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Original article

Individual- and neighborhood-level contextual factors are associated with *Mycobacterium tuberculosis* transmission: genotypic clustering of cases in Michigan, 2004–2012

Grace A. Noppert PhD [a,*,1], Zhenhua Yang MD, PhD [a], Philippa Clarke PhD [a,b], Wen Ye PhD [c], Peter Davidson PhD [d], Mark L. Wilson ScD [a]

[a] Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor
[b] Institute for Social Research, University of Michigan, Ann Arbor
[c] Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor
[d] Michigan Department of Health and Human Services, Lansing, MI

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ABSTRACT

Purpose: Using genotyping data of *Mycobacterium tuberculosis* isolates from new cases reported to the tuberculosis (TB) surveillance program, we evaluated risk factors for recent TB transmission at both the individual- and neighborhood- levels among U.S.-born and foreign-born populations.
Methods: TB cases ($N = 1236$) reported in Michigan during 2004 to 2012 were analyzed using multivariable Poisson regression models to examine risk factors for recent transmission cross-sectionally for U.S.-born and foreign-born populations separately. Recent transmission was defined based on spoligotype and 12-locus-mycobacterial interspersed repetitive unit–variable number tandem repeat typing matches of bacteria from cases that were diagnosed within 1 year of each other. Four classes of predictor variables were examined: demographic factors, known TB risk factors, clinical characteristics, and neighborhood-level factors.
Results: Overall, 22% of the foreign-born cases resulted from recent transmission. Among the foreign-born, race and being a contact of an infectious TB case were significant predictors of recent transmission. More than half (52%) of U.S.-born cases resulted from recent transmission. Among the U.S.-born, recent transmission was predicted by both individual- and neighborhood-level sociodemographic characteristics.
Conclusions: Interventions aimed at reducing TB incidence among foreign-born should focus on reducing reactivation of latent infection. However, reducing TB incidence among the U.S.-born will require decreasing transmission among socially disadvantaged groups at the individual- and neighborhood-levels. This report fills an important knowledge gap regarding the contemporary social context of TB in the United States, thereby providing a foundation for future studies of public health policies that can lead to the development of more targeted, effective TB control.

Introduction

Although the overall incidence of tuberculosis (TB) has been declining in the United States, stark disparities persist in the distribution of disease, particularly by race and nativity. Asian and Pacific Islanders (AI/PI) continue to have the highest incidence of TB in the United States and show no evidence of closing the gap with whites, whose incidence is lowest [1,2]. Moreover, the rate of decline in TB incidence has recently begun to stagnate [3], particularly among foreign-born populations [4], and in both urban and rural populations [5,6].

From a clinical perspective, measures of individual immune status and infectiousness are key to predicting transmission of *Mycobacterium tuberculosis (MTB)* [7]: individuals with underlying comorbidities, those with a positive sputum-smear, and those with abnormal chest radiography results are more likely to be associated with recent transmission. However, previous studies have also found both individual-level and neighborhood-level sociodemographic factors to be predictors of recent TB transmission. Individual-level sociodemographic characteristics such as younger age [8–10], minority race/ethnicity status [8,11], male sex [9,10],

* Corresponding author. Department of Epidemiology, University of Michigan School of Public Health, 1415 Washington Heights, Ann Arbor, MI 48109.
E-mail address: grace.noppert@duke.edu (G.A. Noppert).
[1] Present affiliation: Center for the Study of Aging and Human Development, Duke University, 201 Trent Dr. Durham, NC 27710; email: grace.noppert@duke.edu.

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and being native-born [8,11–13] have been associated with recent TB transmission. In addition, "known TB risk factors" as defined by the Centers for Disease Control and Prevention (CDC) surveillance forms [14], such as homelessness [8,9,13], incarceration [8], and drug use [13] have also been linked to recent transmission. Neighborhood-level studies have demonstrated that area-based measures of disadvantage are associated with increased incidence and transmission of TB, a finding particularly pronounced for those who are U.S.-born [15]. Several studies have also suggested the predictors of recent transmission are different for foreign-born and U.S.-born populations [16], highlighting the importance of investigating these two groups separately.

In 2012, Michigan had an annual incidence rate of 1.28 TB cases per 100,000 [17], notably lower than the U.S. national average incidence of 3.2 per 100,000 [4]. Despite Michigan's lower incidence, there is evidence of persistent disparities in TB risk, particularly by race and nativity [17]. Using TB surveillance data collected by the Michigan Department of Health and Human Services (MDHHS), we evaluated risk factors for recent transmission at both the individual- and neighborhood-levels among U.S.-born and foreign-born populations separately.

Methods

Study population and data collection

Our study subsample included only those cases with complete genotype data, both spacer oligonucleotide (spoligotype) and 12-locus-mycobacterial interspersed repetitive unit–variable number tandem repeat typing (MIRU-VNTR) results, and address information. The genotyping data are part of the CDC-based National Tuberculosis Genotyping Service [18]. Cases were excluded if they had incomplete genotyping data and/or were missing address information. The state of Michigan employs universal genotyping such that greater than 90% of TB cases reported to the state of Michigan were genotyped. At the state level, genotyping was done on the first isolate of a given episode. Isolates from subsequent episodes that were at least 12 months apart were subjected to the same criteria for determining genotypic clusters as described in the following.

Demographic characteristics, risk factor information, and clinical characteristics of each case, as well as residential address, were drawn from TB surveillance data collected by MDHHS using the "Report of a Verified Case of TB" form developed by the CDC [14]. Thus, the variables included were defined on the basis of the CDC classifications.

