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Risk Factors for Tuberculosis and Effect of Preventive Therapy Among Close Contacts of Persons With Infectious Tuberculosis

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Abstract

Background.—Close contacts of persons with pulmonary tuberculosis (TB) have high rates of TB disease.

Methods.—We prospectively enrolled TB patients and their close contacts at 9 US/Canadian sites. TB patients and contacts were interviewed to identify index patient, contact, and exposure risk factors for TB. Contacts were evaluated for latent TB infection (LTBI) and TB, and the effectiveness of LTBI treatment for preventing contact TB was examined.

Results.—Among 4490 close contacts, multivariable risk factors for TB were age ≤5 years, US/Canadian birth, human immunodeficiency virus infection, skin test induration ≥10 mm, shared bedroom with an index patient, exposure to more than 1 index patient, and index patient weight loss ($P < .05$ for each). Of 1406 skin test–positive contacts, TB developed in 49 (9.8%) of 446 who did not initiate treatment, 8 (1.8%) of 443 who received partial treatment, and 1 (0.2%) of 517 who completed treatment (1951, 290, and 31 cases/100 000 person-years, respectively; $P < .001$). TB

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was diagnosed in 4.2% of US/Canadian-born compared with 2.3% of foreign-born contacts (P = .002), and TB rates for US/Canadian-born and foreign-born contacts who did not initiate treatment were 3592 and 811 per 100 000 person-years, respectively (P < .001).

Conclusions.—Treatment for LTBI was highly effective in preventing TB among close contacts of infectious TB patients. Several index patient, contact, and exposure characteristics associated with increased risk of contact TB were identified. These findings help inform contact investigation, LTBI treatment, and other public health prevention efforts.

Keywords

tuberculosis; risk factors; contacts; preventive therapy; contact investigation

Close contacts of pulmonary tuberculosis (TB) patients have high rates of TB disease [1–7]. Factors that predispose to TB are incompletely understood.

In the United States, Canada, and most countries with low TB incidence, contact investigations are conducted for pulmonary TB patients in order to identify and treat secondary cases of active TB disease and latent TB infection (LTBI) among exposed contacts, thereby interrupting secondary transmission of *Mycobacterium tuberculosis* and preventing progression from LTBI to TB disease [1, 2, 8, 9]. Understanding TB risk factors among exposed contacts is important for determining the optimal timing and expected yield of contact investigations, as well as prioritizing public health prevention efforts among persons at highest TB risk.

We conducted a prospective study of contact investigations at health departments in the United States and Canada. We previously described rates and timing of TB among contacts and risk factors for LTBI treatment default [3, 10]. Here, we examine risk factors for TB disease in the same contact cohort.

METHODS

We prospectively enrolled culture-confirmed adult TB patients and their close contacts at 9 US and Canadian sites in the Tuberculosis Epidemiologic Studies Consortium [11]. Close contacts were defined as described previously [3]. TB patients were interviewed, and contacts were identified, interviewed, and screened for LTBI and TB, then followed for up to 4 years (final follow-up February 2011) [3].

All health departments defined negative tuberculin skin tests (TSTs) as <5 mm and positive TSTs as ≥5 mm induration. Contacts with TB diagnosed >30 days after index case diagnosis were considered incident cases, and those diagnosed ≤30 days after index case diagnosis were considered coprevalent cases [3].

Univariate analyses were performed on potential index patient, contact, and exposure location risk factors for contact TB. We considered variables for multivariable models if their univariate P value was < .20 and kept variables with a P value < .05 in the models. Survival analysis methods were as previously described [3]. Statistically significant

differences were defined as $P < .05$ using the χ^2 or Fisher exact test. SAS software version 9.2 was used for all analyses [12].

Contacts were categorized as not treated for LTBI if they did not initiate treatment, partially treated if they started but did not complete treatment, and completely treated if they completed the required duration of treatment for the regimen received. TB rates for each treatment category were determined by dividing the total number of TB cases by person-years of follow-up and compared with the rate for contacts who received no treatment. Coprevalent cases were excluded from LTBI treatment analyses. Although several treatment regimens were used, most contacts received either isoniazid or rifampin monotherapy.

This study was approved by institutional review boards at the Centers for Disease Control and Prevention and all project sites.

RESULTS

Characteristics of the Study Population

Characteristics of the 718 index patients and 4490 close contacts enrolled are included in Table 1. Of the index patients, 518 (72%) had positive sputum smears and 286 (40%) had cavitation on chest radiograph. Of the contacts, 158 (4%) had TB, 1390 (31%) had LTBI, 1650 (36%) were TST-negative and free of TB, and 1292 (29%) did not complete TST screening. Of 158 TB cases among contacts, 81 were coprevalent and 77 were incident. Of the TB cases, 115 (73%) were diagnosed in TST-positive contacts (57 coprevalent and 58 incident cases), 6 (4%) in TST-negative contacts (3 coprevalent and 3 incident cases), and 37 (23%) in contacts who did not complete TST screening (21 coprevalent and 16 incident cases). A total of 1329 contacts did not complete TST screening (37 with TB and 1292 without TB).

Risk Factors for TB Among Close Contacts

In univariate analyses for all TB among contacts, risk factors significantly associated with TB included contact age ≤5 years, US/Canadian birth, human immunodeficiency virus (HIV) test-positive, and skin test induration ≥10 mm; index patient cavitary disease, bilateral disease, weight loss, night sweats, and current smoking; and household exposure, shared bedroom with the index patient, ≥500 exposure hours, and exposure to more than 1 index patient (Table 2).

