A Multi-institutional Outbreak of Highly Drug-Resistant Tuberculosis

Epidemiology and Clinical Outcomes

Thomas R. Frieden, MD, MPH; Lisa Fine Sherman, MPH; Khin Lay Maw, MBBS, MPH; Paula I. Fujiwara, MD, MPH; Jack T. Crawford, PhD; Beth Nivin, MPH; Victoria Sharp, MD; Dial Hewlett, Jr, MD; Karen Brudney, MD; David Alland, MD; Barry N. Kreiswirth, PhD

Objective.—To investigate a multi-institutional outbreak of highly resistant tuberculosis and evaluate patient outcome.

Design.—Epidemiologic investigation of every tuberculosis case reported in New York City.

Setting.—Patients cared for at all public and nonpublic institutions from January 1, 1990, to August 1, 1993 (43 months).

Patients.—We reviewed medical and public health records and conducted clinical, epidemiologic, drug susceptibility, and restriction fragment length polymorphism (RFLP) analyses. A case was defined as tuberculosis in a patient with an isolate resistant to isoniazid, rifampin, ethambutol hydrochloride, and streptomycin (and rifabutin, if sensitivity testing included it), and, if RFLP testing was done, a pattern identical to or closely related to strain W.

Main Outcome Measures.—Patient survival and the conversion of sputum cultures from positive to negative.

Results.—Of the 357 patients who met the case definition, 267 had identical or nearly identical RFLP patterns; isolates from the other 90 patients were not available for RFLP testing. Among these 267 patients, 86% were human immunodeficiency virus (HIV)–infected, 7% were HIV-negative, and 7% had unknown HIV status. All-cause mortality was 83%. Epidemiologic linkages were identified for 70% of patients, of whom 96% likely had nosocomially acquired disease at 11 hospitals. Survival was prolonged among patients who recieved medications to which their isolate was susceptible, especially capreomycin sulfate, and among patients with a $CD4^+$ T-lymphocyte count greater than 0.200×10^9/L (200/μL). Treatment with isoniazid and a fluoroquinolone antibiotic was also independently associated with longer survival.

Conclusions.—This outbreak accounted for nearly one fourth of the cases of multidrug-resistant tuberculosis in the United States during a 43-month period. Most patients had nosocomially acquired disease, were infected with HIV, and unless promptly and appropriately treated, died rapidly. With appropriate directly observed treatment, especially combinations including an injectable medication, even severely immunocompromised patients had culture conversion and prolonged, tuberculosis-free survival.

JAMA. 1996;276:1229-1235

From the New York City Department of Health, Bureau of Tuberculosis Control (Drs Frieden, Maw, Fujiwara, and Brudney and Mss Sherman and Nivin); the Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Ga (Drs Frieden and Fujiwara); the Division of AIDS, STD, and TB Laboratory Research, National Center for Infectious Disease, Atlanta, Ga (Dr Crawford); St Clare's Hospital, New York, NY (Dr Sharp); Lincoln Medical and Mental Health Center, Bronx, NY (Dr Hewlett); Columbia Presbyterian Medical Center, New York City (Dr Brudney); Howard Hughes Medical Institution, Albert Einstein College of Medicine, Bronx, NY (Dr Alland); and Public Health Research Institute, New York, NY (Dr Kreiswirth). Dr Sharp is now with the Beth Israel Medical Center, New York, NY.

Reprints: Thomas Frieden, MD, MPH, Director, Bureau of Tuberculosis Control, New York City Department of Health, 125 Worth St, Box 74, New York, NY 10013.

THE RESURGENCE of tuberculosis in the United States has been complicated by an increase in the proportion of patients with strains resistant to antituberculosis medications.[1,2] Outbreaks of multidrug-resistant tuberculosis have been documented in hospitals[3-6] and prisons.[7] Drug-resistant tuberculosis, particularly disease caused by strains resistant to isoniazid and rifampin (the 2 most active antituberculosis drugs) is much harder to treat and is often fatal.[3,8]

See also pp 1223 and 1259.

Many outbreaks of drug-resistant strains of *Mycobacterium tuberculosis* occurred in New York, and several have involved 1 strain (referred to as strain W) predictably resistant to at least 6 and usually 7 antituberculosis agents: isoniazid, rifampin, ethambutol hydrochloride, streptomycin sulfate, kanamycin sulfate, rifabutin, and usually ethionamide.[9-11] Susceptibility to pyrazinamide, which may be difficult to test,[1] has been variable.[12] Reported outbreaks have largely, although not exclusively, involved human immunodeficiency virus (HIV)–infected patients and health care workers. Mortality was 80% to 90% in the reported outbreaks, with death occurring a median of 1 to 4 months after disease onset.[3] A molecular analysis of strain W has recently been published.[11]

We conducted an in-depth investigation of every tuberculosis patient reported in New York City from January 1, 1990, to August 1, 1993, to determine the number who had disease caused by the W strain of *M tuberculosis*, the probable location of transmission, and the clinical outcome. Since all patients were documented to have genetically related

