

## CHANGES IN THE TRANSMISSION OF TUBERCULOSIS IN NEW YORK CITY FROM 1990 TO 1999

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### ABSTRACT

**Background** Over the past decade, there has been a reduction in the incidence of tuberculosis in New York City and in the United States. However, the reduction has been confined mainly to U.S.-born persons. Understanding the reasons for the lack of reduction among non-U.S.-born persons may lead to new strategies for tuberculosis control.

**Methods** We performed DNA fingerprinting with the IS6110 insertion sequence of the organisms isolated from patients with culture-positive tuberculosis in northern Manhattan from 1990 to 1999. The goal was to identify the strains responsible for multiple infections, presumably through recent transmission (clusters of cases), as well as the strains found in only one patient, presumably representing reactivation of latent infection.

**Results** Of 546 available isolates of *Mycobacterium tuberculosis*, 261 (48 percent) belonged to a cluster and 285 (52 percent) did not. In multivariate analysis, significant predictors of noncluster status included birth outside the United States (odds ratio for a strain causing a cluster among non-Hispanic foreign-born patients, 0.31; 95 percent confidence interval, 0.14 to 0.66; odds ratio among Hispanic foreign-born patients, 0.51; 95 percent confidence interval, 0.30 to 0.88), age greater than 60 years (odds ratio, 0.37), and diagnosis after 1993 (odds ratio, 0.50). All these characteristics appeared to be associated with reactivation disease rather than with tuberculosis due to recent transmission. Homelessness was associated with clustering (odds ratio, 1.78; 95 percent confidence interval, 0.99 to 3.20) and therefore with recent transmission.

**Conclusions** These findings from northern Manhattan suggest that among foreign-born persons, tuberculosis is largely caused by reactivation of latent infection, whereas among U.S.-born persons, many cases result from recent transmission. Strategies for the control and elimination of tuberculosis among foreign-born persons at high risk should be directed toward the treatment of latent tuberculosis infection. (N Engl J Med 2002;346:1453-8.)

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SINCE reaching a peak of 10.5 cases per 100,000 in 1992, the incidence of tuberculosis in the United States has declined sharply, to just 5.8 cases per 100,000 in 2000.<sup>1</sup> Molecular epidemiologic studies in cities such as San Francisco and New York indicated that 40 percent or more of tuberculosis cases resulted from recent transmission rather than from the reactivation of long-latent disease.<sup>2,3</sup> Measures adopted by tuberculosis-control programs and hospitals with a high case load of patients with tuberculosis included improved surveillance; aggressive implementation of programs of directly observed therapy; education of physicians, aimed largely at increasing their index of suspicion with respect to tuberculosis; improving infection-control policies and practices in hospitals, jails, and prisons; and ensuring the availability of drugs to treat those with active tuberculosis.<sup>4</sup>

Nearly the entire decline in the numbers of cases of tuberculosis since 1992 is accounted for by the decline in cases among U.S.-born persons.<sup>1</sup> By contrast, the number of cases in non-U.S.-born persons has not dropped at all but, rather, has risen slightly. More than half the cases of tuberculosis in the United States in 2000 occurred in non-U.S.-born persons. The predominance of non-U.S.-born persons among those with tuberculosis is greatest where tuberculosis case rates far exceed the national average, as in California and New York City.<sup>5</sup>

There are several possible explanations for the fact that tuberculosis-control measures have been effective in one population (U.S.-born persons) but not in another (non-U.S.-born persons).<sup>6-8</sup> Non-U.S.-born persons may be less likely to seek medical care and therefore more likely to have undiagnosed and infectious tuberculosis for prolonged periods in their immigrant communities.<sup>9</sup> Alternatively, some immigrants may have reactivated latent infections that were acquired in their native countries.<sup>10-12</sup> Our tuberculosis-control measures, which are designed to interrupt transmission, would not be effective among foreign-born persons with reactivation disease.

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To address the hypothesis that non-U.S.-born persons are, in general, not involved in ongoing transmission of tuberculosis and are thus relatively unaffected by current tuberculosis-control measures, we performed a molecular epidemiologic analysis of cases of tuberculosis in the Washington Heights neighborhood of New York City for the years 1990 through 1999. This neighborhood has had a tuberculosis case rate much higher than that of New York City as a whole (in excess of 125 cases per 100,000 persons in 1992, as compared with 50 per 100,000 for the city). The concentration of recent immigrants there is among the highest in the city. Over 40 percent of the residents of Washington Heights were not born in the United States.

