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Impact of Immigration on the Molecular Epidemiology of Tuberculosis in Rhode Island[▽]

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While foreign-born persons constitute only 11% of the population in the state of Rhode Island, they account for more than 65% of incident tuberculosis (TB) annually. We investigated the molecular-epidemiological differences between foreign-born and U.S.-born TB patients to estimate the degree of recent transmission and identify predictors of clustering. A total of 288 isolates collected from culture-confirmed TB cases in Rhode Island between 1995 and 2004 were fingerprinted by spoligotyping and 12-locus mycobacterial interspersed repetitive units. Of the 288 fingerprinted isolates, 109 (37.8%) belonged to 36 genetic clusters. Our findings demonstrate that U.S.-born patients, Hispanics, Asian/Pacific islanders, and uninsured patients were significantly more likely to be clustered. Recent transmission among the foreign-born population was restricted and occurred mostly locally, within populations originating from the same region. Nevertheless, TB transmission between the foreign-born and U.S.-born population should not be neglected, since 80% of the mixed clusters of foreign- and U.S.-born persons arose from a foreign-born source case. We conclude that timely access to routine screening and treatment for latent TB infection for immigrants is vital for disease elimination in Rhode Island.

In the past 2 decades, the decline in tuberculosis (TB) cases in the United States occurred predominantly in the U.S.-born population. Consequently, foreign-born persons have accounted for over 50% of all TB cases since 2001 (10, 12). The failure of TB case rates among foreign-born persons to decline as expected since implementation of measures to control resurgent TB in the United States in the early 1990s is likely due to a higher prevalence of latent TB infection (LTBI) and failure to effectively prevent reactivation of the disease (6, 11, 34). Tuberculosis control policy and strategies in the United States since 1989 have been geared toward disease elimination (8, 9, 14, 24), and much progress has been made. However, recent epidemiologic trend of TB in the United States suggests that TB among foreign-born persons still poses a threat to disease elimination (10). In the state of Rhode Island, the influence of foreign-born individuals is reflected in the TB incidence: while foreign-born persons constitute only 11% of the population of Rhode Island (40), they have accounted for about 65% of the incident cases between 1995 and 2004 (Fig. 1A) (35). Moreover, at the time of our study in 2005, incident TB case rate among foreign-born persons (28.5 per 100,000 population) was 15.8 times higher than that among U.S.-born persons (1.8 per 100,000 population) (35).

As incident TB cases in Rhode Island or the United States retreat into identifiable subpopulations such as foreign-born, there is a need to identify contributing factors that may have implications for targeted control measures. In such a context, the use of molecular tools in combination with conventional epidemiological methods has proven to be indispensable to highlight the TB transmission dynamics and the emergence of new strains due to transcontinental importation (1, 15, 18, 23, 25, 28, 36). In population-based studies, isolates with a unique genotypic profile are considered to reflect reactivation of LTBI as opposed to isolates sharing identical genotypic profiles (clustered isolates) as a result of recently acquired infection (1, 18, 19, 23, 25, 26, 37, 41, 42). The aim of the present study was to investigate the molecular-epidemiological differences between foreign-born and U.S.-born TB patients in Rhode Island. Two different molecular typing methods were used (spoligotyping and 12-locus mycobacterial interspersed repetitive units [MIRUs]) to determine the rate of recently transmitted TB and to identify the circulating genotypic lineages of *M. tuberculosis*. We particularly focused on defining the transmission patterns and predictors of clustering.

MATERIALS AND METHODS

Eligibility for inclusion in study population. Patients with culture-confirmed TB diagnosed between January 1995 and December 2004 in Rhode Island, for whom isolates were available, were eligible for the present study. The study was