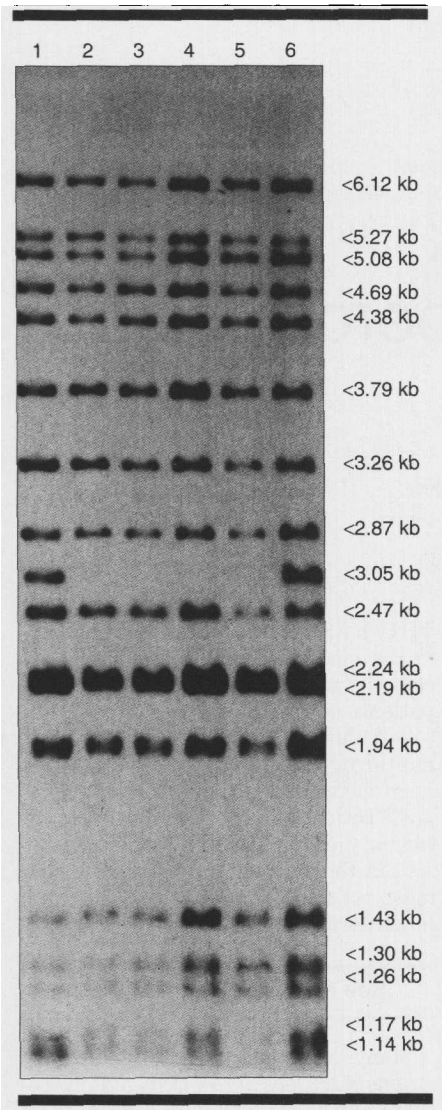

Figure 1.—Southern blot hybridization analysis of highly drug-resistant *Mycobacterium tuberculosis* isolates, New York City. The 17-band hybridization pattern (lanes 2-5) was documented for 237 patients and the 18-band related pattern (lanes 1 and 6) was documented for 22 patients.

strains of *M tuberculosis* with similar susceptibility patterns, analysis of survival as it relates to disease presentation and antituberculosis treatment was also possible.

METHODS

Patients

To meet the case definition, patients had to have isolates of *M tuberculosis* resistant to at least isoniazid, rifampin, ethambutol, and streptomycin, and rifabutin if sensitivity testing included it. If restriction fragment length polymorphism (RFLP) testing was done, patients had to have an identical or closely related pattern. This strain of *M tuberculosis* is characteristically resistant to isoniazid at low (0.2 mg/dL and 1.0 mg/dL) concentrations, but it is susceptible at high (5.0 mg/dL) concentrations. Patients were considered to have RFLP confirmation of relatedness if RFLP revealed the 17-band pattern illustrated in Figure 1 or a pattern differing by 1 to 2 bands. Patients with distinct RFLP patterns were excluded. In 1992, the tuberculosis registry was estimated to be at least 99% complete for patients with culture-proven tuberculosis.[13] Drug susceptibility test results were available for more than 90% of cases reported after 1992; laboratory records were reviewed for drug susceptibility test results on cases reported in 1989 to 1991. Records of all outbreak investigations conducted in New York City and related areas were reviewed. Patients were included in the investigation if their clinical specimen was submitted prior to August 1, 1993. Follow-up was determined through December 31, 1994. Patients who may have become infected with this strain in New York City but who were diagnosed elsewhere as having active tuberculosis were not included in the analysis. Seven of the patients in our series were described in the investigation of Friedman et al.[10]

Forty patients who were determined to have falsely positive cultures attributable to laboratory cross-contamination were excluded. Patients were considered to have falsely positive cultures if all of the following occurred: (1) they had only 1 positive culture with this strain, (2) the specimen from which this positive culture was obtained did not have a positive smear stained for detection of acid-fast bacilli, (3) this culture was processed in the same laboratory on the same date as a specimen from a patient ill with this strain, and (4) clinical course was not consistent with active multidrug-resistant tuberculosis on medical record review. Six patients who met case definition but whose medical records and/or RFLP results were not available at the time of this investigation were not included in this analysis.

Demographic, clinical, bacteriologic, and treatment information was established as accurately as possible with reviews of inpatient and outpatient medical records, New York City Department of Health records, inpatient and outpatient pharmacy records, and private physicians' records. In New York City, physicians and laboratories are required by law to report this information. The primary end points were death among all patients and culture conversion to negative without subsequent positive cultures in patients with pulmonary tuberculosis. Both observed and self-administered treatment was included in our analysis, except where indicated otherwise. Patients were considered HIV-infected if there was documentation of a positive HIV antibody test result in the medical record. The $CD4^+$ T-lymphocyte counts were recorded for the date closest to time of tuberculosis diagnosis.

Homelessness was ascertained from medical record reviews, New York City Department of Health records, and a computer-assisted match with the registry of the New York City Department of Homeless Services. Computer-assisted matches were also done with the New York City jail and the New York State prison databases. Cause of death was determined by medical record review, death certificates, and autopsy reports. In cases where there was a question of cause of death, one of the authors (T.R.F.) reviewed the records.

Laboratory Investigation

In the course of patient care and outbreak investigation, specimens were sent to 1 of 4 national reference laboratories (New York City Department of Health, Centers for Disease Control and Prevention, West Haven Veterans Affairs Hospital, and National Jewish Center for Immunology and Respiratory Medicine) for susceptibility testing. Patients were considered to have primary drug resistance if their isolate was resistant prior to treatment. Patients were considered to have acquired resistance when initial testing showed susceptibility and susceptibility testing following treatment demonstrated resistance. For all patients in whom disease with this strain was suspected, isolates were sought for testing by RFLP analysis,[14,15] which was performed by techniques described previously.[16]

Epidemiologic Investigation

Detailed epidemiologic investigation was conducted for the subset of patients who had RFLP performed. This included review of medical records, review of all New York City Department of Health records, review of admission rosters of hospitals with known outbreaks of this strain of tuberculosis, and review of the shelter and correctional system registries. Patients were considered to be epidemiologically linked if their RFLP fingerprints were identical or if they differed by 1 or 2 bands and they were in the same part of the same institution (eg, hospital ward, jail unit, or homeless shelter) during a time when 1 patient had a positive culture and at least 14 days prior to disease onset in a second patient. Some epidemiologic linkages had been confirmed in prior investigations of nosocomial transmission of tuberculosis, other patients were linked to these

known outbreaks during the current investigation, and in other cases previously unrecognized transmission was documented as a result of this investigation. Records of New York City Department of Health contact investigations were reviewed. Ninety-five patients had multiple exposures. For these patients, the exposure closest to 3 months before disease onset (the median incubation time in several outbreaks[3]) was considered to be the source. For the 43 patients in whom such multiple exposures occurred, the longest exposure was considered the source. Date of exposure was considered to be the date a patient was admitted to an outbreak institution at the time of exposure.

