

Molecular and Geographic Patterns of Tuberculosis Transmission After 15 Years of Directly Observed Therapy

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Context.—Recent studies suggest that one third of tuberculosis cases in urban areas result from recent transmission. Improved tuberculosis control measures such as uniform implementation of directly observed therapy might reduce the proportion of cases resulting from recent transmission.

Objective.—To determine patterns of tuberculosis transmission in Baltimore, Md, after 15 years of community-based directly observed therapy.

Design.—A 30-month (January 1994-June 1996), prospective, city-wide study of all cases of tuberculosis using traditional contact investigations, geographic information systems data, and molecular epidemiologic comparison of *Mycobacterium tuberculosis* isolates with 2 DNA probes.

Patients.—One hundred eighty-two patients with culture-positive tuberculosis.

Main Outcome Measures.—Proportion of disease defined as recently transmitted based on epidemiologic linkage by traditional contact tracing and molecular linkage by DNA fingerprint analysis of isolates; geographic foci of transmission based on linkage of residences by geographic information systems data.

Results.—Of the 182 patients who had isolates of *M tuberculosis* available, 84 (46%) showed molecular clustering with 58 (32%) defined as being recently transmitted. Only 20 (24%) of 84 cases with clustered DNA fingerprints had epidemiologic evidence of recent contact. Geographic analysis showed significant spatial aggregation of the 20 clustered cases with epidemiologic links ($P < .001$), occurring in areas of low socioeconomic status and high drug use. The 64 cases with clustered DNA fingerprints but without epidemiologic links shared common risk factors and demographic features with the 20 clustered patients who did have epidemiologic links.

Conclusions.—Recently transmitted tuberculosis accounts for a high proportion of tuberculosis cases in Baltimore. Recently transmitted cases occur in geographically distinct areas of Baltimore, and location-based control efforts may be more effective than contact tracing for the early identification of cases.

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THE RECENT resurgence of tuberculosis in the United States has focused attention on the dynamics of tuberculosis control. The incidence of tuberculosis in a community is a function of both the rate at which latent *Mycobacterium tuberculosis* infections are reactivated and the number of case contacts who develop primary tuberculosis.¹ The application of molecular typing of *M tuberculosis* isolates² to epidemiologic evaluation of tu-

berculosis has shown that 35% to 50% of tuberculosis cases in urban areas in the United States occur in clusters that share matching restriction fragment length polymorphism (RFLP) types, suggestive of recent transmission.³⁻⁵ An alternative hypothesis is that certain RFLP types are endemic within a region during long periods and that remote transmission of such strains with a period of latent disease prior to reactivation could result in matching types among long-standing residents of the area.⁶

For editorial comment see p 1702 and Patient Page.

Since 1993, US tuberculosis rates have started to decline again.^{7,8} An important factor in this achievement has been the widespread implementation of directly observed therapy (DOT) programs for patients with tuberculosis.⁹ Directly observed therapy has been shown to decrease the incidence of active tuberculosis in the community and to reduce rates of drug-resistant tuberculosis.¹⁰⁻¹² Directly observed therapy decreases tuberculosis transmission by providing greater certainty that patients with active tuberculosis will become noninfectious soon after the initiation of therapy and by reducing the rate of relapse. The rapid improvement of community tuberculosis rates following the implementation of DOT suggests that a significant amount of disease in these populations is recently transmitted rather than reactivation of long-standing latent tuberculosis. Such analyses also predict that the effective implementation of DOT in a community will greatly reduce recently transmitted tuberculosis but will not

have a significant short-term impact on the rates of tuberculosis stemming from reactivation of old disease.

In Baltimore, Md, clinic-based DOT was implemented in 1978 and community-based DOT followed in 1981, well before the reemergence of tuberculosis prompted its use in other areas of the United States. The initiation of DOT in Baltimore led to a steep decline in the tuberculosis rate from 35.6 cases per 100 000 population in 1981 to 14.9 cases per 100 000 population in 1996 (a 58% decrease) and has kept the rate of multidrug-resistant tuberculosis at less than 1% throughout the last decade.¹⁰ To determine what patterns of tuberculosis transmission are occurring in Baltimore after 15 years of community-based DOT, we conducted a prospective molecular epidemiologic and geographic investigation of all cases of culture-positive tuberculosis diagnosed in city residents during a 2.5-year period from 1994 to 1996. We combined our study results with the findings of standard contact investigations to estimate the likelihood of recent vs remote transmission among our cases, and to determine if DNA fingerprinting can be used to infer recent transmission.