Addresses were geocoded and linked with block group–level characteristics derived from the American Community Survey, 5-year estimates for 2012 [19]. The unit of analysis for neighborhood effects was the block group, which serves as a useful proxy for both household-level features such as degradation and vacancy, as well as access to neighborhood resources, both of which are dimensions likely to affect TB transmission. In addition to neighborhood population density and age composition, neighborhood socioeconomic disadvantage was captured using a mean index of six census indicators at the block group level: percent black, percent with less than a high school education, percent unemployed, percent using public assistance, percent of vacant properties, and percent with an income-to-poverty level ratio below 2 (The U.S. Census defines an income-to-poverty ratio below 2 as being "poor or struggling." Thus, we used 2.0 as our cut point to determine the proportion of the block group with an income-to-poverty ratio below 2.0; factor loadings ranged from 0.55 to 0.83, alpha reliability = 0.82). We also sought to examine county-level differences in urban and rural status; however, 94% of cases were identified in a metropolitan region, and thus, we did not include county-level urban/rural status in our investigations.

Genotypic cluster definition

Following previously established methods, genotypically clustered cases were considered a proxy for recently transmitted infections, as defined by those sharing an identical spoligotype and 12-locus-MIRU-VNTR result with at least one other case in the sample, and having a count date within 1 year of one another [5,20]. We used the count date as a proxy for date of diagnosis. Unique ("nonclustered") cases were those that either did not share an identical spoligotype and 12-locus-MIRU-VNTR result or did not have a count date within the 1-year time period and were considered a proxy for reactivation of latent TB infection (LTBI). Genotypic clusters could span more than 1 year if the cluster involved two cases with identical genotypes that had at least one other matching case within a 1-year time frame. Genotypically clustered cases defined as such do not necessarily occur in spatial clusters.

Statistical analysis

We analyzed individual- and neighborhood-level predictors of recent transmission in relation to variables of four types: demographic factors, known TB risk factors (as defined by the CDC [14]), clinical factors, and neighborhood characteristics at the block group level. Demographic factors included nativity, race/ethnicity, age, and gender. Known TB risk factors included HIV status, alcohol use, diabetes, injecting drug use, noninjecting drug use, long-term care facility stay, and homelessness. Clinical risk factors included immunosuppression, sputum-smear status, sputum-culture status, site of TB disease, and initial chest radiography results. Block-group characteristics included population density, proportion of the population over 64 years of age, and the neighborhood disadvantage index, all of which were modeled in quartiles. See Appendix A for details on how each variable was measured.

Univariate, modified Poisson regression models were used to examine the influence of each risk factor individually on recent transmission. For data reduction, we then used stepwise regression to determine which variables, when considered together, were the most significant predictors of recent transmission. Finally, we constructed a final set of multivariable modified Poisson models that included the variables determined to be significant based on the stepwise regression model as well as a priori knowledge.

Modified multivariate Poisson regression models were estimated using generalized estimating equations to account for nesting of cases within block groups [21]. Such models allow for accurate parameter estimation and robust variance estimates by accounting for the correlated observations existing among cases in the same block group. The prevalence ratio of recent transmission and corresponding 95% confidence intervals were calculated using a Poisson regression model with a log-link function.

Because previous research has suggested that the factors influencing transmission are different for U.S.-born and foreign-born populations [9,15,22], models were stratified by nativity, and results for U.S.-born and foreign-born persons are reported separately. For final analyses, a two-tailed alpha level of 0.05 was considered statistically significant. For the stepwise regression, we used alpha = 0.2 to select variables for inclusion in the model, and alpha = 0.05 for retention in the final stepwise regression model. Analyses were undertaken using SAS (version 9.4), Cary, NC.

This study was approved by the University of Michigan Institutional Review Board for Social and Behavioral Sciences and by the MDHHS Institutional Review Board.

Results

Characteristics of the study population

A total of 1800 cases of TB were reported in Michigan from January 1, 2004 to December 31, 2012 (Supplementary Fig. 1). The final study sample consisted of 1236 cases, representing 69% of the 1800 total cases reported by MDHHS during this time period (Table 1). The racial/ethnic composition of these cases was 23% non-Hispanic white, 40% non-Hispanic black/African American, 25% Asian, 10% Hispanic, and 2% other. Most cases (72%) were between the ages of 18 and 64 years. The gender distribution was 60% male and 40% female; 45% of cases were foreign-born and 55% were U.S.-born. More than two-thirds (69%) of cases had exclusively pulmonary TB, 22% exclusively extrapulmonary TB, and 8% both pulmonary and extrapulmonary TB.

Thirty-nine percent ($N = 477$) of individuals were classified as resulting from recent transmission, whereas 61% ($N = 759$) were classified as resulting from reactivation of LTBI. The 477 recent transmission cases belonged to 100 unique genotypes that were shared by 2 to 49 cases. Another six individuals who were identified as recent transmission were considered "singleton" clusters because their genotypic counterparts had been excluded from analysis due to missing information on key covariates. A further examination of the individual genotype clusters showed that in 24% of the genotype clusters, there was evidence of shared transmission between foreign-born and U.S.-born persons.

Risk factor analysis

We investigated the influence of four classes of risk factors on recent transmission: demographic characteristics, known TB risk factors, clinical characteristics, and neighborhood characteristics. In the univariate models for the full sample, 15 variables from the four classes were significantly associated with recent transmission. In particular, nativity was a significant predictor of recent transmission in univariate models. There was a significantly higher proportion of cases resulting from recent transmission among the U.S.-born compared with foreign-born ($P < .001$). Overall, more than half (52%) of the U.S.-born cases were defined as cases resulting from recent transmission compared with less than one-quarter (22%) of the foreign-born.

For the U.S.-born, many factors were significantly associated with recent transmission in univariate models (Table 2). Using stepwise regression, the number of significant variables was reduced to age, sex, homelessness, contact of an infectious TB case, neighborhood population density, and neighborhood disadvantage (results not shown).