Statistical Analysis

Categorical data were compared with the Pearson χ^2 test. Univariate and stratified analyses were performed with the Epi Info computer program, Version 6.03.[17] Analysis of survival and of time to culture conversion was performed using a proportional hazards model; the assumption of proportionality was met.[18] Multivariate survival analysis was conducted by backward elimination of factors potentially associated with survival and culture conversion, using administration of antituberculosis agents for more or less than 12 weeks. The model was tested using treatment as a continuous variable and also using different cutoff points. Various cutoff points for treatment duration were analyzed; the χ^2 for testing the global null hypothesis had the maximum significance level for the 12-week cutoff point and, thus, was used for further analyses. A model that used duration of treatment as a polychotomous variable (0, 1, 2, 3, 4, and ≥5 months of treatment) gave similar results. To control for survivor bias, stratified multivariate analysis was also conducted with patients grouped into those who received at least 3 drugs to which their isolate was susceptible early (ie, within 60 days of presentation), late (60 days or more after presentation), or never. Survival curves were developed using Kaplan-Meier survival analysis.

RESULTS

Patients

Between January 1, 1990, and August 1, 1993, there were 8021 cases reported in New York City with positive cultures for *M tuberculosis*, including 1006 (13%) with multidrug-resistant tuberculosis. There were 649 patients with multidrug-resistant tuberculosis who did not meet case definition (632 with variant drug susceptibility patterns, of whom 178 also had unrelated RFLP patterns, and 17 with consistent drug susceptibility patterns but unrelated RFLP patterns). There were 357 patients (4% of all cases, 35% of multidrug-resistant tuberculosis cases) who met case definition, of whom 267 (75%) had available isolates that were closely related by RFLP testing. Isolates from the other 90 patients who met case definition were not available for RFLP testing because they had not been stored by local hospital laboratories. The RFLP pattern of this *M tuberculosis* strain is characteristic with 17 bands and has been designated 0212072 by the Centers for Disease Control and Prevention and strain W by the Public Health Research Institute.[9-11]

Table 1.—Clinical and Epidemiologic Characteristics of 267 Patients With a Single Strain of Highly Drug-Resistant Tuberculosis in New York City

Characteristic	No. (%)
Age, y	
0-14	1 (0.4)
15-24	9 (3.4)
25-34	80 (30.0)
35-44	118 (44.2)
45-54	31 (11.6)
55-64	14 (5.2)
≥65	14 (5.2)
Median (range) y	38 (<1-90)
Race/ethnicity	
Hispanic	120 (44.9)
Non-Hispanic black	91 (34.1)
Non-Hispanic white	48 (18.0)
Asian	8 (3.0)
Sex	
Male	206 (77.2)
Female	61 (22.8)
Place of birth	
United States/Puerto Rico	239 (89.5)
Outside United States	27 (10.1)
Unknown	1 (0.4)
HIV serostatus at diagnosis	
Infected	230 (86.1)
Not infected	19 (7.1)
Unknown	18 (6.7)
Site of disease at time of diagnosis	
Pulmonary	172 (64.4)
Extrapulmonary	13 (4.9)
Both	82 (30.7)
Chest radiograph at time of diagnosis	
Abnormal	248 (92.9)
Cavitary	31 (11.6)
Died within 12 mo of diagnosis	190 (71.2)

Table 2.—Clinical Characteristics of 267 Tuberculosis Patients With a Simple Strain of Highly Drug-Resistant Tuberculosis in New York City

Characteristic	No. (%)
Psychosocial factors (N=267)	
History of injection drug use	
Yes	146 (54.7)
No	92 (34.5)
Unknown	29 (10.9)
History of alcohol abuse	
Yes	103 (38.6)
No	107 (40.1)
Unknown	57 (21.3)
History of incarceration	
Yes	78 (29.2)
No	189 (70.8)
History of cocaine use	
Yes	82 (30.7)
No	77 (28.8)
Unknown	108 (40.4)
History of homelessness	
Yes	68 (25.5)
No	199 (74.5)
History of "crack" cocaine use	
Yes	40 (15.0)
No	93 (34.8)
Unknown	134 (50.2)
Extrapulmonary sites of disease (n=95)	
Blood	38 (40.0)
Urine	24 (25.3)
Lymph node	17 (17.8)
Cerebrospinal fluid	14 (14.7)
Stool	13 (13.6)
Pleura	7 (7.3)
Bone marrow	7 (7.3)
Soft tissue	7 (7.3)
Other	12 (12.6)
HIV-infected patients (n=230)	
CD4⁺ T-lymphocyte count at diagnosis, $\times 10^9$/L*	
0.0-0.049	104 (45.2)
0.050-0.099	41 (17.8)
0.100-0.149	18 (7.8)
0.150-0.199	8 (3.5)
0.200-0.499	13 (5.7)
≥0.500	3 (1.3)
Not available	43 (18.7)
Mean	0.073
Median	0.033
History of opportunistic infection	191 (83.0)
Opportunistic infection antedated tuberculosis	133 (57.8)
Pneumocystis carinii pneumonia before tuberculosis	81 (35.2)
Opportunistic infection (n=230)	
Mucocutaneous candidiasis	136 (59.1)
P carinii pneumonia	85 (37.0)
Mycobacterium avium complex disease	29 (12.6)
Toxoplasma meningitis	30 (13.0)
Cytomegalovirus retinitis	27 (11.7)
Cryptococcal meningitis	22 (9.6)
Kaposi sarcoma	13 (5.7)

*0.200×10^9/L=200/μL.