In univariate analyses for incident TB among contacts, risk factors significantly associated with TB included contact age ≤5 years, US/Canadian birth, and skin test induration ≥10 mm; index patient bilateral disease, cough ≥3 weeks, and weight loss; and household exposure, ≥500 exposure hours, and exposure to more than 1 index patient (Table 3). Exposure to an index patient with positive sputum smears ($P = .061$) or cavitation on chest radiograph ($P = .081$) and shared bedroom with an index patient ($P = .081$) were not significant for incident TB cases.

In analyses including all TB cases or only incident TB cases, the risk of TB was similar for nonhousehold contacts and household contacts who did not share a bedroom with the index patient.

Univariate analyses of risk factors for coprevalent TB and for incident TB restricted to TST-positive contacts showed similar findings to those reported above (data not shown).

Effectiveness of LTBI Treatment

Of 3161 contacts who completed TST screening, 1505 (48%) were TST-positive. Of these, 57 had coprevalent TB and were excluded from LTBI treatment analyses. Of the remaining 1448 contacts, 517 (37%) completed LTBI treatment, 443 (32%) received a partial treatment course, and 446 (32%) did not initiate treatment; 42 contacts with missing treatment information (16 with TB and 26 without TB) were excluded from analysis.

Incident TB was diagnosed in 49 (9.8%) of 446 contacts who did not initiate treatment, 8 (1.8%) of 443 who received partial treatment, and 1 (0.2%) of 517 who completed treatment (1951, 290, and 31 cases/100 000 person-years of exposure, respectively; $P < .001$ for complete vs no treatment and for partial vs no treatment; Table 4).

Contact Birthplace and TB

TB was diagnosed in 4.2% of US/Canadian-born contacts compared with 2.3% of foreign-born contacts ($P = .002$; Table 2).

Of 446 TST-positive contacts who did not initiate LTBI treatment (Table 4), 197 were US/Canadian-born and 249 were foreign-born. A total of 37 TB cases occurred among US/Canadian-born contacts (37/197 = 18.8%) vs 12 TB cases among foreign-born contacts (12/249 = 4.8%; $P < .001$). TB rates for US/Canadian-born and foreign-born contacts who did not initiate treatment were 3592 and 811 per 100 000 person-years, respectively ($P < .001$).

Disease-free survival was significantly lower for US/Canadian-born contacts compared with foreign-born contacts (Figure 1).

US/Canadian and foreign-born contacts were exposed to index patients with similar smear and chest radiograph findings and were equally likely to initiate and complete LTBI treatment (data not shown). Compared with foreign-born contacts, US/Canadian-born contacts were more likely to be aged ≤5 years (14% vs 2%; $P < .001$).

Multivariable Analyses

In multivariable analysis (Table 5), risk factors for all cases of TB included contact age ≤5 years, US/Canadian birth, HIV test-positive, and skin test size ≥10 mm; exposure to an index case with weight loss; exposure to more than 1 index case; and shared bedroom with the index case. Risk factors for incident TB included contact age ≤5 years, US/Canadian birth, and skin test size ≥10 mm; exposure to an index case with weight loss; and exposure to more than 1 index case. After adjustment for LTBI treatment, risk factors for incident TB included

contact age ≤5 years, US/Canadian birth, exposure to an index case with weight loss, and exposure to more than 1 index case.

DISCUSSION

In our study, 3.5% of all close contacts and 7.6% of TST-positive contacts of culture-confirmed pulmonary TB patients were diagnosed with TB, with a large burden of both coprevalent and incident TB among contacts. Our study identifies factors associated with increased exposure to infectious TB (shared bedroom and exposure to more than 1 index patient), skin test induration ≥10 mm, contact age ≤5 years, and US/Canadian birth as factors associated with TB among contacts. We observed that completion of LTBI treatment was strongly associated with lack of progression to TB disease among exposed contacts. These findings help inform health department decisions on prioritizing contact investigation, LTBI treatment, and other public health prevention efforts to interrupt transmission. These results are also important for infectious disease physicians and general practitioners, the people who often first diagnose active TB and have a relationship with the patient.

In a recent report, we demonstrated that 51% of all TB cases among contacts that occurred over a 5-year period were diagnosed before, at the same time, or within 30 days after the index TB patient was diagnosed [3]. Through analysis of epidemiologic data collected for the same close contact cohort, we have identified independent risk factors for TB. Because the direction of transmission cannot always be established with certainty when index patients and contacts are diagnosed with TB in rapid succession, we did separate analyses of epidemiologic risk factors for all TB cases and incident cases. Our findings have implications for active case finding in high-burden settings as well as secondary prevention of transmission in countries with a low TB burden, such as the United States and Canada.

Skin test reaction size was strongly correlated in multivariable analyses with TB both among all contacts and among incident cases. Increased skin test size is not well characterized as a TB risk factor and is not part of algorithms currently used to prioritize contact investigations in the United States and Canada [1]. Our findings, together with additional observations [13–16], suggest that skin test size could be a useful predictor of TB among exposed contacts and merits consideration in developing future algorithms.

