Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kala Marks Date

Comparing factors for recent transmission of tuberculosis by country of origin — United States, 2011–2014

By

Kala Marks
Master of Public Health

Epidemiology

_____

Dr. John McGowan, Jr., MD
Committee Chair

_____

Anne Marie France, PhD, MPH
Committee Member

_____

Krista Powell, MD, MPH
Committee Member

Comparing factors for recent transmission of tuberculosis by country of origin — United States, 2011–2014

By

Kala Marks

B.S. in Biology
Georgia Institute of Technology
2013

Thesis Committee Chair: John E. McGowan, Jr., MD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2016

Abstract

Comparing factors for recent transmission of tuberculosis by country of origin — United States, 2011–2014

By Kala Marks

Marginalizing conditions, such as homelessness, alcohol use, illicit drug use, and incarceration, have been well established as risk factors for recent transmission of tuberculosis (TB) among U.S.-born cases but have not been well studied among foreign-born cases. Thus, we sought to 1) determine if marginalizing conditions were associated with recent transmission among foreign-born persons in the United States, and 2) to test whether these associations significantly differed between U.S.-born and foreign-born cases. We conducted a nation-wide study using genotyped cases reported to the National TB Surveillance System during January 2011–September 2014. We estimated recent transmission using a novel field-validated plausible source-case approach and used log-binomial regression to evaluate the associations between recent transmission and each of the marginalizing conditions by local and foreign birth. Of the 26,562 analyzed cases, 3,820 (14%) were attributable to recent transmission, including 2,522 of 9,199 (27%) U.S.-born cases and 1,298 of 17,363 (8%) foreign-born cases. Among foreign-born TB cases, recent transmission was positively associated with homelessness (adjusted prevalence ratio [aPR] = 1.7; 95% confidence interval [CI] = 1.4, 2.2), illicit drug use (aPR = 1.4; 95% CI = 1.1, 1.8), and excessive alcohol use (aPR = 1.3; 95% CI = 1.1, 1.6), and negatively associated with incarceration at diagnosis (aPR = 0.5; 95% CI = 0.3, 0.7) after controlling for age (broad age categories) and race/ethnicity. Aside from incarceration at diagnosis, which was more negatively associated with recent transmission among foreign-born persons, there was no evidence to suggest that these associations significantly differed by origin of birth ($p>0.05$). Our results reiterate the need for improved TB control strategies among marginalized populations in the United States and show that marginalizing conditions are important factors for transmission regardless of local or foreign birth.

Comparing factors for recent transmission of tuberculosis by country of origin — United States, 2011–2014

By

Kala Marks

B.S. in Biology
Georgia Institute of Technology
2013

Thesis Committee Chair: John E. McGowan, Jr., MD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2016

ACKNOWLEDGEMENTS

I wish to express my deepest gratitude to my joint field advisors, Dr. Anne Marie France and Dr. Krista Powell, for all of their incredible guidance and mentorship; Dr. John McGowan, Jr., my faculty advisor, for his never-ending encouragement; and finally my friends and family for their unwavering love and support throughout this whole process.

TABLE OF CONTENTS

MANUSCRIPT

Introduction

While the overall incidence of tuberculosis (TB) in the United States has been declining since the 1990s, from 9.7 cases per 100,000 in 1993 to 3.0 cases per 100,000 in 2014, the proportion of TB cases occurring in foreign-born persons has been steadily increasing (1). In 2014, an estimated 66% of the incident TB cases were in foreign-born persons, more than double the proportion reported in 1993, and the TB incidence rate, at 15.4 cases per 100,000, was nearly 13 times higher than the rate among the U.S.-born (1). Thus, addressing TB in foreign-born populations is essential to reaching TB elimination in the United States (1 case per 1,000,000 persons per year) (1).

TB disease can result from infection acquired recently or from reactivation of TB infection acquired in the more distant past. TB genotyping, in combination with spatial and temporal data, is frequently employed as a tool to help identify TB cases that may be involved with recent transmission (2–4). These methods are based upon the assumption that cases related by recent transmission in a geographic area of interest will be infected with strains showing an identical genotype, while cases that were infected in the past, or that were infected outside of the geographic area of interest, will be infected with strains that have a unique genotype (5). However, genotyping is not a perfect predictor of transmission, and not all cases with a shared genotype are related by recent transmission.

Although recent transmission only accounts for an estimated 14% of reported TB cases in the United States, and most transmission is thought to occur among U.S.-born populations, TB outbreaks involving foreign-born persons do occur (6–11). Yet, risk

factors for transmission among foreign-born populations have not been well studied. Given that transmission dynamics have been shown to differ between U.S.-born and foreign-born populations, identification of factors associated with transmission among foreign-born persons may be helpful in prioritizing resources and guiding TB control efforts within these populations (12,13).

Recent transmission is frequently associated with characteristics that are common among marginalized populations, including homelessness, previous incarceration, illicit drug use, and excessive alcohol use (hereinafter referred to as "marginalizing conditions") (12–16). While these marginalizing conditions have been well established as risk factors for recent transmission among U.S.-born populations, few studies have specifically evaluated them as risk factors for recent transmission among foreign-born populations. Moreover, the studies that have analyzed factors associated with recent transmission in foreign-born populations are geographically limited and are dependent upon methods of estimating recent transmission that have not been validated by field epidemiology (12,13,17,18).

Nevertheless, the few field- and genotype-based studies that did compare recent transmission among U.S.-born and foreign-born populations found that the majority of transmission occurred between U.S.-born persons who had at least one marginalizing condition (8,12,13). In contrast, TB transmission among foreign-born persons occurred exclusively in household settings among persons with no social risk factors (12). While these and other studies have shown that marginalizing conditions are less frequent among recent transmission clusters involving foreign-born persons, the studies did not

investigate whether marginalizing conditions are important predictors of recent transmission among foreign-born populations as well (12,13,19).

