Exogenous Reinfection as a Cause of Late Recurrent Tuberculosis in the United States

Julia D. Interrante^{1,2}, Maryam B. Haddad^{1,2,3}, Lindsay Kim¹, and Neel R. Gandhi^{2,4,5}

¹Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, Atlanta, Georgia; and ²Department of Epidemiology, ⁴Department of Global Health, Rollins School of Public Health; ³Laney Graduate School, and ⁵Department of Medicine (Infectious Diseases), School of Medicine, Emory University, Atlanta, Georgia

Abstract

Rationale: The etiology of recurrent tuberculosis is typically presumed to be reactivation of residual *Mycobacterium tuberculosis* infection, but reinfection may account for a greater proportion of recurrent tuberculosis than previously recognized.

Objective: To use *M. tuberculosis* genotyping to characterize the etiology of recurrent tuberculosis occurring 12 months or more after treatment completion.

Methods: The study population for this national population-based cohort was drawn from the estimated 3,039 persons reported to the National Tuberculosis Surveillance System with two episodes of tuberculosis in the United States during 1993–2011, 194 of whom had genotyping results from both the initial and subsequent episode. We analyzed the proportion of recurrent tuberculosis attributable to and risk factors associated with reinfection.

Measurements and Main Results: Among 136 recurrences meeting inclusion criteria, genotypes between episodes were the same

for 116 (85%) recurrences during 1996–2011; the 20 (15%) with differing genotypes were categorized as reinfections. Using exact logistic regression, factors associated with reinfection included Mexican birth with both TB episodes diagnosed in the United States within 12 years of immigration (adjusted odds ratio, 10.7; 95% confidence interval, 1.7–86.3) and exclusive use of directly observed therapy for treatment of the first episode (adjusted odds ratio, 4.5; 95% confidence interval, 1.0–29.2).

Conclusions: Reinfection was the cause of 15% of late recurrent tuberculosis cases in this U.S. cohort. The proportion caused by reinfection increased to 60% in certain subpopulations, such as recent immigrants from Mexico, suggesting that, despite successful treatment for tuberculosis during their first episode, these individuals remain in a social environment where they are reexposed to *M. tuberculosis*. Public health interventions to prevent novel reinfection might require a broader focus in these communities.

Keywords: emigration and immigration; epidemiology; molecular epidemiology; *Mycobacterium*; risk factors

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Correspondence and requests for reprints should be addressed to Maryam B. Haddad, M.S.N., M.P.H., Division of Tuberculosis Elimination, Centers for Disease Control and Prevention, 1600 Clifton Road NE, ME E-10, Atlanta, GA 30329. E-mail: mhaddad@cdc.gov

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Despite 2 decades of steadily declining tuberculosis (TB) rates and a historic low of 9,421 cases in 2014, the United States is not on track to achieve TB elimination, defined as an annual incidence of 1 new case per

1 million population (1, 2). In addition, the annual decrease in the TB rate is slowing (3). In considering strategies to accelerate progress toward the 2050 goal of TB elimination, one potential target is

prevention of recurrent TB. About 5% of TB cases annually occur in individuals with a history of previous TB disease, and this proportion has remained stable for at least 4 decades (1, 4, 5).

The National Tuberculosis Surveillance System considers TB to be recurrent if an individual with a history of TB disease is diagnosed with incident TB 12 months or more after the last clinical encounter for treatment of the first TB episode (1). This explicit exclusion of TB relapses that occur during (i.e., “treatment failure”) or within 12 months following treatment means that the majority of relapses (5–9) are not routinely captured, but rather are considered a continuation of the same incompletely cured TB episode.

Likewise, “late” recurrence (12 mo or later) in a person who successfully completed treatment is typically attributed to incomplete cure of the first TB episode—residual *Mycobacterium tuberculosis* infection with the potential to reactivate (10). However, reinfection with a new strain is another possible etiology. Distinguishing between these two causes is important because the interventions used to curb them differ (11, 12). Interventions to prevent reactivation are focused on ensuring an individual patient’s treatment adherence and completion, but preventing a novel TB reinfection requires a broader focus on curbing *M. tuberculosis* transmission in the patient’s social environment and community.