In the final multivariable model for the U.S.-born, several factors remained significantly associated with recent transmission, including age, sex, contact of an infectious TB case, homelessness, density of the neighborhood, and neighborhood disadvantage after controlling for all other covariates in the model (Table 3). The proportion of cases resulting from recent transmission was 53% lower among those aged 65 years or more compared with those aged 18-64 years ($P < .0001$). The proportion of cases resulting from recent transmission among males was 1.19 times greater than females ($P < .05$). The proportion of cases resulting from recent transmission among those who were a contact of an infectious TB case was 1.27 times greater than among those without such a contact ($P < .05$). Furthermore, the proportion of recent transmission among those who reported a history of homelessness in the past 12 months was 1.25 times greater than that among those who did not ($P < .05$).

In addition, for the U.S.-born, both neighborhood population density and neighborhood disadvantage were significant predictors of recent transmission after controlling for all other covariates in the model. The proportion of cases resulting from recent transmission among cases living in the highest density neighborhoods was 1.30 times greater than that for those living in the lowest density neighborhoods (Q4 vs. Q1; $P < .0001$) (Table 3). The proportion of cases resulting from recent transmission among those living in the most disadvantaged neighborhoods was 1.88 times greater than that for those living in the least disadvantaged neighborhoods (Q4 vs. Q1; $P < .05$).

For the foreign-born population, only three factors were significant predictors of recent transmission in univariate models: individual-level race/ethnicity, injecting drug use, and being a contact of an infectious TB case (Table 2). Only individual-level race/ethnicity and being a contact of an infectious TB case retained significance in the stepwise regression models and were the only two significant predictors in the final multivariable models.

In the final multivariable model for the foreign-born, the proportion of cases resulting from recent transmission among Asians was 2.45 times greater than non-Hispanic whites; Hispanics had a proportion of recent transmission 2.18 times greater than non-Hispanic whites ($P < .05$) (Table 3). Those who were a contact of an infectious TB case had a proportion of recent transmission 1.82 times greater than those without such a contact ($P < .05$).

Among the foreign-born, no associations between the neighborhood environment and recent transmission were found (Table 3). This was also confirmed by testing for interactions in the full set of cases between nativity and neighborhood population density, as well as nativity and neighborhood disadvantage. In the multivariable model for all cases, there was a significant interaction between nativity and neighborhood disadvantage ($P < .001$), but a marginally nonsignificant interaction between nativity and neighborhood population density ($P = .10$) (results not shown).

Table 1
Comparison of the distribution of selected demographic and clinical characteristics among all TB cases ($N = 1800$) and the study population ($N = 1236$) in Michigan, 2004–2012

Characteristic	Total TB cases ($N = 1800$)		Study sample ($N = 1236$)	
	n	%	*n*	%
Race/ethnicity				
Non-Hispanic white	439	24.39	285	23.06
Non-Hispanic black/African American	706	39.22	497	40.21
Asian	423	23.50	304	24.60
Other	38	2.11	28	2.27
Hispanic	194	10.78	122	9.87
Age (y)				
<18	124	6.88	35	2.83
18–64	1263	70.16	891	72.09
65+	413	22.94	310	25.08
Gender				
Male	1047	58.2	735	59.51
Female	752	41.8	500	40.49
Missing	1		1	
Nativity				
Foreign-born	798	44.48	553	44.81
U.S.-born	996	55.52	681	55.19
Missing	6		2	
Site of disease				
Pulmonary	1188	66.22	855	69.29
Extrapulmonary	463	25.81	277	22.45
Both	143	7.97	102	8.27
Missing	6		2	

Classifications of race/ethnicity, age, sex, nativity, and site of disease were defined base on the Report of Verified Case of TB form developed by the Centers for Disease Control and Prevention. See Appendix A for more detailed information of variable measurement.

Discussion

We evaluated risk factors for recent transmission at both the individual and neighborhood levels among U.S.-born and foreign-

Table 2
Results of univariate Poisson regression models estimating the prevalence of recent transmission for each single factor for the sample overall and U.S.-born and foreign-born separately