Thus, we conducted a large nation-wide study using a novel field-validated plausible-source case approach to estimate recent transmission to 1) determine if these marginalizing conditions are associated with recent transmission among foreign-born populations, and 2) to test whether the associations between recent transmission and each of the marginalizing conditions significantly differ between U.S.-born and foreign-born cases (20). Given that TB transmission dynamics differ for U.S.-born and foreign-born populations, we hypothesize that the associations between recent transmission and each of the marginalizing conditions will significantly differ by local versus foreign birth.

Methods

Data Source and Study Population

The study population includes all verified TB cases with valid genotyping results and known country of origin reported to the U.S. National Tuberculosis Surveillance System (NTSS) by 49 states and the District of Columbia during January 1, 2011–September 30, 2014; TB cases reported in Oklahoma were excluded because they lacked sufficient geographic information to be evaluated for recent transmission by the plausible-source case approach. The NTSS includes routinely collected demographic, clinical, and epidemiologic data for each reported TB case in the United States (21). Routine genotyping of all culture-positive TB cases is also conducted as a part of the NTSS and is used to uniquely characterize *M. tuberculosis* isolates. Since 2009, genotypes have been characterized using a standardized protocol for spacer

oligonucleotide typing (spoligotyping) and 24-locus mycobacterial interspersed repetitive unit–variable number of tandem repeats (MIRU–VNTR) typing (18,22).

Marginalizing Conditions

To understand how recent transmission of TB is associated with marginalized populations among U.S.- and foreign-born persons, we analyzed four characteristics captured by the NTSS: homelessness within the past year, excessive alcohol use within the past year, illicit drug use within the past year, and incarceration at the time of diagnosis (23). Due to collinearity between the separate variables, non-injecting drug use and injecting drug use, we combined them into one variable to indicate any illicit drug use.

Country of Origin

The NTSS includes information about country of origin, categorized as either foreign-born or U.S.-born, for all reported TB cases in the United States. In accordance with the U.S. Census Bureau definition of foreign-born, individuals were classified as U.S.-born if they were either born in the U.S. or an associated jurisdiction, or if they were born in a foreign country but had at least one parent who was a U.S. citizen (23). Individuals not meeting this definition were classified as foreign-born. Those with a missing or unknown country of origin were excluded from the analysis.

Estimating Recent Transmission

We evaluated each reported TB case with valid genotyping results from January 1, 2011–September 30, 2014, for recent transmission using a novel field-validated plausible-source case approach (20). Each case was compared to cases reported during the full study period (January 1, 2009–December 31, 2014) to determine if a plausible-

source case could be identified; if a plausible-source case was identified for a given case, then the given case was attributed to recent transmission. To be eligible as a plausible source for a secondary case, the source case must have an infectious form of TB, must have an identical genotype, must reside within 10 miles of the secondary case, and must have been diagnosed within 2 years before or up to 3 months after the secondary case (20). TB cases in foreign-born persons who were diagnosed within 100 days upon arrival to the U.S. were never attributed to recent transmission even if a plausible-source case could be identified (20). Those cases for which at least one plausible source case could be identified were classified as attributable to recent transmission. All others were classified as not attributable to recent transmission.

Statistical Analysis

We used log-binomial regression to evaluate whether the association between recent transmission of TB and each of homelessness, illicit drug use, excess alcohol use, and incarceration at diagnosis significantly differs by country of origin. Because transmission dynamics are different between adults and children, bivariate and multivariable analyses were restricted to persons 15 years of age or older (12). To determine if independent associations with recent transmission and each of homelessness, illicit drug use, excess alcohol use, and incarceration at diagnosis significantly differed by country of origin, we created one multivariable model that included interaction terms between origin of birth and each of the aforementioned variables. All statistical analyses were evaluated at an alpha level of 0.05. We assessed for confounding by age (broad age categories), race/ethnicity, sex, and HIV status by evaluating the change in prevalence ratio estimates with and without each variable. If the change in estimate was less than

10%, the variable was not considered a confounder and was not included in the model. We conducted collinearity diagnostics to detect any potential collinearity problems; variables with VIFs >10 were considered to be collinear. All statistical analyses were performed using SAS 9.3 (Cary, NC).

Ethics Statement

We analyzed data routinely collected by the CDC for disease surveillance and control purposes. The analysis was not considered human subjects research by the CDC or the Emory University Institutional Research Board (IRB), and does not require IRB approval. The only potentially identifying information included in the NTSS is a state case number assigned to each verified case; all state case numbers were removed prior to analysis.

Results

During January 1, 2011–September 30, 2014, a total of 36,674 verified TB cases in the 50 states and the District of Columbia were reported to the NTSS (Figure 1). Of these, 28,283 (77%) were culture-confirmed and 26,793 (73%) had valid genotyping results; 71% of U.S.-born cases and 75% of foreign-born cases were genotyped. After excluding cases reported by Oklahoma and those with unknown country of origin, we were left with a study sample of 26,562 cases: 17,363 (65%) among foreign-born persons and 9,199 (35%) among U.S.-born persons. Overall, 3,820 (14%) cases in the study population were attributed to recent transmission, including 2,522 of 9,199 (27%) U.S.-born persons and 1,298 of 17,363 (8%) foreign-born persons.

Table 1 provides descriptive analyses comparing patient characteristics for all TB cases as well as those cases attributed to recent transmission, stratified by country of

origin. The proportion of TB cases associated with homelessness, illicit drug use, excess alcohol use, or incarceration at diagnosis is notably higher among the U.S.-born. Among all U.S.-born cases, 2,091 (23%) reported excessive alcohol use, 1,601 (17%) reported illicit drug use, 1,072 (12%) reported homelessness, and 450 (5%) were incarcerated at diagnosis. Among all foreign-born cases, 1,273 (7%) reported excessive alcohol use, 572 (3%) reported illicit drug use, 493 (3%) reported homelessness, and 590 (3%) were incarcerated at diagnosis.

Table 2 provides results from bivariate analyses between patient characteristics and recent transmission. Among both U.S.-born and foreign-born populations, racial and ethnic minorities (vs. white race), males (vs. females), and persons 15–24 years old (vs. 25–44 years old) were more likely to be involved with recent transmission, while persons 65 years or older (vs. 25–44 years old) were considerably less likely to be involved with recent transmission. For incarcerated TB cases, recent transmission is most positively associated with residency in local jails and is most negatively associated with residency in immigration and customs enforcement detention centers. The majority of incarcerated U.S.-born cases are housed in local jails, and a large proportion of foreign-born cases are held in immigration and customs enforcement detention centers (Table 1).