Although reactivation appears to be the primary cause of TB recurrence in the United States (9, 11, 13), Western Europe (14–17), and Australia (18), molecular data from South Africa (19–21) suggest that reinfection may be responsible for a larger proportion of TB recurrences in high-incidence settings. Regardless, without the *M. tuberculosis* genotyping results of both the initial and subsequent TB episode, the proportion of recurrent TB attributable to reinfection is rarely certain (11, 12). In our earlier study of recurrent TB in the United States (22), we had genotyping results from both TB episodes for only 24 patients, similar to other previous studies of recurrent TB (9, 13–15, 17–21).

Reinfection may account for a greater proportion of recurrent cases in the United States than previously recognized. Recent TB outbreaks and other studies suggest ongoing TB transmission, particularly in certain disadvantaged subpopulations, such as recent immigrants, people experiencing homelessness, and patients with HIV infection (11–13, 15, 19–23). Now that *M. tuberculosis* genotyping has become routine, it is possible to compare the

episode genotypes rather than having to presume that TB recurrence reflects incomplete cure of the first TB episode. To better understand the proportion of recurrent TB attributable to reinfection in the United States, as well as its associated risk factors, we examined a nationally representative sample of patients with recurrent TB.

Methods

In this retrospective, observational study, we used the National Tuberculosis Surveillance System, which collects standardized data of all TB cases in the 50 U.S. states, Puerto Rico, and the District of Columbia (1). TB cases that occurred between 1993 and 2011 and reported as of June 25, 2012, were eligible for inclusion. This study used a previously developed matching algorithm (22) that is based on date of birth, sex, self-reported race, and country of origin, as well as state and year of the first episode, to identify recurrent TB episodes and match them to the earlier episodes. When previously validated using 1993–2006 records (22), this algorithm successfully identified 1,533 of 2,702 persons who appeared to be living in the United States for both of their TB episodes (i.e., sensitivity of 56.7%), with a positive predictive value for correctly identifying recurrent TB of 97.6% (22).

Systematically linked to the National Tuberculosis Surveillance System, the National Tuberculosis Genotyping Service was launched in 2004 to offer rapid genotyping of isolates from every culture-positive TB case in the United States. Before 2004, genotyping was available upon request in certain circumstances (e.g., to help investigate outbreaks or suspected false-positive cultures). Earlier methods were based on IS6110-based restriction fragment-length polymorphism (RFLP) analysis patterns and additional spacer oligonucleotide (spoligotyping) for RFLP patterns with fewer than six bands. Beginning in 2004, spoligotyping and 12-locus mycobacterial interspersed repetitive unit variable number tandem repeats (MIRU-VNTR) were routinely performed for each isolate nationwide. In 2009, MIRU-VNTR analysis expanded from 12 to 24 loci to increase discriminatory power (24–27). Genotyping of culture-positive cases increased from 51% in 2004

to 94% in 2012 (26, 27). The isolate submission form for the National Tuberculosis Genotyping Service includes a field for public health laboratory personnel to note any suspicion that an isolate represents a false-positive culture, which can occur if patient specimens are mislabeled or cross-contaminated. To help with investigation, these personnel have the option to submit multiple isolates for genotyping.

For this retrospective study of reinfection, spoligotype patterns and MIRU-VNTR loci were examined for both episodes. For older cases without MIRU-VNTR results, the number and length of specific DNA fragments in RFLP patterns were compared. We defined reactivation as recurrent TB in which the two episodes matched by spoligotype and differed by no more than a single MIRU-VNTR locus or one RFLP band; genotype patterns with more differences were classified as reinfection. None of the initial or subsequent isolates in any of the cases in this study had been flagged as a potential false-positive culture result.

Analyses

All TB recurrences with genotyping data for both episodes were eligible for the study. To increase model specificity (i.e., to include only patients not expected to have recurrent TB), our primary analysis was restricted to persons considered to have completed an adequate course of treatment for their first TB episode (i.e., reason treatment was stopped was that it was “completed”).

