MAJOR ARTICLE

Active Case Finding and Prevention of Tuberculosis Among a Cohort of Contacts Exposed to Infectious Tuberculosis Cases in New York City

Holly A. Anger,[1] Douglas Proops,[1] Tiffany G. Harris,[1] Jiehui Li,[1] Barry N. Kreiswirth,[2] Elena Shashkina,[2] and Shama D. Ahuja[1]

[1]Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, New York; and [2]Public Health Research Institute Tuberculosis Center, Newark, New Jersey

Background. Tuberculosis contact investigation identifies individuals who may be recently infected with tuberculosis and are thus at increased risk for disease. Contacts with latent tuberculosis infection (LTBI) are offered chemoprophylaxis to prevent active disease; however, the effectiveness of this intervention is unclear as treatment completion is generally low.

Methods. A retrospective cohort study of 30 561 contacts identified during investigation of 5182 cases of tuberculosis diagnosed in New York City, 1997–2003, was performed. We searched the NYC tuberculosis registry to identify contacts developing active tuberculosis within 4 years of follow-up. We estimated the following: number of contacts undergoing evaluation (ie, tuberculin skin test and/or chest radiograph) per prevalent case diagnosed; number of contacts with LTBI that need to be treated with standard chemoprophylaxis to prevent 1 active case.

Results. Of 30 561 contacts, 27 293 (89%) were evaluated and 268 prevalent cases were diagnosed (102 contacts evaluated per prevalent case diagnosed, 95% confidence interval [CI], 90–115). LTBI was diagnosed in 7597 contacts, including 6001 (79%) who initiated chemoprophylaxis, 3642 (61%) who later completed treatment, and 2359 (39%) who did not complete treatment. During 4 years of follow-up, active tuberculosis was diagnosed in 46 contacts with LTBI, including 22 of 6001 (0.4%) who initiated chemoprophylaxis and 24 of 1596 (1.5%) who did not initiate treatment. The absolute risk reduction afforded by chemoprophylaxis initiation was 1.1% (95% CI, .6%–1.9%), leading to an estimated 88 contacts treated to prevent 1 tuberculosis case (95% CI, 53–164).

Conclusions. Contact investigation facilitates active case finding and tuberculosis prevention, even when completion rates of chemoprophylaxis are suboptimal.

Contact investigation is a core tuberculosis control strategy widely employed in countries with low to intermediate tuberculosis incidence [1, 2]. Contact investigation helps identify and evaluate individuals who have been recently exposed to an infectious tuberculosis case and therefore are at increased risk for active tuberculosis or latent tuberculosis infection (LTBI) [3, 4]. By identifying contacts with active disease, tuberculosis control programs reduce further transmission by ensuring prompt treatment of existing, undiagnosed cases in the community [4, 5]. By identifying contacts with LTBI, programs also provide chemoprophylaxis to recently infected individuals, of whom 5%–10% would develop active tuberculosis if left untreated [6, 7].

Prevention of tuberculosis among contacts with LTBI is contingent upon their acceptance and completion of a lengthy chemoprophylaxis regimen [8]. Although clinical trials demonstrate efficacy of chemoprophylaxis ranging from 90% to 93% [9–12], treatment completion observed outside of clinical trials averages 40%–60% [4, 13], casting uncertainty over the effectiveness of

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Correspondence: Holly A. Anger, MPH, Bureau of Tuberculosis Control, New York City Department of Health and Mental Hygiene, 42-09 28th St, 21st Floor, Long Island City, New York, 11101 (hollyannanger@gmail.com).

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chemoprophylaxis provision. Further, because contacts seldom undergo regular follow-up subsequent to chemoprophylaxis, data are scarce regarding the long-term impact of chemoprophylaxis on preventing future tuberculosis cases and whether contacts diagnosed with active tuberculosis have the same infecting organism as the presumed index case.

To assess the impact of contact investigation as an active case-finding modality and an opportunity for tuberculosis prevention, we conducted a retrospective cohort study of contacts who developed active tuberculosis after exposure to an infectious tuberculosis case in New York City.