## METHODS

### Patient Population

Study patients included all persons with culture-proved tuberculosis who were treated at Columbia Presbyterian Medical Center between 1990 and 1999 and who resided in New York City. Columbia Presbyterian Medical Center is located in Washington Heights, a leading destination among recent immigrants to New York City, with a total of 28,824 new residents between 1990 and 1994, 82 percent of whom were from the Dominican Republic.<sup>13</sup> Columbia Presbyterian Medical Center is the major inpatient health care provider in northern Manhattan and also provides care to many patients from adjacent Central and East Harlem, the population of which is 80 percent black and composed mostly of U.S.-born persons.

### Restriction-Fragment–Length Polymorphism Analysis

Restriction-fragment–length polymorphism (RFLP) analysis (DNA fingerprinting with the IS6110 insertion sequence) was performed at the Public Health Research Institute in New York according to internationally standardized methods.<sup>14</sup> Briefly, *Mycobacterium tuberculosis* DNA was extracted, digested with *PvuII*, subjected to electrophoresis, and hybridized by Southern blotting with a fragment of the insertion element IS6110. *M. tuberculosis* strains with fingerprints of five or fewer bands were subjected to secondary DNA analysis with spoligotyping (spacer oligonucleotide typing).<sup>15–17</sup> These low-band RFLP patterns were assigned to the category of strains causing clusters of cases only if their spoligotypes were identical and specific to the IS6110 fingerprint. If they were not, they were classified as causing unique cases.

Identical strains recovered from different patients comprised a cluster of cases. Strains found in only one person were considered unique. Clustered cases were assumed to represent recent transmission, whereas a unique case was considered to result from the reactivation of latent disease. Data on clustered and unique cases were subjected to univariate and multivariate analysis; information on clinical, social, and demographic variables was obtained from the registry of the Tuberculosis Control Program at the New York City Department of Health. Study participants' addresses in New York City were mapped, and the addresses were matched to Census-block information with Topologically Integrated Geographic Encoding and Referencing system (TIGER) files, the geographic locator system of the U.S. Census. Mapping was performed with geographic-information-systems software. The study was approved by the institutional review boards of the Columbia University College of Physicians and Surgeons and the New York City Department of Health, which determined that informed consent was not required.

### Statistical Analysis

In univariate analysis, chi-square tests were performed to test associations of categorical variables with cluster status. All unknown

values were excluded from the analysis. The Wilcoxon test was used to test associations of continuous variables with cluster status. A marked decrease in the risk of clustering occurred for patients around the age of 60 years, and therefore age was categorized as 60 years or less or greater than 60 years. A significant drop in the risk of clustering occurred among patients in whom tuberculosis was diagnosed after 1993; therefore the year of diagnosis was analyzed as a categorical variable (1990–1993 or 1994–1999).

Variables significantly associated with cluster status ( $P < 0.05$ ) were entered into logistic-regression models with all unknown values represented by indicator variables. Odds ratios have been used to represent the odds of having an *M. tuberculosis* isolate that belonged to a cluster of isolates; that is, an odds ratio greater than 1 is associated with having a case that belongs to a cluster (presumably, a case resulting from recent transmission), and an odds ratio of less than 1 is associated with a strain's having a unique RFLP pattern (presumably, a case resulting from reactivation of latent infection). All statistical analyses were conducted with SAS software (SAS Institute, Cary, N.C.).

## RESULTS

### Study Population

Of 812 cases of tuberculosis diagnosed at Columbia Presbyterian Medical Center between 1990 and 1999, 745 (91.7 percent) were culture-positive. In 575 of the 745 cases (77.2 percent), DNA analysis could also be performed. Twenty-nine patients with tuberculosis were excluded from the study either because their residence was not in New York City or because they could not be matched to the case-registry data, leaving a final study population of 546. This represented 73.3 percent of all culture-positive cases diagnosed in the study period.

Forty-six percent of the patients resided in the Washington Heights health district, and 27 percent lived in the Central and East Harlem health districts. The remainder were distributed among the Bronx (16 percent), the rest of Manhattan (7 percent), Queens (3 percent), and Brooklyn (2 percent), with one patient from Staten Island. Thirty-seven percent of the patients were born in countries other than the United States; by far the largest single group was from the Dominican Republic, making up 55.4 percent of the total foreign-born population. Forty-three percent of the patients were black, and 45 percent were Hispanic. These and other clinical and demographic characteristics are shown in Table 1. The patients in our cohort were statistically similar to all patients in the New York City Tuberculosis Case Registry in terms of median age and age distribution, sex, human immunodeficiency virus (HIV) status, birth within or outside the United States, and the proportion of foreign-born persons who had been in the United States for up to nine years before the diagnosis of tuberculosis.