Factor	U.S.-born, $N = 681$	Foreign-born, $N = 553$
	Prevalence ratio (95% CI)	
Demographic factors		
Nativity		
U.S.-born versus FB		
Race/ethnicity		
Asian versus NH white	**0.79 (0.23–2.66)**†	**2.54 (1.28–5.03)***
NH black versus NH white	**1.96 (1.58–2.43)**	**1.35 (0.55–3.29)**
Other versus NH white	**1.58 (0.95–2.61)**	**1.98 (0.49–8.03)**
Hispanic versus NH white	**1.73 (1.11–2.71)**	**2.52 (1.21–5.25)**
Age (y)		
<18 versus 18–64	**1.05 (0.76–1.47)**†	1.57 (0.81–3.06)
65+ versus 18–64	**0.39 (0.30–0.50)**	0.79 (0.51–1.22)
Gender		
Male versus female	**1.29 (1.10–1.52)***	0.93 (0.68–1.28)
Known TB risk factors		
Diabetes		
Diabetes versus no diabetes	0.78 (0.52–1.18)	1.08 (0.58–2.02)
HIV		
HIV+ versus HIV−	**1.22 (1.0–1.50)**†	1.30 (0.60–2.80)
HIV not done versus HIV−	**0.74 (0.59–0.92)**	0.87 (0.53–1.42)
HIV unknown versus HIV−	**0.67 (0.40–1.13)**	1.17 (0.49–2.79)
HIV refused versus HIV−	**0.69 (0.49–0.96)**	1.24 (0.79–1.95)
Alcohol use		
Alcohol use versus none	**1.26 (1.08–1.48)***	0.94 (0.38–2.29)
Injecting drug use (IDU)		
IDU versus none	**1.37 (1.09–1.73)***	**3.16 (1.40–7.15)***
Non−injecting drug use (non-IDU)		
Non-IDU use versus none	**1.45 (1.24–1.70)**†	1.36 (0.42–4.43)
Long-term care facility		
LTC versus no LTC	0.81 (0.57–1.16)	1.84 (0.62–5.44)
Homelessness		
Homeless versus not	**1.62 (1.38–1.89)**†	0.91 (0.33–2.53)
Incarceration		
Incarcerated versus not	1.11 (0.75–1.64)	NA
DOT time		
<18 wk versus >31 wk	0.77 (0.60–0.98)	1.22 (0.73–2.01)
19–25 wk versus >31 wk	0.82 (0.63–1.07)	1.08 (0.66–1.78)
26–31 wk versus > 31 wk	0.90 (0.72–1.13)	0.89 (0.54–1.47)
DOT missing versus > 31 wk	0.90 (0.75–1.09)	0.82 (0.48,1.42)
Infectious contact		
Infectious contact versus not	**1.34 (1.11–1.63)***	**2.18 (1.40–3.37)**†
Incomplete LTBI treatment		
Incomplete LTBI versus not	1.07 (0.59–1.92)	0.50 (0.08–3.22)
Clinical risk factors		
End-stage renal disease (ESRD)		
ESRD versus not	0.64 (0.13–3.17)	1.53 (0.31–7.63)
Organ transplant or TNF-a antagonist therapy		
Transplant/therapy versus not	1.12 (0.69–1.82)	1.54 (0.60–3.92)
Immunosuppression		
Immunosuppressed versus not	0.75 (0.45–1.25)	1.94 (0.98–3.87)
Sputum-smear status		
SSP versus SSN	**1.15 (0.96–1.37)***	1.00 (0.70–1.44)
SSND versus SSN	**0.80 (0.63–1.02)**	0.78 (0.52–1.19)
SS unknown versus SSN	**1.98 (1.69–2.30)**	NA
Site of TB disease		
PTB versus EPTB	1.13 (0.92–1.40)	1.44 (0.98–2.12)
Both PTB/EPTB versus EPTB only	1.32 (0.97–1.79)	1.00 (0.52–1.92)
Initial chest radiography		
Abnormal versus normal	1.04 (0.81–1.33)	1.64 (1.01–2.66)
Not done versus normal	0.87 (0.53–1.43)	1.01 (0.37–2.77)
Unknown versus normal	0.56 (0.57–3.02)	3.41 (0.79–14.64)
Block group characteristics		
Density (population per square mile)		
Q2 versus Q1	**1.19 (0.90–1.57)**†	1.05 (0.68–1.62)
Q3 versus Q1	**1.38 (1.06–1.79)**	0.92 (0.59–1.43)
Q4 versus Q1	**1.85 (1.47–2.34)**	0.95 (0.60–1.49)
Proportion over 64 y		
Q2 versus Q1	0.90 (0.73–1.11)	0.82 (0.55–1.22)
Q3 versus Q1	0.80 (0.64–0.99)	0.76 (0.47–1.25)
Q4 versus Q1	0.83 (0.67–1.03)	1.14 (0.77–1.69)
Index of neighborhood disadvantage		
Q2 versus Q1	**1.58 (1.02–2.44)**†	0.86 (0.59–1.26)
Q3 versus Q1	**2.72 (1.86–3.98)**	0.83 (0.54–1.27)
Q4 versus Q1	**2.85 (1.96–4.14)**	1.42 (0.89–2.27)

CI = confidence interval; SSP = sputum-smear positive; SSN = sputum-smear negative; SSND = sputum-smear not done; PTB = pulmonary TB; EPTB = extrapulmonary TB; those indicated as PTB had exclusively PTB, whereas those indicated as EPTB had exclusively EPTB; NA = not applicable due to a lack of cases within levels of the variables; Q = quartile.
Results are based on univariate Poisson regression models. All models are adjusted for all other covariates. See Appendix A for more detailed information of variable measurement. Values in bold indicate statistical significance.
* Indicates a P-value $\leq .05$.
† indicates a P-value $\leq .001$.

born populations separately using a combination of genotyping and surveillance data from 1236 new TB cases reported in Michigan during 2004 through 2012.

Using time-restricted genotypic clusters as the proxy for recent transmission, we found significant differences between the U.S.-born and the foreign-born in the proportion of cases attributable to recent transmission. However, we also found evidence that there is transmission occurring between the two groups. The factors predicting recent transmission for the foreign-born were notably different than those for the U.S.-born, except for that of being an infectious TB case contact. For the U.S.-born, recent transmission was influenced more by individual-level and neighborhood-level sociodemographic factors than by clinical risk factors. These findings point to the importance of the social and physical context in influencing TB transmission in a high-disparity environment, particularly among U.S.-born populations. The differences in the proportion of recent transmission between the U.S.-born and foreign-born could partly be due to many of the foreign-born cases immigrating from high TB burden countries where they had been infected with MTB before entering the United States [23–25].

For the U.S.-born, the predictors of recent transmission spanned both individual-level sociodemographic factors such as age and sex, as well as neighborhood-level factors such as population density and disadvantage. In fact, the neighborhood environment was only a salient predictor of presumed transmission for the U.S.-born. Neighborhood studies have found evidence of higher TB incidence in socioeconomically disadvantaged neighborhoods [26–28], but few have focused on recent transmission at the neighborhood level and/or the effects of nativity on these trends. Acevedo-Garcia hypothesized in a 2000 report there were both direct and indirect pathways by which the neighborhood environment may influence TB risk [29]; indirect pathways being those operating through an intervening mechanism. Our finding of an association between neighborhood population density and recent transmission, after controlling for neighborhood disadvantage, supports a direct pathway hypothesis. The likelihood of transmission of TB is a function of the size of the susceptible pool and how densely such susceptibles are distributed in a given space [30–32]. Thus, an active case of TB in a high-population-density neighborhood likely results in a greater number of secondary cases than if the case were in a low-population-density neighborhood.