METHODS

All infectious tuberculosis cases were interviewed to identify individuals whom they may have exposed during their infectious period, defined programmatically as 3 months before initiation of antituberculosis treatment [14]. Evaluation of contacts included symptom screening for active tuberculosis, a tuberculin skin test (TST), and a chest radiograph for contacts with tuberculosis symptoms or positive TST results. Chemoprophylaxis was recommended for all contacts with newly diagnosed LTBI. A negative TST result was considered valid when administered >8 weeks after the end of the index case's infectious period in order to account for the *Mycobacterium tuberculosis* incubation period ("window" period) [15, 16]. Contacts aged <5 years or those with human immunodeficiency virus (HIV) infection were given chemoprophylaxis during the window period once active tuberculosis was excluded, regardless of TST result.

The NYC TB registry was used to identify contacts to infectious tuberculosis cases diagnosed in New York City during 1997–2003 and to obtain information on demographics, exposure location, clinical characteristics, and laboratory results for cases and contacts. We excluded contacts to index cases aged <5 years because they are generally considered not infectious and contacts to cases of multidrug-resistant tuberculosis (ie, resistance to isoniazid and rifampin) because there is no standard chemoprophylaxis regimen in these circumstances. We also excluded contacts with the following: unknown date of birth, treatment for active tuberculosis within 1 year before the index case's diagnosis, nonresidence in New York City, and death or relocation outside New York City during contact evaluation. For individuals identified as a contact multiple times during 1997–2003, the last exposure and evaluation outcome was used in analyses.

The NYC TB registry was used to identify contacts diagnosed with active tuberculosis in New York City from 1997 to 2007 using the Centers for Disease Control and Prevention tuberculosis case definition [17]. We limited analysis to active tuberculosis occurring within 4 years after exposure, the maximum potential follow-up time for all contacts. We also performed a New York City death registry match to identify contacts who died during the follow-up period.

Since 2001, 2 genotyping techniques (spacer oligonucleotide typing and IS*6110* restriction fragment length polymorphism) are performed on *M. tuberculosis* isolates recovered from all New York City tuberculosis patients [18]. Before 2001, genotyping was performed only on selected isolates. When available, we compared genotyping results of cases and their contacts with active tuberculosis.

Prevalent and Incident Tuberculosis

Contacts with active tuberculosis diagnosed within 9 months of the index case's diagnosis were considered "prevalent." Cases diagnosed among contacts >9 months after the index case's diagnosis were considered "incident." The 9-month period was chosen because in New York City, it takes approximately 9 months to identify, evaluate, and initiate chemoprophylaxis for contacts. Contacts were categorized as evaluated if a TST or chest radiograph was performed within 9 months of the index case's diagnosis.

We reported the following rates and proportions by year after exposure: Tuberculosis incidence rate (IR) among contacts per 100 000 person-years of observation, proportion of incident cases among contacts who were culture-positive for *M. tuberculosis*, and proportion of incident cases among contacts with genotypes concordant to their index case. The Poisson distribution was used to calculate 95% confidence intervals (CIs) for IRs. Observations were censored on the date of death or at 4 years of follow-up. An estimate and 95% CI for the number of contacts evaluated per prevalent case identified was calculated using the inverse of the proportion diagnosed with prevalent tuberculosis among all contacts evaluated [19].

We compared contacts with and without prevalent tuberculosis by contact characteristics (age, HIV status, region of birth, exposure location, contact evaluation, TST) and index case characteristics (age, HIV status, acid-fast bacilli [AFB] sputum smear results, chest radiograph findings, and isoniazid resistance). TST status was categorized as follows: (1) *TST-positive* from contact investigation; (2) *TST-negative* if performed ≥8 weeks after index cases' diagnosis; (3) *window TST-negative* if performed within the window period without a subsequent result; (4) ineligible for TST due to prior tuberculosis diagnosis; (5) ineligible for TST due to a known prior positive TST result; or (6) not tested, if eligible and no TST was administered during contact investigation. Crude and adjusted odds ratios (AORs) and corresponding 95% CIs for prevalent tuberculosis were calculated using logistic regression, applying generalized estimating equations to account for correlation among contacts to the same index case.