Clinical and epidemiologic information on these 267 patients is presented in Tables 1 and 2. Median age was 38 years, 45% were Hispanic, 77% were male, 12% had cavitary disease on chest radiograph, and 78% had pulmonary specimens that were smear positive for acid-fast bacilli during their illness. HIV-serostatus was documented for 249 patients (93%), of whom 230 (92%) were HIV-infected. Of the 18 patients with unknown HIV serostatus, 6 (33%) had 1 or more risk factor, clinical, or laboratory features suggestive of HIV infection (a history of injection drug use [n=6]; an opportunistic infection [n=2]; and a CD4⁺ T-lymphocyte count $<0.200 \times 10^9$/L [200 cells/μL] [n=1]). Nineteen patients (7%) had diabetes. Thirty-one patients (12%) had a reported prior history of tuberculosis and may have been reinfected with this strain. Patients resided in all boroughs and most ZIP codes in the city, were cared for at 41 different hospitals, and were hospitalized for a cumulative total of 19 740 days in the time reviewed. Patients with this strain were far more likely to have documented HIV infection than other patients with positive cultures for tuberculosis in New York City (86% vs 37%; $P<.001$), although data collection was more complete for case patients. All-cause mortality was 83%.

Overall, 89% of patients had at least

Table 3.—Drug Susceptibility of 267 Tuberculosis Patients With a Simple Strain of Highly Drug-Resistant Tuberculosis in New York City

Drug	Initial Testing, No.	Primary Resistance, No. (%)	Follow-up Testing Performed, No.	Acquired Resistance, No. (%)
Pyrazinamide	188	104 (55.3)	19	6 (31.6)
Ethionamide	204	110 (53.9)	40	6 (15.0)
Capreomycin sulfate	204	10 (4.9)	65	13* (20.0)
Ciprofloxacin/ofloxacin	195	0 (0.0)	61	14* (23.0)
Cycloserine	200	2 (1.0)	63†	1 (1.6)
Kanamycin sulfate	208	191 (91.8)	8	1 (12.5)
Aminosalicylic acid	120	1 (0.8)	48	0 (0.0)

*Among patients whose isolates acquired resistance to capreomycin or a fluoroquinolone, a median of 228 and 173 days, respectively, elapsed between the last susceptible culture and the first drug-resistant culture; patients received a median of 153 and 133 days of treatment with these drugs before resistance was documented.
†Forty-five of 63 patients received cycloserine for a median of 151 days before repeat susceptibility testing.

Table 4.—Antituberculosis Drug Treatment for 267 Patients With Tuberculosis

Antituberculosis Drug	Patients Who Received Drug, No. (%)	Treatment, Median d
Isoniazid	240 (90)	50
Rifampin	237 (89)	43
Pyrazinamide	236 (88)	55
Ethambutol hydrochloride	214 (80)	53
Ciprofloxacin	175 (66)	43
Cycloserine	120 (45)	155
Ethionamide	116 (44)	72
Capreomycin sulfate	109 (41)	119
Kanamycin sulfate	100 (37)	26
Ofloxacin	87 (33)	162
Clofazimine	53 (20)	43
Aminosalicylic acid	48 (18)	168
Streptomycin sulfate	30 (11)	17
Imipenem	13 (5)	15
Amoxicillin/clavulanate potassium	7 (3)	33

Table 5.—Factors Associated With Survival Among 179 HIV-Infected Patients With Highly Drug-Resistant Tuberculosis in New York City*

Factor	No. of Patients	Median Survival, wk	Multivariate Analysis		Stratified by Early, Late, or No Effective Treatment Regimen	
			Adjusted† OR (95% CI)	P	Adjusted† OR (95% CI)	P
Capreomycin sulfate treatment						
≤12 wk	141	6	...	...	...	...
>12 wk	38	77	7.3 (3.0-17.6)	<.001	7.9 (3.0-21.0)	<.001
CD4⁺ T-lymphocyte count, ×10⁹/L†						
<0.200	163	8	...	...	...	...
≥0.200	16	39	4.2 (1.6-11.0)	.004	3.8 (1.4-10.5)	.009
Ciprofloxacin/ofloxacin treatment						
≤12 wk	119	5	...	...	...	...
>12 wk	60	57	3.5 (2.0-6.3)	<.001	2.9 (1.5-5.5)	.001
Isoniazid treatment						
≤12 wk	124	6	...	...	...	...
>12 wk	55	32	2.3 (1.5-3.7)	<.001	2.1 (1.3-3.3)	.004

*OR indicates odds ratio; CI, confidence interval.
†Using backward elimination.
‡0.200×10⁹/L=200/μL.

1 susceptibility result performed at 1 of 4 reference institutions. Resistance to kanamycin was found in 92% of isolates tested. Resistance to ethionamide and pyrazinamide was common, and resistance to pyrazinamide became more common later in the outbreak (χ^2 for linear trend, 37.4; $P<.001$) (Table 3). A minority of patients had follow-up susceptibility testing; of these, many acquired resistance to additional second-line drugs. Acquisition of resistance to cycloserine was less common than to capreomycin sulfate and the fluoroquinolones (1/63 [2%] vs 13/65 [20%] vs 14/61 [23%], respectively; $P=.001$) (Table 3). Antituberculosis drugs used to treat the patients are shown in Table 4.

The isolates of these 267 patients revealed 8 closely related RFLP patterns (Figure 1). There were 237 isolates (89%) with an identical RFLP pattern (strain W). Twenty-two (8%) had another pattern that differed from the predominant pattern by a single band in an identical location (referred to as "W1"[11]), and 8 others (3%) had isolates with 6 other patterns that differed by 1 to 2 bands, including 3 with an identical pattern. Eight of the 22 patients and 2 of the 3 patients with strains closely related to strain W but identical to each other were epidemiologically linked.

Factors Associated With Patient Survival and Culture Conversion

The median survival for the 230 HIV-infected patients was 66 days. Whether multivariate analyses were stratified for early, late, or no effective treatment regimen or not, treatment with capreomycin and, to a lesser extent, with a fluoroquinolone or isoniazid (unstratified adjusted odds ratio [OR], 7.3, 95% confidence interval [CI], 3.0-17.6; unstratified adjusted OR, 3.5, 95% CI, 2.0-6.3; and unstratified adjusted OR, 2.3, 95% CI, 1.5-3.7, respectively) was associated with prolonged survival on multivariate analysis (Table 5). Patients with CD4⁺ T-lymphocyte counts of at least 0.200×10^9/L also had longer survival (unstratified adjusted OR, 4.2; 95% CI, 1.6-11.0). Treatment with capreomycin improved survival of patients with low CD4⁺ T-lymphocyte counts to the survival level of patients with higher CD4⁺ T-lymphocyte counts (Figure 2). In all models, capreomycin use was the strongest predictor of survival, even stronger than CD4⁺ T-lymphocyte count. Results were unchanged when only the 237 patients with identical RFLP patterns were included in the survival analysis.