Household contacts are traditionally thought to be at the highest TB risk [1, 2]. In our study, household contacts who shared a bedroom with the index patient had high TB risk; however, those who did not had risk similar to that of nonhousehold contacts. The correlation of sharing a bedroom with an index patient and higher TB risk likely reflects both more close contact, with more frequent shared airspace and increased risk of sharing infectious aerosols, and greater duration of contact, with shared airspace at night and during the day. The fact that nonhousehold contacts were at equal risk of TB as household contacts who did not share the index case bedroom underscores the importance of a concentric circle approach to contact investigations, which incorporates all spheres of daily activities rather than exclusively the household [1, 2, 17].

We evaluated exposure duration, location, and closeness as well as the number of infectious patients to whom a contact was exposed in an effort to examine the relationship between exposure and TB risk. It is plausible that greater duration or closeness of exposure would result in higher disease risk by increasing the likelihood that contacts share infectious aerosols with an index patient as well as serving as a marker for an increased exposure "dose" of *M. tuberculosis*. Indeed, our findings that greater hours of exposure to an index patient, greater closeness of exposure through sharing a bedroom, and exposure to more than 1 index patient are all correlated with increased TB risk are consistent with this hypothesis. Although the latter 2 factors were independent predictors of TB, an association for exposure hours was not demonstrated in multivariate analysis. A likely explanation is that household contacts who shared a bedroom with the index patient or were exposed to more than 1 index patient were many of the same persons with a higher number of exposure hours. Thus, the likely colinearity of the different exposure measures resulted in only 2 identified as independent predictors of TB.

Young children had the highest TB risk, which is consistent with several previous studies [4, 8, 18, 19]. In multivariable analysis, young age was a predictor of both coprevalent and incident TB. Thus, children had both rapid development of disease and high overall TB risk. This underscores the importance of prioritizing rapid screening, diagnosis of TB and LTBI, and initiation of treatment for this high-risk group.

US/Canadian birth was associated with increased TB risk, with the rate among persons who did not initiate LTBI treatment more than 4-fold per 100 000 person-years higher than for foreign-born contacts. This finding was unexpected since TB case rates in the United States are 15 times higher among foreign-born than US-born residents [20], and more than 70% of all TB cases reported in the US are foreign-born [20]. US/Canadian-born and foreign-born contacts in our study were exposed to index patients with a similar clinical profile and were equally likely to initiate and complete LTBI treatment. Thus, it is unlikely that our findings could be the result of differences in exposure or treatment. A higher proportion of US/Canadian-born contacts were aged ≤5 years, which could contribute to our findings. However, age and US/Canadian birth were both independent predictors of TB risk, so age differences alone do not explain this finding. Further, the inclusion of several sites with a predominance of US-born TB patients could help explain the larger proportion of US-born TB patients in the study compared with national reporting but does not explain the differences in TB risk between US/Canadian-born and foreign-born contacts that we observed. A possible explanation is that foreign-born contacts have a higher likelihood of previous TB exposure (and previous infection or disease) [8, 9, 21–26] than contacts born in low-incidence areas such as the United States and Canada and are thus at lower risk of developing disease from the recent exposure [27]. These findings can inform TB prevention strategies in the United States and Canada, including modeling and cost analyses for TB elimination.

HIV infection is the strongest known predictor of TB [5, 8, 15, 17, 28]. Consistent with this, HIV was an independent predictor of TB in multivariate analysis of all TB cases among contacts in our study. However, neither index case positive smear nor cavitary chest radiograph, traditionally recognized risk factors for transmission [1, 2, 29, 30], were

identified in multivariable analysis as risk factors for contact TB in our study. Positive sputum smear, cavitation, bilateral disease, cough, and smoking could be risk factors for transmission but not risk factors for progression to TB disease, or not independent risk factors after other markers of the extent of TB infection are included. *Mycobacterium tuberculosis* transmission and progression to TB disease are separate biologic processes [31]. Thus, it is not surprising that the risk factors for transmission and progression to TB disease were different.

Fifty years ago, the lifetime TB risk in individuals with LTBI was estimated to be 5%–10%, with half of all cases identified within 2 years following exposure [8, 9]. Our recent previous report provides evidence that the vast majority of secondary cases identified within 5 years after exposure occur within the first year, with the highest rates in the first 3 months [3]. Thus, recently exposed close contacts with a new LTBI diagnosis are at high risk of rapidly progressing to TB disease. LTBI treatment has been associated with a substantial decrease in TB disease risk [8, 9]. In an earlier analysis of preliminary data from our cohort, LTBI treatment with isoniazid for 6 or more months was associated with lower TB rates compared with shorter treatment [10]. In the current analysis, which excludes coprevalent TB cases, limits analyses to the first contact exposure, and includes several different treatment regimens, contacts who completed LTBI treatment had the lowest TB rates, those with partial treatment had somewhat higher rates, and untreated contacts had markedly higher TB rates than contacts with either partial or complete treatment. Moreover, we demonstrated that even a partial LTBI treatment course had some effectiveness in preventing TB among recently exposed close contacts. These findings emphasize the importance of rapid initiation and thorough conduct of contact investigation, not only as an important means for identifying persons with active disease but also to diagnose LTBI and initiate treatment, thus preventing progression to active TB disease.