Prevention of Incident Tuberculosis

To assess the effect of chemoprophylaxis, we restricted analysis to TST-positive contacts and applied the following exclusion criteria: prevalent tuberculosis, died or relocated while taking chemoprophylaxis, initiated treatment for active tuberculosis but subsequently found not to have tuberculosis disease, chemoprophylaxis regimen other than isoniazid or rifampin, and radiographic evidence of prior tuberculosis disease. IRs and 95% CIs were compared by initiation and completion of chemoprophylaxis. A 2-sided Wilcoxon rank-sum test was used to compare incident tuberculosis by median duration of chemoprophylaxis among those who initiated and did not complete treatment. Poisson regression incorporating generalized estimating equations was used to compare contact characteristics by chemoprophylaxis initiation to determine if characteristics associated with higher tuberculosis risk were associated with treatment initiation. Clustered Cox proportional hazards regression was used to calculate crude and adjusted hazard ratios (HRs) and 95% CIs for incident tuberculosis by initiation and completion of chemoprophylaxis.

To estimate the number of contacts needed to initiate chemoprophylaxis in order to prevent 1 tuberculosis case within 4 years after exposure, we calculated the absolute risk reduction (ARR) and associated 95% CI for chemoprophylaxis initiation. The inverse of the ARR was used to estimate the number needed to initiate chemoprophylaxis in order to prevent 1 tuberculosis case [19, 20]. We repeated this analysis incorporating age adjustment. Additional details regarding study definitions and analysis are included in the Supplementary Methods.

This study was approved by the NYC Department of Health and Mental Hygiene (DOHMH) Institutional Review Board.

RESULTS

We identified 36 606 contacts to 5731 infectious tuberculosis cases diagnosed in New York City from 1997 to 2003. We excluded 6045 contacts (Figure 1). The final study population was 30 561 contacts to 5182 cases.

Active tuberculosis was diagnosed in 378 (1%) contacts: 268 (71%) prevalent cases and 110 (29%) incident cases occurred during 4 years of follow-up (Table 1). The New York City death registry match revealed that 452 (1%) contacts died during the follow-up period. Contacts had 118 616 person-years of observation. IRs were highest in the first 2 years after diagnosis of index cases and declined thereafter. The proportion of contacts with culture-confirmed tuberculosis was smallest for cases diagnosed within the first 9 months (53%) compared with subsequent time periods (range, 71%–94%); this trend was consistent when restricting analysis to adult contacts (73% with culture-confirmed tuberculosis in the first 9 months vs 81%–94% in subsequent time periods). Because *M. tuberculosis* isolates were not routinely genotyped until 2001, genotyping results were available for 103 of 233 (44%) contacts with culture-confirmed disease; 88 (85%) had concordant genotypes with the index case. The proportion of concordant genotypes was highest among prevalent cases (92%); the majority of incident cases had concordant results in all subsequent time periods (range, 63%–85%).

Prevalent Tuberculosis

There were 268 prevalent cases (1.0%, 95% CI, .9–1.1) identified among 27 293 contacts evaluated, resulting in 102 contacts (95% CI, 90–115) screened per prevalent case. Most (174 [65%]) prevalent cases were diagnosed within 3 months following the index cases' diagnoses (Supplementary Figure 1). Multivariate analysis revealed that prevalent tuberculosis was associated with exposure to an index case with AFB smear-positive sputum and was more common among contacts who were aged <5 years, US-born, HIV-infected, or had household exposure (Table 2). Compared to TST-negative status, a prior tuberculosis diagnosis was associated with the highest odds of prevalent tuberculosis (AOR, 98.4 [95% CI, 33.4–289.5]), followed by TST-positive (AOR, 84.0 [95% CI, 38.5–183.4]), prior TST-positive (AOR, 30.3 [95% CI, 12.7–72.3]), window TST-negative (AOR, 16.0 [95% CI, 6.50–39.5]), or never tested (AOR, 13.3 [95% CI, 4.79–37.1]).