As the outbreak progressed, physicians prescribed prompt and appropriate treatment more commonly. In institutions with recognized outbreaks, patients with prior non–tuberculosis-related admissions who were readmitted with symptoms suggestive of tuberculosis were given initial antituberculosis regimens that included capreomycin, cycloserine, a fluoroquinolone, and aminosalicyclic acid when this drug became available. Of 15 patients whose conditions were diagnosed in 1990, 4 (27%) were treated with at least 3 of these drugs ever, and none received them within 60 days of submitting their first

positive culture; among 47 patients whose conditions were diagnosed in 1993, 24 (51%) were treated with at least 3 of these drugs ever, and 10 (21%) received them within 60 days of diagnosis ($P<.001$). The HIV-infected patients who were started on a regimen of at least 3 of the agents to which their isolate was susceptible within 60 days of their first positive culture survived a median of 262 days after the start of this treatment. Of these 30 patients, 13 survived at least 2 weeks after starting treatment, had at least 80% of prescribed treatment under direct observation, and had a sufficient number of follow-up sputum cultures to determine conversion. Of these 13, 10 (77%) had culture conversion a median of 60 days after treatment began and survived a median of 262 days after the start of treatment. Two of the 3 patients whose sputum remained culture-positive for *M tuberculosis* had isolates that were resistant to ciprofloxacin, 1 of which was also resistant to capreomycin.

Culture conversion could be assessed in 221 HIV-infected patients with positive cultures from a pulmonary source. On univariate analysis, treatment with antituberculosis medications and $CD4^+$ T-lymphocyte count of at least 0.200×10^9/L were associated with culture conversion. On multivariate analysis with backward elimination, only treatment with capreomycin (adjusted OR, 2.2; 95% CI, 1.0-4.8; $P=.04$) was independently associated with culture conversion in patients with the predominant strain. Of the 43 HIV-infected patients whose sputum cultures converted to negative, 39 (91%) received capreomycin (median, 250 days). Patients who received capreomycin for at least 12 weeks and whose isolates were not resistant to capreomycin were more likely to have culture conversion to negative than patients who received less than 12 weeks of capreomycin (30/45 [67%] vs 13/45 [29%]; OR, 4.9; 95% CI, 1.8-13.4; $P<.001$).

There were 19 patients (7%) who were documented to be HIV-negative. Four of these patients died; 1 patient with underlying diabetes and another with carcinoma of the lung died of progressive tuberculosis. Neither of these patients received effective therapy, and both died within 1 year of diagnosis. The remaining 2 patients died of unrelated causes (drug overdose and multiorgan failure unrelated to tuberculosis); both had received effective therapy with resultant sputum conversion. Of the 11 HIV-negative patients whose sputum culture was documented to convert to negative, 7 (64%) received capreomycin (median, 226 days).

There were 20 patients (7%) who were health care workers prior to disease onset (including 6 nurses' aides, 5 physicians, and 4 nurses), of whom 15 (75%) were linked to institutions with confirmed nosocomial transmission of this strain of tuberculosis. Duration of symptoms from onset to diagnosis ranged from 8 to 250 days (median, 24 days). Of the 20 health care workers, 13 (65%) had documented HIV infection and 5 (25%) were documented to be HIV-negative, 2 of whom had diabetes. Twelve health care workers (60%) died, 11 of whom were HIV-infected; the non–HIV-infected health care worker died after taking an intentional drug overdose 2 weeks after beginning treatment with cycloserine.

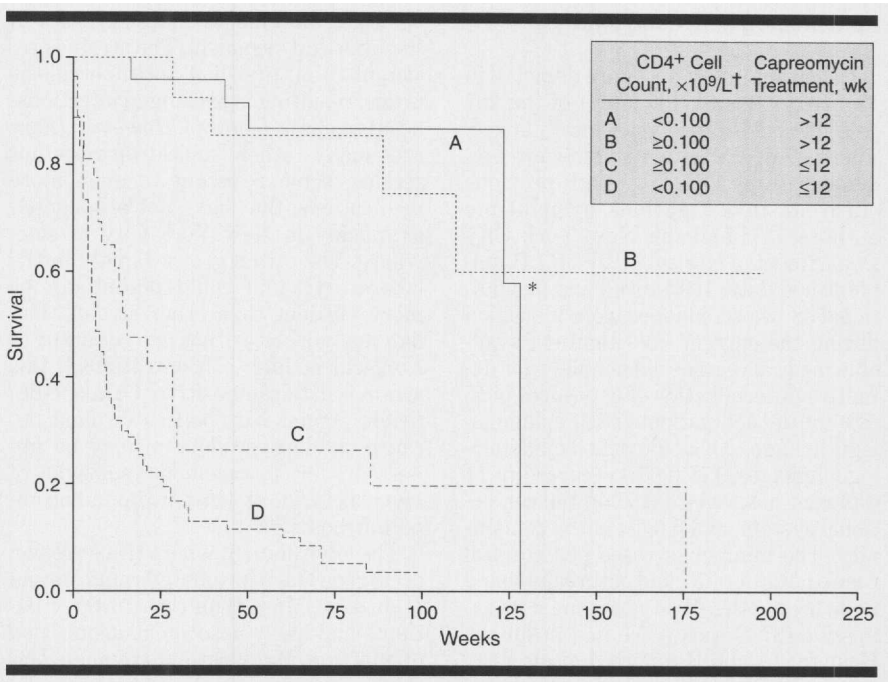

Figure 2.—Survival in patients with highly drug-resistant tuberculosis in New York City from January 1, 1990, to August 1, 1993. The asterisk indicates 1 patient who became noncompliant with antituberculosis treatment. †0.100×10^9/L=100/μL.