Although our recent report suggests that fewer TB cases among contacts can be prevented than previously anticipated [3], data in the current report demonstrate that LTBI treatment was still highly effective in preventing TB, with a reduction in TB rates per person-year of 85% for partial treatment and 98% for complete treatment. These findings contrast with 2 reports in which LTBI treatment was not effective [5] or of lower efficacy [4] among contacts. A likely reason for this difference is that in the other studies, treatment appears to have been initiated later (up to 180 days in Amsterdam [4] and approximately 270 days in New York [5] compared with an average of less than 60 days in our study [32]). Given the rapid decline in TB diagnosis rates among contacts beyond the first several months after index case diagnosis demonstrated in our recent report [3], the efficacy of LTBI treatment would be expected to decrease progressively the later it is initiated since fewer and fewer cases can be prevented. This underscores the importance of evaluating contacts and initiating LTBI treatment as soon as possible in order to have the biggest impact on disease prevention. The effectiveness of even a partial LTBI treatment course is also noteworthy and reemphasizes the benefit of initiating treatment for all exposed contacts with newly documented LTBI [1].

In our study, nearly one-third of contacts did not complete skin testing, and this group had a 5-fold higher TB risk than skin test–negative contacts. Many, but not all, of the contacts with

TB and no skin test results had coprevalent TB and may not have completed screening because of a concurrent TB diagnosis. Nevertheless, the large number of contacts who did not complete screening emphasizes the importance of developing strategies to improve testing of contacts as well as acceptance and completion of treatment in infected contacts [9, 10]. Engaging providers outside of health departments is one potential approach to consider that this study can help to inform.

Study limitations include incomplete HIV testing data for many contacts, incomplete TST screening for some contacts, and the possibility that skin test size could have contributed to TB diagnosis for some coprevalent cases. The large number of contacts with TB included in our study, complete LTBI treatment data for most contacts, the prospective and protocol-driven nature of data collection, and collection of information on numerous epidemiologic factors, including systematic interviewing to quantify hours of exposure, were study strengths.

In conclusion, our study provides important new information on risk factors for TB disease and the effectiveness of LTBI treatment in contacts with recent exposure to infectious TB patients. Our findings underscore the importance of contact investigation as a mechanism for identifying and treating new cases of active TB among contacts and emphasizes the importance of prompt screening and LTBI treatment. These findings have important implications for tuberculosis prevention efforts [1, 33, 34].

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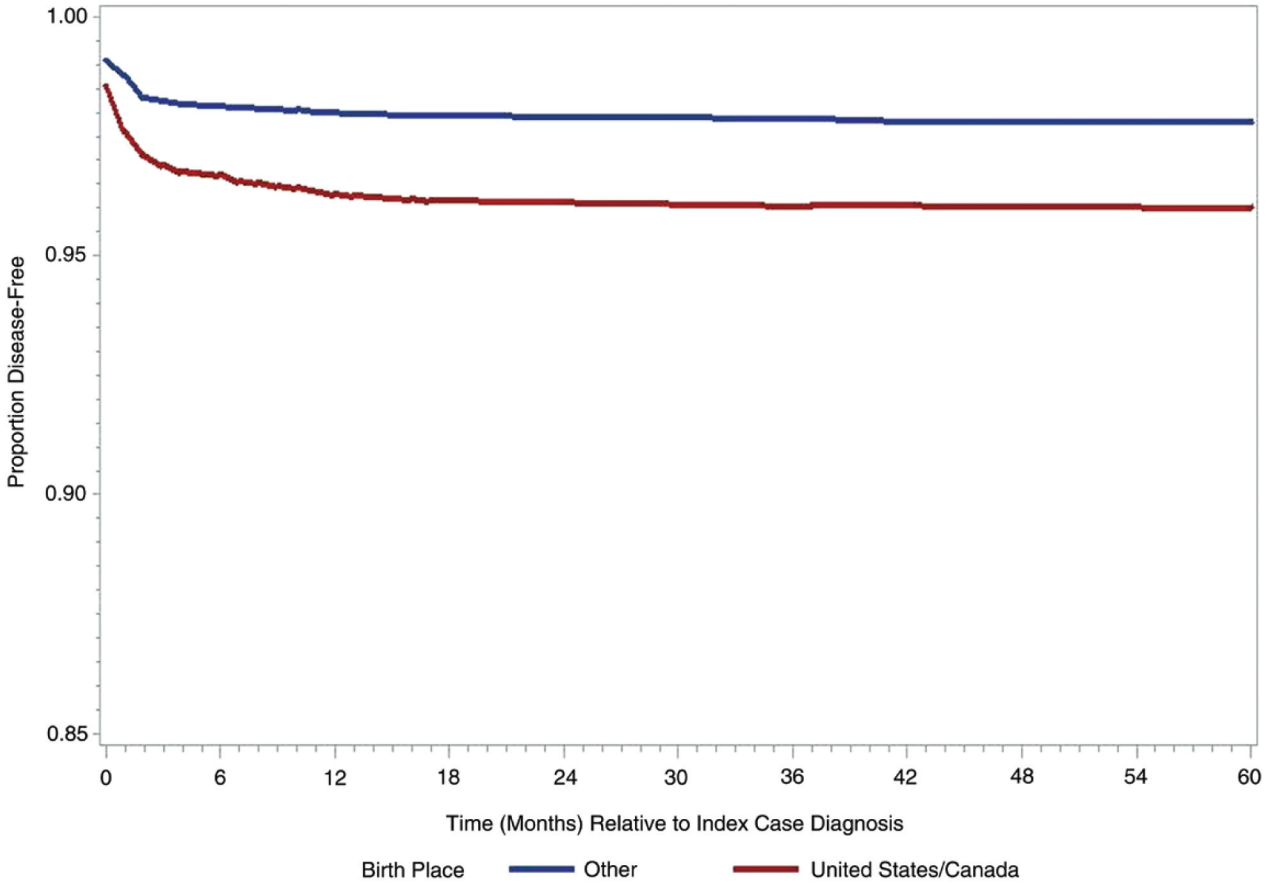

Figure 1.