METHODS

Study Participants and Contact Investigations

Baltimore city residents with culture-positive *M tuberculosis* who reported to the Baltimore City Health Department from January 1994 to June 1996 were candidates for this study. Contact investigations were conducted for all cases in the study. Case patients and family members or caretakers were interviewed no more than 2 weeks following diagnosis to collect information on contacts and tuberculosis risk factors. A concentric circle approach was used to identify those persons most likely to be exposed to infection.¹³ A *contact* was defined as a person who shared airspace with a case patient for at least 4 hours when the case patient was symptomatic, prior to diagnosis and treatment. The results of DNA fingerprinting and geographic analysis were not known to the contact investigation team who assessed each case patient for epidemiologic links. Tuberculosis risk factors among case patients were determined prospectively by interview at the time of contact investigation and were defined as follows: injection drug use, noninjection drug use, homelessness any time within the 12 months prior to diagnosis, and unemployment any time during the 24 months prior to diagnosis. Excessive alcohol use was defined according to the Centers for Disease Control and Pre-

vention guidelines for reports of verifiable cases of tuberculosis. Directly observed therapy is provided free through the Baltimore City Health Department for about 90% of city cases, with the remainder receiving care in the private sector at the request of their physician; contacts of cases who meet the Centers for Disease Control and Prevention–American Thoracic Society criteria for secondary prophylaxis are offered free isoniazid preventive therapy.^{9,10,14}

Laboratory Analysis of *M tuberculosis* RFLPs

Mycobacterium tuberculosis clinical isolates were cultivated on Lowenstein-Jensen medium, harvested, and killed using heat. Genomic DNA was isolated and *Pvu*II-IS6110 RFLP analysis was performed according to standardized methods¹⁵ using a 245–base pair, right-sided probe and the BioImage Whole Band Analyzer, version 3.0 software (Genomic Solutions, Ann Arbor, Mich) with a 10% error tolerance. Isolates with 6 or fewer IS6110 bands were further analyzed with a probe specific for the *M tuberculosis* polymorphic GC-rich repetitive sequence (PGRS). A 3.8-kilobase *Eco*RI-*Hind*III fragment from plasmid pTBN12 was used to probe *Alu*I-cleaved genomic DNA.^{5,16,17} For questionable IS6110 matches, Southern blots were repeated side-by-side on the same gel for direct comparison; this was routinely done for PGRS matches.

Patient Categories

Study patients were classified according to DNA fingerprint and epidemiologic data. Each case was reviewed by the Baltimore City Health Department contact investigation team, the nurse interviewers, and medical staff involved in the study to identify epidemiologic linkages.¹⁸ Epidemiologic links were defined as sharing a mutual residence, place of employment, or social activity, or as a family relationship with a case patient or as being identified as a possible contact by a case patient.

Three groups of patients were identified: cases with a DNA fingerprint match and an epidemiologic link to another case (group 1); cases with matching DNA fingerprints but no epidemiologic link (group 2); and cases with unique DNA fingerprints (group 3).

Statistical Analyses

The proportion and confidence intervals of cases occurring in RFLP clusters were determined by the binomial method. Comparisons between groups were performed using the 2-tailed Fisher exact test or χ^2 analysis; multivariate analysis was done using the least squares

regression method.¹⁹ After dividing cases into 3 groups, spatial aggregation was tested using the approach of Cuzick and Edwards,²⁰ and the significance of spatial aggregation of the clusters within each group was tested using the Simes modified Bonferroni method for comparing multiple probabilities.²¹ Maps of cases were generated using the MapInfo version 4.0 software package (MapInfo Corp, Troy, NY). The intracluster distance was calculated as the mean of the distances of case addresses from the geometric center of the cluster.

