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Risk factors for transmission of tuberculosis among United States-born African Americans and Whites

M. A. Pagaoa[*], **R. A. Royce**[†], **M. P. Chen**[*], **J. E. Golub**[‡], **A. L. Davidow**[§], **Y. Hirsch-Moverman**[¶], **S. M. Marks**[*], **L. D. Teeter**[#], **P. M. Thickstun**[**], and **D. J. Katz**[*] **for the Tuberculosis Epidemiologic Studies Consortium**

[*]Centers for Disease Control and Prevention, Atlanta, Georgia [†]RTI International, Durham, North Carolina [‡]Johns Hopkins School of Medicine, Baltimore, Maryland [§]New Jersey Medical School at Rutgers, Newark, New Jersey [¶]Columbia University, New York, New York [#]Houston Methodist Research Institute, Houston, Texas [**]Texas Department of State Health Services, Austin, Texas, USA

SUMMARY

SETTING —Tuberculosis (TB) patients and their contacts enrolled in nine states and the District of Columbia from 16 December 2009 to 31 March 2011.

OBJECTIVE —To evaluate characteristics of TB patients that are predictive of tuberculous infection in their close contacts.

DESIGN —The study population was enrolled from a list of eligible African-American and White TB patients from the TB registry at each site. Information about close contacts was abstracted from the standard reports of each site.

RESULTS —Close contacts of African-American TB patients had twice the risk of infection of contacts of White patients (adjusted risk ratio [aRR] 2.1, 95%CI 1.3–3.4). Close contacts of patients whose sputum was positive for acid-fast bacilli on sputum smear microscopy had 1.6 times the risk of tuberculous infection compared to contacts of smear-negative patients (95%CI 1.1–2.3). TB patients with longer (>3 months) estimated times to diagnosis did not have higher proportions of infected contacts (aRR 1.2, 95%CI 0.9–1.6).

CONCLUSION —African-American race and sputum smear positivity were predictive of tuberculous infection in close contacts. This study did not support previous findings that longer estimated time to diagnosis predicted tuberculous infection in contacts.

Keywords

epidemiologic factors; contact tracing; infection

TUBERCULOSIS (TB) control programs need to know which TB patient characteristics best predict transmission in order to allocate limited resources to screening of contacts most

Correspondence to: Melissa Pagaoa, Centers for Disease Control and Prevention, 1600 Clifton Road NE MS-D18, Atlanta, GA 30333, USA. Tel: (+1) 404 639 5959. mpagaoa@cdc.gov.

at risk for latent tuberculous infection (LTBI) and disease progression.[1,2] Previously identified predictors of transmission include longer times from symptom onset to TB diagnosis, presence of acid-fast bacilli (AFB) in sputum smears, and pulmonary cavities on chest radiography.[3–6]

We hypothesized that TB cases with delayed diagnosis, defined as a longer time from symptom onset to TB diagnosis, would be more likely to transmit TB to their contacts. We evaluated delayed time to TB diagnosis as a risk factor for transmission of *Mycobacterium tuberculosis* from US-born African-American and White TB cases to their contacts.

STUDY POPULATION AND METHODS

The Tuberculosis Epidemiologic Studies Consortium (TBESC) was funded by the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) to conduct research on TB prevention and control at 21 sites across the United States and Canada.[7] One study focused on the differences in time to diagnosis between African Americans and Whites. This study was conducted at seven TBESC sites and three additional collaborating TB programs that accounted for 36.8% of TB cases among US-born Blacks and 15.8% of cases among US-born Whites reported to the CDC's National Tuberculosis Surveillance System during the enrollment period from 16 December 2009 to 31 March 2011 (Table 1). The following analysis was conducted on contact investigation data collected for the study.

To be eligible, patients listed on the site's TB registry had to 1) have a TB diagnosis that met CDC case verification criteria,[8] 2) be US-born; 3) be non-Hispanic; 4) be African American, White, or a combination that included either race; 5) be at least 15 years old at the time of diagnosis; and 6) be first reported to a local health department as a presumptive TB case from 16 August 2009 to 31 December 2010.

The institutional review boards at the CDC and the local institutions approved the study. All living participants provided written informed consent.

