given isolate was categorized as resistant, susceptible, not tested, or test results unknown.

Univariate analyses of the study variables and drug-susceptibility results were performed for each year and for both years combined. The proportion of isolates susceptible to a specific drug was calculated for only those isolates that were tested for that drug. Since adequate therapy requires susceptibility to at least two drugs, we calculated resistance to the first line drugs separately and in combinations.

We estimated the annual number of drug-resistant cases for 1992 based on the proportion of 1992 cases reported in the first quarter. Proportions were compared with the chi-square statistic, relative risk, and 95 percent confidence intervals using Epi info version 5 (*8*).

Results

A total of 637 culture-positive TB cases were reported to the NYC DOH in the first quarter of 1991, and 588 in the first quarter of 1992. In all cases the organisms identified were *Mycobacterium tuberculosis*. Susceptibility testing against one or more drugs was documented on 82 percent (520 ÷ 637) of culture-positive cases in 1991 and 88 percent (517 ÷ 588) in 1992. Among cases in which susceptibility results were documented, in 1991 23 percent were reported to the health department and 77 percent were identified by laboratory record search. In 1992, however, 82 percent were reported to the health department and 18 percent were found by laboratory search.

In this study, 71 percent (735 ÷ 1,038) had results available for testing against four first line drugs of INH, RIF, streptomycin (SM), and ethambutol (EMB); 275 of these (37 percent) were also tested against pyrazinamide (PZA). When comparing patients for whom drug susceptibility testing of isolates was done with those for whom it was not done, we did not detect a statistically significant difference between groups with regard to sex, age group, race or ethnicity, or country of origin.

'Combined resistance to four first-line anti-TB medications (INH, RIF, SM, and EMB) was seen in 6 percent of patients in 1991 and 8 percent in 1992.'

In previous studies, prior treatment with anti-TB drugs has consistently been a major risk factor for the development of drug resistant organisms. The TB surveillance system does not consistently collect data on history of treatment; however, it does specify whether the case is new or recurrent. We initially stratified the data by new versus recurrent to see if this variable could be used as a proxy for prior treatment. In 1991, persons reported as having had TB previously were more likely to have organisms resistant to one or more drugs than those without a reported history of TB, 57 percent (12 ÷ 21) versus 24 percent (125 ÷ 500), respectively. However, this difference was not found in 1992; the proportions were 21 percent (4 ÷ 19) versus 24 percent (108 ÷ 498), respectively. Because reported history of TB did not appear to be a reliable proxy for prior treatment with anti-TB drugs, further analysis was not stratified by this variable.

The proportion of patients with organisms resistant to one or more anti-TB drugs was 26 percent (137 ÷ 520) in the first quarter of 1991 and 24 percent (122 ÷ 517) in the first quarter of 1992. Resistance to INH was most common, followed by resistance to RIF (table 1). Resistance to INH was 22 percent in 1991 and 19 percent in 1992. Similarly, resistance to RIF was 15 percent and 14 percent, respectively. Resistance to both INH and RIF was 15 percent and 14 percent, respectively. Combined resistance to four first-line anti-TB medications (INH, RIF, SM, and EMB) was seen in 6 percent of patients in 1991 and 8 percent in 1992.

For patients tested for both INH and RIF susceptibility, we compared patients with combined INH and RIF resistance to those who had both INH-

Table 1. Cases of drug-resistant tuberculosis (TB) among those with a history and those who had no history of anti-TB treatment, New York City, first quarters of 1991 and 1992

Drug	1991			1992		
	Results available	Drug resistant		Results available	Drug resistant	
		Number	Percent		Number	Percent
First line anti-tuberculosis drug:						
Isoniazid (INH)	515	115	22	515	98	19
Rifampin (RIF)	509	75	15	511	72	14
Streptomycin (SM)	495	48	10	473	59	12
Pyrazinamide (PZA)	159	20	13	116	8	7
Ethambutol (EMB)	464	28	6	468	47	10
INH and RIF	446	70	15	474	64	14
INH, RIF, SM, and EMB	372	22	6	363	29	8
Second line anti-tuberculosis drugs:						
Ethionamide	152	11	7	195	27	14
Capreomycin	38	4	11	28	2	7
Cycloserine	45	4	9	27	0	. . .
Kanamycin	49	3	6	9	0	. . .
Amikacin	33	1	3	0	0	. . .
Para-aminosalicylic acid	35	0	. . .	52	0	. . .
Rifabutin	1	0	. . .	0	0	. . .
Ciprofloxacin	32	0	. . .	3	0	. . .
Ofloxacin	2	0	. . .	0	0	. . .
Other	5	0	. . .	0	0	. . .

Table 2. Relative risk of combined resistance to isoniazid and rifampin of persons with tuberculosis in New York City, by sex, race-ethnicity, country of origin, first quarters of 1991 and 1992, combined

Category	Results available	Drug resistant		Relative risk	95 percent confidence interval
		Number	Percent		
Sex:					
Male	651	99	15.2	1.26	0.88–1.80
Female	289	35	12.1	[1] 1.00	. . .
Age group: [2]					
0–14 years	11	2	18.2	2.55	0.58–11.09
15–24 years	59	8	13.6	1.90	0.70–05.18
25–44 years	574	93	16.2	2.27	1.03–5.01
45–64 years	211	25	11.9	1.66	0.71–03.90
65 years or older	84	6	7.1	[1] 1.00	. . .
Race-ethnicity:					
Asian-Pacific Islanders	56	11	19.6	1.32	0.65–02.68
Hispanic	227	38	16.7	1.13	0.65–01.95
Non-Hispanic black	555	70	12.6	0.85	0.51–01.42
American Indian-Alaskan Native	1	0	0.0	0.00	. . .
Non-Hispanic white	101	15	14.9	[1] 1.00	. . .
Country of origin:					
Foreign born	184	27	14.7	1.04	0.70–01.53
U.S. born	756	107	14.2	[1] 1.00	. . .