Among U.S.-born persons, excessive alcohol use (prevalence ratio [PR] =1.6; 95% confidence interval [CI] = 1.5, 1.7), illicit drug use (PR = 1.7; 95% CI = 1.6, 1.9), homelessness (PR = 2.0; 95% CI = 1.9, 2.2), and incarceration at diagnosis (PR= 1.3; 95% CI = 1.1, 1.5) were all positively associated with recent transmission. Among foreign-born persons, excessive alcohol use (PR=1.6; 95% CI = 1.4, 1.9), illicit drug use (PR = 1.8; 95% CI = 1.6, 1.9), and homelessness (PR = 2.2; 95% CI = 1.8, 2.7) were all

positively associated with recent transmission, while incarceration at diagnosis (PR= 0.7; 95% CI = 0.5, 1.0) was negatively associated with recent transmission.

Results from the multivariable analyses show similar associations as those from the bivariate analyses (Table 3). The risk factors, homelessness, illicit drug use, excessive alcohol use, and incarceration at diagnosis, were associated with recent transmission for both U.S.-born and foreign-born populations after adjusting for age (broad age groups) and race/ethnicity. Gender and HIV status were also evaluated as confounders, but they did not meaningfully change the prevalence ratio estimates and were not included in the model. While the associations between recent transmission and each of the marginalizing conditions are slightly stronger among the foreign-born, the estimates, aside from incarceration at diagnosis, are not significantly different across strata ($p > 0.05$).

Among the U.S.-born, homelessness (adjusted PR [aPR] = 1.6; 95% CI = 1.5, 1.7), illicit drug use (aPR = 1.2; 95% CI = 1.1, 1.3), and excessive alcohol use (aPR = 1.2; 95% CI = 1.1, 1.3) were positively associated with recent transmission, and incarceration at diagnosis (aPR = 0.9; 95% CI = 0.8, 1.1) was negatively associated with recent transmission after adjusting for age and race/ethnicity. Similarly, among the foreign-born, homelessness (aPR = 1.7; 95% CI = 1.4, 2.2), illicit drug use (aPR = 1.4; 95% CI = 1.1, 1.8), and excessive alcohol use (aPR = 1.3; 95% CI = 1.1, 1.6) were also positively associated with recent transmission, while incarceration at diagnosis (aPR = 0.5; 95% CI = 0.3, 0.7) was negatively associated with recent transmission after adjusting for age and race/ethnicity.

Discussion

This cross-sectional study is the first nation-wide analysis to evaluate factors for recent transmission of TB among foreign-born populations in the United States. Using a novel field-validated plausible-source case approach, we found that recent transmission was independently associated with each of homelessness, illicit drug use, excessive alcohol use, and incarceration at diagnosis among foreign-born persons. With the exception of incarceration at diagnosis, there was no evidence to suggest that these associations significantly differed between U.S.-born and foreign-born cases. The results from this study reiterate the need for improved TB control strategies among marginalized populations in the United States and show that marginalizing conditions are important factors for transmission regardless of local or foreign birth.

Of the 26,562 cases included in this 3-year study, an estimated 14% were attributable to recent transmission, including 27% of U.S.-born cases and 8% of foreign-born cases. While these results support the notion that the most transmission in the United States occurs among U.S.-born persons (12,14,15), our estimates of recent transmission are considerably lower than those observed by previous genotype-based studies of U.S. populations (24–26). One explanation for this difference is that we evaluated recent transmission using a novel plausible-source case approach. Unlike previous methods of evaluating recent transmission, the plausible-source case approach was validated using field epidemiology and requires identification of a plausible-source case to attribute cases to recent transmission (20). This method has a calculated accuracy of 94% when the expected prevalence of recent transmission is between 10-15% (20).

Despite the fact that marginalizing conditions are not frequently associated with foreign-born TB cases (19), our results suggest that homelessness, excessive alcohol use, and illicit drug use are important predictors of recent transmission among foreign-born persons. These findings are not unexpected, though, as marginalized populations are known to be disproportionally affected by TB disease (27). Outbreaks of TB in the United States predominantly occur among marginalized populations (8), and numerous molecular epidemiologic studies have shown that patients with marginalizing conditions are more likely to be involved with recent transmission (6,14,15). These findings are further substantiated by one study that showed genotype clusters were at a substantially increased risk of becoming an outbreak if any one of the first three patients reported at least one marginalizing condition (28).

Persons experiencing homelessness are among the most marginalized populations in the United States (29) and were found to have the greatest magnitude of independent association with recent transmission among foreign-born cases. Our results are supported by outbreaks that have been detected among persons experiencing homelessness (8,30–32,11,33,34), and are consistent with previous genotype-based studies that have evaluated factors for recent transmission (6,14,15,35). Transmission is believed to be elevated among the homeless due to a number of host and environmental factors. First, persons experiencing homelessness are regularly associated with substance use, HIV infection, and malnutrition, all of which physiologically increase the likelihood of developing active disease among those who have been infected (36–38). Second, homeless persons often lack access to or are unwilling to seek medical care (39–41), which prevents timely diagnosis of TB (42,43) and results in prolonged infectious periods (8). Third, homeless

persons often congregate in overcrowded and poorly ventilated shelters, further facilitating transmission among these populations (44,45). Lastly, difficulties in contact tracing may also contribute to transmission among these populations, as homeless persons often have many transient contacts (9,11,46) and other comorbidities, such as substance abuse or mental illness, that may decrease a patient's willingness or ability to name contacts (47–49).