The outcome of interest was novel reinfection. Independent variables of interest included HIV, sex, race, time between episodes, and age at second episode. Characteristics of the first episode included treatment duration; whether treatment was administered exclusively by directly observed therapy; anatomic site of disease; and, for pulmonary TB, whether disease was cavitary or smear-positive and whether sputum conversion was documented. The U.S. state in which the two TB episodes occurred, the patient’s country of origin, and the number of years living in the United States at the time of the second episode were also considered. Other variables included social risk factors for TB, including homelessness, incarceration, and substance abuse in either episode.

For each independent variable, descriptive statistics were calculated to obtain an unadjusted degree of association

with reinfection (vs. reactivation). Fisher's exact tests of association were used for categorical variables, and Wilcoxon's signed-rank tests were performed for continuous variables. Those variables with $P < 0.1$ in unadjusted analysis were screened into the initial exact logistic regression model (28, 29). Interactions between all screened-in variables were assessed and dropped from the model using backward P value–based elimination. Individual variables were dropped using change-in-estimate elimination (28). Unadjusted and adjusted odds ratios (ORs), along with 95% confidence intervals (CIs), were computed. Statistical significance for all calculations was assessed by setting $\alpha = 0.05$. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC).

Our supplemental analysis included all recurrences, regardless of whether treatment of the first episode was completed (i.e., included loss to follow-up, refused treatment, or unknown outcome), to examine whether the distribution of reinfection versus reactivation or risk factors for reinfection would differ with a more inclusive definition of recurrent TB.

Also, because the paucity of genotyping results in the early years of this study meant that our final study population included TB recurrences during 1996–2011 only, we repeated our analysis restricting the years to 2000–2011 and to 2005–2011, when the most complete data were available, to examine whether the reinfection proportion or risk factors would differ.

Ethical Considerations

This study was determined not to require human subject review by the Centers for Disease Control and Prevention and the Emory University Institutional Review Board, because the data collected by the National Tuberculosis Surveillance System and the National Tuberculosis Genotyping Service are part of routine public health surveillance. The identities of persons were held confidential in accordance with Section 308(d) of the U.S. Public Health Service Act (42 U.S.C. § 242m).

Results

Among the 312,589 total TB cases reported in the United States during 1993–2011, 6,078 cases appeared to represent two

episodes of TB in the same person (i.e., 3,039 individual persons). A total of 194 individuals had genotyping results available from both episodes during 1996–2011, and 136 (70%) were eligible for our primary analysis (Figure 1). Recurrences were distributed among 36 U.S. states and Puerto Rico (data not shown); however, 59 (43%) of these recurrent cases were in 4 large U.S. states in which approximately half the country's TB cases are reported annually (1).

Thirty-five patients (26%) were female. Among U.S.-born persons ($n = 78$; 57%), 30 (38%) were black non-Hispanic and 12 (15%) were Hispanic (Table 1). Foreign-born persons with recurrent TB ($n = 58$; 43%) had immigrated a median of 12 years earlier at the time their second TB episode in the United States was diagnosed (interquartile range [IQR], 7–20). Mexico was the most frequently reported country of origin of these immigrants ($n = 19$; 14%). Treatment of the first episode was administered exclusively by directly observed therapy for 88 patients (65%), completely self-administered for 13 patients (10%), and a combination of both administration methods for 34 patients (25%) (data not shown). Median duration of treatment for the first episode was 7 months (IQR, 6–10).

Primary Analysis

Of the 136 recurrences meeting the inclusion criteria for the primary analysis, 20 (15%) were classified as reinfections on the basis of genotype differences (Table 2) and 116 (85%) as reactivations on the basis of genotype similarities. Both groups had similar proportions of pulmonary, cavitary, and smear-positive disease. The median number of months between episodes was equivalent in both groups at 26 months, and the majority of second-episode TB strains were from the Euro-American lineage.

However, the characteristics of the two groups differed in a few distinct factors. Patients with reinfection were a median of 7 years younger at the time of their second episode (Table 1). The median number of years living in the United States when the TB recurrence was diagnosed was also shorter for foreign-born persons with reinfection (9 yr vs. 14 yr). Among foreign-born persons with recurrent TB, a higher proportion of those from Mexico and Africa had reinfection.