RESULTS

Tuberculosis Incidence

From January 1, 1994, to June 30, 1996, there were 246 reported cases of tuberculosis in Baltimore, 2 of which (0.8%) were determined to be laboratory cross-contaminants on DNA fingerprint and epidemiologic investigation. Of the remaining 244 cases, 2 were relapses (0.8%) in patients already enrolled in the study, both with isolates proven to be identical to the original strain by DNA fingerprinting.²² There were 10 additional relapse cases in which the initial case of tuberculosis occurred before the study started, and these were included in the analysis. Of the 242 patients who entered our study, 43 (17.8%) had culture-negative tuberculosis, and there were 17 culture-positive patients (7.0%) for whom the *M tuberculosis* isolate was lost or unobtainable. Investigation of the cases for whom isolates were unobtainable failed to reveal any common features that might bias subsequent analysis. The isolates from the remaining 182 patients (91% of all culture-positive cases) were analyzed by DNA fingerprinting. The annual incidence rates for tuberculosis in the city for 1994, 1995, and 1996 were 14.8, 14.0, and 14.9 per 100 000, respectively. Demographic features of our study population are shown in Table 1.

Results of DNA Fingerprinting of *M tuberculosis* Isolates

Our initial analysis with the IS6110 probe revealed that 94 (52%) of 182 isolates matched DNA of at least 1 other patient isolate in the study (Table 2). These matches were grouped into 21 clusters with a mean cluster size of 4.5 members. Although a total of 21 clusters were found, 2 large, low band number clusters—IS6110 clusters A and B—accounted for a large proportion (37/94 [39.4%]) of the clustered isolates. Because the discriminative power of RFLP analysis is reduced in low band number clusters, we performed secondary fingerprinting using the PGRS of *M tuberculosis*^{5,23,24} for

Table 1.—Risk Factors by Group Assignment for Cases of Culture-Positive Tuberculosis in Baltimore (N = 182)*

Variables	Percentage With Variable (n/N)	Percentage With Variable			Probability of Differing Risks (P Values)			
		Total Study Group	Group 1 (n = 20)	Group 2 (n = 64)	Group 3 (n = 98)	Groups 1 and 2 vs 3, All Clustered vs Unclustered	Group 1 vs 2	Group 2 vs 3
Age <54 y	50 (91/182)	70 (Median age, 44 y)	66 (Median age, 46 y)	36 (Median age, 64 y)	.001	.72	.001	.006
Male	69 (125/182)	65	77	64	.17	.31	.10	.95
Black	75 (137/182)	65	86	70	.10	.05	.02	.61
Intravenous drug use	21 (33/156)	32	35	10	.001	>.99	.001	.02
Pulmonary tuberculosis	85 (155/182)	95	92	79	.007	>.99	.02	.12
Heavy alcohol use	32 (41/130)	44	44	22	.008	>.99	.01	.11
Homeless	7 (12/182)	5	12	3	.04	.68	.03	.53
HIV seropositive	33 (39/118)	16	50	35	.10	.01	.01	.53
Foreign born	3 (6/173)	0	2	5	.21	>.99	.40	.59
Nonintravenous drug use	3 (4/122)	8	6	1	.29	>.99	.23	.28

*Group 1, DNA clustering with epidemiologic link (recent transmission); group 2, DNA clustering with no epidemiologic link (recent transmission probable); and group 3, no DNA clustering (remote transmission). HIV indicates human immunodeficiency virus.

clustered isolates containing 6 bands or fewer. Overall, our use of combined IS6110 and PGRS DNA fingerprints led to a reduction in the number of isolates that showed clustering from 94 cases (52%) to 84 cases (46%), increased the number of clusters from 21 to 26, and reduced the mean cluster size from 4.5 to 3.2 cases per cluster (Table 2). Assuming that 1 case per cluster resulted from reactivation of remote infection and that the remainder resulted from the spread of the recently transmitted disease, 58 (32%) of 182 isolates could be defined as recently transmitted tuberculosis.

Epidemiologic Linkages Between Tuberculosis Cases

Using data from contact investigations and interviews, 10 epidemiologic links were found involving 22 patients. An epidemiologic link (among the patients in cluster Q) was discovered as a result of the DNA fingerprint match and was excluded because it was not identified by standard contact tracing.¹⁸ The remaining 20 patients (11%) with matching DNA fingerprints and identifiable epidemiologic links were classified as group 1 in our study. Tuberculosis was almost certainly the result of recent transmission among these patients (Table 2). Of the 182 patients, 64 (35%) had *M tuberculosis* strains that were clustered but could not be linked epidemiologically (group 2). Group 3 patients (unique DNA fingerprints) were considered likely to have acquired their tuberculosis remotely in time. As would be expected for remote transmission, none of the 98 patients in group 3 shared epidemiologic links. Thus, for patients with DNA fingerprint clustering, 20 (24%) of 84 had epidemiologic evidence of recent transmission, while none of the 98 patients with unique isolates had epidemiologic linkages.