Substance use, including excessive alcohol and illicit drug use, is commonly associated with marginalized populations and is the most prevalent TB risk factor among outbreaks in the United States (8,37). During 2002–2008, 18 of the 27 reported outbreaks in the United States were characterized by substance abuse (≥50% of outbreak patients within a cluster reported substance abuse) (8). Although our study period is later, this association seems to hold, as we found both excessive alcohol use and illicit drug use to be positively associated with recent transmission among foreign-born persons. The physiological effects of substance abuse, along with the environment and risk behaviors of substance users, have been shown to contribute to the increased prevalence of recent transmission among these populations (36). Research indicates that substance use may cause impairment of the immune system (50), which not only increases an individual's susceptibility to active TB, but also facilitates development of more advanced and infectious disease (19,36,37,51). Substance users are also more likely to delay seeking medical care (19,46), which in combination with the physiological effects, leads to longer periods of infectivity (8). Additionally, substance use is likely to occur in confined and poorly ventilated settings, such as drug houses (49,52,47), bars (46,53), and vehicles (51), which all facilitate close and prolonged contact.

Contrary to findings from previous molecular epidemiologic studies, we did not find a positive association between recent transmission and incarceration at diagnosis for both U.S.-born and foreign-born cases (14,15). One possible explanation for this difference is that previous studies evaluated the association between recent transmission and past incarceration, rather than incarceration at diagnosis. The positive associations observed in previous studies might have been an artifact of the population this variable was capturing, as persons with a history of incarceration are more likely to be involved with other risk factors for TB transmission, such as substance abuse and homelessness (19,54). As further support for this hypothesis, another study that evaluated the association between incarceration at diagnosis and recent transmission also observed a negative effect (25). However, given that inmates are frequently transferred in and out of correctional facilities (54), the degree of recent transmission among incarcerated individuals might have been underestimated by the plausible source-case approach due to the geospatial constraints imposed by the method.

Although TB transmission dynamics differ between U.S.-born and foreign-born persons (12,13), our results suggest that there is no significant difference in the associations between recent transmission and each of homelessness, excessive alcohol use, and illicit drug use by country of origin. While these associations were not statistically significant, they were slightly stronger among foreign-born cases, suggesting that these factors may be more predictive of recent transmission for foreign-born persons. The only marginalizing condition that significantly differed between U.S.-born and foreign-born persons was incarceration at diagnosis; foreign-born cases that were incarcerated at diagnosis were significantly less likely to be involved with recent

transmission than were U.S.-born cases that were incarcerated at diagnosis. However, this difference is likely confounded by correctional facility type, as most U.S.-born persons were diagnosed in local jails, which have the strongest positive association with recent transmission, and a large proportion of foreign-born persons were diagnosed in immigration and customs enforcement detention centers, which have the strongest negative association with recent transmission. Differences in transmission dynamics by correctional type are likely due to the characteristics of persons that are housed in each facility. The majority of cases diagnosed in immigration and customs enforcement detention centers are in recent arrivals from countries with endemic TB, thus these cases likely represent remote transmission of TB (i.e., transmission that occurred outside of the United States). In contrast, cases diagnosed in local jails typically originate from disadvantaged, marginalized populations and are more likely to engage in behaviors that are associated with recent transmission. Ideally, we would have evaluated the association between recent transmission and correctional facility type, rather than overall correctional involvement, but there were not enough cases to analyze the data in this manner.

This analysis has several important limitations. First, TB genotyping can only be performed for cases with a cultured *Mycobacterium tuberculosis* isolate, and among those that do have a positive culture, isolate submission for genotyping is voluntary, thus our analysis does not include all reported TB cases for the study period. However, aside from young age, which is disproportionally represented among non-genotyped cases and likely represents recent transmission, we found no meaningful difference with regards to demographic and social risk factors between cases with and without genotyping results (data not shown). Although the proportion of cases attributable to recent transmission is

likely underestimated, we do not anticipate any systematic bias due to missing genotype results, as our analyses were restricted to persons 15 years of age or older.

Second, in the absence of detailed epidemiologic data, genotype clustering only serves as a proxy for differentiating between recent transmission and reactivation TB. While the plausible source-case approach has been validated through field epidemiology, this method, like any method based on genotyping data without epidemiologic information on transmission links, has the potential for misclassification errors. There are some circumstances in which cases related by recent transmission will not cluster, such as when related cases fall outside of the spatial or temporal frame of analysis or if mutation results in a change in the genotype. Conversely, cases may be falsely classified as attributable to recent transmission if they were infected with the same genotype elsewhere but developed TB after resettlement in the same location (e.g., immigrants from TB endemic countries who resettle in the same neighborhood), or if they were infected with a common genotype that has been circulating in the population for many years. In addition, because isolate submission is incomplete, recent transmission might be misclassified as reactivation TB if related cases were not detected due to missing genotype results. However, non-genotyped cases are more likely to have clinical markers of less infectious TB (i.e., negative sputum smear results and non-cavitary disease) and are more frequently characterized by non-pulmonary disease (data not shown). Thus, non-genotyped cases may be less likely to be source cases (55), so the degree of misclassification due to missing genotype results might not be that great.

Lastly, although the study population was large, there were not enough data to assess effect modification by country of birth or by time since arrival in the United States

among foreign-born persons. Results from previous studies have shown that risk factors for recent transmission differ by country of birth (56), and there is evidence to suggest that foreign-born persons become more similar to U.S.-born persons with increasing time in the United States (57). Thus, our analysis likely masked differences between these groups that are potentially important for guiding TB control efforts among foreign-born persons.

In conclusion, we found that recent transmission is positively associated with homelessness, excessive alcohol use, and illicit drug use among foreign-born persons. However, there was no evidence that these associations significantly differed between U.S.-born and foreign-born persons. While our results suggest that incarceration at diagnosis is negatively associated with recent transmission, this can be primarily attributed to the large proportion of foreign-born cases that were diagnosed in immigration and customs enforcement detention centers shortly after arrival to the United States. Given that TB becomes increasingly concentrated within marginalized populations as the incidence of TB declines (27), our results reiterate the importance of addressing TB in marginalized populations regardless of local or foreign birth.