Among the 10 recent immigrants from Mexico, 6 (60%) with TB diagnosed twice in the United States during the 1996–2011 period appeared to have reinfection as the etiology for their second TB episode. Among the four recent immigrants from Africa, two (50%) had reinfection. Three factors were individually significant for reinfection in unadjusted analysis: State A residence, African birth, and Mexican birth with recent immigration to the United States. Because of small numbers, African birth was too unstable to be retained in the multivariate model (Table 3). After we adjusted for demographics, HIV status, and treatment factors, two factors remained statistically significant for reinfection: exclusive use of directly observed therapy for treatment of the first episode of TB (adjusted OR, 4.5; 95% CI, 1.0–29.2) and Mexican birth with both TB episodes diagnosed in the United States within 12 years of immigration (adjusted OR, 10.7; 95% CI, 1.7–86.3).

Supplemental Analyses

The supplemental analysis, where treatment completion of the first TB episode was not required, included 188 recurrences: 164 (87%) due to reactivation and 24 (13%) due to reinfection. Although the more inclusive definition of recurrent TB added 48 reactivations and 4 reinfections, the relative proportion of recurrence due to reinfection did not substantially change (i.e., only 2% of the total were reclassified). Fourteen of the fifteen whose first TB episode was treated for less than 2 months experienced reactivation. HIV, homelessness, and incarceration continued to be prevalent among all TB recurrences but remained unassociated with reinfection.

When we restricted our study population to 2000–2011 or 2005–2011 TB recurrences, the reinfection proportion changed minimally from 15% to 16%. Risk factors for reinfection were not substantially different (data not shown).

Discussion

In this national population-based cohort of persons with recurrent TB in the United States, we used genotyping to discriminate between the two etiologies of recurrent TB. We found that approximately 15% of recurrent cases were due to reinfection with a new TB strain rather than to the typically

Figure 1. Derivation of study cohort: recurrent tuberculosis (TB) in the United States, 1993–2011. Bubble plot shows all tuberculosis recurrences identified by study algorithm, with corresponding year of first episode (x-axis) and year of recurrent episode (y-axis). Darker inset circles show the subset of recurrences with genotype results available for both episodes. Size of bubble or circle is proportional to the number of recurrences.

presumed reactivation of the first TB episode. After adjustment for other factors, previous TB treatment by directly observed therapy and recent immigration were associated with reinfection. In fact, among certain subgroups, such as recent immigrants from Africa and Mexico, the proportion of recurrences due to reinfection increased to 50% and 60%, respectively.

Few previous studies of recurrent TB in low-incidence settings have had genotyping

data available from both episodes, preventing discrimination between the etiologies of reactivation and reinfection. Among those that have, the number of paired isolates ranged from 8 to 75 (9, 13–15, 17, 18), limiting statistical power to examine reinfection as an outcome. Additionally, as other authors have noted (5, 10–12), different definitions of recurrent TB disease result in great variations in both estimated overall recurrent TB incidence and the proportion attributable to

reinfection. In particular, the National Tuberculosis Surveillance System definition of recurrence excludes TB relapses that occur as a consequence of treatment failure or immediately following treatment. A more inclusive definition would presumably increase the proportion of recurrences attributable to reactivation (9), which was not the outcome of interest in the present study.

Our study was focused on recurrences 12 months or more after previous TB

Table 1. Characteristics of 136 persons with recurrent tuberculosis 12 months or longer after treatment completion—United States, 1996–2011