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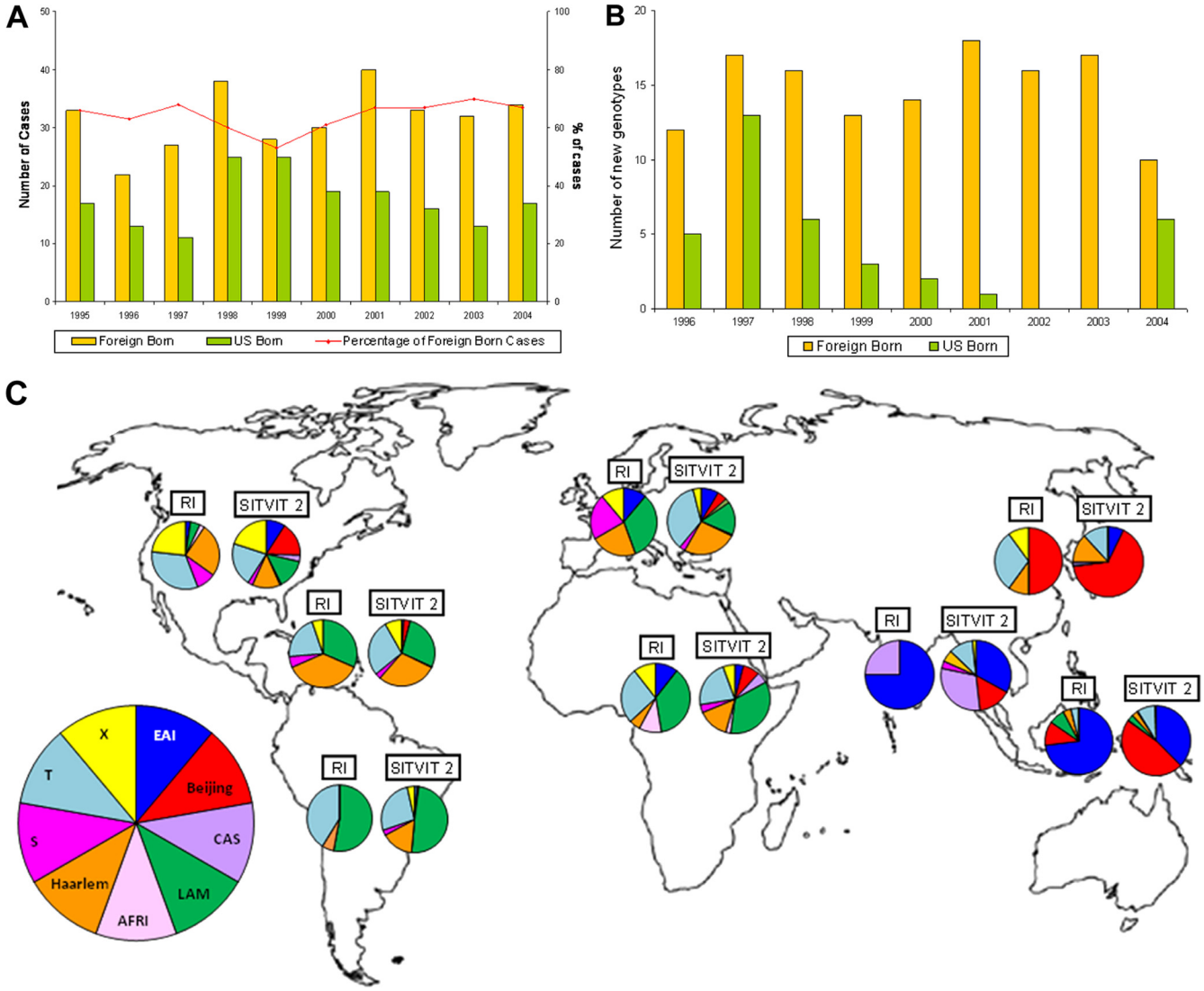

FIG. 1. (A) Number and proportion of all reported TB cases in Rhode Island by country of birth, 1995 to 2004. (B) Number and proportion of new isolated genotypes in TB cases in Rhode Island by country of birth, 1996 to 2004. (C) Distribution of major *M. tuberculosis* lineages according to patient region of origin: comparison between all unique strains isolated in TB patients of Rhode Island (RI) between January 1995 and December 2004, and all strains included in the international genotyping database (SITVIT 2). (The world outline map used in the figure was obtained from WorldAtlas.com and is used with permission.).

reviewed and approved by the Institutional Review Board for Studies on Human Subjects of both the Rhode Island Department of Health and The Miriam Hospital.

Definitions. Persons born in any of the 50 states and the District of Columbia were considered U.S.-born. All other persons were classified as foreign-born. Foreign-born persons who presented with active TB within 5 years of residence in the United States were classified as "recent immigrants," while those in whom TB occurred after 5 years were classified as "remote immigrants." The duration of U.S. residence was used as a surrogate marker for duration of Rhode Island residence since the time of migration to Rhode Island was not available.

Data collection and DNA fingerprinting. Using a standardized form, trained persons abstracted data on demographics, TB risk factors, clinical characteristics, and treatment outcome from outpatient medical records. The data were obtained from the Rhode Island Department of Health electronic records for eligible patients for whom outpatient charts had incomplete data. Contact tracing data was reviewed to identify known epidemiological links between the patients.

DNA fingerprinting of prospectively archived *M. tuberculosis* isolates was performed at the Centers for Disease Control and Prevention (CDC) and the Institut Pasteur de Guadeloupe by spoligotyping (26) and 12-locus MIRU typing (39) using published protocols. Clusters were defined as two or more patients infected with isolates showing identical spoligotyping and 12-locus MIRU typing patterns, in contrast to patients with unique strains. The percentage of TB attributed to recent transmission was calculated according to the "$n - 1$ method" (37). The source case of a cluster was defined as the earliest case to show TB symptoms.

Database comparison and phylogenetic analysis. Spoligotypes in binary format and 12-digit MIRU patterns were entered in the SITVIT2 proprietary database of the Institut Pasteur de Guadeloupe, which is an updated version of the previously released SpolDB4 database (5) (available online at http://www.pasteur-guadeloupe.fr:8081/SITVITDemo). At the time of the present study, SITVIT2 contained genotyping information on more than 70,000 *M. tuberculosis* clinical isolates from 160 countries of origin. In this database, spoligotype international type (SIT) and MIRU international type (MIT) designate spoligotyping and 12-locus MIRU patterns shared by two or more patient isolates. Major spoligotyping-based phylogenetic clades were assigned according to signatures provided in SpolDB4 (5).