Data collection on tuberculosis patients

TB patients were interviewed in person about their demographics, behavioral risk factors, medical history, TB symptoms and symptom onset dates, and care seeking for TB and other conditions. Clinical information was abstracted from health department records and CDC Reported Verified Case of Tuberculosis (RVCT) surveillance reports. For eligible persons who died before they could be interviewed, study researchers abstracted relevant information from death certificates, health department records, and RVCT reports.

Data collection on tuberculosis contacts

TB contacts' demographics, places and duration of exposure to the TB patient, LTBI and TB disease history, and local determination of whether the contact was close, high risk, or high priority, were abstracted from health department contact investigation reports; no personal identifiers were collected.

Study variables

Tuberculous infection in a contact was determined from the results of the tuberculin skin test (TST) or either of the commercially available interferon-gamma release assays (IGRAs)—QuantiFERON® (Cellestis, Carnegie, VIC, Australia) and T-SPOT®.*TB* (Oxford Immunotec, Abingdon, UK)—as recorded in the health department contact investigation records. Contacts were defined as having tuberculous infection if they had 1) a positive interpretation noted on the first or second IGRA or TST; 2) ≥5 mm induration recorded on the first or second TST; or 3) a diagnosis of TB disease. Contacts were defined as not having tuberculous infection if they had negative interpretations of their most recent IGRAs or TSTs, or <5 mm induration recorded as the most recent TST result. Contacts with positive test results were regarded as recently infected with *Mycobacterium tuberculosis* if they did not have a previous positive TB test, LTBI diagnosis, or TB diagnosis.[9]

TB patients were asked to provide the month and year of symptom onset, and the 15th of the month was selected as the day. For those who did not remember or had died before the interview, the earliest symptom date in the medical record was used. The date of TB diagnosis was defined as the recorded date the patient first received TB medication. In preliminary analyses, time from symptom onset to diagnosis was treated as a continuous and dichotomous variable with values based on a review of the literature[4,10] and the distribution of the study data. Two dichotomous variables were used for the final analyses: <2 months vs. ≥2 months, and <3 months vs. ≥3 months.

Statistical analysis

As outcomes of tuberculous infection in contacts of the same TB patient were unlikely to be independent of each other,[4,11,12] generalized estimating equations (GEE) were used to control for intra-cluster dependence.[13] Relative risks (RRs) and 95% confidence intervals (CIs) were calculated using adjusted and unadjusted GEE models. All predictor variables with a *P* value of <0.25 in unadjusted analyses were included in the adjusted model. Although time to diagnosis did not meet the threshold for inclusion, it was included in the model as it was the main exposure variable of interest. Final models were formed using a backward elimination strategy and the *Z*-statistic. Data were analyzed using Statistical Analysis Software (SAS, version 9.3; SAS Inc, Cary, NC, USA).

RESULTS

Of 1014 eligible patients, 128 (13%) died before they could be interviewed and 886 (87%) were approached for recruitment. A final 601 patients were enrolled, 126 deceased and 475 living, with a total of 9525 contacts.

Patients were excluded from analysis if 1) no contacts were listed ($n = 116$); 2) they had an unknown site of disease or had no pulmonary, laryngeal, or pleural involvement, as transmission from such patients was unlikely ($n = 26$);[14,15] or 3) time to diagnosis could not be determined ($n = 77$) (Figure 1). After exclusion of these patients, 382 patients and 8275 contacts remained.

Contacts other than those designated by health departments as close, high priority, or high risk (hereafter, referred to as close contacts) were excluded, to focus on those most likely to acquire tuberculous infection (n =3895) (Figure 1).[15–18] Also excluded were contacts likely to have old infections[2] (previous positive TB test, LTBI diagnosis, or TB diagnosis, n=545) and those with unknown infection status (n = 534).

After these exclusions, 277 patients (46% of total) remained, 33 deceased and 244 living, and their 3301 (35% of total) close contacts. Compared to the patients excluded from the study, the included patients were younger at TB diagnosis, less likely to have had a previous TB diagnosis, less educated, more likely to report drug and alcohol use, more likely to report a cough lasting at least 2 weeks in the year before TB diagnosis, to have positive sputum smears, and to have pulmonary cavities (Table 2).