Our finding that among the U.S-born those living in more disadvantaged neighborhoods had an increased rate of transmission

Table 3
Results of final multivariable Poisson regression models estimating the prevalence of recent transmission among the U.S.-born and foreign-born separately

Factor	U.S.-born ($N = 681$)	Foreign-born ($N = 553$)
	Prevalence ratio (95% CI)	
Demographic factors		
Nativity		
U.S.-born versus foreign-born		
Race/ethnicity		
Asian versus non-Hispanic white	0.57 (0.19–1.73)	**2.45 (1.23–4.89)***
Non-Hispanic black versus non-Hispanic white	1.20 (0.94–1.52)	**1.18 (0.46–3.00)**
Other versus non-Hispanic white	1.22 (0.63–2.37)	**1.93 (0.47–7.93)**
Hispanic versus non-Hispanic white	1.35 (0.92–1.97)	**2.18 (1.03–4.61)**
Age (y)		
<18 versus 18–64	**1.07 (0.79–1.44)†**	1.43 (0.67–3.06)
65+ versus 18–64	**0.47 (0.36–0.61)**	0.85 (0.54–1.35)
Gender		
Male versus female	**1.19 (1.02–1.39)***	0.88 (0.64–1.21)
Clinical characteristics		
Sputum-smear		
SSP versus SSN	1.07 (0.91–1.25)	1.01 (0.70–1.45)
SSND versus SSN	0.99 (0.79–1.23)	0.76 (0.51–1.15)
Known TB risk factors		
Infectious contact		
Infectious contact versus not	**1.27 (1.04–1.55)***	**1.82 (1.19–2.78)***
Homeless		
Homeless versus not	**1.25 (1.08–1.45)***	0.85 (0.31–2.33)
Block group characteristics		
Density (population per square mile)		
Q2 versus Q1	**0.90 (0.72–1.14)†**	0.97 (0.63–1.50)
Q3 versus Q1	**1.03 (0.83–1.28)**	0.91 (0.57–1.45)
Q4 versus Q1	**1.30 (1.06–1.61)**	0.87 (0.53–1.44)
Proportion of population over 64 y		
Q2 versus Q1	1.07 (0.87–1.31)	0.87 (0.58–1.30)
Q3 versus Q1	1.02 (0.83–1.25)	0.76 (0.46–1.26)
Q4 versus Q1	1.16 (0.95–1.41)	1.19 (0.77–1.85)
Index of neighborhood disadvantage		
Q2 versus Q1	**1.42 (0.92–2.19)***	0.94 (0.64–1.35)
Q3 versus Q1	**1.91 (1.27–2.89)**	0.91 (0.58–1.43)
Q4 versus Q1	**1.88 (1.25–2.84)**	2.21 (1.32–3.69)

CI = confidence interval; SSP = sputum-smear positive; SSN = sputum-smear negative; SSND = sputum-smear not done.
Results are based on multivariable Poisson regression models. All models are adjusted for all other covariates. See Appendix A for more detailed information of variable measurement. Analytic sample for U.S.-born: 666 of 681 (2% of the sample was dropped due to missingness). Analytic sample for foreign-born: 550 of 553 (0.5% of the sample was dropped due to missingness). Values in bold indicate statistical significance.
* Indicates a P-value $\leq .05$ based on type-3 effects.
† Indicates a P-value $\leq .001$ based on type-3 effects.

may also be evidence that the neighborhood indirectly influences TB transmission. Living in a disadvantaged neighborhood may limit the resources available for treatment of TB, thereby increasing duration of infectiousness among those infected [29]. Previous studies have found similar effects of disadvantage both in incidence of TB overall [28,33], as well as specifically for transmission [15].

Although many studies have reported racial disparities in recent transmission, in our multivariable models, race/ethnicity was not a significant predictor of recent transmission for the U.S.-born when neighborhood factors were included. These results suggest that race/ethnicity is only a meaningful predictor of recent TB transmission in so far as it represents much larger social patterns. For TB, individual-level race/ethnicity is likely a proxy for disadvantage, and more specifically in our study, neighborhood-level disadvantage.

Other studies have also reported that the effects of the neighborhood environment differ by race/ethnicity [9,15,22,34]. It may be that the neighborhood environment has different meanings and confers different risks, depending on an individual's racial and ethnic identity. For the U.S.-born, the neighborhood in which a person resides is not only indicative of the physical environment to which one is exposed but may also reflect the influences of structural racism tied to one's racial/ethnic identity [35]. Thus, the neighborhood environment can indirectly pattern the distribution of TB through such mechanisms as poverty, housing conditions, social disorganization, access to health care [29], political disinvestment, and the stress of living in such disadvantage neighborhoods [36–38]. Based on our findings, and consistent with other U.S.-based studies, transmission of TB among the U.S.-born is happening in insular, disadvantaged communities defined by their sociodemographic makeup, at both the individual- and neighborhood- levels [9].

The factors predicting recent transmission were markedly different for the foreign-born. The only significant predictor of recent transmission besides being a contact of an infectious TB case was race/ethnicity. Asians had an increased proportion of recent transmission compared with whites after controlling for measures of the neighborhood environment and other social risk factors. More work is needed to understand how the Asian population as a whole differs from other foreign-born populations. Future studies would benefit from disaggregating the Asian group into the ethnically diverse groups that compose it.

There are several limitations to our study. First, inferences regarding individual-level risk based on group-level factors are vulnerable to the ecological fallacy. However, we are not assuming a causal relationship between neighborhood level factors and one's individual risk of TB transmission.

Our analyses were based on available genotype data, and thus, some cases that lacked culture confirmation (which allows for genotyping) were excluded. This could have biased our results if those cases were significantly different than the genotyped culture–positive cases included in the analysis. We also only examined predictors of transmission among a group of TB cases. There may be important predictors of TB transmission that were missed by not comparing cases with the larger, TB-free population.