Statistical analyses. All analyses were carried out using Stata statistical software, release 10.0 (StataCorp, College Station, TX). An initial descriptive analysis compared the frequency of different demographic, clinical, and treatment characteristics between foreign-born and U.S.-born patients. A second univariate analysis was performed to identify risk factors for clustering. For categorical variables, differences between groups were assessed by using the chi-square test (or the Fisher exact test where necessary). P values of <0.05 were considered as statistically significant. A stepwise multivariate regression analysis was performed including sex, age group, and all variables associated with clustering according to the univariate analysis ($P < 0.20$) to identify independent predictors of clustering. Statistical significance was assessed by using likelihood ratio tests for all of the categorical variables. A multiple imputation parameter model (29) was used to estimate the missing values of the variable "medical insurance" ($n = 52$).

RESULTS

Study population. Between January 1995 and December 2004, 496 cases of active TB were reported in Rhode Island, of which 327 were culture confirmed. Of the culture-confirmed cases, 288 (88.1%) patients had stored isolates available and were successfully fingerprinted by spoligotyping and 12-locus MIRU typing. A total of 265 (81.0%) patients had data available on demographics, TB risk factors, clinical characteristics, and treatment outcome and were included in the epidemiological analysis.

Country of birth and characteristics of the foreign-born patients. Of the 265 patients included in the epidemiological analysis, 176 (66.4%) were foreign born from 42 different countries; 68.2% did not speak English. The predominant country of birth of the foreign-born persons was Cambodia (12.5%), followed by Guatemala (10.8%), Dominican Republic (10.2%), Laos (6.3%), the Philippines (5.1%), and Portugal (5.1%). The mean duration of U.S. residence prior to TB presentation was 10.3 years (standard deviation, 12.2; range, 0 to 80 years) among the foreign-born patients. The duration of U.S. residence was greater than 5 years in 56.5% of the patients and within 5 years in 43.5%. Prior to presentation with TB symptoms, only 31 (20.3%) of the foreign-born patients were previously diagnosed with LTBI.

Epidemiological profiles of foreign-born and U.S.-born patients. Demographic and epidemiological profiles of the patients showed important dissimilarities between the foreign-born and U.S.-born persons (Table 1). The age distribution varied significantly between groups as there were more patients aged <30 years and fewer aged >65 years in the foreign-born patients. All six U.S.-born pediatric patients had foreign-born parents. Foreign-born patients were significantly more likely than U.S.-born patients to be Hispanic or a Asian/Pacific Islander. They were more likely to be employed and yet also more likely to be without health insurance. In addition, foreign-born patients were more likely to have no underlying medical conditions (other than HIV infection) and no history of drug-use. The mean time from the onset of TB symptoms to the first presentation at a health facility was 72 days, and from time of presentation to diagnosis was 36 days among the foreign-born patients, which were not different from those noted among U.S.-born patients (76 and 36 days, respectively).

The proportions of drug-resistant cases were significantly higher among foreign-born patients than in U.S.-born patients (21.0% versus 6.7%; $P < 0.01$). Among the foreign-born patients, 37 (21.0%) were resistant to any first-line drug, 18 (10.2%) were resistant to isoniazid, 9 (5.1%) were resistant to streptomycin, and 8 (4.5%) were resistant to both isoniazid and streptomycin. The proportions of multidrug resistance (i.e., resistant to both rifampin and isoniazid) was similar among foreign-born and U.S.-born populations (2.3% versus 0.6%; $P = 0.22$).

Fingerprinting and cluster analysis. Spoligotyping and 12-locus MIRU typing were used to assess the genetic diversity among the isolated *M. tuberculosis* strains and to define genetic clusters. Among the 288 fingerprinted clinical isolates, 215 distinct SIT-MIT combinations could be identified, 131 (60.9%) of which preexisted in the SITVIT 2 database. Figure 1B shows the occurrence of new genotypes, i.e., SIT-MIT combinations that were not present in the study population in the preceding year(s), in the U.S.-born and foreign-born patients. Overall, 78.7% of the 169 genotypes newly identified after 1995 occurred in foreign-born patients, with the highest number of new genotypes introduced between 2001 and 2003. In some years, all of the new genotypes that were identified occurred in only foreign-born patients (Fig. 1B).

A total of 109 clustered isolates (37.8%) were found to be distributed in 36 clusters containing from 2 to 16 isolates (Table 2), the remaining 179 isolates were considered unique (62.2%). Of the 97 clustered TB patients for which country of origin was known, 44 (45.4%) were in 10 clusters with mixed U.S.-born and foreign-born patients, 22 (22.7%) were in 12 clusters containing only U.S.-born patients and 31 (32.0%) were in 14 clusters containing only foreign-born patients. In the 10 mixed clusters, the source case was foreign-born in 8 clusters (80%). Assuming that each cluster contains one source case and that all other cases in the cluster were due to recent transmission, we estimated the proportion of TB cases attributed to recent transmission be 25.3%. Among the cases involved in recent transmission, 54.1% were foreign-born and 45.9% were U.S.-born.