	Total Recurrences, N = 136*	Recurrent TB, n (Row %)		P Value†
		Reactivation	Reinfection	
Type of recurrence, n (%)		116 (85.3)	20 (14.7)	
Characteristics				
Age at second episode of TB (yr), median [IQR]	50 [37–60]	51 [37–61]	44 [34–52]	0.163
Female, n (%)	35	32 (91.4)	3 (8.6)	0.282
U.S.-born, n (%)	78	70 (89.7)	8 (10.3)	0.140
Race/ethnicity, n (%)				0.311
Black, non-Hispanic	30	25 (83.3)	5 (16.7)	
Hispanic	12	12 (100.0)	0 (0.0)	
White and other,‡ non-Hispanic	36	33 (91.7)	3 (8.3)	
Foreign-born, n (%)	58	46 (79.3)	12 (20.7)	0.140
Country/region of birth,§ n (%)				0.006
Mexico	19	12 (63.2)	7 (36.8)	
Africa	5	2 (40.0)	3 (60.0)	
Asia	24	23 (95.8)	1 (4.2)	
Latin America/Caribbean	5	4 (80.0)	1 (20.0)	
Eastern Europe	5	5 (100.0)	0 (0.0)	
Among foreign-born, number of years living in United States at time second episode of TB was diagnosed, median [IQR]	12 [7–20]	14 [8–26]	9 [4–13]	0.039
Resident of one of the four large U.S. states that report approximately half the country's TB cases, n (%)	59	48 (81.4)	11 (18.6)	0.065
State A	22	15 (68.2)	7 (31.8)	
State B	25	21 (84.0)	4 (16.0)	
State C or D	12	12 (100.0)	0 (0.0)	
Homeless in previous 12 mo, n (%)	22	17 (77.3)	5 (22.7)	0.320
Incarcerated at time of TB diagnosis, n (%)	4	3 (75.0)	1 (25.0)	0.475
Substance abuse in previous 12 mo, n (%)	57	49 (86.0)	8 (14.0)	1.000
Alcohol	48	41 (85.4)	7 (14.6)	1.000
Noninjection drug use	31	29 (93.5)	2 (6.5)	0.160
Injection drug use	7	5 (71.4)	2 (28.6)	0.277
HIV coinfection, n (%)¶	18	14 (77.8)	4 (22.2)	0.305
Pulmonary anatomic site of disease at first TB episode, n (%)	127	108 (85.0)	19 (15.0)	1.000
Cavitary disease	47	39 (83.0)	8 (17.0)	0.616
Smear-positive sputum	92	77 (83.7)	15 (16.3)	0.606
First TB episode treatment administered exclusively by directly observed therapy, n (%)	88	71 (80.7)	17 (19.3)	0.045
First TB episode treatment duration (mo), median [IQR]	7 [6–10]	7 [6–10]	9 [7–10]	0.157
Time between episodes (mo), median [IQR]	26 [19–44]	26 [19–43]	26 [17–60]	0.818
TB lineage at second episode, n (%)**				0.081
Euro-American	86	71 (82.6)	15 (17.4)	
East Asian	31	30 (96.8)	1 (3.2)	
Indo-Oceanic	3	3 (100.0)	0 (0.0)	
East African Indian	4	2 (50.0)	2 (50.0)	

Definition of abbreviations: IQR = interquartile range; TB = tuberculosis.

*Among the 312,589 total TB cases reported in the United States during 1993–2011, 6,078 cases appeared to represent two episodes of TB in the same person (i.e., 3,039 individual persons); 194 individuals had genotyping results available from both episodes; and 136 were eligible for the primary analysis. See Figure 1 for additional details.

†Fisher's exact tests were used for categorical variables, and Wilcoxon's signed-rank tests were used for continuous variables.

‡This category includes one U.S.-born person whose race was reported as "multiple." "Other" category includes Asian, American Indian/Alaska Native, Hawaiian/Pacific Islander, and multiracial non-Hispanic.

§Mexican-born persons experienced 19 of the 136 recurrences in this study. Ten of these nineteen had both TB episodes diagnosed in the United States within 12 yr of immigration (i.e., 4 of the 12 reactivations and 6 of the 7 reinfections). Africa category includes Ethiopia, Somalia, Sudan, and Zimbabwe. Three of those born in Africa experienced reinfection, including two of the four who had immigrated within the previous 12 years. Asian category includes Cambodia, Democratic People's Republic of Korea, Hong Kong, India, Laos, People's Republic of China, the Philippines, Republic of Korea, Taiwan, Thailand, and Vietnam. Latin American/Caribbean category includes El Salvador, Haiti, Honduras, and Trinidad and Tobago. Eastern European category includes Bosnia-Herzegovina, Russia, and Ukraine.

||Identities of individual states are concealed in accordance with the National Tuberculosis Surveillance System guidelines for publication of data. Whereas the overall (Type III) *P* value was 0.26, a *post hoc* Fisher's exact test for State A (referent is all other states) yielded a *P* value of 0.02. The data for the other three large states were nonsignificant at $\alpha = 0.05$ level. Also note that any statistically significant unadjusted association between a particular state and reinfection disappeared after adjustment for other factors (Table 3).