The 214 African-American and 63 White TB patients had a median of three close contacts (range 1–438). Compared to Whites, African Americans with TB disease were more likely to have human immunodeficiency virus (HIV) infection, be less educated, and younger (data not shown). The median estimated time to diagnosis was 2 months (range <1 month–237 months; interquartile range 4 months) (Figure 2). Of the 3301 close contacts included in the analysis, 464 (14%) had tuberculous infection; 22 (4.7%) of those infected had TB disease. Of the close contacts with TB disease, 19 (86.4%) were African-American, one contact (4.6%) was White, and two contacts (9.1%) were of unknown race. Of the 2870 close contacts who were negative on their initial TST/IGRA, 1104 (38.5%) did not have a second TST/IGRA result available. Sixty-three contacts (2%) who were negative on their initial TST/IGRA were positive on their second TST/IGRA. The majority of contacts (89%) were tested using TST; 5% of Whites and 3% of African-Americans were tested using IGRAs (P < 0.05). Although a large amount of information was missing for contacts for most variables (>65%), available data for sex (85% complete) and race (73% complete) showed that the majority of close contacts were male (63%) and African American (53%). Infection was more common among females than males (16% vs. 12%, P < 0.01), and among African Americans than Whites (15% vs. 9%, P < 0.0001). African-American TB patients (81%) were more likely than Whites (12%) to have African-American close contacts (P < 0.0001). In unadjusted GEE analysis, close contacts were at higher risk of tuberculous infection if their index TB patient was African-American, had pulmonary cavities, was sputum smear-positive, or reported drug use. Close contacts were at lower risk of tuberculous infection if their index patient was homeless or had a previous diagnosis of TB (Table 3). Time to diagnosis at the 3-month cut-off had a smaller P value (P = 0.44) than the 2-month cut-off (P = 0.70), and was therefore included in the adjusted model (Table 4).

In the adjusted model, close contacts of African-American TB patients had twice the risk of tuberculous infection as close contacts of White patients. Further analyses were conducted to determine the specific differences in factors associated with infectiousness between African-American and White TB patients. However, models stratified on race did not produce results that changed conclusions of the study. Close contacts of sputum smear-positive patients had 1.6 times the risk of tuberculous infection compared to close contacts of sputum smear-negative patients (Table 4). The TB patients' time to diagnosis was not associated with

tuberculous infection in their contacts (aRR 1.18, 95%CI 0.86–1.63). Controlling for study site in the adjusted model did not change these conclusions (data not shown).

DISCUSSION

The presence of AFB on sputum smear microscopy is a marker of both the severity of TB disease and its infectiousness.[19] Sputum smear positivity has long been associated with increased risk for tuberculous infection in contacts, and our results support other studies that found an increased risk of tuberculous infection in contacts exposed to patients with advanced TB disease.[2,5–7,16,18,20–23]

While some studies have found an association between African-American race and TB transmission,[4,5,21,24–27] others did not.[19,28–32] Our study found that close contacts of US-born non-Hispanic African Americans were twice as likely to have tuberculous infection as close contacts of US-born non-Hispanic Whites; African-American patients were also more likely than White patients to have African-American close contacts. However, the association between race and tuberculous infection may be a reflection of the generally higher prevalence of LTBI in the African-American community rather than an indication of recent TB transmission. The 2008 National Health and Nutrition Examination Survey (NHANES) found that US-born non-Hispanic African Americans had a significantly higher prevalence of LTBI than non-Hispanic Whites (5.7% vs. 1.1%).[33]

Previous studies found that longer time to diagnosis results in TB transmission in the community. A Maryland study that included 54 US-born patients and their 310 close contacts reported that 40% of close contacts of patients who had a time to diagnosis of ≥90 days had positive TSTs compared to 24% of contacts with <90 days' delay ($P < 0.01$).[4] While our definition of a close, high risk, or high priority contact varied across sites, the local health departments in Maryland shared a similar definition of close contact,[4] reducing the variance of exposure and increasing the power to find an association between time to diagnosis and TB transmission. The Maryland study reported more than twice as many contacts with tuberculous infection (35%)[4] as found in our study (14%), while earlier studies reported even higher proportions of close contacts with tuberculous infection (18–43%).[1,2,16,18] The lower proportion of infection in our study may reflect the continuing reduction in overall TB rates in the US-born population.[34] In addition, our study used IGRAs as well as the TST to diagnose infection in contacts, while previous studies relied primarily on TST.[1,2,4,16,18] Higher specificity has been reported for IGRAs than for the TST,[35] and may have influenced our study's tuberculous infection results. Lastly, our study had a smaller proportion of patients with delayed diagnosis (47%) than the Maryland study (56%).[4] The lower proportion of delayed diagnosis in patients, coupled with the lower proportion of infection in contacts, may have contributed to our inability to determine time to diagnosis as a risk factor for TB transmission.