Of the clustered cases, 17.4% had identifiable local epidemiological links, and one cluster with three family members had both foreign-born and U.S.-born persons within the cluster. There was another family cluster of two U.S.-born children, but the suspected source case (foreign-born relative) was not part of our study population. Clustered cases for which no evident local epidemiological link could be identified often shared the same country or continent of birth (Table 2). For example, the Beijing-type, the largest cluster of 16 patients occurred predominantly in patients born in Asia and the United States. Similar continental patterns were observed for the Haarlem 3, Latino-American, and Mediterranean (LAM) 9, S, and X2 clades. Moreover, the distribution of *M. tuberculosis* clades among TB cases assumed to result from reactivation of latent infection (unique cases) differs according to the patient's continents of origin and reflects the global distribution of major *M. tuberculosis* clades reported in the global spoligotyping database (Fig. 1C; based on unpublished data from Institut Pasteur de Guadeloupe).

Risk factors for recent transmission of tuberculosis. Overall, the odds of being a clustered case did not change significantly between 1995 and 2004 (odds ratio [OR] per additional year = 1.09; 95% confidence interval [CI] = 0.99 to 1.20; $P = 0.07$). The variables found to represent significant predictive risk for membership in a cluster were birth in the United States (adjusted OR = 5.80; 95% CI = 2.37 to 14.17); Hispanic race

TABLE 1. Sociodemographic, clinical and treatment characteristics of U.S.-born and foreign-born patients, Rhode Island, 1995–2004

Characteristic	Foreign-born subjects (n = 176)		Native-born subjects (n = 89)		Foreign-born vs U.S.-born	
	No.	%	No.	%	OR (95% CI)	P^a
Sex						
Female	71	40.3	30	33.7	1.00 (reference)	0.29
Male	105	59.7	59	66.3	0.75 (0.42–1.32)	
Age group (yr)						
0–29	52	29.5	11	12.4	1.00	<0.01
30–44	45	25.6	10	11.2	0.95 (0.37–2.45)	
45–64	52	29.5	27	30.3	0.41 (0.18–0.91)	
>65	27	15.3	41	46.1	0.14 (0.06–0.31)	
Race/ethnicity						
Black	29	16.5	15	16.9	1.00	<0.01
White	22	12.5	65	73.0	0.18 (0.08–0.39)	
Hispanic	73	42.1	1	1.1	37.76 (4.77–299.07)	
Asian/Pacific Islander	52	29.0	7	7.9	3.84 (1.41–10.50)	
Medical insurance						
No	79	44.9	13	14.6	1.00	<0.01
Yes	70	39.8	50	56.2	0.23 (0.11–0.48)	
Unknown*	27	15.3	26	29.2		
Employment						
No	49	27.8	44	49.4	1.00	<0.01
Yes	84	47.7	27	30.3	2.79 (1.48–5.30)	
Unknown*	43	24.4	18	20.2		
HIV status						
Negative	122	69.3	49	55.1	1.00	0.54
Positive	17	9.7	9	10.1	0.76 (0.30–2.07)	
Unknown*	37	21.0	31	34.8		
History of latent TB						
No	123	69.9	57	64.0	1.00	0.24
Yes	31	17.6	9	10.1	1.60 (0.68–4.06)	
Unknown*	22	12.5	23	25.8		
Prior history of active TB						
No	162	92.0	78	87.6	1.00	0.43
Yes	8	4.5	6	6.7	0.64 (0.19–2.33)	
Unknown*	6	3.4	5	5.6		
Sputum AFB smear result						
Negative	87	49.4	41	46.1	1.00	0.95
Positive	62	35.2	31	34.8	0.98 (0.54–1.80)	
Unknown*	27	15.3	17	19.1		
Site of disease						
Extrapulmonary	39	22.2	20	22.5	1.00	0.95
Pulmonary	137	77.8	69	77.5	1.01 (0.55–1.88)	
History of drug use						
No	170	96.6	77	86.5	1.00	<0.01[b]
Yes	2	1.1	8	9.0	0.11 (0.01–0.59)	
Unknown*	4	2.3	4	4.5		
Excessive alcohol use						
No	133	75.6	56	62.9	1.00	0.27
Yes	37	21.0	22	24.7	0.71 (0.37–1.38)	
Unknown*	6	3.4	11	12.4		
Underlying medical condition						
No	137	77.8	55	61.8	1.00	<0.01
Yes	39	22.2	34	38.2	0.46 (0.25–0.84)	

Continued on following page

TABLE 1—*Continued*

Characteristic	Foreign-born subjects (n = 176)		Native-born subjects (n = 89)		Foreign-born vs U.S.-born	
	No.	%	No.	%	OR (95% CI)	P^a
Drug resistance						
No	139	79.0	83	93.3	1.00	<0.01
Yes	37	21.0	6	6.7	3.68 (1.45–11.09)	
Treatment outcome						
Completed treatment	145	82.4	68	76.4	1.00	<0.01
Died before treatment completed	21	11.9	0	0.0		
Lost to follow up	5	2.8	14	15.7	0.17 (0.06–0.48)	
Unknown*	5	2.8	7	7.9		

[a] *, Not included in the χ^2 and OR calculation.
[b] Fisher exact P value.