Relationship of Demographic and Behavioral Factors to Tuberculosis Transmission

Factors associated with having an *M tuberculosis* isolate that was a member of an IS6110/PGRS cluster are shown in Table 1. Injection drug use, age younger than 54 years (the median age of patients in the study), alcoholism, pulmonary infection as the major site of disease, and homelessness were significantly associated with having a shared DNA fingerprint. We did not find a significant association between DNA fingerprint clustering and race, sex, human immunodeficiency virus (HIV) status, US birth, or nonintravenous drug use. Having extrapulmonary tuberculosis was significantly associated with infection by a strain with a unique DNA fingerprint type.

Multivariate analysis was conducted to determine whether these factors were independent predictors of membership in a cluster. Together, none of the 5 above-mentioned risk factors (injection drug use, age younger than 54 years, alcoholism, pulmonary tuberculosis, or homelessness) were significant independent predictors of IS6110/PGRS clustering. When age was removed from the 5 variable regression analysis, we did observe that injection drug use was a significant independent predictor of clustering, with an odds ratio of 4.0 (95% confidence interval, 1.3-12.7; $P = .02$). No other risk factors were found to be independent determinants of clustering in alternative combinations of 4 variable regression analyses, though it is possible that with a larger sample size other predictors might be found.

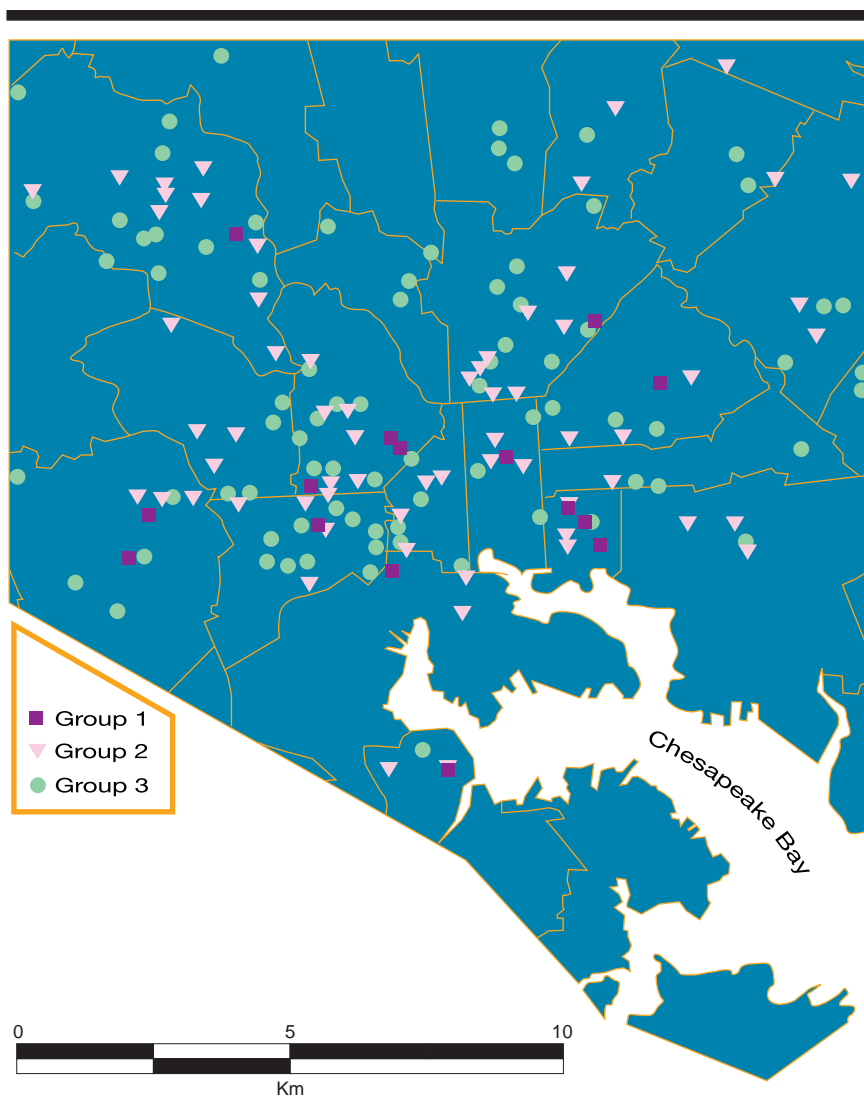
We next compared group 2 patients (DNA match and no epidemiologic link) with group 1 (DNA match and an epidemiologic link) and group 3 (no DNA match