¶HIV status is based on positive test result versus other (missing, unknown, not offered, or refused in 26 reactivations and 4 reinfections).

**Lineage not determined for seven reactivations and one reinfection where the genotyping methods for both episodes did not include spoligotyping methods.

Table 2. *Mycobacterium tuberculosis* genotyping results for 20 persons who appeared to have novel reinfection as the etiology for their tuberculosis recurrence—United States, 1996–2011

Duration between Episodes (mo)	Genotyping Results, Initial Episode/Subsequent Episode		
	Spoligotype	12-Locus MIRU-VNTR	RFLP bands, n
12	00000000002771/77777777777777	223325173533/226225173433	Not performed
13	00000000003771/777776777760601	223325173534/224325153323	Not performed
15	777776777760771/777737774020771	125325153225/225326153323	Not performed
16	64001377777600*/777777607760771	232224263322/124326153220	Not performed
16	77777777720771/00003777760770	225326153322/333125153326	Not performed
18	77773777760771/70007677760671	223125153322/224325153324	Not performed
18	— [†]	— [‡]	17/10
19	00000000003771/67677377777600*	223325143533/2y2324253322	Not performed
22	77637777760751/77777760020611	333325153222/225325141323	Not performed
25	703777740000771/401777606060771	224325173533/224126152321	Not performed
26	777776777760601/777776777760771	224325153324/223325143223	Not performed
27	777776777760771/700036777760731	125325143224/222325143223	Not performed
38	77777607720771/000000004020771	224315153324/224315153324	Not performed
53	77773777760731/776137607760771	224325163421/226228153323	Not performed
60	77777607760771/missing	124316153322/225313153324	Not performed
60	77777777760731/77777763460771	224312153321/223425143322	Not performed
64	00000000003771/77777760060771	223225173433/223325143323	Not performed
71	776377776760771/776137607760771	232325153326/224226153324	Not performed
73	777000377760771/703377400001771	225125113322/227425113434	Not performed
103	77777777760771/60377740003771	223125153324/226425153533	Not performed

Definition of abbreviations: MIRU-VNTR = 12-locus mycobacterial interspersed repetitive units variable number tandem repeats analysis; RFLP = IS6110-based restriction fragment-length polymorphism pattern.

**Mycobacterium bovis* strain within the *Mycobacterium tuberculosis* complex. Both had a pulmonary site of disease.

[†]Not performed because RFLP so different.

[‡]Not performed because before 2004.

treatment completion. Our finding that novel reinfection accounted for approximately 15% of cases dropped only slightly when all recurrences, regardless of previous treatment completion status, were included.

Directly observed therapy and lengthier treatment of the previous TB episode were individually associated with reinfection. One interpretation for this finding is that patients who self-administer treatment or receive fewer doses are less likely to achieve

cure, predisposing them to experience reactivation.

In this study of the etiology of recurrent TB, reinfection was associated with both TB episodes occurring within 12 years of immigration to the United States.

Table 3. Predictors of tuberculosis reinfection 12 months or more after treatment completion—United States, 1996–2011

Characteristic	Outcome (Reinfection vs. Reactivation)*			
	Unadjusted		Adjusted	
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value
Female sex	0.5 (0.1–1.8)	0.365	0.5 (0.1–2.1)	0.435
Living in State A for both TB diagnoses [†]	3.6 (1.0–11.7)	0.043	2.1 (0.5–8.3)	0.384
Born in Mexico with both TB episodes diagnosed in the United States within 12 yr of immigration [‡]	11.6 (2.4–63.3)	0.001	10.7 (1.7–86.3)	0.008
African birth	9.8 (1.0–124.9)	0.046	Not calculated [§]	
HIV infection	1.8 (0.4–6.8)	0.517	1.5 (0.2–7.1)	0.863
First TB episode treated ≥9 mo	2.6 (0.9–8.0)	0.081	1.9 (0.6–6.6)	0.363
First TB episode treatment administered exclusively by directly observed therapy	3.6 (1.0–20.0)	0.062	4.5 (1.0–29.2)	0.042

Definition of abbreviations: CI = confidence interval; TB = tuberculosis.