(adjusted OR = 8.56; 95% CI = 2.96 to 24.71) and Asian/Pacific Islander race (adjusted OR = 6.05; 95% CI = 2.00 to 18.26) compared to the black race; and having no medical insurance (adjusted OR = 0.41; 95% CI = 0.19 to 0.86) (Table 3). Further analysis showed that both recent immigrants and remote immigrants with TB were less likely than U.S.-born patients to have clustered strains (OR = 0.51 [95% CI = 0.27 to 0.99] and OR = 0.52 [95% CI = 0.28 to 0.96], respectively). However, follow-up of the association revealed that increasing duration of U.S. residence prior to TB presentation was not associated with an increasing risk of being in a case cluster (OR = 1.00; 95% CI = 0.99 to 1.01).

Similar analyses were performed to identify risk factors for membership to a mixed cluster of foreign-born and U.S.-born patients, reflecting ongoing transmission between these two populations. Only membership to a large cluster (a cluster of >3 patients) remained significant after adjustment for possible confounders (Table 4). In addition, specific analysis of foreign-born clustered cases showed that remote immigrants were significantly more likely than recent immigrants to be a part of a mixed cluster of foreign-born and U.S.-born patients (OR = 3.97; 95% CI = 1.12 to 14.0).

DISCUSSION

During the past decade in Rhode Island, the relatively small population of foreign-born persons disproportionately bore the burden of incident TB disease. Our data not only support the hypothesis that reactivation of *M. tuberculosis* infection likely acquired prior to migration to Rhode Island was a major contributor to incident cases but also demonstrates that prolonged residence in Rhode Island prior to TB presentation for foreign-born patients was associated with recent transmission between foreign-born and U.S.-born persons. The high proportion of new genotypes found in foreign-born persons, as well as the phylogeographical distribution of *M. tuberculosis* clades among the foreign-born unique cases, is consistent with our hypothesis that most of foreign-born patients developed reactivation disease from infection acquired prior to residing in Rhode Island.

Targeted screening and treatment of LTBI remains the primary means of controlling TB in the foreign-born population once they reside in the United States (2, 13), but widespread implementation of this strategy remains a major challenge. Political involvement, managerial capability, cost-effectiveness, effective information delivery, and access to high-risk groups are as important constraints as medical challenges to the implementation of targeted testing for LTBI (24, 27, 32). The analysis of the sociodemographic and clinical characteristics of the foreign-born TB patients revealed several possible barriers, including language difficulties, lack of medical insurance, young age, and/or absence of other medical conditions that will cause patient to seek medical attention. Therefore, expanded TB screening services that actively move into at-risk communities outside of traditional health clinic sites will be important in reaching these persons during the window period of latent infection. Involving community-based organizations has proved effective in increasing cure rates, detecting new cases, and decreasing costs compared to traditional practices (22, 32, 33). In addition, application of current screening guidelines that emphasize screening of recent immigrants within 5 years of immigration would miss a large proportion of the foreign-born persons who developed TB, since more than 56% of them had resided in the United States for >5 years before developing disease, and most of these remote migrants (69.4%) acquired disease through reactivation of latent infection. This is consistent with the finding that among immigrants from high-incidence countries, the risk of developing active tuberculosis from latent infection can persist at least for some decades following entry (43). Thus, targeted LTBI screening guidelines should be updated to classify all foreign-born persons from high-incidence countries as a high-risk population irrespective of time since entry into the United States and should be tested for LTBI as proposed by other researchers in a recent guideline (2), since TB case rates remain higher in foreign-born than in U.S.-born persons even more that 20 years after arrival (7).

In the U.S.-born population, the lack of perceived risk of TB might have contributed to delayed LTBI diagnosis. Primary care clinicians receive little ongoing education services, and a large proportion of them demonstrated a lack of knowledge in TB screening and treatment guidelines (30, 38). Keeping frontline clinicians informed of the problem and current screening and treatment guidelines through continuing medical education in the face of declining case rates is necessary to maintain TB expertise.

The proportion of Rhode Island TB patients attributed to recent transmission was estimated at 25%, which is smaller

TABLE 2. Genotypes and country of birth of clustered patients, Rhode Island, 1995-2004