Prevention Analysis

When analyzing the preventive benefit of chemoprophylaxis for infected contacts, we excluded 673 TST-positive contacts (Figure 1). Of the remaining 7597 infected contacts, 3642 (48%) initiated and completed chemoprophylaxis, 2359 (31%) initiated but did not complete (2219 defaulted, 140 discontinued due to adverse reactions), and 1596 (21%) never initiated treatment (Figure 1). Of those initiating chemoprophylaxis, 5361 (89%) received isoniazid, of whom 3201 (60%) completed treatment, and 640 (11%) received rifampin, of whom 441 (69%) completed treatment. Of 46 incident cases among TST-positive contacts, 11 completed chemoprophylaxis (IR, 76 [95% CI, 31–121]), 11 initiated but did not complete (IR, 117 [95% CI, 48–187]) and 24 never initiated (IR, 384 [95% CI, 230–537]). Contacts who developed incident tuberculosis after completing chemoprophylaxis took the following regimens: isoniazid, 6 months (n = 6); isoniazid, 9 months (n = 4); and rifampin, 4 months (n = 1). The association between treatment duration and incident tuberculosis among contacts who initiated but did not complete was only examined among contacts receiving isoniazid, as all incident cases occurring among contacts who initiated and did not complete received isoniazid. Median treatment duration was 1 month (range, 1–5) and 2 months (range, 1–8) among contacts with and without incident tuberculosis, respectively (P = .46). Treatment initiation was associated with