### Analysis of Cluster Status

IS6110 DNA fingerprinting and spoligotyping determined that in 261 of the 546 patients (48 percent), the disease was caused by isolates that had at least one

**TABLE 1.** DEMOGRAPHIC, SOCIAL, AND CLINICAL CHARACTERISTICS AND THEIR ASSOCIATION WITH CLUSTER STATUS IN THE UNIVARIATE ANALYSIS.\*

CHARACTERISTIC	ALL PATIENTS (N=546)	PATIENTS WITH CLUSTERED CASES (N=261)	PATIENTS WITH UNIQUE CASES (N=285)	ODDS RATIO FOR CLUSTERING (95% CI)
<b>Demographic</b>				
Median age — yr	41	38	45	
Male sex — no. (%)	369 (67.6)	190 (72.8)	179 (62.8)	1.58 (1.10–2.28)
Race or ethnic group — no. (%)				
Asian	22 (4.0)	4 (1.5)	18 (6.3)	0.23 (0.08–0.69)
Hispanic	247 (45.2)	103 (39.5)	144 (50.5)	0.64 (0.45–0.90)
Black	234 (42.9)	141 (54.0)	93 (32.6)	2.43 (1.71–3.43)
White	43 (7.9)	13 (5.0)	30 (10.5)	0.45 (0.23–0.87)
Foreign birth — no. (%)	204 (37.4)	74 (28.4)	130 (45.6)	0.47 (0.33–0.67)
Median years in U.S.†	16	14	17	NS
Age >60 yr — no. (%)	98 (17.9)	23 (8.8)	75 (26.3)	0.27 (0.16–0.45)
Diagnosis after 1993 — no. (%)	208 (38.1)	79 (30.3)	129 (45.3)	0.52 (0.36–0.75)
Residence — no. (%)				
Washington Heights	250 (45.8)	123 (47.1)	127 (44.6)	NS
Harlem	146 (26.7)	75 (28.7)	71 (24.9)	NS
Other	150 (27.5)	63 (24.1)	87 (30.5)	NS
<b>Social</b>				
Homelessness — no. (%)‡	69 (13.1)	48 (19.1)	21 (7.6)	2.86 (1.65–4.93)
Injection-drug use — no. (%)§	52 (22.3)	32 (34.8)	20 (14.2)	3.23 (1.70–6.11)
Median income — dollars	19,069	19,195	18,650	
<b>Clinical</b>				
Cavitary disease — no. (%)¶	116 (24.7)	56 (24.6)	60 (24.9)	1.02 (0.67–1.55)
HIV infection — no. (%)	198 (51.4)	116 (58.0)	82 (44.3)	1.73 (1.16–2.60)
Pulmonary source of isolate — no. (%)**	466 (86.0)	236 (91.5)	230 (81.0)	2.52 (1.49–4.27)
Drug resistance — no. (%)				
Any drug	45 (8.2)	22 (8.4)	23 (8.1)	1.05 (0.57–1.93)
Isoniazid only	24 (4.4)	12 (4.6)	12 (4.2)	1.09 (0.48–2.49)
Rifampin only	2 (0.4)	0	2 (0.7)	—
MDR	19 (3.5)	10 (3.8)	9 (3.2)	1.22 (0.49–3.06)

\*In the calculation of odds ratios, the patients without the given characteristic served as the reference group. CI denotes confidence interval, NS not significant, HIV human immunodeficiency virus, and MDR multidrug-resistant (i.e., tuberculosis was resistant to at least isoniazid and rifampin).

†Only foreign-born persons are included.

‡Data were missing for 10 patients in the clustered group and 10 in the unique group.

§Data were missing for 169 patients in the clustered group and 144 in the unique group.

¶Data were missing for 33 patients in the clustered group and 44 in the unique group.

||Data were missing for 61 patients in the clustered group and 100 in the unique group.

\*\*Data were missing for three patients in the clustered group and one in the unique group.