SIT	Binary spoligotype	Clade	12-locus MIRU	MIT	Total no. of patients	Foreign-born patients		Birth country of foreign-born patients (no. of patients)
						No.	%	
1		Beijing	223325173533	17	16	7	43.8	Cambodia (5), Korea (1), Senegal (1)
19		EAI2-Manilla	254326223432	56	6	3	50.0	Philipinnes (2), Cambodia (1)
42		LAM9	224226133321	464	5	1	20.0	Philipinnes (1)
42		LAM9	124326153326	816	5	4	80.0	Puerto Rico (2), Ecuador (1), Salvador (1)
34		S	333325153222	279	5	0	0.0	
8		EAI variant	25432A223633	850	4	4	100.0	Guatemala (1), Mexico (1), Haiti (1), Dominican Republic (1)
61		LAM10-CAM	223315153323	12	3	2	66.7	Portugal (1), Liberia (1)
137		X2	224225153323	22	3	1	33.3	Sweden (1)
33		LAM3	223426153321	1,045	3	2	66.7	Puerto Rico (1), Costa Rica (1)
33		LAM3	224326133323	251	3	3	100.0	Guatemala (3)
92		X3	225325153324	46	3	3	100.0	Guatemala (3)
20		LAM1	223226153321	128	3	3	100.0	Portugal (3)
1		Beijing	223321153643	569	3	0	0.0	
50		Haarlem3	225325153323	45	3	1	33.3	Dominican republic (1)
50		Haarlem3	223325153323	116	2	2	100.0	Guatemala (1), Colombia (1)
50		Haarlem3	227326153323	1,148	2	0	0.0	
50		Haarlem3	224325153323	33	2	0	0.0	
457		Haarlem3 variant	225323153324	222	2	2	100.0	Dominican Republic (2)
457		Haarlem3 variant	225123153324	1,141	2	1	50.0	Dominican Republic (1)
47		Haarlem 1	225313153323	42	2	0	0.0	
47		Haarlem 1	125325153323	520	2	1	50.0	Laos (1)
45		Haarlem 1 variant	224325143323	30	2	0	0.0	
354		T2 variant	204225223533	1,147	2	2	100.0	Cambodia (1), Thailand (1)
451		H37Rv	233226133321	50	2	0	0.0	
53		T1	223425153323	382	2	2	100.0	Guatemala (2)
40		T4	223321153314	1,145	2	2	100.0	Cambodia (1), Bolivia (1)
336		T variant	223225153324	169	2	0	0.0	
137		X2	224325153323	33	2	0	0.0	
137		X2	225325153323	45	2	1	50.0	
70		X3 variant	214325141326	1,143	2	0	0.0	
93		LAM5	224226153321	25	2	2	100.0	Dominican Republic (2)
376		LAM3 variant	223326133323	846	2	2	100.0	Guatemala (2)
1		Beijing	223325163533	83	2	2	100.0	Vietnam (1), Senegal (1)
26		CAS1-Delhi	226425173423	374	2	0	0.0	
236		EAI5	264225223533	59	2	2	100.0	Cambodia (1), Laos (1)
89		EAI2-nonthaburi	254326223432	56	2	2	100.0	Laos (2)

than the transmission rates observed in similar studies conducted in the United States (in the range of 28 to 52%) (1, 17, 18, 36). However, we did not observe a decrease of the number of clustered cases with time, in contrast to previous long-term population-based studies (18, 25). Recent transmission should therefore not be neglected, and more effective measures should be taken to break the TB transmission chains. Since early recognition of disease symptoms and institution of effective treatment is a key factor in prevention of transmission (3, 20, 21), particular efforts should be made to reduce the delays in diagnosis observed in both foreign-born and U.S.-born patients. Education of health care professionals may decrease the time to diagnosis once the patient has presented for care, but patient delays in seeking care will require more complex interventions addressing social factors contributing to health disparity access.

TABLE 3. Univariate and multivariate analysis of risk factors for clustering, Rhode Island, 1995-2004

Characteristic[a]	Unique and clustered strains				Clustered vs unique		
	Unique (n = 168)		Clustered (n = 97)		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Sex							
Female	68	40.5	33	34.0	1.00 (reference)	1.00	0.53
Male	100	59.5	64	66.0	1.32 (0.76–2.30)	1.20 (0.68–2.14)	
Age group (yr)							
0–29	36	21.4	27	27.8	1.00	1.00	0.64
30–44	37	22.0	18	18.6	0.65 (0.31–1.38)	0.76 (0.32–1.80)	
45–64	49	29.2	30	30.9	0.82 (0.42–1.60)	0.85 (0.39–1.82)	
>65	46	27.4	22	22.7	0.64 (0.31–1.30)	0.60 (0.24–1.49)	
Country of origin							
Foreign born	121	72.0	55	56.7	1.00	1.00	<0.01
US born	47	28.0	42	43.3	1.97 (1.12–3.43)	5.54 (2.25–13.65)	
Race/ethnicity							
Black	37	22.0	7	7.2	1.00	1.00	<0.01
White	50	29.8	37	38.1	3.91 (1.57–9.74)	3.35 (1.20–9.33)	
Hispanic	41	24.4	33	34.0	4.25 (1.68–10.77)	8.58 (2.97–24.75)	
Asian/Pacific Islander	39	23.2	20	20.6	2.71 (1.03–7.16)	6.00 (1.98–18.18)	
Medical insurance							
No	51	30.4	41	42.3	1.00	1.00	0.03
Yes	82	48.8	38	39.2	0.58 (0.32–1.05)	0.41 (0.18–0.93)	
Unknown*	35	20.8	18	18.6			
Employment							
No	50	29.8	43	44.3	1.00		
Yes	75	44.6	36	37.1	0.56 (0.30–1.03)		
Unknown*	43	25.6	18	18.6			
HIV status							
Negative	111	66.1	60	61.9	1.00		
Positive	19	11.3	7	7.2	0.68 (0.23–1.82)		
Unknown*	38	22.6	30	30.9			
History of latent TB							
No	112	66.7	68	70.1	1.00		
Yes	27	16.1	13	13.4	0.79 (0.35–1.72)		
Unknown*	29	17.3	16	16.5			
Prior history of active TB							
No	150	89.3	90	92.8	1.00		
Yes	10	6.0	4	4.1	0.67 (0.15–2.40)		
Unknown*	8	4.8	3	3.1			
Sputum AFB smear result							
Negative	80	47.6	52	53.6	1.00		
Positive	61	36.3	33	34.0	0.83 (0.46–1.49)		
Unknown*	27	16.1	12	12.4			
Site of disease							
Extrapulmonary	37	22.0	22	22.7	1.00		
Pulmonary	131	78.0	75	77.3	0.96 (0.51–1.85)		
History of drug use							
No	158	94.0	89	91.8	1.00		
Yes	5	3.0	5	5.2	1.78 (0.40–7.92)		
Unknown*	5	3.0	3	3.1			
Excessive alcohol use							
No	126	75.0	63	64.9	1.00		
Yes	33	19.6	26	26.8	1.58 (0.83–2.98)		
Unknown*	9	5.4	8	8.2			