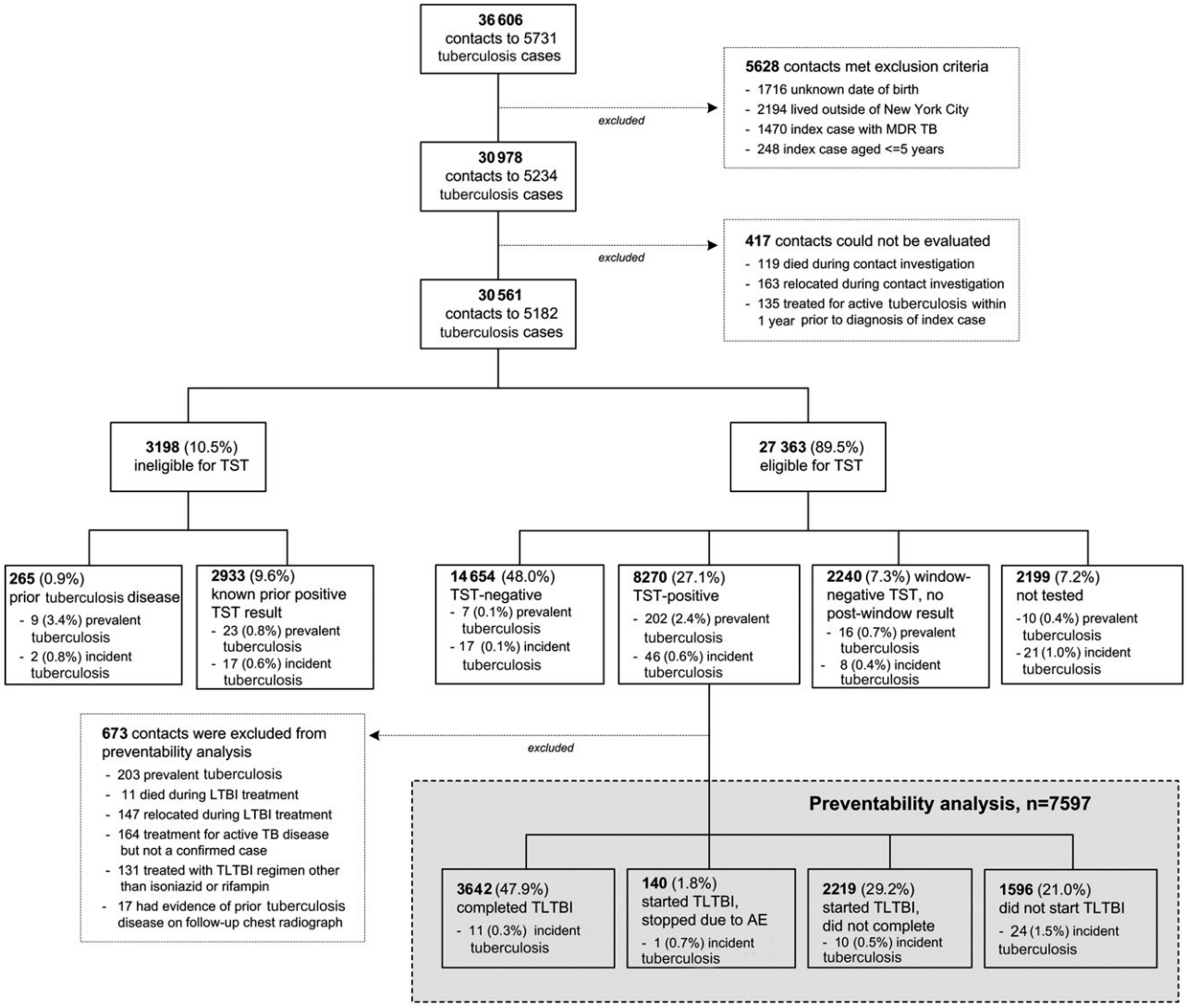

Figure 1. Study population, prevalence, and incidence of active tuberculosis among contacts to New York City tuberculosis cases, 1997–2003. AE, adverse events; MDR TB, multidrug-resistant tuberculosis; TLTBI, treatment of latent tuberculosis infection; TST, tuberculin skin test.

some characteristics suggestive of higher tuberculosis risk, including younger age, household exposure, and exposure to an index case with AFB smear-positive sputum; however, HIV infection and US birth were inversely associated with treatment initiation (Supplementary Table 1).

Multivariate analysis revealed that chemoprophylaxis completion (adjusted HR, 0.16 [95% CI, .07–.41]) and initiation without completion (adjusted HR, 0.24 [95% CI, .11–.54]) was associated with a lower risk of incident tuberculosis compared with no chemoprophylaxis (Table 3). Additionally, increased risk of tuberculosis was associated with age of 18–44 years, US birth, and household exposure. When applying the same multivariate model and excluding those who did not initiate chemoprophylaxis, tuberculosis risk did not significantly differ by chemoprophylaxis completion (data not shown).

The ARR afforded by chemoprophylaxis initiation was 1.1% (95% CI, .6%–1.9%; Table 4). Assuming 63% completion among contacts who initiate chemoprophylaxis (as observed in our cohort), an estimated 88 infected contacts (95% CI, 53–164) need to be treated to prevent 1 tuberculosis case within 4 years after exposure. Age adjustment revealed that chemoprophylaxis initiation did not significantly reduce the tuberculosis risk in the 2 oldest age groups. Further, only 6 contacts (95% CI, 2–22) aged 0–4 years need to be treated to prevent 1 case arising from this age group.

DISCUSSION

Although contact investigation is a widely used tuberculosis control strategy, this report is novel in its documentation of

Table 1. Incidence Rate of Tuberculosis and Genotyping Results Among Contacts to Infectious Tuberculosis Cases by Year After Exposure

Year After Exposure	Person-Years of Observation, No.	Cases, No. (%)	Incidence Rate (95% Confidence Interval)[a]	Culture-Positive Cases, No. (%)	Cases Culture-Positive With Genotyping Results, No.	Cases With Concordant Genotyping Results, No. (%)[b]
All contacts						
0–9 months[c]	22 630.7	268 (71)	1184 (1042–1326)	141 (53)	63	58 (92)
>9–12 months	7716.1	34 (9)	441 (293–589)	24 (71)	13	11 (85)
2 years	30 139.1	41 (11)	136 (94–178)	35 (85)	12	9 (75)
3 years	29 956.3	18 (5)	60 (32–88)	17 (94)	8	5 (63)
4 years	29 799.4	17 (4)	57 (30–84)	16 (94)	7	5 (71)
Total	118 616	378 (100)	319 (287–351)	233 (62)	103	88 (85)
Adults (≥18 years)						
0–9 months[c]	16 412.4	157 (62)	957 (807–1106)	114 (73)	51	46 (90)
>9–12 months	5450.4	26 (10)	477 (293–660)	21 (81)	11	9 (82)
2	21 688.5	37 (15)	171 (116–226)	33 (89)	12	9 (75)
3	21 509.8	17 (7)	79 (41–117)	16 (94)	7	4 (57)
4	21 355.4	15 (6)	70 (35–106)	14 (93)	5	4 (80)
Total	86 416.5	252 (100)	292 (256–328)	198 (79)	86	72 (84)