One possible limitation of our study is that over one third of the contacts had a negative result on their initial TSTor IGRA, and a second TSTor IGRA result was unavailable. Some of these contacts could thus have been misclassified as negative, as they might have been tested before their immune systems mounted a reaction to tuberculous infection. However,

our data show that only a small percentage of contacts (2%) who had negative results on the initial TSTor IGRA had positive results on their second test. The effect of misclassification on our study results was therefore probably minimal.

Differences in testing methods by race could also have caused systematic bias. However, the great majority of contacts (89%) were tested using TST, and the difference in proportions of White contacts tested with IGRAs (5%) compared to African Americans (3%), while statistically significant, was small. An analysis that excluded contacts who received IGRAs did not change the study conclusions.

The study excluded a large number of patients (54%) and their contacts (65%) from the analysis. However, 36% of those who were excluded had no contacts listed, and 69% of the eliminated contacts were not close, high priority, or high risk. We therefore do not believe inclusion of these patients and contacts would have changed our study results.

Despite these limitations, a major strength of our study is that the study population included a large number of patients and their contacts from diverse jurisdictions, which supports both its reliability and generalizability.

CONCLUSIONS

Our large, multisite study found African American race and sputum smear positivity to be independent risk factors for *M. tuberculosis* infection in close contacts. Sputum smear positivity has long been incorporated into contact investigation screening algorithms, and our results support the findings of higher LTBI prevalence in US-born African Americans observed in previous publications. The lower proportion of infection in our study may correspond to the lower overall rates of TB in the US-born population, possibly a reflection of the success of the TB program. Similarly, the lower proportion of patients with delayed diagnosis may demonstrate the efforts made by clinicians and health departments to reduce the time from symptom onset to TB diagnosis and treatment in order to reduce TB disease severity and sequelae. The CDC has designated the treatment of LTBI as a major tool in achieving the national goal of TB elimination.[9] Our study emphasizes the importance of contact investigations as a method to find persons with LTBI who could benefit from preventive treatment.

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Conflicts of interest: none declared.

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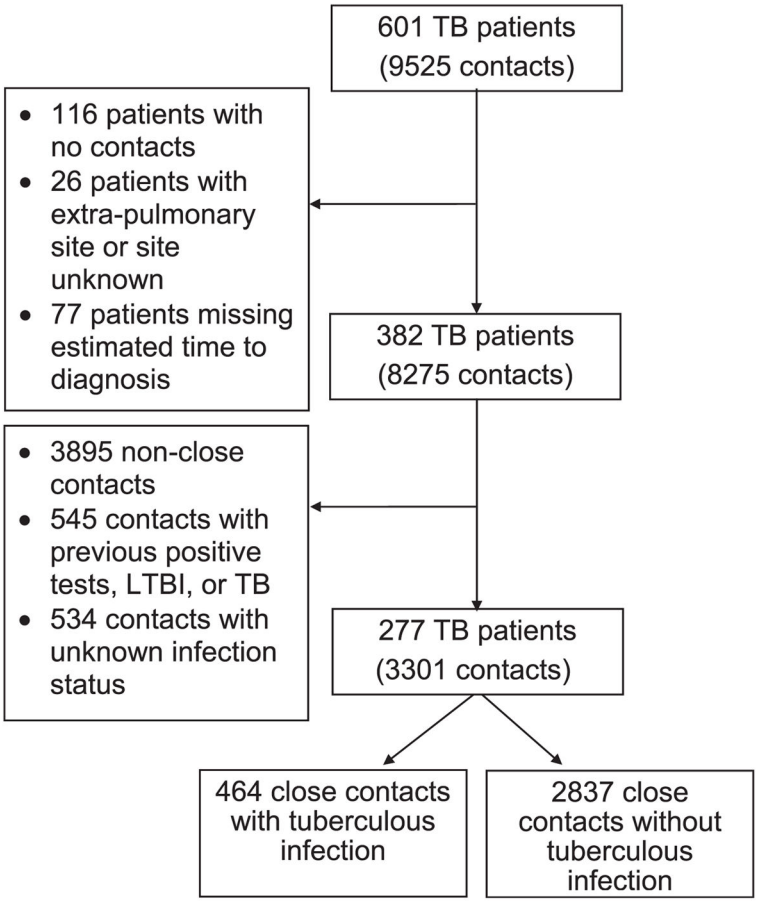