We also recognize that the data included for these analyses are not the most current data. However, we believe these data are still of value given that there have not been significant changes in neither the total population of Michigan, nor the demographic composition of the population in terms of native-born to foreign-born in the intervening time period.

In addition, although we believe that time restriction added greater specificity to our classification of recent transmission, misclassification was still possible. In particular, the estimates of the proportion of cases arising from recent transmission at the beginning and end of our study period (2004 and 2012) are likely underestimates because cases occurring in those years were not linked to cases in 2003 or 2013. However, such misclassification would likely be nondifferential, biasing the observed results toward the null. Moreover, 12-locus-MIRU-VNTR and spoligotyping results can lack discriminatory power compared with methods such as 24-locus-MIRU-VNTR, which were not available for the entire study period. Because of this lower discriminatory power, there may been situations in which we misclassified reactivation of LTBI as recent transmission. However, we did sensitivity analyses comparing the distribution of known TB risk factors for recent transmission (male gender, black race, younger age, drug use, being a contact of an infectious TB case, positive sputum-smear status, and having exclusive pulmonary TB) among those cases only genotypically clustered and those cases that were both genotypically clustered and diagnosed within a 1-year time frame of another case. For nearly all of the factors we checked, we saw an increase in the prevalence of known risk factors for recent transmission among those that were genotypically clustered with the time restriction compared with those

only genotypically clustered (data not shown). This gives us even more confidence that the use of a time restriction in our definition of recent transmission reduces the likelihood of misclassification.

Finally, cases that lacked address information were excluded. Of the 1800 cases reported in Michigan, 104 (6%) were missing address information and included people whose address was missing altogether, those coded as homeless, and those with an address listed as a hospital or laboratory. These cases were significantly different than those with complete address information by race/ethnicity, nativity, geographic area, and site of disease (Supplementary Table 1). However, given the small proportion missing address information, these differences seem unlikely to have biased our findings.

Conclusions

Our findings point to the need for considering socioeconomic context in designing interventions aimed at reducing MTB transmission. Although a focus on individual-level factors in TB control may have reduced overall TB incidence in the United States during the last decades, our results suggest that this is insufficient to address enduring disparities in TB incidence that are largely patterned by social and economic disadvantages. Reducing disparities in TB incidence will require strategies that target high-risk groups which may be most effectively defined based on ecologic factors such as neighborhood poverty [35], rather than on individual-level factors. This report fills an important knowledge gap regarding the contemporary social context of TB in the United States, thereby providing a foundation for future studies of public health policies that can lead to the development of more targeted, effective TB control.

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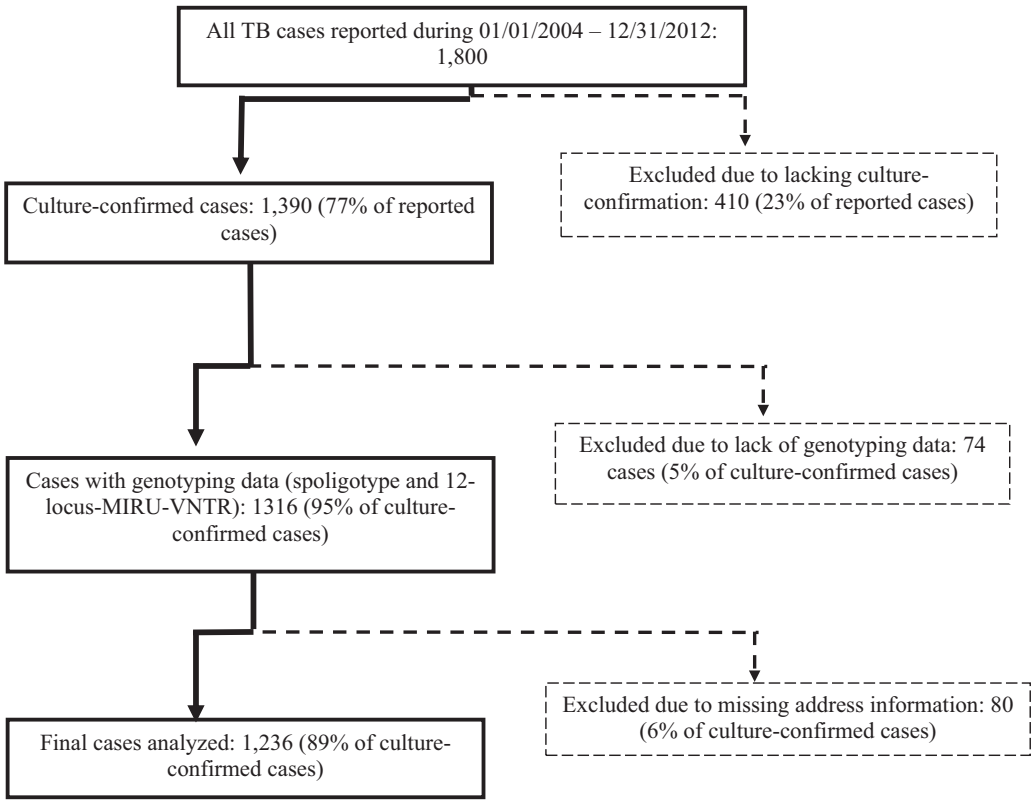
Appendix



Supplementary Fig. 1. Flowchart illustrating the selection of the study sample from the 1800 total TB cases reported in Michigan during 2004 to 2012.