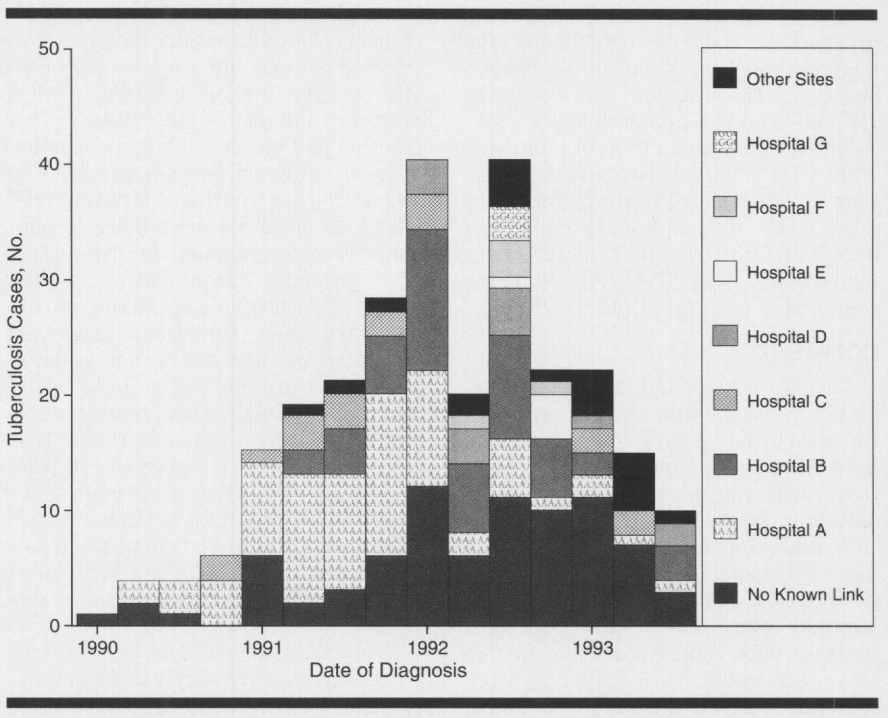

Figure 3.—Cases by time of onset and location of transmission. Other sites include patients with suspected nosocomial transmission (n=12), patients whose source of community-acquired disease was known (n=5), and patients suspected to have contracted infection in a correctional facility (n=3).

Epidemiologic Investigation

Cases by time of onset are depicted in Figure 3. Overall, 186 (70%) of the 267 patients could be epidemiologically linked. There were 128 patients who were epidemiologically linked through previous outbreak investigations by multiple authors[3,4,19,20] and the New York City Department of Health (T.R.F., P.I.F., unpublished data, 1992-1996), and an additional 58 whose linkages were identified during the current investigation; available medical records did not allow for definitive determination of exposures in 15 (8%) of the 186 patients with epidemiologic linkages. Of all identified epidemiologic linkages, 178 (96%) occurred in 11 different hospitals, 3 (2%) in the correctional system, and 5 (3%) in the community. The number of cases per hospital ranged from 1 to 76, and outbreaks lasted up to 38 months. Most nosocomial transmission (87%) took place in 4 hospitals. Hospitals A and B reported most of the cases, with 76 and 48 cases diagnosed over 38 and 26 months, respectively. Hospitals C and D had 18 and 13 cases diagnosed over 30 and 17 months (Figure 3).

Among 146 patients for whom the date of exposure could be determined, the median time from exposure to disease onset was 17 weeks and was shorter in HIV-infected patients with lower $CD4^+$ T-lymphocyte counts: 15 weeks for those with $CD4^+$ T-lymphocyte counts less than 0.050×10^9/L, 19 weeks for those with $CD4^+$ T-lymphocyte counts of 0.050×10^9/L to 0.099×10^9/L, and 23 weeks for patients with $CD4^+$ T-lymphocyte counts of at least 0.100×10^9/L ($P=.01$).

COMMENT

This is the most extensive and most highly resistant tuberculosis outbreak reported to date. The 357 cases described here were more than one third of patients with multidrug-resistant tuberculosis in New York City during the time studied, a period during which New York City had more than 60% of all multidrug-resistant tuberculosis cases in the United States.[2] Thus, New York City patients with tuberculosis due to this strain accounted for nearly 1 in 4 patients in the United States with multidrug-resistant tuberculosis in this 43-month period. Based on the number of days in the hospital alone, the estimated direct cost of care for these patients exceeded $25 million, and there were other patients who were infected in New York City and became ill elsewhere.[11]

The remarkable size and speed of this outbreak was related to the patients exposed to and infected with this organism and the environments where transmission occurred, but it may have also been attributable to characteristics of the infecting organism. The strain is resistant to all first-line antituberculosis drugs, resulting in prolonged infectiousness (weeks to months). However, there are many other multidrug-resistant strains, some resistant to even more medications, that have not propagated as quickly in New York City or elsewhere. The strain grows rapidly in the laboratory[21] and could potentially be more virulent than other strains. Unlike many isolates that are resistant to isoniazid at high concentrations,[22] this strain is catalase-positive. Catalase-deficient strains may be less virulent because catalase production may be important for intracellular survival of mycobacteria, at least in immunocompetent hosts.[22,23]