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TABLE 3—*Continued*

Characteristic[a]	Unique and clustered strains				Clustered vs unique		
	Unique (n = 168)		Clustered (n = 97)		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Underlying medical condition							
No	123	73.2	69	71.1	1.00		
Yes	45	26.8	28	28.9	1.11 (0.61–2.00)		
Drug resistance							
No	134	79.8	87	89.7	1.00		
Yes	34	20.2	9	9.3	0.40 (0.16–0.91)		
Unknown*	0	0.0	1	1.0			
Treatment outcome							
Completed treatment	134	79.8	79	81.4	1.00		
Died before treatment completed	17	10.1	4	4.1	0.40 (0.13–1.23)		
Lost to follow-up	11	6.5	8	8.2	1.23 (0.48–3.20)		
Unknown*	6	3.6	6	6.2			

[a] *, Not included in χ^2 and OR calculations.

Our findings demonstrate high clustering of foreign-born patients by continent of birth with little clustering between patients from different continents. This could indicate that recent transmission in the U.S.-born and foreign-born populations occurs locally, within populations originating from the same region. Moreover, the tendency of TB transmission exclusively within specific subgroups is more pronounced in recent immigrants, as suggested by their predominant membership to clusters of foreign-born patients only. A similar trend was observed in other studies and is probably due to the fact that new arrivals are more likely to live with other foreign-born persons in their own ethnic communities (4, 41). In the foreign-born population of Rhode Island, people originating from Central America, the Caribbean, and Southeast Asia seem to be the most involved in local transmission chains. In addition, recent transmission seems to occur within specific ethnic groups, particularly Hispanics and Asians/Pacific Islanders, as suggested by the significant ethnic disparities between clustered and unique cases. Several contributory factors such as stigma, illegal immigration status, fear of inability to legalize immigration status, language difficulties, and poverty were observed in our study and could explain the delays on the part of these high-risk groups to seek TB services (16, 44). Some of these concerns need to be addressed through focused patient education programs or campaigns using selected lay print media, radio, and television advertisements, as well as linguistically appropriate informational handouts.

Nevertheless, nearly one-third of the clusters involved both U.S.-born and foreign-born patients, suggesting ongoing transmission between these populations. Transmission occurred mainly from the foreign-born to the U.S.-born population, since foreign-born patients were identified as the source case in 80% of these clusters. Moreover, these mixed clusters were significantly larger than unmixed clusters and involved widespread TB strain types. These clusters could have arisen from particularly transmissible or virulent strains, therefore not restrained to specific subpopulations, as suggested by other studies (19).

Some limitations should be taken into account when interpreting the results of the present study. First, the restriction of the study to culture-confirmed cases diagnosed in a defined time period and failure to type all cases during that period may have missed some members of potential clusters and misclassified some strains as unique or missed persons with epidemiological links. In addition, the use of spoligotyping with classical 12-locus MIRU as typing methods likely overestimated the proportion of clustered cases belonging to the Beijing clade, since it has been shown that the combination of these techniques is not sufficient to fully discriminate Beijing isolates (31). Second, the assumption that isolates in clusters result from recent transmission from a single source should be taken with care, since TB in clustered patients may have occurred through coincidental reactivation from LTBI during the observation period. In addition, clusters of exclusively foreign-born persons may have arisen from importation of prevalent circulating strains in their birth country, leading to an overestimation of the rate of recent transmission. Although this cohort looks at patients diagnosed between 1995 and 2004, the issues of foreign-born contribution to the U.S. TB burden remains relevant today; 2009 incident data for the United States continues to demonstrate that 60.2% of all cases are in the foreign-born (10). To reach elimination ongoing characterization of transmission is required to design and maintain support for targeted testing and treatment programs.