Table 2.—Summary of DNA Fingerprint Matching*

IS6110 Typing Alone	
No. of clusters	21
Average No. of cases per cluster	4.5
Member of an IS6110 cluster, No. (%)	94 (52)
Unclustered, No. (%)	88 (48)
Combined IS6110/PGRS Typing	
No. of clusters	26
Average No. of cases per cluster	3.2
Member of an IS6110/PGRS cluster, No. (%)	84 (46)
Member of an IS6110/PGRS cluster with an epidemiologic link to other members of the same cluster, group 1, No. (%)	20 (11)
Member of an IS6110/PGRS cluster with no epidemiologic link to other members of the same cluster, group 2, No. (%)	64 (35)
Unclustered, group 3, No. (%)	98 (54)

*PGRS indicates polymorphic GC-rich repetitive sequence. Group 1 had recent transmission; group 2, recent transmission probable; and group 3, remote transmission.

and no epidemiologic link) patients. Group 2 patients were predominantly US born, black, and male and had a higher prevalence of homelessness and HIV infection than patients in groups 1 and 3 (Table 1). They were distinct from group 3 and similar to group 1 patients in that they tended to be young (median age, 46 years) and had high proportions of subjects reporting injection drug use, noninjection drug use, and excessive alcohol intake. With the exception of HIV status, there were no statistically significant risk factors that distinguished patients in group 1 from group 2 patients. In contrast, there were at least 7 variables that distinguished group 2 patients from those in group 3. Patients in group 2 were significantly more likely than group 3 patients to be younger than 54 years, black, homeless, and HIV seropositive, to use injection drugs or excessive alcohol, and to have pulmonary tuberculosis (Table 1). In addition, group 2 patients were more frequently male (77%) vs group 3 patients (64%) ($P = .10$). Although this analysis may be limited by the small size of group 1, we conclude that group 2



Geographic distribution of 182 culture-positive cases of tuberculosis in Baltimore, Md. Squares indicate home addresses of group 1 cases (DNA clustering, known epidemiologic link); triangles, addresses of group 2 cases (DNA clustering, no epidemiologic link); and circles, addresses of group 3 cases (no DNA clustering, no epidemiologic link). Patients whose home addresses mapped to the same 100s block or were less than 250 m apart are shown as a single point. The solid lines indicate postal code demarcations.

patients strongly resemble group 1 patients, suggesting that their tuberculosis was acquired by recent (as in group 1) rather than remote (as in group 3) transmission.

Geographic Patterns of Tuberculosis Transmission

We then evaluated the residential addresses of the patients in our study to determine if there are neighborhoods in Baltimore that are associated with tuberculosis transmission. Of the 182 patients, 6 patients (3.3%) were excluded from the geographic analysis. While 12 patients (6.6%) reported episodes of homelessness in the 12 months prior to diagnosis, only 2 (1.1%) had no consistent residential address during the entire study period and could not be included in geographic analyses. Also, 4 persons (2.2%) gave addresses

that could not be geographically located. Thus, the residences of 96.7% of the patients in our study could be assigned a geographic location.

We evaluated the spatial distributions of groups 1 through 3 as shown in the Figure. Group 1 patient addresses were spatially aggregated when compared with those of group 2 patients (Simes correction for multiple comparisons, $P < .001$) or group 3 patients (Simes correction for multiple comparisons, $P < .001$). Group 1 residences were clustered in areas of low socioeconomic status, high unemployment, high drug use, and poor housing stocks as assessed by the US Census Bureau and Baltimore police records. Group 2 patients tended to reside along the periphery of these same areas. Group 3 residences tended to be more widely distributed and were associated with the lower

middle-class neighborhoods of the city. Calculations of the intracluster distance supported the observation that group 2 patients were more dispersed than those in group 1. As shown in Table 3, the mean intracluster distance for group 2 clusters (3.10 km) was significantly greater than for clusters containing group 1 patients (1.72 km) ($P = .04$).