Disease-free survival for 4490 contacts (158 with and 4332 without tuberculosis), by birthplace (United States/Canada shown in red, other countries shown in blue).

Table 1.

Clinical and Demographic Characteristics of Index Tuberculosis Patients and Close Contacts

Characteristic	No. (%) Index Cases (n = 718)	Contacts (n = 4490)
Total	718	4490
Age (y)		
0–14	0 (0)	879 (20)
15–44	393 (55)	2288 (51)
≥45	325 (45)	1173 (26)
Unknown	0 (0)	150 (3)
Sex, Male	440 (61)	2301 (51)
Race/Ethnicity		
White	96 (13)	548 (12)
Black	360 (50)	2234 (50)
Asian/Pacific Islander	81 (11)	266 (6)
Hispanic	146 (20)	1064 (24)
Other	35 (5)	378 (8)
Birthplace, United States/Canada	436 (61)	2946 (66)
Age (y) (y (irthplace		
United States/Canada		
0–5	…	420 (14)
6–14	…	359 (12)
15–44	…	1279 (43)
≥45	…	862 (29)
Unknown	…	26 (1)
Other		
0–5	…	32 (2)
6–14	…	68 (4)
15–44	…	1009 (65)
≥45	…	311 (20)
Unknown	…	124 (8)
Place of contact household	…	2794 (62)
Diagnostic outcome		
TB	…	158 (4)
LTBI	…	1390 (31)
No LTBI or TB	…	1650 (36)
No TST result	…	1067 (24)
Not eligi(le for testing[a]	…	225 (5)
TST result		
Positive	…	1505 (34)
Negative	…	1656 (37)

Characteristic	No. (%) Index Cases (n = 718)	Contacts (n = 4490)
Other[b]	…	1329 (30)

Abbreviations: LTBI, latent tuberculosis infection; TB, tuberculosis; TST, tuberculin skin test.

[a] A total of 225 contacts were not eligible for TST screening due to prior positive TST or TB.

[b] A total of 1329 contacts did not complete TST screening (1292 contacts without TB and 37 contacts with TB).

Table 2.

Univariate Analysis of Risk Factors for Tuberculosis

Characteristic[a]	Total (N = 4490) n (%)	TB (n = 158) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Total	4490	158	4332	3.5	…	…	…
Contact age (y)							
0–5	452	49 (31)	403 (9)	10.8	4.0	(2.8, 5.7)	**<.001**
6–14	427	8 (5)	419 (10)	1.9	…	…	
15–24	814	26 (16)	788 (18)	3.2	(Referent age >5)	…	…
25–44	1474	42 (27)	1432 (33)	2.9	…	…	…
45–64	955	28 (18)	927 (21)	2.9	…	…	…
≥65	218	3 (2)	215 (5)	1.9	…	…	…
Unknown	150	2 (1)	148 (3)	…	…	…	…
Contact race/ethnicity							
White	548	9 (6)	539 (12)	1.6	Referent	…	…
Black	2234	95 (60)	2139 (49)	4.3	2.7	(1.3, 5.3)	**.006**
Asian	266	16 (10)	250 (6)	6.0	3.8	(1.7, 8.8)	**.002**
Hispanic	1064	30 (19)	1034 (24)	2.8	1.7	(0.8, 3.7)	.150
First Nations	146	8 (5)	138 (3)	5.5	3.5	(1.3, 9.2)	**.012**
Other	232	0 (0)	232 (5)	…	…	…	…
Contact birthplace							
United States/Canada	2946	123 (78)	2823 (65)	4.2	1.8	(1.3, 2.7)	**.002**
Foreign-born	1544	35 (22)	1509 (35)	2.3	Referent	…	…
Contact human immunodeficiency virus							
Positive	16	4 (3)	12 (0)	23.1	4.8	(1.6, 14.9)	**.006**
Negative	1039	54 (34)	985 (23)	0.4	Referent	…	…
Unknown	3435	100 (63)	3335 (77)	…	…	…	…
TST result[b]							
Positive	1505	115 (73)	1390 (32)	7.6	22.8	(10.0, 51.9)	**<.001**
Negative	1656	6 (4)	1650 (38)	0.4	Referent		