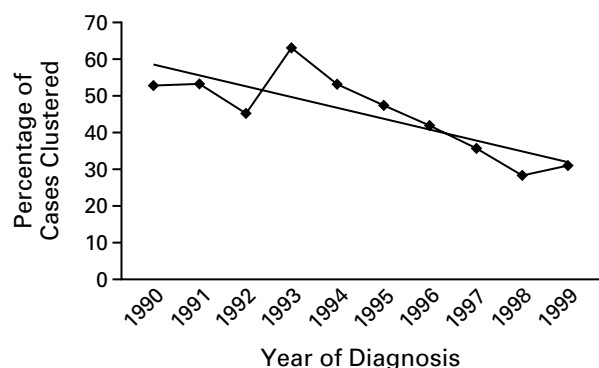
matching isolate in the cohort and that were therefore designated as belonging to a cluster. In 285 of the 546 patients (52 percent), the disease was caused by an isolate that was unique, implying reactivation of latent infection. This number included 31 patients whose isolates were “low-banders” (with five or fewer bands) and that had a match on IS6110 DNA fingerprinting but not on spoligotyping; these cases were therefore not classified as belonging to a cluster. The clusters comprised a mean of 5.2 cases (median, 3; mode, 2) and had a total of 51 distinct RFLP patterns.

On the basis of previous studies of the epidemiology of tuberculosis in which molecular techniques were used, we inferred that the cases in the clustered group represented the proportion of our study pop-

ulation with disease due to recent transmission. The proportion of cases caused by clustered isolates (i.e., cases of tuberculosis due to recent transmission) decreased from 63.2 percent in 1993 to 31.4 percent in 1999 (Fig. 1). As a result, the cases of tuberculosis in northern Manhattan at the end of the study period were largely those caused by unique strains.

#### Risk Factors for Tuberculosis Due to Recent Transmission

Table 1 shows the odds ratios for having an isolate in the clustered rather than the unique group according to clinical, social, and demographic characteristics. Characteristics significantly associated with clustering according to the univariate analysis were male sex (odds ratio, 1.58), black race (odds ratio, 2.43), home-



**Figure 1.** Linear Regression Model Showing the Relation between the Proportion of Tuberculosis Cases Occurring in Clusters (Representing Recent Transmission) and the Year of Diagnosis.

From 1990 to 1999, the percentage of clustered cases peaked at 63 percent in 1993 and fell to 31 percent by 1999.  $P$  for trend = 0.006 by the chi-square test;  $r^2 = 0.675$ . The straight line is the regression line.

lessness (odds ratio, 2.86), injection-drug use (odds ratio, 3.23), HIV infection (odds ratio, 1.73), and a pulmonary source of the isolate (odds ratio, 2.52). Multidrug-resistant tuberculosis, cavitary disease, and income level were not significantly associated with clustering.

In contrast, factors associated with unique RFLP patterns, representing the development of disease through reactivation of latent infection, were Asian race (odds ratio for clustering, 0.23), Hispanic ethnic background (odds ratio, 0.64), white race (odds ratio, 0.45), foreign birth (odds ratio, 0.47), diagnosis after 1993 (odds ratio, 0.52), and age of more than 60 years (odds ratio, 0.27) (Table 1).

In the multivariate analysis, birth outside the United States was strongly associated with infection with organisms not belonging to a tuberculosis cluster (Table 2). Both non-Hispanic foreign-born patients (odds ratio for clustering, 0.31) and Hispanic foreign-born patients (odds ratio, 0.51) were significantly less likely to be infected with an organism in a clustered group. Other characteristics found to be independently associated with the likelihood of having a unique RFLP pattern were an age of more than 60 years (odds ratio for clustering, 0.37) and diagnosis after 1993 (odds ratio, 0.50). Figure 2 shows the distribution of cases among U.S.-born and foreign-born patients in northern Manhattan in 1992 and 1993 and in 1998 and 1999. In the multivariate analysis, homelessness had an odds ratio for clustering of 1.78 (95 percent confidence interval, 0.99 to 3.20).