Geographic analysis was also used to look for evidence of casual recent transmission as indicated by geographic aggregation in the absence of epidemiologic linkages. We studied 7 evaluable clusters (clusters with ≥ 3 patients) accounting for 28 patients, all of which included at least 2 subjects from group 1 (clusters A5, B3, G, L, C, E, and K) (Table 3). Four clusters showed significant geographic aggregation (A5, C, K, and L), accounting for 16 (57%) of the 28 patients. For 6 (37.5%) of the 16 patients in these 4 clusters, no epidemiologic links were identifiable other than residing in close proximity to other cluster members. These 6 patients are likely to have acquired their tuberculosis by casual recent transmission. We were also able to evaluate 10 clusters in group 2 (representing 58 patients). Significant geographic aggregation was found for 3 (30%) of the 10 clusters and involved 11 (19%) of 58 patients. Hence, a greater proportion of clusters containing group 1 patients showed geographic aggregation than group 2 clusters, and a greater proportion of patients in group 1 were in geographically aggregated clusters than in group 2. This suggests that patients with tuberculosis in clusters with no epidemiologic links (group 2) either tend to acquire disease outside their home community or that they are more transient in their places of residence than their counterparts in clusters with epidemiologic links.

COMMENT

Our data illustrate recent advances in molecular typing of *M tuberculosis*, which have modified our understanding of tuberculosis transmission dynamics. In Baltimore, 46% of tuberculosis patients have isolates that are clustered and 32% of cases may be considered recently transmitted, similar to results from San Francisco, Calif; New York, NY; and Denver, Colo.³⁻⁵ Our results indicate that tuberculosis clusters occur within geographic localities, demographic groups, or individuals sharing certain behaviors and lifestyles, as has been suggested in other reports.^{25,26} Although some earlier studies relied on a single DNA probe to establish DNA fingerprint type, our data confirm the need for a second probe (PGRS) in strains with low copy numbers of IS6110.^{17,23,27}

In this prospective, city-wide study, the retrieval of 91% of all culture-positive

cases during a 30-month interval permits a comprehensive comparison of DNA clustering with epidemiologic transmission links. Our observation of 52% clustering of *M tuberculosis* isolates by IS6110 and 46% by IS6110/PGRS is similar to observations of molecular epidemiologic studies of tuberculosis transmission in other US cities. DNA fingerprint clustering was found in 40% of cases from San Francisco,³ 38% of cases from the Bronx, NY,⁴ 59% to 71% of cases among urban residents of central Los Angeles, Calif,^{28,29} and 46% of cases from Denver.⁵ The average of 35% to 50% clustering, which appears to hold relatively constant in US urban areas, may not prevail in other areas. For example, studies from rural Arkansas, the Netherlands, and Berne, Switzerland, revealed only 33%,⁶ 20%,³⁰ and 28%³¹ clustering, respectively.

A major observation of this study is that intensive contact tracing and patient interviews established epidemiologic links among only 20 (24%) of the 84 clustered patients. Since clustering is believed to be indicative of recent transmission, we anticipated that our tracing efforts would have led to a higher yield. One possible explanation for the low number of identified transmission links is that some clustered isolates may result from remote transmission of strains endemic in the city throughout many years. We tested this hypothesis by examining the demographic and behavioral traits of the clustered patients who lacked epidemiologic links (group 2) and found that they most resembled patients with DNA fingerprint matches and firm epidemiologic links (group 1), who almost certainly had recently transmitted tuberculosis. This suggests that remote transmission does not account for a significant proportion of clustering in Baltimore. The substantial geographic clustering of patients in DNA clusters who lacked epidemiologic linkages (group 2) also supports the hypothesis of ongoing recent transmission of tuberculosis among patients with DNA fingerprint matches.