References

1. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2014. Atlanta, GA: 2015.
2. Barnes PF, Cave MD. Molecular epidemiology of tuberculosis. *N. Engl. J. Med.* 2003;349:1149–56.
3. Kammerer JS, Shang N, Althomsons SP, et al. Using statistical methods and genotyping to detect tuberculosis outbreaks. *Int. J. Health Geogr.* 2013;12(1):15.
4. Ghosh S, Moonan PK, Cowan L, et al. Tuberculosis Genotyping Information Management System: Enhancing Tuberculosis Surveillance in the United States. *Infect. Genet. Evol.* 2012;12(4):782–788.
5. Burgos M V, Pym AS. Molecular epidemiology of tuberculosis. *Eur. Respir. J.* 2002;20:54s–65s.
6. Yuen C, Kammerer S, Marks K, et al. Recent transmission of tuberculosis — United States, 2011-2014. *PLoS One*. 2016;11(4):e0153728.
7. Mitruka K, Blake H, Ricks P, et al. A tuberculosis outbreak fueled by cross-border travel and illicit substances: Nevada and Arizona. *Public Health Rep.* 2014;129:78–85.
8. Mitruka K, Oeltmann JE, Ijaz K, et al. Tuberculosis outbreak investigations in the United states, 2002-2008. *Emerg. Infect. Dis.* 2011;17(3):425–431.
9. Moreau D, Gratrix J, Kunimoto D, et al. A shelter-associated tuberculosis outbreak: A novel strain introduced through foreign-born populations. *Can. J. Public Heal.* 2012;103(6):408–412.
10. Zwerling A, Hanrahan C, Dowdy DW. Ancient Disease, Modern Epidemiology: A Century of Progress in Understanding and Fighting Tuberculosis. *Am. J. Epidemiol.* 2016;183(5):407–414.
11. Centers for Disease Control and Prevention. Tuberculosis Outbreak Associated with a Homeless Shelter — Kane County, Illinois, 2007-2011. *MMWR Morb. Mortal. Wkly. Rep.* 2012;61(11):186–189.
12. Cronin WA, Golub JE, Lathan MJ, et al. Molecular epidemiology of tuberculosis in a low- to moderate-incidence state: are contact investigations enough? *Emerg. Infect. Dis.* 2002;8(11):1271–1279.
13. Chin DP, DeRiemer K, Small PM, et al. Differences in contributing factors to tuberculosis incidence in US-born and foreign-born persons. *Am. J. Respir. Crit. Care Med.* 1998;158(6):1797–1803.
14. Nava-Aguilera E, Andersson N, Harris E, et al. Risk factors associated with recent transmission of tuberculosis: systematic review and meta-analysis [Review article]. *Int. J. Tuberc. Lung Dis.* 2009;13(1):17–26.
15. Fok, A. YN, Schulzer M, FitzGerald MJ. Risk factors for clustering of tuberculosis cases: a systematic review of population-based molecular epidemiology studies [Review Article]. *Int. J. Tuberc. Lung Dis.* 2008;12(5):480–492.

16. Kempf MC, Dunlap NE, Lok KH, et al. Long-term molecular analysis of tuberculosis strains in Alabama, a state characterized by a largely indigenous, low-risk population. *J. Clin. Microbiol.* 2005;43(2):870–878.

17. Jasmer RM, Hahn JA, Small PM, et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991-1997. *Ann. Intern. Med.* 1999;130(12):971–978.

18. Centers for Disease Control and Prevention. Tuberculosis Genotyping in the United States. Atlanta, GA: 2012.

19. Oeltmann JE, Kammerer JS, Pevzner ES, et al. Tuberculosis and substance abuse in the United States, 1997-2006. *Arch. Intern. Med.* 2009;169(2):189–197.

20. France AM, Grant J, Kammerer JS, et al. A Field-Validated Approach Using Surveillance and Genotyping Data to Estimate Tuberculosis Attributable to Recent Transmission in the United States. *Am. J. Epidemiol.* 2015;182(9):799–807.

21. Centers for Disease Control and Prevention. Report of Verified Case of Tuberculosis (RVCT) Form. 2009.(http://www.cdc.gov/tb/programs/rvct/)

22. Kamerbeek J, Schouls LEO, Kolk A, et al. Simultaneous Detection and Strain Differentiation of Mycobacterium tuberculosis for Diagnosis and Epidemiology. *J. Cinical Microbiol.* 1997;35(4):907–914.

23. Centers for Disease Control and Prevention. Report of Verified Case of Tuberculosis (RVCT) Instruction Manual. 2009.

24. Ricks PM, Cain KP, Oeltmann JE, et al. Estimating the burden of tuberculosis among foreign-born persons acquired prior to entering the U.S., 2005-2009. *PLoS One*. 2011;6(11):e27405.

25. Moonan PK, Ghosh S, Oeltmann JE, et al. Using Genotyping and Geospatial Scanning to Estimate Recent Mycobacterium tuberculosis Transmission, United States. *Emerg. Infect. Dis.* 2012;18(3):458–465.

26. Shea KM, Kammerer JS, Winston C a., et al. Estimated rate of reactivation of latent tuberculosis infection in the United States, overall and by population subgroup. *Am. J. Epidemiol.* 2014;179(2):216–225.

27. World Health Organization. Towards tuberculosis elimination: an action framework for low-incidence countries. Geneva: 2014.

28. Althomsons SP, Kammerer JS, Shang N, et al. Using Routinely Reported Tuberculosis Genotyping and Surveillance Data to Predict Tuberculosis Outbreaks. *PLoS One*. 2012;7(11):1–8.

29. Levinson D. Encyclopedia of Homelessness, Volume 1. Thousand Oaks, CA: SAGE Publications; 2004.

30. Lathan M, Mukasa LN, Hooper N, et al. Cross-jurisdictional transmission of Mycobacterium tuberculosis in Maryland and Washington, D.C., 1996-2000, linked to the homeless. *Emerg. Infect. Dis.* 2002;8(11):1249–1251.

31. Centers for Disease Control and Prevention. Notes from the Field: Tuberculosis Cluster Associated with Homelessness — Duval County, Florida, 2004-2012.

MMWR Morb. Mortal. Wkly. Rep. 2012;61(28):539.