A separate model was created to evaluate the role

**TABLE 2.** RESULTS OF THE MULTIVARIATE ANALYSIS.\*

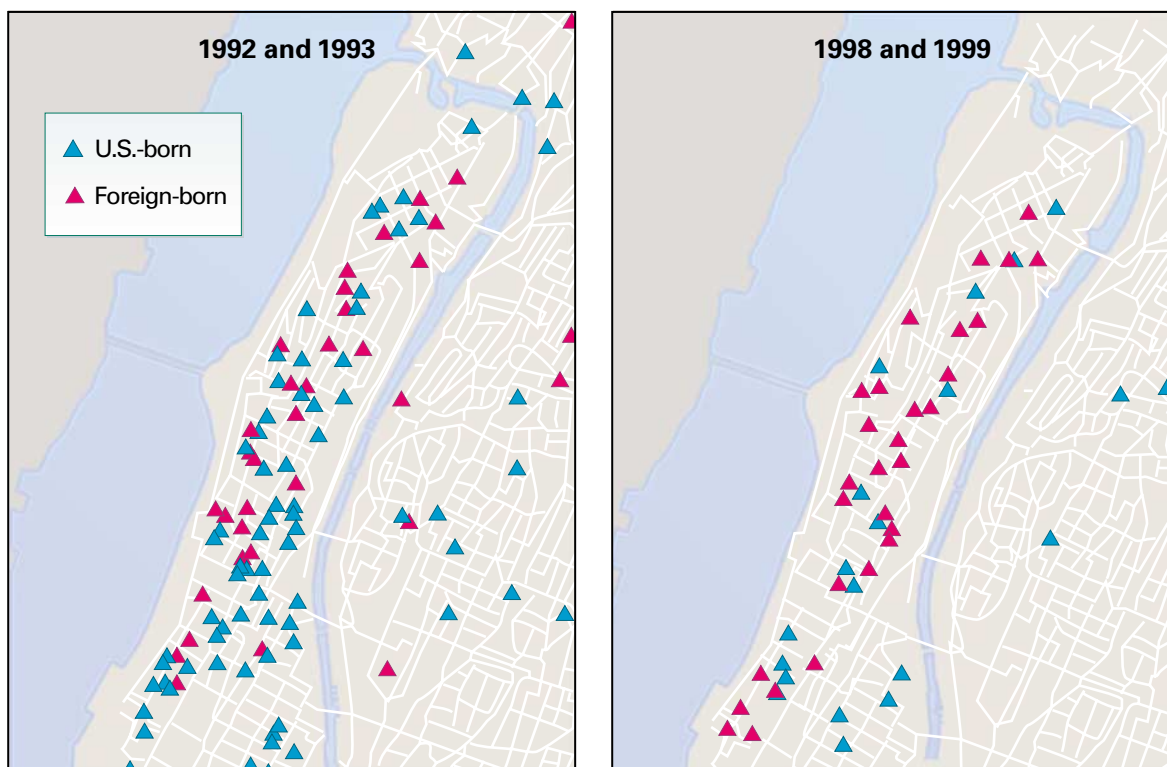
CHARACTERISTIC	ADJUSTED ODDS RATIO FOR CLUSTERING (95% CI)
Foreign birth, non-Hispanic ethnic background	0.31 (0.14–0.66)
Foreign birth, Hispanic ethnic background	0.51 (0.30–0.88)
Age >60 yr	0.37 (0.21–0.63)
Diagnosis after 1993	0.50 (0.33–0.76)

\*In the calculation of the odds ratios, patients born in the United States served as the reference group. CI denotes confidence interval. Odds ratios have been adjusted for homelessness, source of isolate, human immunodeficiency virus infection, and sex.

of predictors of clustering that were specific to foreign-born persons. Although there was no significant difference overall between the percentage of HIV-infected and non-HIV-infected foreign-born patients with organisms belonging to a tuberculosis cluster (43 percent vs. 57 percent,  $P = 0.69$ ), there was a significant interaction between years of residence in the United States and HIV infection. Among foreign-born persons with HIV infection, increasing length of residence in the United States was independently associated with increasing odds of clustering (odds ratio, 1.15 per year of residence; 95 percent confidence interval, 1.10 to 1.19). In contrast, among foreign-born persons without HIV infection, the opposite was found: increasing length of residence in the United States was independently associated with decreasing odds of clustering (odds ratio, 0.93; 95 percent confidence interval, 0.90 to 0.97). Thus, among persons who were born outside the United States, tuberculosis was significantly more likely to result from recent transmission among those who were HIV-infected and more likely to result from the reactivation of latent infection among those who were not infected with HIV (Fig. 3).

## DISCUSSION

Our study results show that over a period in which tuberculosis case rates have fallen from recent high levels, the proportion of cases occurring as a result of recent transmission dropped sharply, as manifested by the declining proportion of isolates of *M. tuberculosis* with RFLP patterns that matched at least one other case in the area we studied. In addition, we found that tuberculosis was unlikely to result from recent transmission in persons born outside the United States, since relatively few such persons had tuberculosis caused by an isolate that matched another in the sample. Rather, cases among foreign-born persons were