Two other explanations could account for the low frequency of transmission links in clustered patients. The 64 individuals who had clustering but no epidemiologic link (group 2) may constitute a population with socioenvironmental risk factors for casual exposure to infectious tuberculosis cases. In support of this hypothesis, we found that group 2 patients tended to be young, US-born, black males with higher rates of homelessness, HIV infection, drug use, and alcohol use than group 3 patients. Transmission of tuberculosis among such individuals may be facilitated by both behavioral traits and the increased susceptibility to disease asso-

Table 3.—Characteristics of IS6110/PGRS Clusters and Their Epidemiologic Links*

Cluster	IS6110 Bands, No.	Patients, No.	Patients Linked, No.	Intracluster Distance, Mean (SD), km	Nature of Epidemiologic Link
Clustered With Epidemiologic Links					
A5	2	4	2	3.65 (1.98)	Familial (brother/sister)
B2	4	2	2	0.27	Familial (uncle/nephew)
B3	4	5	2	1.68 (0.70)	Social (boyfriend/girlfriend)
G	8	3	2	1.67 (0.48)	Work (coworkers)
L	10	3	2	1.49 (0.65)	Social/work (friends/coworkers)
C	11	5	4	0.01 (0.00)	Social (neighborhood)
E	11	4	2	3.99 (3.27)	Social (neighborhood)
K	12	4	2	2.40 (1.23)	Social (neighborhood)
I	13	2	2	0.36	Familial (aunt/niece)
Mean intracluster distance = 1.72 (1.43)					
Clustered With No Epidemiologic Link					
A1	2	4	0	1.57 (0.27)	...
A2	2	4	0	3.51 (2.61)	...
A3	2	5	0	4.00 (1.79)	...
A4	2	4	0	5.75 (2.24)	...
S	3	2	0	2.45	...
B1	4	3	0	2.61 (1.61)	...
N	6	3	0	2.44 (1.07)	...
O	6	2	0	7.14	...
M	9	2	0	4.86	...
R	9	3	0	3.47	...
U	9	4	0	2.44 (1.47)	...
Q	10	2	2†	4.06	Nosocomial (bronchoscopy)
D	10	5	0	0.95 (0.45)	...
F	10	3	0	3.36 (1.67)	...
V	10	2	0	1.69	...
P	11	2	0	2.03	...
J	12	2	0	0.36	...
Mean intracluster distance = 3.10 (1.73)					

*Ellipses indicate data not applicable. PGRS indicates polymorphic GC-rich repetitive sequence.
 †These patients were included in group 2, rather than group 1, because their epidemiologic link was discovered as a result of our intervention (ie, the DNA fingerprinting study).¹⁸

ciated with drug use and HIV infection. A second explanation for the low frequency of epidemiologic links among clustered cases may be that recently transmitted infection among contacts who are easy to trace is efficiently identified and interrupted with isoniazid preventive therapy before active disease develops. On the other hand, the unknown recipients of casually transmitted infection do not benefit from preventive therapy programs and are at risk for developing early active disease with strains matching others in the city.

A second major observation of this study is that clustered strains of *M tuberculosis* occur among patients whose residences are geographically aggregated. The neighborhoods associated with clustered cases and recent transmission were characterized by low socioeconomic status, inadequate housing, and high rates of drug abuse and crime. In contrast, unclustered cases—those associated with reactivation of old infection—resided in middle-class neighborhoods. Thus, the risk of recent tuberculosis infection in Baltimore continues to be highest in impoverished neighborhoods despite improvements that have resulted from DOT.

Historically, tuberculosis control has emphasized case detection and treatment as a means of reducing transmission and case rates. Baltimore has been highly successful in this respect with a 58% decrease in tuberculosis incidence since community-based DOT was introduced.¹⁰ In this setting, one might suspect that reactivated, remotely transmitted tuberculosis would account for most cases.³² However, our data suggest that despite a 15-year history of community-based DOT, which led to substantial decreases in tuberculosis incidence, about one third of tuberculosis cases continue to occur in microepidemics of recent tuberculosis transmission—a level as high as that reported in other cities with much shorter experiences with DOT. Recently transmitted disease in Baltimore appears to be propagated among a core population of difficult-to-serve patients.^{29,33} While implementation of comprehensive DOT and of preventive services has dramatically reduced the incidence of tuberculosis in Baltimore, the dynamics of transmission may not have been altered.

Although there has been renewed enthusiasm for the idea that tuberculosis is controllable, even eradicable, with more

widespread implementation of DOT, our findings sound a cautionary note. While community-based DOT has reduced the overall incidence of tuberculosis in Baltimore from 35.6 to 14.9 cases per 100 000 population during the past 15 years, it is apparent that a high proportion of disease in the city continues to be propagated by casual, recent transmission among individuals in impoverished neighborhoods in the city. Despite the usefulness of DOT, additional innovative approaches for providing tuberculosis care, such as location-based screening, may be necessary to further improve tuberculosis control in urban areas.

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