Our findings demonstrate that incident TB among foreign-born persons who accounted for the majority cases in Rhode Island is a manifestation of reactivation of infection likely acquired before arrival in the state. Furthermore, there was a prolonged period of time between the time of U.S. immigration and the development of disease that provides an opportunity for implementation of preventive measures. The profile of the foreign-born patients suggests that there are potential barriers to a passive screening for LTBI. Bold expansion of screening and treatment for LTBI to effectively reach this population will be necessary for TB elimination. Recent transmission occurred within specific ethnic communities, as well as

TABLE 4. Univariate and multivariate analysis of risk factors for membership to a mixed cluster of foreign-born and U.S.-born patients, Rhode Island, 1995-2004

Characteristic[a]	Clustered strains				Mixed vs unmixed		
	Unmixed (n = 53)		Mixed (n = 44)		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Sex							
Female	16	30.2	17	38.6	1.00 (reference)	1.00	0.87
Male	37	69.8	27	61.4	0.69 (0.27–1.74)	0.92 (0.34–2.52)	
Age group (yr)							
0–29	19	35.8	8	18.2	1.00	1.00	0.09
30–44	11	20.8	7	15.9	1.51 (0.43–5.31)	1.92 (0.44–8.32)	
45–64	14	26.4	16	36.4	2.71 (0.91–8.11)	3.19 (0.88–11.49)	
>65	10	18.9	13	29.5	3.43 (1.04–11.22)	5.18 (1.29–20.87)	
Country of origin							
Foreign-born	31	58.5	24	54.5	1.00		
Native-born	22	41.5	20	45.5	1.17 (0.48–2.84)		
Race/ethnicity							
Black	9	17.0	11	25.0	1.00		
White	5	9.4	2	4.5	2.94 (0.50–17.14)		
Hispanic	22	41.5	11	25.0	1.25 (0.21–7.51)		
Asian/Pacific Islander	17	32.1	20	45.5	3.05 (0.47–19.66)		
Medical insurance							
No	29	54.7	12	27.3	1.00		
Yes	17	32.1	21	47.7	2.99 (1.07–8.41)		
Unknown*	7	13.2	11	25.0			
Employment							
No	20	37.7	23	52.3	1.00		
Yes	24	45.3	12	27.3	0.43 (0.16–1.19)		
Unknown*	9	17.0	9	20.5			
HIV status							
No	41	77.4	19	43.2	1.00		
Yes	2	3.8	5	11.4	5.39 (0.77–59.82)		
Unknown*	10	18.9	20	45.5			
History of latent TB							
No	39	73.6	29	65.9	1.00		
Yes	7	13.2	6	13.6	1.15 (0.29–4.49)		
Unknown*	7	13.2	9	20.5			
Prior history of active TB							
No	53	100.0	37	84.1	1.00		
Yes	0	0.0	4	9.1			
Unknown*	0	0.0	3	6.8			
Sputum AFB smear result							
No	25	47.2	27	61.4	1.00		
Yes	21	39.6	12	27.3	0.53 (0.20–1.41)		
Unknown	7	13.2	5	11.4			
Site of disease							
Extrapulmonary	12	22.6	10	22.7	1.00		
Pulmonary	41	77.4	34	77.3	1.00 (0.38–2.58)		
History of drug use							
No	50	94.3	39	88.6	1.00		
Yes	2	3.8	3	6.8	1.92 (0.21–23.91)		
Unknown*	1	1.9	2	4.5			
Excessive alcohol use							
No	33	62.3	30	68.2	1.00		
Yes	15	28.3	11	25.0	0.81(0.29–2.23)		
Unknown*	5	9.4	3	6.8			

Continued on following page

TABLE 4—*Continued*

Characteristic[a]	Clustered strains				Mixed vs unmixed		
	Unmixed (n = 53)		Mixed (n = 44)		Crude OR (95% CI)	Adjusted OR (95% CI)	P
	No.	%	No.	%			
Underlying medical condition							
No	39	73.6	30	68.2	1.00		
Yes	14	26.4	14	31.8	1.30 (0.49–3.44)		
Drug resistance							
No	46	86.8	42	95.5	1.00		
Yes	7	13.2	2	4.5	0.31 (0.03–1.79)		
Treatment outcome							
Completed treatment	48	90.6	31	70.5	1.00		
Died before treatment completed	2	3.8	2	4.5	1.55 (0.21–11.57)		
Lost to follow up	1	1.9	7	15.9			
Unknown*	2	3.8	4	9.1			
Cluster size							
Small cluster (≤3 patients)	44	83.0	16	36.4	1.00	1.00	<0.01
Large cluster (>3 patients)	9	17.0	28	63.6	9.89 (3.55–27.57)	2.67 (1.64–4.34)	

[a] *, Not included in χ^2 and OR calculations.

between the foreign-born and U.S.-born population, suggesting the need to improve public health interventions in both populations.

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