Supplementary Table 1
Comparison of the distribution of key covariates among all cases ($N = 1800$) comparing those with address information to those without address information

Characteristic	Cases with address information ($N = 1696$)		Cases missing address information ($N = 104$)		P
	n	%	n	%	
Race/ethnicity					
Non-Hispanic white	410	24.17	29	27.88	.55
Non-Hispanic black/African American	662	39.03	44	42.31	
Asian	405	23.88	18	17.31	
Other	35	2.06	3	2.88	
Hispanic	184	10.85	10	9.62	
Age groups (y)					
<18	117	6.9	7	6.73	.7782
18–64	1187	69.99	76	73.08	
65+	392	23.11	21	20.19	
Gender					
Male	976	57.55	71	68.27	.0971
Female	719	42.39	33	31.73	
Missing	1	0.06	0	0	
Nativity					
Foreign-born	759	44.75	39	37.5	<.0001
U.S.-born	935	55.13	61	58.65	
Missing	2	0.12	4	3.85	
Site of disease					
Exclusively pulmonary	1116	65.8	72	69.23	<.0001
Exclusively extrapulmonary	441	26	22	21.15	
Both pulmonary and extrapulmonary	137	8.08	6	5.77	
Missing	2	0.12	4	3.85	

Supplementary Table 2
Comparison of the distribution of selected covariates between those cases resulting from recent transmission and those resulting from reactivation of latent TB infection

Factor	Recent transmission		Reactivation of latent TB infection		*P*
	n	%	*n*	%	
Total	477	38.59	759	61.41	
Demographic factors					
Nativity					
U.S.-born	354	74.21	327	43.08	<.0001
Foreign-born	121	25.37	432	56.92	
Missing	2	0.42	0	0	
Race/ethnicity					
Non-Hispanic white	74	15.51	211	27.8	<.0001
Non-Hispanic black	277	58.07	220	28.99	
Asian	78	16.35	226	29.78	
Other	11	2.31	17	2.24	
Hispanic	37	7.76	85	11.2	
Age (y)					
<18	18	3.77	17	2.24	<.0001
18–64	391	81.97	500	65.88	
65+	68	14.26	242	31.88	
Gender					
Male	308	64.57	427	56.26	.0059
Female	168	35.22	332	43.74	
Missing	1	0.21	0	0	
Known TB risk factors					
Diabetes					
Diabetes	23	4.82	46	6.06	.3558
No diabetes	454	95.18	713	93.94	
HIV					
HIV test positive	40	8.39	29	3.82	.0024
HIV test negative	313	65.62	477	62.85	
HIV test not done	71	14.88	144	18.97	
HIV test refused	39	8.18	82	10.8	
HIV test unknown	14	2.94	27	3.56	
Alcohol use					
Alcohol use	86	18.03	66	8.7	<.0001
No alcohol use	365	76.52	670	88.27	
Missing	26	5.45	23	3.03	
Injecting drug use (IDU)					
IDU use	27	5.66	12	1.58	<.0001
No IDU use	428	89.73	732	96.44	
Missing	22	4.61	15	1.98	
Non–injecting drug use (IDU)					
Non-IDU drug use	68	14.26	33	4.35	<.0001
No non-IDU drug use	381	79.87	707	93.15	
Missing	28	5.87	19	2.5	
Stay in a long-term care (LTC) facility					
LTC stay	20	4.19	27	3.56	.8093
No LTC stay	454	95.18	726	95.65	
Missing	3	0.63	6	0.79	
Homelessness					
Homeless	47	9.85	23	3.03	<.0001
Not Homeless	420	88.05	729	96.05	
Missing	10	2.1	7	0.92	
Incarceration in last 12 mo					
Incarcerated	11	2.31	9	1.19	.2736
Not incarcerated	464	97.27	745	98.16	
Missing	2	0.42	5	0.66	
Directly observed therapy time					
<18 wk	81	16.98	134	17.65	.1537
19–25 wk	67	14.05	129	17	
26–31 wk	90	18.87	169	22.27	
>31 wk	99	20.75	129	17	
DOT missing	140	29.35	198	26.09	
Contact of an infectious TB case					
Infectious contact	53	11.11	35	4.61	<.0001
No infectious contact	424	88.89	724	95.39	
Incomplete latent TB infection (LTBI) treatment					
Incomplete LTBI	6	1.26	12	1.58	.6443
No incomplete LTBI	471	98.74	747	98.42	
Clinical risk factors					
End-stage renal disease					
ESRD	2	0.42	4	0.53	.7908
No ESRD	475	99.58	755	99.47	
Organ transplant or TNF-a antagonist therapy					

(*continued on next page*)

Supplementary Table 2 (*continued*)

Factor	Recent transmission		Reactivation of latent TB infection		*P*
	n	%	*n*	%	
Transplant/therapy	11	2.31	11	1.45	.2674
No transplant/therapy	466	97.69	748	98.55	
Immunosuppression					
Immunosuppression	14	2.94	21	2.77	.8622
No immunosuppression	463	97.06	738	97.23	
Sputum-smear (SS) status					
SS positive	251	52.62	305	40.18	<.0001
SS negative	122	25.58	212	27.93	
SS not done	102	21.38	241	31.75	
SS unknown	2	0.42	0	0	
SS missing	0	0	1	0.13	
Culture status					
Both sputum and other tissue sample positive	30	6.29	52	6.85	<.0001
Positive sputum culture only	309	64.78	389	51.25	
Positive other tissue culture only	138	28.93	318	41.90	
Negative culture	0	0	0	0	
Culture missing	0	0	0	0	
Site of TB disease					
Exclusively pulmonary TB (PTB)	359	75.26	496	65.35	.0012
Exclusively extrapulmonary TB (EBTB)	81	16.98	196	25.82	
Both PTB and EPTB	37	7.76	65	8.56	
Missing	0	0	2	0.26	
Initial chest radiography (X-ray)					
Normal chest X-ray	51	10.69	127	16.73	.0101
Abnormal chest X-ray	407	85.32	591	77.87	
Chest X-ray not done	16	3.35	37	4.87	
Chest X-ray unknown	3	0.63	2	0.26	
Missing	0	0	2	0.26	
Block group characteristics					
Density (population per square mile)					
Q1	96	20.13	213	28.06	<.0001
Q2	113	23.69	196	25.82	
Q3	116	24.32	193	25.43	
Q4	152	31.87	157	20.69	
Proportion of population over 64 y					
Q1	118	24.74	191	25.16	.5887
Q2	117	24.53	192	25.30	
Q3	113	23.69	196	25.82	
Q4	129	27.04	180	23.72	
Index of neighborhood disadvantage					
Q1	70	14.68	239	31.49	<.0001
Q2	79	16.56	230	30.3	
Q3	135	28.3	175	23.06	
Q4	193	40.46	115	15.15	

Q = quartile.
Results based on χ^2 test comparing the distribution of covariates among those cases defined as recent transmission and those cases defined as resulting from reactivation of latent TB infection. See Appendix A for more detailed information of variable measurement.