Characteristic[a]	Total (N = 4490) n (%)	TB (n = 158) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Not tested	1086	19 (12)	1067	1.8	…	…	…
Not eligible[c]	243	18 (11)	225	7.4	…	…	…
TST size (mm)							
0–4	1656	6 (4)	1650 (38)	0.4	Referent	…	…
5–9	98	1 (1)	97 (2)	1.0	2.8	(0.3, 23.8)	.337
10–14	418	26 (17)	392 (9)	6.2	18.2	(7.5, 44.6)	**<.001**
15–19	455	39 (25)	416 (10)	8.6	25.8	(10.8, 61.3)	**<.001**
≥20	529	49 (31)	480 (11)	9.3	28.1	(12.0, 66.0)	**<.001**
Other[d]	1334	37 (23)	1297 (30)	2.8	…	…	…
Index case smear (+)							
No	686	21 (13)	665 (15)	3.7	Referent	…	…
Yes	3745	137 (87)	3608 (83)	3.1	1.2	(0.7, 1.9)	.439
Not done	59	0 (0)	59 (1)	…	…	…	…
Index case cavitary chest radiograph							
No	2434	74 (47)	2360 (54)	3.0	Referent	…	…
Yes	1981	83 (53)	1898 (44)	4.2	1.4	(1.0, 1.9)	**.049**
Unknown	75	1 (1)	74 (2)				
Index case bilateral disease[e]							
No	3300	99 (63)	3201 (64)	3.0	Referent	…	…
Yes	1190	59 (37)	1131 (26)	5.0	1.7	(1.2, 2.3)	**.003**
Index case cough ≥3 weeks							
No	687	18 (11)	669 (15)	2.6	Referent	…	…
Yes	2910	125 (79)	2785 (64)	4.3	1.6	(1.0, 2.7)	**.053**
Unknown	893	15 (9)	878 (20)	…	…	…	…
Index case weight loss							
No	1280	27 (17)	1253 (29)	2.1	Referent	…	…
Yes	3135	131 (83)	3004 (69)	4.2	1.9	(1.3, 3.0)	**.001**
Unknown	75	0 (0)	75 (2)	…	…	…	…

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Characteristic[a]	Total (N = 4490) n (%)	TB (n = 158) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Index case fever							
No	1908	63 (40)	1845 (43)	3.3	Referent	…	…
Yes	2558	95 (60)	2463 (57)	3.7	1.1	(0.8, 1.6)	.461
Unknown	24	0 (0)	24 (1)	…	…	…	…
Index case night sweats							
No	2090	61 (39)	2029 (47)	2.9	Referent	…	…
Yes	2371	97 (61)	2274 (52)	4.1	1.4	(1.02, 1.96)	**.035**
Unknown	14	0 (0)	14 0)	…	…	…	…
Index case smoking[f]							
No	2672	79 (50)	2593 (60)	4.4	Referent	…	…
Yes	1816	79 (50)	1737 (40)	3.0	1.5	(1.1, 2.0)	**.017**
Unknown	2	0 (0)	2 (0)				
Index case status at diagnosis							
Alive	4404	155 (98)	4249 (98)	Referent	…	…	…
Dead	86	3 (2)	83 (2)	1.0	(0.3, 3.2)	.991	…
Exposure location							
Household	2794	115 (73)	2679 (62)	4.1	1.6	(1.1, 2.3)	**.008**
Workplace	708	9 (6)	699 (16)	1.3	…	…	…
Social place	844	26 (16)	818 (19)	3.1	(Referent nonhousehold)	…	…
School	144	8 (5)	136 (3)	5.6	…	…	…
Exposure environment							
Nonhousehold	1734	43 (27)	1691 (39)	2.5	Referent	…	…
Household, no shared bedroom	2237	75 (47)	2162 (50)	3.4	1.4	(0.9, 2.0)	.109
Household, shared bedroom	460	39 (25)	421 (10)	8.5	3.4	(2.2, 5.3)	**.001**
Unknown	59	1 (1)	58 (1)	…	…	…	…
Number of exposures[g]							
1	4393	138 (87)	4255 (98)	3.1	Referent	…	…
2	67	10 (6)	57 (1)	14.9	4.8	(2.4, 9.4)	**.001**

Characteristic[a]	Total (N = 4490) n (%)	TB (n = 158) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
3	15	10 (6)	5 (0)	66.7	21.2	(9.4, 48.1)	**.001**
Unknown	15	0 (0)	15 (0)	…	…	…	…
Exposure hours							
<250	1312	36 (23)	1276 (29)	2.7	(Referent <500 hours)	…	…
250–499	1112	27 (17)	1085 (25)	2.4	…	…	…
≥500	2057	95 (60)	1962 (45)	4.6	1.8	(1.3, 2.5)	**.001**
Unknown	9	0 (0)	9 (0)	…	…	…	…

Statistically significant associations are marked in bold.

Abbreviations: TB, tuberculosis; TST, tuberculin skin test.

[a]No significant associations were observed for contact gender, diabetes mellitus, smoking, or alcohol use; these variables are not shown.

[b]TST-positive defined as ≥5 mm induration; TST-negative defined as <5 mm induration.

[c]A total of 243 contacts were not eligible for TST screening due to prior positive TST or TB.

[d]A total of 1334 contacts were not eligible for TST screening, eligible but not tested, or missing TST size; includes 1297 contacts without TB and 37 contacts with TB.

[e]Bilateral is disease in both the left and right lung fields on chest radiograph.

[f]Cigarette smoking in the past 6 months.

[g]Number of exposures is the number of tuberculosis cases to which a given contact was exposed.

Table 3.