The environment where transmission occurred clearly promoted rapid spread of disease. More than two thirds of patients had likely nosocomial acquisition of infection. Many patients remained infectious from disease onset to death, did not survive to leave the hospital, and were located on wards where many other patients with HIV infection received care, allowing rapid *M tuberculosis* transmission. Outbreaks among HIV-infected persons can progress very rapidly because of short incubation times between infection and disease (3-4 months) and because a high proportion of newly infected persons progress to active disease (perhaps 30%-50%).[24,25] Hospitals often did not adhere to published recommendations for prevention of nosocomial transmission of disease.[3,4,6,26] In particular, patients who did not have their conditions diagnosed promptly or who were not isolated promptly were allowed to leave isolation rooms for nonmedical reasons while infectious, were housed in rooms that were not at negative pressure in relation to the hallway, and were often not placed on appropriate antituberculosis regimens.[3,4,6] Improved diagnosis, treatment, and infection control have since curtailed nosocomial transmission of disease.[27,28]

Prompt diagnosis and appropriate treatment improve survival and emphasize the need for faster diagnostic technology. Capreomycin, which was virtually always used with at least 1 to 2 other agents to which this organism was susceptible, was the strongest predictor of both survival and culture conversion, even stronger than $CD4^+$ T-lymphocyte count. Although this finding is most likely related to the biological activity of capreomycin, ensured compliance with injectable medications or impaired absorption of oral antituberculosis medications may also play a role. For patients with isolates that are resistant to isoniazid and rifampin, injectable medications should be administered for as long as feasible, and at least 4 to 6 months after culture conversion to negative for patients with pulmonary disease or 4 to 6 months after clinical response in patients with extrapulmonary disease.[29] Fluoroquinolone and isoniazid use also improved survival somewhat. There may be a role for isoniazid in the treatment of patients with resistant isolates such as this one that are susceptible to isoniazid at high concentrations (5.0 mg/dL). High-dose (15 mg/kg) intermittent (2 or 3 times weekly) treatment may be more effective than daily therapy with isoniazid,[30] although we were unable to evaluate this possibility.

Although this outbreak strain overwhelmingly involved HIV-infected patients and health care workers, it also affected at least 19 patients who were HIV-seronegative. Since approximately half of the risk of active tuberculosis occurs in the first 2 years after infection in immunocompetent persons,[31] a similar number of HIV-negative patients can be expected to develop disease with this organism in the future, particularly since regimens to prevent disease in patients infected with multidrug-resistant strains have unproven efficacy[32] and may be poorly tolerated.[33]

This investigation has several limitations. First, treatment regimens, although variable, were not randomized or standardized, complicating the evaluation of the contribution of treatment to survival analysis and culture conversion. Second, bacteriologic follow-up was not standardized. Cultures were not collected at the same intervals and susceptibility results were not always available from 1 of the 4 reference laboratories. Third, we conducted limited investigations of epidemiologic linkages in the community and thus may not have identified community linkages among patients who had exposure in hospital. However, we also did not review records of outpatient and emergency department visits, during which tuberculosis transmission may occur.[34] Thus, a larger number of patients than we identified to have possible nosocomially acquired infection may have become infected in health care facilities.

It is likely, given that more than 350 patients had disease due to this strain and that many persons infected with *M tuberculosis* do not become ill until years after infection, that at least several hundred more persons became infected with this highly drug-resistant strain of tuberculosis in New York City in recent years. Hospitals may be important sites for *M tuberculosis* trans-

mission, especially among HIV-infected persons, but nosocomial transmission can be effectively prevented.[27,28,35] We found, as have others,[36] that appropriate treatment using directly observed therapy with injectable and other medications to which patients' isolates are susceptible can improve outcome even among patients with highly drug-resistant tuberculosis (from 2 to 3 months to more than 1 year among HIV-infected persons).[37-39] Since this investigation ended, there have been 82 additional RFLP-confirmed patients that meet case definition; the outbreak began with 15 RFLP-confirmed cases in 1990, peaked with 122 cases in 1992, and decreased to 19 cases in 1995 (T.R.F., P.I.F., L.F.S., K.L.M., unpublished data, 1996). To prevent similar outbreaks from occurring in the future, prompt diagnostic evaluation, including susceptibility testing, must be ensured, directly observed treatment must be used whenever possible, effective treatment must be given promptly to patients with multidrug-resistant tuberculosis, and patients with active tuberculosis should be treated and housed separately from immunocompromised persons.

The authors thank Lucille Palumbo, MA, James Tsung, MD, Katherine Deely Fehrenbach, and Kervyn Mark for assistance with collection of data and specimens, Patricia M. Simone, MD, and Kenneth G. Castro, MD, for helpful comments on the manuscript, Sukhminder Osahan, PhD, for assistance with multivariate analysis, Deborah Lew for assistance with manuscript preparation, and public health advisors and other health care workers from throughout New York City for their dedication and commitment to providing care for patients with tuberculosis.