Supplementary Table 3
Measurement values for the neighborhood indices

Variable	Q1	Q2	Q3	Q4
Density (population per square mile)	≤1997.15	>1997.15, ≤3816.35	>3816.35, ≤6343.48	>6343.48
Proportion over 64 y (proportion of the total block group population that is greater than 64 y)	≤0.07	>0.07, ≤0.12	>0.12, ≤0.17	>0.17
Index of neighborhood disadvantage (proportion of the total block group population in poverty)	≤0.11	>0.11, ≤0.19	>0.19, ≤0.33	>0.33

Q = quartile.

Appendix A

A complete list of the variables used in the analyses, the source of each variable, and how each is measured in the data

Variable	Source	Measurement
Demographic factors		
Nativity	RVCT	Defined as U.S.-born or foreign-born.
Race/ethnicity	RVCT	Defined as white, black/African American, Asian.
Age	RVCT	Defined as 18–64 y, 65+ y.
Gender	RVCT	Defined as male or female.
Diabetes	RVCT	Defined as having reported diabetes mellitus.
HIV	RVCT	The RVCT classifies HIV status into the following seven categories: negative, positive, indeterminate, refused, HIV test not offered, HIV test done (results unknown), and unknown. We then collapsed those categories into the following five categories: negative (containing only HIV negative results), positive (containing only HIV positive results), HIV not done (containing who did not have an HIV test offered to them), HIV unknown (containing those with an indeterminate test result, those with the HIV test done but results unknown, and those classified as unknown), and HIV refused (containing those who refused testing).
Alcohol use	RVCT	Defined as reporting excess alcohol use within the past year with three levels: yes, no, unknown.
Injecting drug use	RVCT	Defined as reported injecting drug use within the past year with three levels: yes, no, unknown.
Non–injecting drug use	RVCT	Defined as reported non–injecting drug use within the past year with three levels: yes, no, unknown.
Long-term care facility	RVCT	Defined as being a resident of a long-term care facility at the time of TB diagnosis with three levels: yes, no, unknown.
Homelessness	RVCT	Defined as having reported homelessness in the past year with three levels: yes, no, unknown.
Incarceration	RVCT	Defined as being a resident of a correctional facility at the time of TB diagnosis with three levels: yes, no, unknown.
DOT therapy time	RVCT	Defined as the number of weeks receiving directly observed therapy (DOT). We then split the therapy time into quartiles with the following levels: <18 wk of DOT, 19–25 wk of DOT, 26–31 wk of DOT, >31 wk of DOT, and DOT missing.
Infectious contact	RVCT	Defined as being a contact of an infectious TB patient.
Incomplete LTBI treatment	RVCT	Defined as having not completed treatment for latent TB infection (LTBI).
End-stage renal disease	RVCT	Defined as having reported end-stage renal disease (ERSD)
Organ transplant or TNF-a antagonist therapy	RVCT	Defined as either reporting postorgan transplantation or having received TNF-a antagonist therapy.
Immunosuppression	RVCT	Defined as reporting immunosuppression not related to HIV/AIDS.
Sputum-smear status	RVCT	Defined based on laboratory diagnostics of sputum-smear samples (SSP) with the following categories: SSP positive, SSP negative, SSP not done, and SSP unknown.
Site of TB disease	RVCT	The RVCT allows for reporting of exact site of TB disease on diagnosis. We then classified the sites into three categories: pulmonary (PTB, those cases having TB diagnosed in the lungs only), extrapulmonary (EPTB, those cases having TB diagnosed in any site outside of the lungs), and both PTB and EPTB (those cases having TB diagnosed in the lungs in addition to a site outside of the lungs).
Initial chest radiography results	RVCT	Defined based on laboratory information on initial chest radiography with the following categories: normal, abnormal, not done, and unknown.
Block group density	ACS	Defined by the ACS as the population density per square mile of the block group. We then split this variable into quartiles with quartile 1 being the lease densely population block group and quartile 4 being the most densely populated block group. Quartile 1 was the referent category.
Block group proportion over 64 y	ACS	We created this variable by summing the total population in all age groups over 64 y in the block group and dividing the result by the total population (all ages) of the block group. We then split this variable into quartiles with quartile 1 being the block groups with a lower proportion of a population over 64 y old and quartile 4 being those block groups with a greater proportion of those over 64 y old. Quartile 1 was the referent category.
Index of neighborhood disadvantage	ACS	We created the neighborhood disadvantage index by summing the values of the following block group characteristics and taking the mean of the sum: percent black, percent with less than a high school education, percent unemployed, percent using public assistance, percent of properties in the block group that are vacant, and percent of the block group with a poverty to income ratio <2. We then split the resulting variable into quartiles with quartile 1 as the least disadvantaged block groups and quartile 4 being the most disadvantaged block groups. Quartile 1 was used as the referent category.

RVCT = Report of Verified Case of TB form developed by the Centers for Disease Control and Prevention and used for state surveillance; ACS = American Community Survey, 5-y estimates for 2012.