Figure 1.
Selection of TB patients and contacts: included TB patients and contacts are on the right, exclusions on the left. TB = tuberculosis; LTBI = latent tuberculous infection.

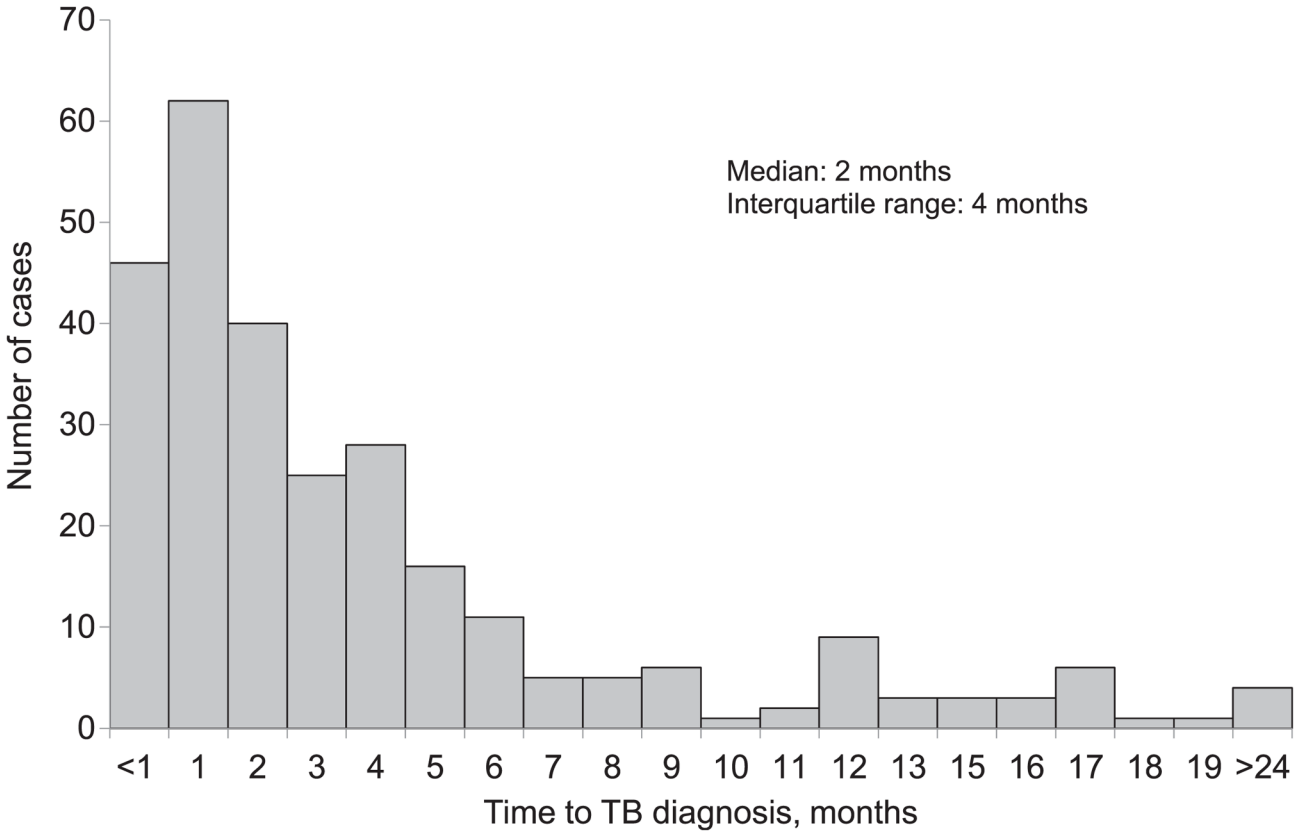

Figure 2.
Distribution of estimated time to TB diagnosis. TB = tuberculosis.