[a] Incidence rate in cases per 100 000 person-years of observation.

[b] Contacts with infected with organisms having concordant genotypes to those of their index case's.

[c] Tuberculosis diagnosed within 9 months of exposure is considered to be prevalent tuberculosis diagnosed during contact investigation activities.

concrete gains in tuberculosis prevention occurring as a result of routine contact investigation. This study also lends support to previous studies demonstrating that contact investigation is an effective strategy to identify and treat active tuberculosis [4, 5, 13, 21, 22]. Among adult contacts, only 73% of prevalent cases had bacteriological confirmation compared with 88% of incident cases, suggesting that contact investigation facilitates early diagnosis of active tuberculosis before cases become infectious. Our analysis of risk factors for prevalent tuberculosis also confirms the importance of prompt evaluation of child contacts [13, 23] and contacts with a history of tuberculosis [22].

Provision of chemoprophylaxis to infected contacts was an effective intervention, despite a 48% completion rate. This modest completion is consistent with previous reports from various settings [4, 13, 24, 25]. Contacts who completed chemoprophylaxis had the lowest incidence, although those who initiated and did not complete also had decreased incidence compared with contacts who did not initiate treatment. Overall, the 79% treatment initiation rate among infected contacts resulted in substantial gains in tuberculosis prevention. For contacts who did not complete chemoprophylaxis, analysis did not reveal a significant association between duration of treatment and tuberculosis incidence; this finding conflicts with previous reports, although the small number of incident cases in this analysis may explain this discrepancy [26].

Several factors may impact our estimate of the number of infected contacts needed to initiate chemoprophylaxis to prevent 1 tuberculosis case. This estimate was heavily influenced by age, as just 6 infected contacts <5 years old need to be treated to prevent 1 case arising from this age group, lending support to current Centers for Disease Control and Prevention and World Health Organization guidelines that prioritize chemoprophylaxis for this vulnerable age group [15, 27]. Also, infected contacts were not randomized by chemoprophylaxis initiation, and those who initiated treatment differed from those who did not. Some tuberculosis risk factors were associated with a higher likelihood of treatment initiation, whereas others were inversely associated with initiation (Supplementary Table 1); however, the protective effect of chemoprophylaxis increased in multivariate analysis of incident tuberculosis. Hence, the risk reduction afforded by chemoprophylaxis is likely underestimated, and the number needed to treat is likely overestimated. Further, the impact of chemoprophylaxis among our cohort appears underestimated when compared with a recent study from Canada, where contacts who did not initiate chemoprophylaxis had a 26-fold higher risk of active tuberculosis compared with contacts who completed; however, this study did not account for prevalent cases diagnosed during contact investigation and were thus unlikely to benefit from chemoprophylaxis [23]. In our study, we excluded cases of tuberculosis that occurred within 9 months of the index case's diagnosis to better understand the impact of chemoprophylaxis, because 9 months provided substantial time for diagnosis of active cases or initiation of chemoprophylaxis for infected contacts. Conversely, there is potential for overestimation of the

Table 2. Univariate and Multivariate Logistic Regression[a] of Demographic and Clinical Factors Associated With Prevalent Tuberculosis Among Contacts to New York City Tuberculosis Cases