Univariate Analysis of Risk Factors for Incident Tuberculosis

Characteristic[a]	Total (N = 4409) n (%)	Incident TB (n = 77) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Total	4409	77	4332	1.7	…	…	…
Contact age (y)							
0–5	423	20 (26)	403 (9)	4.7	3.5	(2.1, 6.0)	**<.001**
6–14	421	2 (3)	419 (10)	0.5	…	…	…
15–24	803	15 (19)	788 (18)	1.9	(Referent age >5)	…	…
25–44	1449	17 (22)	1432 (33)	1.2	…	…	…
45–64	947	20 (26)	927 (21)	2.1	…	…	…
≥65	216	1 (1)	215 (5)	0.5	…	…	…
Unknown	150	2 (3)	148 (3)	…	…	…	…
Contact race/ethnicity							
White	545	6 (8)	539 (12)	1.1	Referent	…	…
Black	2183	44 (57)	2139 (49)	2.0	1.8	(0.8, 4.4)	.161
Asian	260	10 (13)	250 (6)	3.9	3.6	(1.3, 10.0)	**.014**
Hispanic	1045	11 (14)	1034 (24)	1.1	1.0	(0.4, 2.6)	.929
First Nations	144	6 (8)	138 (3)	4.2	3.9	(1.2, 12.3)	**.020**
Other	232	0 (0)	232 (5)	…	…	…	…
Contact birthplace							
United States/Canada	2884	61 (79)	2823 (65)	2.1	2.0	(1.2, 3.5)	**.010**
Foreign-born	1525	16 (21)	1509 (35)	1.1	Referent	…	…
Contact human immunodeficiency virus							
Positive	13	1 (1)	12 (0)	7.7	2.73	(0.34, 21.73)	.341
Negative	1015	30 (39)	985 (23)	3.0	Referent	…	…
Unknown	3381	46 (60)	3335 (77)	…	…	…	…
TST result[b]							
Positive	1448	58 (75)	1390 (32)	4.0	22.9	(7.2, 73.4)	**<.001**
Negative	1653	3 (4)	1650 (38)	0.2	Referent	…	…

Characteristic[a]	Total (N = 4409) n (%)	Incident TB (n = 77) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Not tested	1077	10 (12)	1067	0.8	…	…	…
Not eligible[c]	231	6 (11)	225	2.6	…	…	…
TST size (mm)							
0–4	1653	3 (4)	1650 (38)	0.2	Referent	…	…
5–9	103	0 (0)	97 (2)	0.0	…	…	…
10–14	416	12 (16)	403 (10)	2.8	8.6	(3.5, 21.1)	**<.001**
15–19	451	22 (29)	438 (10)	4.7	14.5	(6.4, 32.8)	**<.001**
≥20	521	26 (34)	507 (12)	4.8	27.4	(8.3, 91.1)	**<.001**
Other[d]	1308	16 (21)	1292 (30)	1.2	…	…	…
Index case smear (+)							
No	671	6 (8)	665 (15)	0.9	Referent	…	…
Yes	3679	71 (92)	3608 (83)	1.9	2.2	(0.94, 5.0)	.061
Not done	59	0 (0)	59 (1)	…	…	…	…
Index case cavitary chest radiograph							
No	2395	35 (45)	2360 (54)	1.5	Referent	…	…
Yes	1940	42 (55)	1898 (44)	2.2	1.5	(0.9, 2.3)	.081
Unknown	74	0 (0)	74 (2)	…	…	…	…
Index case bilateral disease[e]							
No	3250	49 (62)	3201 (64)	1.5	Referent	…	…
Yes	1159	28 (36)	1131 (26)	2.4	1.6	(1.01, 2.6)	**.043**
Index case cough ≥3 weeks							
No	676	7 (9)	669 (15)	1.0	Referent	…	…
Yes	2851	66 (86)	2785 (64)	2.3	2.3	(1.03, 5.0)	**.036**
Unknown	882	4 (5)	878 (20)	…	…	…	…
Index case weight loss							
No	1262	9 (12)	1253 (29)	0.7	Referent	…	…
Yes	3072	68 (88)	3004 (69)	2.2	3.2	(1.6, 6.3)	**<.001**
Unknown	75	0 (0)	75 (2)	…	…	…	…

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Characteristic[a]	Total (N = 4409) n (%)	Incident TB (n = 77) n (%)	Not TB (n = 4332) n (%)	TB Risk (%)	Odds Ratio	95% Confidence Interval	*P* Value
Index case smoking[f]							
No	2634	41 (53)	2593 (60)	1.6	Referent	…	…
Yes	1773	36 (47)	1737 (40)	2.0	1.31	(0.83, 2.06)	.240
Unknown	2	0 (0)	2 (0)	…	…	…	…
Exposure location							
Household	2743	64 (79)	2679 (62)	2.3	2.32 (1.35, 3.90)	**.002**	…
Workplace	700	1 (1)	699 (16)	0.1	…	…	…
Social place	832	14 (17)	818 (19)	1.7	(Referent nonhousehold)	…	…
School	138	2 (2)	136 (3)	1.5	…	…	…
Exposure environment							
Nonhousehold	1717	26 (34)	1691 (39)	1.5	Referent	…	…
Household, no shared bedroom	2201	39 (51)	2162 (50)	1.8	0.85	(0.52, 1.40)	.531
Household, shared bedroom		433	12 (16)	421 (10)	2.8	1.9	(0.93, 3.7)
Unknown	58	0 (0)	58 (1)	…	…	…	…
Number of exposures[g]							
1	4318	63 (82)	4255 (98)	1.5	Referent	…	…
2	60	7 (9)	57 (1)	10.9	8.3	(3.6, 18.9)	**<001**
3	12	7 (9)	5 (0)	58.3	94.6	(29.2, 305.9)	**<001**
Unknown	15	0 (0)	15 (0)	…	…	…	…
Exposure hours							
<250	1298	22 (29)	1276 (29)	1.7	(Referent <500)	…	…
250–499	1095	10 (13)	1085 (25)	0.9	…	…	…
≥500	2007	45 (58)	1962 (45)	2.2	1.7	(1.08, 2.68)	**.022**
Unknown	9	0 (0)	9 (0)	…	…	…	…

A total of 81 contacts with coprevalent tuberculosis were excluded. Coprevalent TB is TB diagnosed before or within 30 days after TB diagnosis for the index patient; incident TB is TB diagnosed in a contact more than 30 days after TB diagnosis for the index patient. Statistically significant associations are marked in bold.