[1] Reference group.
[2] 1 case with unknown age excluded from analysis. Chi-square for linear trend showed a significant inverse association between increasing age and resistance to isoniazid and rifampin (P=0.03).

and RIF-susceptible TB. Since we did not find differences in demographic characteristics of persons with drug-resistant TB, such as sex and race or ethnicity or in rates of resistance according to year, the data for 1991 and 1992 were pooled for these analyses. Analysis showed no association by sex, race-ethnicity, or country of origin (table 2). When compared with the 65 or older group, only the 25 to 44 year age group showed a significant association with INH–RIF resistance. Chi-square for linear trend found a significant inverse association between increasing age and resistance to INH–RIF ($P = 0.03$).

When examined by zip code of residence, TB cases were reported from 80 percent (143 ÷ 179) of the zip codes in New York City. Four was the median number of TB cases reported per zip code (range 1–28). INH- and RIF-resistant cases were reported in 39 percent (69 ÷ 179) of zip codes.

Discussion

Drug-resistant TB has become common in New York City. Of greatest concern, 20.7 percent of TB patients had resistance to at least INH, and 14.4 percent had resistance to at least RIF, the two most effective drugs presently available for the treatment of TB. Current recommendations for initial treatment of new TB cases, pending availability of drug susceptibility results, consist of a regimen of four first-line anti-TB agents including INH, RIF, and PZA, with EMB or SM as the fourth drug (*9*). When drug susceptibility results become available, the regimen can be adjusted acccordingly. Among patients with susceptible isolates or those with tubercle bacilli resistant to INH or SM alone, short course regimens containing these drugs have been shown to be 94 to 97 percent effective among compliant patients. However, among patients with tubercle bacilli resistant to RIF, the four-drug regimen previously described is not effective when given for only 6 months (*9*). In addition, INH, the recommended drug for preventive treatment of infected contacts, may not be adequate for infected contacts of 20 percent of cases in New York City. Alternate regimens may be required in cases in which the index patient is known to have a drug-resistant isolate (*10*).

Among all TB cases, the proportion of patients with organisms resistant to one or more anti-TB drugs was not statistically different between years. Based on the proportion of 1992 cases reported in the first quarter, it is possible to estimate the magnitude of drug-resistant disease on an annualized basis. The 588 cultures-positive cases reported in the first quarter represented 15.7 percent of the 3,745 culture-positive cases for the entire year (unpublished data, CDC). In this survey, in New York City, 122 were cases resistant to one or more drugs, including 64 resistant to INH and RIF. It is estimated for all of 1992, there may have been as many as 777 cases resistant to one or more drugs and 407 cases resistant to INH and RIF. This may be a conservative estimate since only 88 percent (517 ÷ 588) of culture-positive cases reported had drug susceptibility results.

'Drug resistance has been associated with younger age groups. Older persons are less likely to have disease caused by drug-resistant organisms if they were infected before use of anti-TB drugs became widespread and now have reactivation disease.'

The level of drug resistance identified in this study is somewhat lower than the resistance level found in the April 1991 survey of patients with positive mycobacterial cultures in New York City (*5*). This difference is most likely due to methodological differences in the two studies. The April 1991 study was based on incident and prevalent TB patients with positive mycobacterial cultures, while our study was based on incident TB cases with positive mycobacterial cultures.

Traditionally, analyses of drug resistance have looked at patients with a history of TB treatment separately from those without any treatment in an attempt to separate initial from acquired resistance since risk factors for the two groups are likely to be different (*5,11*). Since the TB case report data analyzed in this study did not include consistent information about history of anti-TB therapy, we could not evaluate risk factors for these groups separately. Further, previous history of TB did not appear to be a reliable proxy for prior treatment with anti-TB drugs.

Primary drug resistance has been associated with younger age groups (*6,12,13*). Older persons are less likely to have disease caused by drug-resistant organisms if they were infected before use of anti-TB drugs became widespread and now have reactivation disease. In our study, when compared with the 65 and older age group, only the 25 to 44 year age group showed a significant association with INH–RIF resistance. This was the age group of most persons with multidrug-resistant TB in the New York City outbreaks (*1,3*). And, chi-square for linear trend

showed that younger patients were more likely than older patients to have INH–RIF-resistant organisms. Disease in younger persons is suggestive of recent transmission of TB, rather than reactivation disease.

Prior studies reporting increased rates of drug resistance among foreign-born persons indicated that resistance was most common to INH and in combinations including SM and PAS, reflecting the prescription practices in those countries (*13–15*). Rifampin, a relatively expensive drug, has not been used widely in other countries. The data in our study suggest, however, that combined INH–RIF drug resistance in New York City is as likely to be found among persons born in the United States as among foreign-born persons. One possible explanation for this lack of association with the foreign-born is that recent transmission of INH–RIF resistance has primarily involved patients born in the United States (*1,3*).

Our data are limited by the following factors:

1. The susceptibility studies were conducted in different laboratories; factors that affect the comparability of susceptibility results such as type of media and test used have not been considered.
2. Not all cases had susceptibility testing reported although the proportion is very high.

The findings of our study underscore the importance of susceptibility testing in all TB cases and of reporting susceptibility results to the health department. Drug susceptibility results should be collected routinely as part of ongoing TB surveillance. Because the case report data collected in the current surveillance system did not include consistent information on previous treatment of TB, evaluation of risk factors for drug resistance will require more detailed epidemiologic studies. Aggressive TB control measures including intensified efforts to increase case completion, isolation until patients are no longer infectious, and directly observed therapy to ensure adherence, are required to contain drug resistance (*10*).

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