Demographics	Contacts Without Prevalent Tuberculosis, No, (%)	Contacts With Prevalent Tuberculosis, No. (%)	Prevalent Tuberculosis Among Contacts, OR (95% CI)	Prevalent Tuberculosis Among Contacts, AOR (95% CI)
Total	30 293	268	…	…
Index case characteristics				
Male sex	17 974 (59)	149 (56)	0.85 (.64–1.15)	…
Age (years)				…
5–17	1448 (5)	11 (4)	0.98 (.46–2.08)	…
18–44	16 928 (56)	189 (71)	1.44 (.98–2.11)	…
45–64	7752 (25)	60 (22)	Ref	…
≥65	4165 (14)	8 (3)	0.25 (.12–.58)	
HIV coinfection				
HIV-infected	5792 (19)	48 (18)	0.82 (.53–1.28)	…
Not HIV-infected	17 314 (57)	174 (65)	Ref	…
Unknown	7187 (24)	46 (17)	0.64 (.45–.90)	…
AFB sputum smear-positive	20 642 (68)	238 (89)	3.71 (2.48–5.55)	2.54 (1.69–3.82)
Cavities on chest radiograph	8463 (28)	102 (38)	1.56 (1.18–2.12)	1.09 (.80–1.48)
Resistance to isoniazid				
Resistant	2046 (7)	11 (4)	0.59 (.32–1.08)	…
Susceptible	28 247 (93)	257 (96)	Ref	…
Contact characteristics				
Male sex	14 887 (49)	145 (54)	1.22 (.94–1.59)	…
Age (years)				
0–4	2262 (7)	68 (25)	3.90 (2.64–5.76)	6.08 (3.95–9.34)
5–17	6200 (20)	43 (16)	0.90 (.55–1.46)	1.26 (.78–2.05)
18–44	14 050 (46)	102 (38)	0.94 (.67–1.33)	1.06 (.74–1.52)
45–64	5970 (20)	46 (17)	Ref	Ref
≥65	1811 (6)	9 (3)	0.65 (.31–1.33)	0.68 (.32–1.41)
Country of birth				
US-born	11 101 (37)	127 (47)	1.62 (1.18–2.23)	2.66 (1.82–3.90)
Not US-born	11 881 (39)	84 (31)	Ref	Ref
Unknown	7311 (24)	57 (21)	1.10 (.78–1.56)	2.11 (1.46–3.05)
HIV coinfection				
HIV-infected	307 (1)	9 (3)	2.19 (.99–4.83)	3.08 (1.23–7.60)
Not HIV-infected	3359 (11)	45 (17)	Ref	Ref
Unknown	26 627 (88)	214 (80)	0.60 (.43–.84)	0.75 (.52–1.07)
Exposure setting				
Household	13 293 (44)	167 (62)	2.11 (1.63–2.74)	1.62 (1.24–2.13)
Nonhousehold	17 000 (56)	101 (38)	Ref	Ref
Contact evaluation				
Extent of evaluation				
TST only	17 002 (56)	0 (0)	…	…
Chest radiograph only	1871 (7)	41 (15)	0.79 (.55–1.12)	…
TST and chest radiograph	8152 (27)	227 (85)	Ref	…
Not evaluated	3268 (11)	0 (0)	…	…
TST status				
Positive	8067 (27)	203 (76)	52.7 (24.7–112.3)	84.0 (38.5–183.4)
Negative	14 647 (48)	7 (3)	Ref	Ref
Window TST-negative	2224 (7)	16 (6)	15.1 (6.11–37.1)	16.0 (6.50–39.5)
Prior tuberculosis diagnosis	256 (1)	9 (3)	73.6 (27.2–198.7)	98.4 (33.4–289.5)
Prior TST-positive	2910 (10)	23 (9)	16.5 (7.09–38.6)	30.3 (12.7–72.3)
Not tested	2189 (7)	9 (3)	9.56 (3.47–26.3)	13.3 (4.79–37.1)

Abbreviations: AFB, acid-fast bacilli; AOR, adjusted odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; Ref, reference; TST, tuberculin skin test.

[a] Logistic regression incorporating generalized estimating equations.