References

1. Frieden TR, Sterling T, Pablos-Méndez A, Kilburn JO, Cauthen GM, Dooley SW. The emergence of drug-resistant tuberculosis in New York City. *N Engl J Med.* 1993;328:521-526.
2. Bloch AB, Cauthen GM, Onorato IM, et al. Nationwide survey of drug-resistant tuberculosis in the United States. *JAMA.* 1994;271:665-671.
3. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons—Florida and New York, 1988-1991. *MMWR Morb Mortal Wkly Rep.* 1991; 40:585-591.
4. Coronado VG, Beck-Sague CM, Hutton MD, et al. Transmission of multidrug-resistant *Mycobacterium tuberculosis* among persons with human immunodeficiency virus infection in an urban hospital: epidemiologic and restriction fragment length polymorphism analysis. *J Infect Dis.* 1993;168:1052-1055.
5. Small PM, Shafer RW, Hopewell PC, et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *N Engl J Med.* 1993;328:1137-1144.
6. Pearson ML, Jereb JA, Frieden TR, et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis*: a risk to patients and health care workers. *Ann Intern Med.* 1992;117:191-196.
7. Valway SE, Greifinger RB, Papania M, et al. Multidrug-resistant tuberculosis in the New York State prison system, 1990-1991. *J Infect Dis.* 1994; 170:151-156.
8. Goble M. Drug-resistant tuberculosis. *Semin Respir Infect.* 1986;1:220-229.
9. Plikaytis BB, Marden JL, Crawford JT, Woodley CL, Butler WR, Shinnick TM. Multiplex PCR assay specific for the multidrug-resistant strain W of *Mycobacterium tuberculosis*. *J Clin Microbiol.* 1994;32:1542-1546.
10. Friedman CR, Stoeckle MY, Kreiswirth BN, et al. Transmission of multidrug-resistant tuberculosis in a large urban setting. *Am J Respir Crit Care Med.* 1995;152:355-358.
11. Bifani PJ, Plikaytis BB, Kapur V, et al. Origin and interstate spread of a New York City multidrug-resistant *Mycobacterium tuberculosis* clone family. *JAMA.* 1996;275:452-457.
12. Hewlett D Jr, Horn DL, Alfalla C. Drug-resistant tuberculosis: inconsistent results of pyrazinamide susceptibility testing. *JAMA.* 1995;273:916-917.
13. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City: turning the tide. *N Engl J Med.* 1995;333:229-233.
14. Hermans PW, van Soolingen D, Dale JW, et al. Insertion elements IS986 from *Mycobacterium tuberculosis*: a useful tool for diagnosis and epidemiology of tuberculosis. *J Clin Microbiol.* 1990;28: 2051-2058.
15. Cave MD, Eisenach KD, McDermott PF, Bates JH, Crawford JT. IS6110: conservation of sequence in the *Mycobacterium tuberculosis* complex and its utilization in DNA fingerprinting. *Mol Cell Probes.* 1991;5:73-80.
16. 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.
17. Dean AG, Dean JA, Coulombier D, et al. *Epi Info, Version 6.03: A Word Processing, Database, and Statistics Program for Public Health on IBM-Compatible Microcomputers.* Atlanta, Ga: Centers for Disease Control and Prevention; 1995.
18. SAS Institute Inc. *SAS/STAT Software: Syntax Version 6.* Cary, NC: SAS Institute Inc; 1993.
19. Azmeh W, Ziegenfuss R, Lutfey M, et al. Clinical, microbiologic, and epidemiologic evaluation of an outbreak of multi-drug resistant tuberculosis (MDR-TB). In: Programs and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy; October 17-20, 1993; New Orleans, La. Abstract 604.
20. Alfalla C, Hewlett D, Horn D, et al. An outbreak of multidrug resistant tuberculosis among 28 patients at a New York City hospital. In: Programs and abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy; October 11-14, 1992; Anaheim, Calif. Abstract 551.
21. Sathyakumar C, Palumbo LA, Ebrahimzadeh A, Reimer SM. Time to detect growth of multidrug-resistant *Mycobacterium tuberculosis*. Presented at the 95th General Meeting of the American Society for Microbiology; May 21-25, 1995; Washington, DC. Abstract U-146.
22. Cohn ML, Kovitz C, Oda U, Middlebrook G: Studies on isoniazid and tubercle bacilli, II: the growth requirements, catalase activities, and pathogenic properties of isoniazid-resistant mutant. *Am Rev Tuberc.* 1954;70:641-644.
23. Ausina V, Riutort N, Viñado B, et al. Prospective study of drug-resistant tuberculosis in a Spanish urban population including patients at risk for HIV infection. *Eur J Clin Microbiol Infect Dis.* 1995;14:105-110.
24. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: an analysis using restriction-fragment-length polymorphisms. *N Engl J Med.* 1992;326:231-235.
25. Valway S, Greifinger R. Risk of HIV-positive persons becoming infected and developing disease after exposure to multidrug-resistant tuberculosis, New York. In: Programs and abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy; October 17-20, 1993; New Orleans, La. Abstract 607.
26. Centers for Disease Control. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. *MMWR Morb Mortal Wkly Rep.* 1990;39 (RR-17):1-27.
27. Wenger PN, Otten J, Breeden A, Orfas D, Beck-Sague CM, Jarvis WR. Control of nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis* among health care workers and HIV-infected patients. *Lancet.* 1995;345:235-240.
28. Maloney SA, Pearson ML, Gordon MT, Del Castillo R, Boyle JF, Jarvis WR. Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Ann Intern Med.* 1995;122: 90-95.
29. Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med.* 1993;329:784-791.
30. Mitchison DA, Dickinson JM. Laboratory aspects of intermittent drug therapy. *Postgrad Med J.* 1971;47:737-741.
31. Comstock GW, Livesay VT, Ferebee Woolpert S. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol.* 1974; 99:131-138.
32. Villarino ME, Dooley SW Jr, Geiter LJ, Castro KG, Snider DE Jr. Management of persons exposed to multidrug-resistant tuberculosis. *MMWR Morb Mortal Wkly Rep.* 1992;41(RR-11):59-71.
33. Horn DL, Hewlett D, Alfalla C, et al. Limited tolerance of ofloxacin and pyrazinamide prophylaxis in health care workers following exposure to rifampin-isoniazid-streptomycin-ethambutol-resistant tuberculosis. *Infect Dis Clin Pract.* 1995;4: 219-225.
34. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital—Florida. *MMWR Morb Mortal Wkly Rep.* 1989;38:313-320, 325.
35. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health care facilities. *MMWR Morb Mortal Wkly Rep.* 1994;43(RR-13): 1-132.
36. Telzak EE, Sepkowitz K, Alpert P, et al. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med.* 1995;333:907-911.
37. Turett GS, Telzak EE, Torian LV, et al. Improved outcomes for patients with multidrug-resistant tuberculosis. *Clin Infect Dis.* 1995;21:1238-1244.
38. Saloman N, Perlman DC, Friedmann P, Buchstein S, Kreiswirth BN, Mildvan D. Predictors and outcome of multidrug-resistant tuberculosis. *Clin Infect Dis.* 1995;21:1245-1252.
39. Fischl MA, Daikos GL, Uttamchandani RB, et al. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug-resistant bacilli. *Ann Intern Med.* 1992; 117:184-190.