**Figure 2.** Cases of Tuberculosis among Foreign-Born and U.S.-Born Patients in New York City.

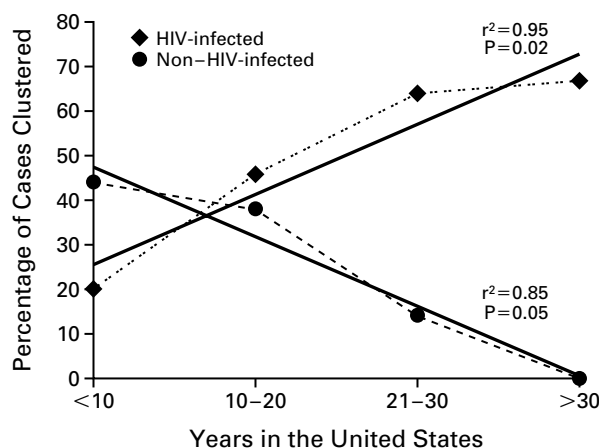
As the two maps of northern Manhattan show, the proportion of cases in foreign-born persons increased during the period we studied, from 28 percent in 1992 and 1993 to 59 percent in 1998 and 1999.

substantially more likely to develop as a result of the reactivation of latent tuberculosis infection. The main exception was that HIV infection modified the effect of foreign birth and was associated with an increased likelihood of acquiring tuberculosis by recent transmission. Although our study was confined to only a part of New York City, the data are both robust and broadly applicable because of the high percentage of isolates available for IS6110 DNA fingerprinting relative to the total number of cases of tuberculosis diagnosed, the long period during which the data were collected, and the high proportion of immigrants in the neighborhoods studied. These results should have direct implications for tuberculosis-control programs in other large urban areas in the United States.<sup>1,18</sup>

During the previous decade, the number of cases of tuberculosis in New York City fell from a peak of 3811 in 1992 to 1350 in 2000, a decline of 65 percent. The causes of this rapid decline included widespread provision of medication through programs of directly observed therapy, improvements in policies and practices of infection control related to tuberculosis, and standardization of initial drug-treatment reg-

imens for patients with active disease.<sup>4</sup> These interventions were all aimed at curing patients with active disease quickly, which has the effect of reducing transmission in the community. Our study demonstrated that 63.2 percent of all cases belonged to a cluster in 1992, but by 1999 that figure had dropped to 31.4 percent.

Our findings provide insight into the apparent “immunity” of non-U.S.-born persons to the tuberculosis-control measures used for most of the past decade. IS6110 DNA fingerprinting of *M. tuberculosis* isolates from non-U.S.-born patients in the Washington Heights neighborhood of New York City demonstrates that cases in this patient population occur sporadically rather than in clusters, as a result of recent transmission. Thus, the failure of tuberculosis-control measures to decrease disease rates among non-U.S.-born persons did not occur because patients escaped these measures but, rather, because the measures used did not address the development of tuberculosis in such foreign-born persons. To decrease the prevalence of tuberculosis among non-U.S.-born persons in this country, widespread treatment of latent tuberculosis



**Figure 3.** Proportion of Cases of Tuberculosis among Foreign-Born Patients Occurring in Clusters, According to the Length of Residence in the United States and the Presence or Absence of Human Immunodeficiency Virus (HIV) Infection.

Among foreign-born patients infected with HIV, the proportion in whom tuberculosis was caused by a strain occurring in clusters increased as the length of residence in the United States increased. Among foreign-born patients without HIV infection, the opposite relation is evident: the proportion of cases caused by a clustering strain decreased over time. The straight lines are the regression lines.

infection must be implemented. Our results support the recommendations for the treatment of latent infection in the Institute of Medicine's recent landmark report.<sup>19</sup>

The U.S. government requires that persons planning to emigrate to the United States be screened for active tuberculosis before their departure. Until recently, however, little emphasis was placed on the diagnosis and treatment of latent infection. The situation is further complicated by the generally poor acceptance and completion rates for treatment of latent tuberculosis infection.<sup>20,21</sup> Newly revised guidelines issued by the Centers for Disease Control and Prevention, the American Thoracic Society, and the Infectious Disease Society of America encourage testing for and treatment of latent infection in persons from countries where the prevalence of tuberculosis is high who have been in the United States for less than five years.<sup>22</sup> The recommended treatment regimen is nine months of isoniazid. A two-month regimen of rifampin and pyrazinamide has been shown to be effective in treating latent tuberculosis infection in patients with HIV infection, although there is some concern about the safety of this regimen.<sup>23</sup> Shorter and safer regimens for the treatment of latent tuberculosis infection are urgently needed if tuberculosis is to be completely controlled and eliminated in the United States and elsewhere.

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