Table 1

Catchment areas for participant recruitment

TBESC site	Recruitment area	Dates of enrollment	TB patients (*n* = 277) *n*	Contacts (*n* = 3301) *n*
Maryland	Statewide, District of Columbia *, and Virginia (statewide) *	Maryland: December 2009–March 2011; District of Columbia: May 2010–March 2011; Virginia: January 2010–September 2010	42	417
North Carolina	Statewide	December 2009–March 2011	56	334
New Jersey	Statewide and Philadelphia, Pennsylvania *	New Jersey: December 2009–March 2011; Philadelphia: September 2010–March 2011	4	12
Georgia	Clayton Health District, Cobb/Douglas Health District, DeKalb Health District, Fulton Health District, Gwinnett/Rockdale Health Districts, East Central Health District, West Central Health District, and North Central Health District	January 2010–March 2011	39	1751
Tennessee	Shelby County, Davidson County, Mid-Cumberland Region: Stewart County, Houston County, Humphreys County, Montgomery County, Dickson County, Robertson County, Cheathum County, Williamson County, Sumner County, Truesdale County, Wilson County, and Rutherford County	Shelby County, Davidson County: December 2009–March 2011; Mid-Cumberland Region: December 2010–March 2011	37	257
New York Texas	New York City	December 2009–March 2011	30	147
	City of Houston, and Dallas County	December 2009–March 2011	69	383

* District of Columbia and Virginia were sub-contract sites of Maryland; Philadelphia, Pennsylvania was a sub-contract site of New Jersey.

TBESC = Tuberculosis Epidemiologic Studies Consortium; TB = tuberculosis.

Table 2

Characteristics of TB patients included and excluded in final analysis

Characteristics	TB patients included (*n* = 277) *n* (column %)*	TB patients excluded (*n* = 324) *n* (column %)*	*P* value†
Race			
African American	214 (77)	243 (75)	0.52
White	63 (23)	81 (25)	
Sex			
Male	184 (66)	224 (69)	0.48
Female	93 (34)	100 (31)	
Age at TB diagnosis, years			
<49	138 (50)	111 (34)	0.0003
≥49	138 (50)	213 (66)	
Data missing	1 (0)	0	
Highest level of schooling completed			
<High school	107 (39)	112 (35)	0.01
≥High school	164 (59)	187 (58)	
Data missing	6 (2)	25 (8)	
Homeless			
Yes	42 (15)	52 (16)	0.62
No	235 (85)	271 (84)	
Data missing	0	1 (0)	
Excess alcohol use			
Yes	93 (34)	64 (20)	<0.0001
No	183 (66)	249 (77)	
Data missing	1 (<1)	11 (3)	
Drug use			
Yes	99 (36)	69 (21)	0.0003
No	172 (62)	243 (75)	
Data missing	6 (2)	12 (4)	
Intravenous drug use			
Yes	6 (2)	12 (4)	0.43
No	267 (96)	305 (94)	
Data missing	4 (1)	7 (2)	
HIV status			
Positive	50 (18)	67 (21)	0.002
Negative	214 (77)	217 (67)	
Data missing	13 (5)	40 (12)	
Sputum smear status			
Positive	161 (58)	115 (35)	<0.0001
Negative	112 (40)	185 (57)	
Data missing	4 (1)	24 (7)	

Characteristics	TB patients included (*n* = 277) *n* (column %)*	TB patients excluded (*n* = 324) *n* (column %)*	*P* value†
Pulmonary cavities			
Yes	127 (46)	87 (27)	<0.0001
No	141 (51)	186 (57)	
Data missing	9 (3)	51 (16)	
Previous diagnosis of TB			
Yes	12 (4)	19 (6)	0.04
No	261 (94)	289 (89)	
Data missing	4 (1)	16 (5)	
Cough in year before TB diagnosis			
Yes	219 (79)	106 (33)	<0.0001
No	49 (18)	155 (48)	
Data missing	9 (3)	63 (19)	

*Column percentages may not add up to 100% due to rounding.