32. McElroy PD, Southwick KL, Fortenberry ER, et al. Outbreak of tuberculosis among homeless persons coinfected with human immunodeficiency virus. *Clin. Infect. Dis.* 2003;36(5):1305–1312.
33. Centers for Disease Control and Prevention. Notes from the Field: Outbreak of Tuberculosis Associated with a Newly Identified Mycobacterium tuberculosis Genotype — New York City, 2010–2013. *MMWR Morb. Mortal. Wkly. Rep.* 2013;62(45):904.
34. Mindra G, Haddad MB, Wortham J, et al. Tuberculosis Outbreaks in the United States, 2009-2015.
35. Sahly HM El, Adams GJ, Soini H, et al. Epidemiologic Differences between United States— and Foreign-Born Tuberculosis Patients in Houston, Texas. *J. Infect. Dis.* 2001;183(3):461–468.
36. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and illicit drug use: review and update. *Clin. Infect. Dis.* 2009;48(1):72–82.
37. Rehm J, Samokhvalov A V, Neuman MG, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health*. 2009;9:450.
38. Frieden TR, Sterling TR, Munsiff SS, et al. Tuberculosis. *Lancet*. 2003;362(9387):887–899.
39. Hwang SW, Ueng JJM, Chiu S, et al. Universal health insurance and health care access for homeless persons. *Am. J. Public Health*. 2010;100(8):1454–1461.
40. Gelberg L, Gallagher TC, Andersen RM, et al. Competing priorities as a barrier to medical care among homeless adults in Los Angeles. *Am. J. Public Health*. 1997;87(2):217–220.
41. Baggett TP, O'Connell JJ, Singer DE, et al. The Unment Health Care Needs of Homeless Adults: A National Study. *Am. J. Public Health*. 2010;100(7):1326–1333.
42. Tan de Bibiana J, Rossi C, Rivest P, et al. Tuberculosis and homelessness in Montreal: a retrospective cohort study. *BMC Public Health*. 2011;11(1):833.
43. Sherman LF, Fujiwara P!., Cook S V, et al. Patient and health care system delays in the diagnosis and treatment of tuberculosis. *Int J Tuberc Lung Dis*. 1999;3(12):1088–1095.
44. Lofy KH, McElroy PD, Lake L, et al. Outbreak of tuberculosis in a homeless population involving multiple sites of transmission. *Int. J. Tuberc. Lung Dis.* 2006;10(6):683–689.
45. Curtis AB, Ridzon R, Novick LF, et al. Analysis of Mycobacterium tuberculosis transmission patters in a homeless shelter outbreak. *Int.J.Tuberc.Lung Dis.* 2000;4(4):308–313.
46. Diel R, Meywald-Walter K, Gottschalk R, et al. Ongoing outbreak of tuberculosis in a low-incidence community: A molecular-epidemiological evaluation. *Int. J.*

Tuberc. Lung Dis. 2004;8(7):855–861.

47. Asghar RJ, Patlan DE, Miner MC, et al. Limited utility of name-based tuberculosis contact investigations among persons using illicit drugs: Results of an outbreak investigation. *J. Urban Heal.* 2009;86(5):776–780.
48. Cavanaugh JS, Powell K, Renwick OJ, et al. An Outbreak of Tuberculosis Among Adults With Mental Illness. *Am. J. Psychiatry*. 2012;169(6):569–575.
49. Pevzner ES, Robison S, Donovan J, et al. Tuberculosis transmission and use of methamphetamines in Snohomish County, WA, 1991-2006. *Am. J. Public Health*. 2010;100(12):2481–2486.
50. Friedman H,Newton C KT. Microbial infections inmunomodulation and drugs of abuse. *Clin Microbiol Rev*. 2003;16(16):209–219.
51. Oeltmann JE, Oren E, Haddad MB, et al. Tuberculosis Outbreak in Marijuana Users, Seattle, Washington, 2004. *Emerg. Infect. Dis.* 2006;12(7).
52. Malakmadze N, González IM, Oemig T, et al. Unsuspected recent transmission of tuberculosis among high-risk groups: implications of universal tuberculosis genotyping in its detection. *Clin. Infect. Dis.* 2005;40(3):366–373.
53. Kline SE, Hedemark LL, Davies SF. Outbreak of tuberculosis among regular patrons of a neighborhood bar. *N. Engl. J. Med.* 1995;333:222–227.
54. Centers for Disease Control and Prevention. Prevention and Control of Tuberculosis in Correctional and Detention Facilities: Recommendations from CDC. *MMWR Recomm. Reports*. 2006;55(RR09):1–44.
55. Tostmann A, Kik S V, Kalisvaart N a, et al. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. *Clin. Infect. Dis.* 2008;47(9):1135–1142.
56. Suwanpimolkul G, Jarlsberg LG, Grinsdale J a, et al. Molecular epidemiology of tuberculosis in foreign-born persons living in San Francisco. *Am. J. Respir. Crit. Care Med.* 2013;187(9):998–1006.
57. Argeseanu Cunningham S, Ruben JD, Venkat Narayan KM. Health of foreign-born people in the United States: A review. *Heal. Place*. 2008;14(4):623–635.

Tables and Figures

Figure 1. Inclusion and exclusion criteria for reported cases of TB in the United States.