Abbreviations: TB, tuberculosis; TST, tuberculin skin test.

[a]No significant associations were observed for contact gender, diabetes mellitus, smoking, or alcohol use and these variables are not shown.

[b] TST-positive defined as ≥5mm induration; TST-negative defined as <5 mm induration.

[c] A total of 243 contacts were not eligible for TST screening due to prior positive TST or TB.

[d] A total of 1308 contacts were not eligible for TST screening or eligible but not tested; includes 1292 contacts without TB and 16 contacts with TB.

[e] Bilateral is disease in both the left and right lung fields on chest radiograph.

[f] Cigarette smoking in the past 6 months.

[g] Number of exposures is the number of tuberculosis cases to which a given contact was exposed.

Table 4.

Rates of Incident Tuberculosis (TB) in Tuberculin Skin Test–positive Close Contacts With Complete, Partial, and No Treatment for Latent TB Infection

Latent TB Infection[a] Treatment	Persons Treated, n	TB Cases, n	Follow-up, Person-years	TB Cases/10^5 Person-years (95% Confidence Interval)[b,c]	*P* Value[d]
Complete	517	1	3210	31 (2, 154)	<.001
Partial	443	8	2756	290 (135, 551)	<.001
No treatment	446	49	2511	1951 (1459, 2559)	Referent

Abbreviation: TB, tuberculosis.

[a]Tuberculin skin test–positive contacts were categorized as not treated for latent TB infection if they did not initiate treatment, partially treated if they initiated but did not complete treatment, and completely treated if they completed the required duration of treatment for the regimen received. The duration of treatment was unknown for 4 contacts with partial treatment. TB rates for partial treatment and complete treatment were compared with the rate for contacts who received no treatment using the χ^2 test, with associated *P* values for each comparison presented in the table.

[b]TB rates for each treatment category were calculated by dividing the total number of TB cases by the person-years of follow-up.

[c]Only TB events among contacts diagnosed 30 or more days after index case diagnosis were counted.

[d]*P* values presented in the table are for comparisons using the no treatment group as the referent. When partial treatment was compared with complete treatment as the referent group, the result was $P = .04$.

Table 5.

Multivariable Analysis of Risk factors for Tuberculosis

	All TB (n = 158)		Incident TB (n = 77)		Incident TB Adjusted for Latent TB Infection Treatment (n = 58)[a]	
Risk Factor	**aOR (95% CI)**	***P* Value**	**aOR (95% CI)**	***P* Value**	**aOR (95% CI)**	***P* Value**
Contact factors						
Age 0–5 y	7.2 (4.6–11.2)	<.001	6.1 (3.2–11.7)	<.001	6.3 (2.6–14.8)	<.001
US/Canadian-born	3.0 (1.9–4.6)	<.001	3.2 (1.7–6.3)	<.001	4.0 (1.9–8.5)	<.001
TST size, mm						
0–4	Referent	…	…	…	…	…
5–9	5.5 (0.6–47.3)	.12	[b]	…	…	…
10–14	33.5 (13.0–86.4)	<.001	13.8 (5.4–35.3)	<.001	…	…
15–19	49.7 (19.8–124.8)	<.001	27.4 (11.5–65.3)	<.001	…	…
≥20	52.6 (21.0–131.8)	<.001	31.8 (13.2–76.2)	<.001	…	…
No TST or missing mm	12.9 (5.2–32.2)	<.001	[c]	…	[c]	…
HIV-positive	7.9 (1.8–35.0)	.007	…	…	…	…
HIV-unknown	0.6 (0.4–0.9)	.013	…	…	…	…
Index case factors						
Weight loss	1.6 (1.04–2.6)	.03	3.5 (1.5–8.5)	.004	3.7 (1.4–9.9)	.004
Exposure factors						
Household shared bedroom	2.9 (1.8–4.9)	<.001	…		…	…
Number of exposures						
≥2 vs 1	3.7 (1.7–8.2)	<.001	12.9 (5.9–28.2)	<.001	9.7 (3.6–26.3)	<.001
Latent TB infection treatment						
TST-positive, no treatment	…	…	…	…	Referent	…
TST-positive, partial treatment	…	…	…	…	.07 (0.03–0.16)	<.001
TST-positive, complete treatment	…	…	…	…	.10 (0.04–0.24)	<.001
TST-negative	…	…	…	…	.01 (0.002–0.02)	<.001

Incident TB is TB in a contact diagnosed >30 days after index TB patient treatment initiation (n = 77); partial LTBI treatment = treatment initiated but not completed; complete LTBI treatment = treatment completed.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; TB, tuberculosis; TST, tuberculin skin test.

[a] Includes adjustment for latent TB infection treatment as a potential confounder, with TST-positive no treatment as the referent group. For this model, the last factors removed by backward elimination were total hours of exposure >500 ($P = .08$) and index case cough for >3 weeks ($P = .15$).

[b] Unestimated as a result of 0 incident cases for contacts with skin test size 5–9 mm.

[c] For skin tests, no skin test or missing millimeter reading was included as a separate term for the analysis of all TB cases but coded as missing for the 2 incident TB models.