†χ^2 test.

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 3

Unadjusted association of TB patient characteristics with tuberculous infection in close contacts

Characteristics	TB patients (*n* = 277) *n* (column %)	Close contacts with tuberculous infection (*n* = 464) *n* (row %)	Close contacts without tuberculous infection (*n* = 2837) *n* (row %)	GEE unadjusted *P* value
Time from symptom onset to diagnosis, months				
≥2	169 (61)	320 (17)	1546 (83)	0.70
<2	108 (39)	144 (10)	1291 (90)	
Time from symptom onset to diagnosis, months				
≥3	129 (47)	278 (19)	1176 (81)	0.44
<3	148 (53)	186 (10)	1661 (90)	
Race				
African American	214 (77)	431 (15)	2491 (85)	0.01
White	63 (23)	33 (9)	346 (91)	
Sex				
Male	184 (66)	357 (14)	2271 (86)	0.62
Female	93 (34)	107 (16)	566 (84)	
Age at TB diagnosis, years				
<49	138 (50)	352 (14)	2098 (86)	0.39
≥49	138 (50)	112 (13)	736 (87)	
Highest level of schooling completed				
<High school	107 (39)	221 (12)	1674 (88)	0.77
≥High school	164 (59)	242 (17)	1143 (83)	
Homeless				
Yes	42 (15)	114 (18)	517 (82)	0.20
No	235 (85)	350 (13)	2320 (87)	
Excess alcohol use				
Yes	93 (33)	205 (15)	1128 (85)	0.99
No	183 (66)	258 (13)	1702 (87)	
Drug use				
Yes	99 (36)	231 (12)	1670 (88)	0.22
No	172 (62)	227 (17)	1138 (83)	
Intravenous drug use				
Yes	6 (2)	1 (5)	19 (95)	0.26
No	267 (96)	461 (14)	2808 (86)	
HIV status				
Positive	50 (18)	75 (11)	632 (89)	0.95
Negative	214 (77)	385 (15)	2161 (85)	
Sputum smear status				
Positive	161 (58)	353 (16)	1849 (84)	0.03
Negative	112 (40)	111 (10)	982 (90)	
Pulmonary cavities				
Yes	127 (46)	309 (16)	1610 (84)	0.03

Characteristics	TB patients (*n* = 277) *n* (column %)	Close contacts with tuberculous infection (*n* = 464) *n* (row %)	Close contacts without tuberculous infection (*n* = 2837) *n* (row %)	GEE unadjusted *P* value
No	141 (51)	145 (11)	1155 (89)	
Previous diagnosis of TB				
Yes	12 (4)	3 (6)	51 (94)	0.14
No	261 (94)	460 (14)	2761 (86)	
Cough in year before TB diagnosis				
Yes	219 (79)	395 (15)	2209 (85)	0.29
No	49 (18)	65 (10)	609 (90)	

TB = tuberculosis; GEE = generalized estimating equations; HIV = human immunodeficiency virus.

Table 4

TB patient characteristics in unadjusted and adjusted GEE model that describe tuberculous infection among close contacts

Characteristics	GEE unadjusted RR (95%CI)	*P* value	GEE adjusted RR (95%CI)	*P* value
Time from symptom onset to diagnosis, months				
≥3	1.14 (0.82–1.58)	0.44	1.18 (0.86–1.63)	0.31
<3	Referent		Referent	
Race				
African American	1.98 (1.20–3.27)	0.01	2.09 (1.27–3.43)	0.004
White	Referent		Referent	
Homeless				
Yes	0.73 (0.46–1.18)	0.20		
No	Referent			
Drug use				
Yes	1.24 (0.88–1.73)	0.22		
No	Referent			
Sputum smear status				
Positive	1.50 (1.05–2.18)	0.03	1.58 (1.10–2.27)	0.01
Negative	Referent		Referent	
Pulmonary cavities				
Yes	1.44 (1.03–2.02)	0.03		
No	Referent			
Previous diagnosis of TB				
Yes	0.41 (0.13–1.34)	0.14		
No	Referent			

TB = tuberculosis; GEE = generalized estimating equations; RR = risk ratio; CI = confidence interval.