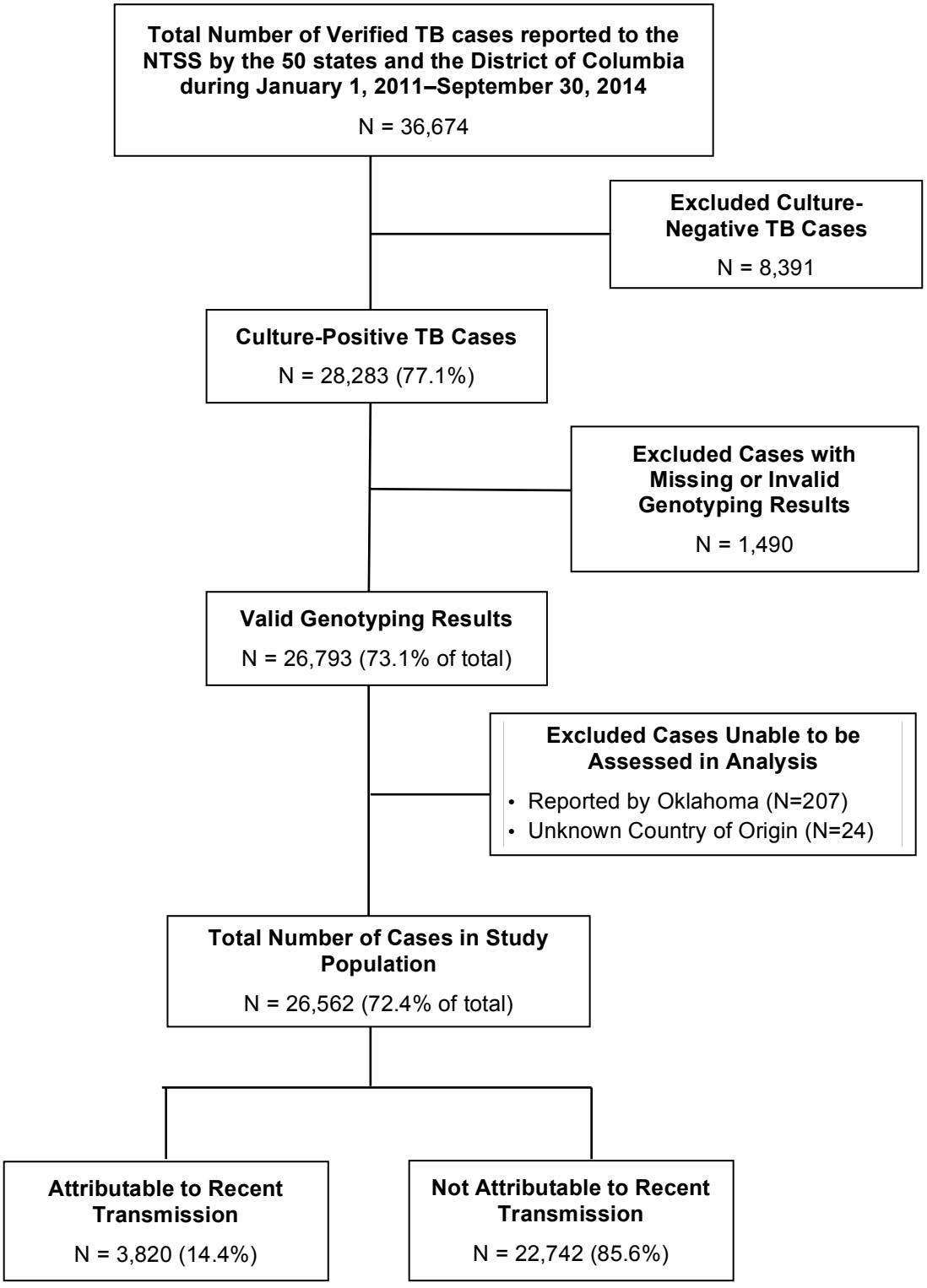

Table 1. Frequency of patient characteristics among total cases (N=26,562) and those classified as attributable to recent transmission for U.S.-born (N=2,522) and foreign-born (N=1,298) TB cases in the United States. Column percentages are presented.

Characteristic	U.S.-born		Foreign-born	
	Total (%)	Attributable to RT (%)	Total (%)	Attributable to RT (%)
Overall	9,199 (34.6)	2,522 (27.4)	17,363 (65.4)	1,298 (7.5)
Age				
≤4	259 (2.8)	144 (5.7)	14 (0.1)	1 (0.1)
5-14	141 (1.5)	53 (2.1)	88 (0.5)	7 (0.5)
15-24	918 (10.0)	337 (13.4)	1,867 (10.8)	204 (15.7)
25-44	2,087 (22.7)	678 (26.9)	6,343 (36.5)	491 (37.8)
45-64	3,542 (38.5)	1,077 (42.7)	4,823 (27.8)	373 (28.7)
≥65	2,252 (24.5)	233 (9.2)	4,226 (24.3)	222 (17.1)
Gender				
Female	3,046 (33.1)	791 (31.4)	6950 (40.0)	452 (34.8)
Male	6,151 (66.9)	1,730 (68.6)	10,413 (60.0)	846 (65.2)
Race/Ethnicity[a]				
American Indian/Alaska Native	354 (3.9)	143 (5.7)	4 (0.0)	0 (0.0)
Asian	290 (3.2)	73 (2.9)	8,031 (46.3)	517 (39.8)
Black	3,549 (38.6)	1,280 (50.8)	2,166 (12.5)	156 (12.0)
Hispanic	1,643 (17.9)	457 (18.1)	5,930 (34.2)	577 (44.5)
Multiple Races	66 (0.7)	15 (0.6)	338 (1.9)	14 (1.1)
Native Hawaiian/Other Pacific Islander	140 (1.5)	53 (2.1)	42 (0.2)	2 (0.2)
White	3,145 (34.2)	498 (19.8)	823 (4.7)	30 (2.3)
Excessive Alcohol Use				
Yes	2,091 (22.7)	762 (30.2)	1,273 (7.3)	149 (11.5)
No	6,972 (75.8)	1,724 (68.4)	15,839 (91.2)	1,134 (87.4)
Unknown	136 (1.5)	36 (1.4)	251 (1.4)	15 (1.2)
Illicit Drug Use				
Yes	1,601 (17.4)	646 (25.6)	572 (3.3)	77 (5.9)
No	7,453 (81.0)	1,839 (72.9)	16529 (95.2)	1,209 (93.1)
Unknown	145 (1.6)	37 (1.5)	262 (1.5)	12 (0.9)
Homeless				
Yes	1,072 (11.7)	509 (20.2)	493 (2.8)	77 (5.9)
No	8,075 (87.8)	1,996 (79.1)	16,726 (96.3)	1,217 (93.8)
Unknown	52 (0.6)	17 (0.7)	144 (0.8)	4 (0.3)
Incarcerated at Diagnosis				
Yes	450 (4.9)	149 (5.9)	590 (3.4)	31 (2.4)
No	8,722 (94.8)	2,362 (93.7)	16,731 (96.4)	1,265 (97.5)
Unknown	27 (0.3)	11 (0.4)	42 (0.2)	2 (0.2)
Correctional Type				
Federal Prison	27 (0.3)	6 (0.2)	122 (0.7)	5 (0.4)
State Prison	181 (2.0)	51 (2.0)	31 (0.2)	1 (0.1)
Local Jail	224 (2.4)	88 (3.5)	249 (1.4)	22 (1.7)
Immigrations and Customs Enforcement	2 (0.0)	0 (0.0)	162 (0.9)	2 (0.2)
Unknown	11 (0.1)	3 (0.1)	17 (0.1)	1 (0.1)
None	8,754 (95.2)	2,374 (94.1)	16,782 (96.7)	1,267 (97.6)
HIV Status				
Positive	736 (8.0)	286 (11.3)	905 (5.2)	81 (6.2)
Negative	7,157 (77.8)	1,977 (78.4)	14,339 (82.6)	1,110 (85.5)
Unknown[b]	1,306 (14.2)	259 (10.3)	2,119 (12.2)	107 (8.2)