*Exact logistic regression.

[†]One of the four large U.S. states that report approximately half the country's TB cases. The patient was living in that state for both TB episodes.

[‡]Mexican-born persons experienced 19 of the 136 recurrences in this study. Ten of these nineteen had both TB episodes diagnosed in the United States within 12 yr of immigration (i.e., 4 of the 12 reactivations and 6 of the 7 reinfections).

[§]Because of small numbers, African birth was too unstable to be retained in the final adjusted model. Only five recurrences were in persons of African birth: three were reinfections, including two with both TB episodes diagnosed in the United States within 12 yr of immigration.

^{||}Missing, unknown, not offered, or refused HIV test in 26 reactivations and 4 reinfections.

In TB epidemiology, recent immigration is typically perceived as a risk factor for imported infection (23, 30), so finding reinfection, which is more suggestive of postarrival transmission in the United States, is similar to a finding in Italy (15) but somewhat surprising. On the one hand, an etiology of reinfection provides some reassurance about the success of treating TB in newly arriving immigrants. On the other hand, social factor similarities among more recent immigrants (e.g., residing, working, or socializing in settings with other recently arrived immigrants) could increase their exposure to new TB strains, increasing their risk of a novel TB reinfection despite prior successfully treated TB disease.

Although the National Tuberculosis Surveillance System upon which this study was based is nationally representative, the generalizability of our study to TB recurrences outside the United States is unknown. In addition, although about 5% of U.S. residents diagnosed with TB each year have a history of TB 12 months or more prior (1), our study population was drawn from the 1% whose previous TB episode occurred in the United States in 1993 or later (i.e., an estimated 3,039 persons through the end of 2011). As Figure 1 shows, most of our final cohort (i.e., the 194 persons with genotyping results from both episodes) had their first TB episode in 2004 or later. A further limitation of the present study is that our reactivation versus reinfection distinction is subject to

misclassification. Although TB genotyping methods became increasingly discriminatory during the study period, particularly with the addition of 24-locus MIRU-VNTR to the National Tuberculosis Genotyping Service in 2009, these methods are not as discriminatory as whole-genome sequencing. Thus, we might have underestimated the rate of reinfection if our genotyping methods suggested that the initial and recurrent isolates were similar when they actually differed; employing more discriminatory methodology would have yielded a proportion of reinfection cases higher than 15%. Additionally, a person might have been misclassified as having reactivation if he or she was actually reinfecting with the same circulating TB strain (e.g., in outbreak settings). Finally, HIV was the factor most frequently associated with reinfection in most (9, 13, 19, 20) but not all (15, 21) previous studies. In our study, persons with HIV infection experiencing recurrent TB had 1.5 times the odds (95% CI, 0.2–7.1) of reinfection, but this finding was not statistically significant. Reporting of HIV status to the National Tuberculosis Surveillance System varies among states; for example, some report only positive HIV results, whereas others report both positive and negative results. We therefore performed sensitivity analysis with varying proportions of persons with HIV coinfection, but our results did not change (data not shown). Despite these limitations, this study is the first nationally representative study of recurrent TB using

genotyping data and, to our knowledge, also the largest to have genotyping results available for so many pairs of TB episodes.

In conclusion, whereas genotyping evidence suggests that the etiology of most recurrent TB in the United States is reactivation of residual *M. tuberculosis* infection from the first TB episode, certain recent immigrants may have a substantial risk of novel reinfection following TB treatment. Although routine long-term follow-up of patients who successfully complete TB treatment is no longer recommended (6–8), the risk of TB persists if the patients remain in a social environment where they are reexposed to *M. tuberculosis* (23). Public health interventions to prevent reinfection as a cause of late recurrence might require a broader focus on these communities to stop *M. tuberculosis* transmission in areas of residence, work, and recreation. ■

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