Abbreviation: RT, recent transmission.

[a] Persons of Hispanic ethnicity might be of any race; non-Hispanic persons were categorized as American Indian/Alaskan Native, Asian, black, white, Native Hawaiian or other Pacific Islander, or of multiple races

[b] Unknown HIV status includes those who refused testing, were not offered testing, had indeterminate results, or had a test done but the results were unknown

Table 2. Bivariate associations between patient characteristics and recent transmission of TB, stratified by local and foreign-birth. Crude prevalence ratios and 95% confidence intervals are presented.

Characteristic	U.S.-born		Foreign-born	
	Crude PR	95% CI	Crude PR	95% CI
Age				
15-24	1.1	1.0, 1.3	1.4	1.2, 1.7
25-44	*Reference*		*Reference*	
45-64	0.9	0.9, 1.0	1.0	0.9, 1.1
≥65	0.3	0.3, 0.4	0.7	0.6, 0.8
Gender				
Female	*Reference*		*Reference*	
Male	1.1	1.0, 1.2	1.3	1.1, 1.4
Race/Ethnicity[a]				
American Indian/Alaska Native	2.5	2.1, 2.9	--	--
Asian	1.3	1.0, 1.7	1.8	1.2, 2.5
Black	2.3	2.1, 2.5	2.0	1.3, 2.9
Hispanic	1.6	1.5, 1.9	2.7	1.9, 3.8
Multiple Races	1.4	0.8, 2.3	1.1	0.6, 2.1
Native Hawaiian/Other Pacific Islander	2.3	1.8, 3.0	1.3	0.3, 5.3
White	*Reference*		*Reference*	
Excessive Alcohol Use				
Yes	1.6	1.5, 1.7	1.6	1.4, 1.9
No	*Reference*		*Reference*	
Unknown	1.1	0.9, 1.5	0.8	0.5, 1.4
Illicit Drug Use				
Yes	1.7	1.6, 1.9	1.8	1.5, 2.3
No	*Reference*		*Reference*	
Unknown	1.1	0.8, 1.5	0.6	0.4, 1.1
Homeless				
Yes	2.0	1.9, 2.2	2.2	1.8, 2.7
No	*Reference*		*Reference*	
Unknown	1.2	0.8, 1.9	0.4	0.2, 1.0
Incarcerated at Diagnosis				
Yes	1.3	1.1, 1.5	0.7	0.5, 1.0
No	*Reference*		*Reference*	
Unknown	1.6	1.0, 2.5	0.6	0.2, 2.4
Correctional Type				
Federal Prison	0.9	0.4, 1.7	0.5	0.2, 1.3
State Prison	1.1	0.9, 1.4	0.4	0.1, 2.9
Local Jail	1.5	1.3, 1.8	1.2	0.8, 1.8
Immigrations and Customs Enforcement	--	--	0.2	0.0, 0.7
Unknown	1.1	0.4, 2.8	0.8	0.1, 5.2
None	*Reference*		*Reference*	
HIV Status				
Positive	1.4	1.3, 1.6	1.2	0.9, 1.4
Negative	*Reference*		*Reference*	
Unknown[b]	0.6	0.5, 0.7	0.7	0.5, 0.8

Abbreviation: PR, prevalence ratio; CI, confidence interval.
[a] Persons of Hispanic ethnicity might be of any race; non-Hispanic persons were categorized as American Indian/Alaskan Native, Asian, black, white, Native Hawaiian or other Pacific Islander, or of multiple race
[b] Unknown HIV status includes those who refused testing, were not offered testing, had indeterminate results, or had a test done but the results were unknown

Table 3. Multivariable associations between recent transmission and each of illicit substance use, homelessness, incarceration at diagnosis, and excessive alcohol use stratified by local and foreign-birth. Prevalence ratios are adjusted for age and race/ethnicity. Statistical interactions between origin of birth and each risk factor were assessed in one multivariable model.

	U.S.-born		Foreign-born		Statistical Interaction
	aPR	**95% CI**	**aPR**	**95% CI**	**p-value**
Excessive Alcohol Use					
Yes	1.2	1.1, 1.3	1.3	1.1, 1.6	0.191
Unknown	1.3	0.9, 1.8	1.3	0.7, 2.4	0.971
No	*Reference*		*Reference*		
Illicit Drug Use					
Yes	1.2	1.1, 1.3	1.4	1.1, 1.8	0.155
Unknown	0.8	0.6, 1.1	0.7	0.3, 1.3	0.658
No	*Reference*		*Reference*		
Homeless					
Yes	1.6	1.5, 1.7	1.7	1.4, 2.1	0.480
Unknown	1.1	0.7, 1.7	0.5	0.2, 1.4	0.192
No	*Reference*		*Reference*		
Incarcerated at Diagnosis					
Yes	0.9	0.8, 1.1	0.5	0.3, 0.7	<0.001
Unknown	1.2	0.8, 1.7	1.1	0.3, 4.4	0.910
No	*Reference*		*Reference*		

Abbreviation: aPR, adjusted prevalence ratio; CI, confidence interval