Table 3. Clustered Cox Proportional Hazards Regression Models for Risk of Developing Incident Tuberculosis Within 4 Years After Tuberculosis Exposure Among 7597 Contacts With Positive Tuberculin Skin Test Results

Factors	Contacts Without Active Tuberculosis, No. (%)	Contacts With Active Tuberculosis, No. (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Total	7551 (100)	46 (100)	…	…
Index case characteristics				
Male sex	4782 (63)	31 (67)	1.20 (.63–2.29)	…
Age (years)				
5–17	359 (5)	0 (0)	…	…
18–44	4779 (63)	31 (67)	0.79 (.40–1.56)	…
45–64	1591 (21)	13 (28)	Ref	…
≥65	822 (11)	2 (4)	0.30 (.07–1.32)	…
HIV coinfection				
HIV-infected	993 (13)	9 (20)	1.43 (.69–2.97)	…
Not HIV-infected	4714 (63)	30 (65)	Ref	…
Unknown	1844 (24)	7 (15)	0.60 (.24–1.50)	…
AFB sputum smear-positive	5703 (76)	38 (83)	1.54 (.72–3.29)	1.77 (.81–3.85)
Cavities on chest radiograph	2539 (34)	13 (28)	0.78 (.39–1.57)	0.78 (.39–1.54)
Resistance to isoniazid				
Resistant	516 (7)	3 (7)	0.95 (.30–3.00)	…
Susceptible	7035 (93)	43 (93)	Ref	…
Contact characteristics				
Male sex	4182 (55)	27 (59)	1.15 (.64–2.05)	…
Age (years)				
0–4	242 (3)	3 (6)	4.22 (1.01–17.6)	4.49 (.76–26.5)
5–17	1046 (14)	3 (6)	0.98 (.23–4.12)	1.35 (.26–6.97)
18–44	4089 (54)	30 (65)	2.50 (.99–6.23)	3.44 (1.38–8.58)
45–64	1713 (23)	5 (11)	Ref	Ref
≥65	461 (6)	5 (11)	3.76 (1.01–13.0)	3.16 (.89–11.2)
Region of birth				
US-born	1476 (20)	18 (39)	2.45 (1.29–4.62)	2.69 (1.21–5.97)
Non–US-born	5005 (66)	25 (54)	Ref	Ref
Unknown	1070 (14)	3 (7)	0.56 (.17–1.87)	0.45 (.14–1.47)
HIV status				
Infected	34 (1)	2 (4)	9.24 (1.97–43.3)	3.65 (.75–17.8)
Not infected	1304 (17)	8 (17)	Ref	Ref
Unknown	6213 (82)	36 (78)	0.94 (.44–2.05)	0.85 (.37–1.96)
Exposure setting				
Household	3863 (51)	43 (66)	1.47 (.82–2.63)	1.97 (1.07–3.65)
Nonhousehold	3669 (49)	22 (34)	Ref	Ref
LTBI treatment				
Did not start	1572 (21)	24 (52)	Ref	Ref
Started, did not complete	2348 (31)	11 (24)	0.31 (.15–.63)	0.24 (.11–.54)
Completed	3631 (48)	11 (24)	0.20 (.09–.43)	0.16 (.07—.41)

Abbreviations: AFB, acid-fast bacilli; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; LTBI, latent tuberculosis infection; Ref, reference.

protective effect of chemoprophylaxis and underestimation of the number needed to treat, because prevalent cases may have gone undetected among infected contacts who did not receive a follow-up chest radiograph during contact investigation. Such misclassification of prevalent tuberculosis as incident tuberculosis was differential by chemoprophylaxis initiation, because contacts who did not receive a chest radiograph were unlikely to start treatment; however, as previously mentioned, a generous 9-month time period was applied in which cases were considered nonpreventable, minimizing this misclassification.

Our results offer insight regarding how greater gains in tuberculosis prevention may be attained with programmatic

Table 4. Crude and Age-Adjusted Estimates of Number of Infected Contacts Needed to Initiate Chemoprophylaxis to Prevent 1 Tuberculosis Case Within 4 Years After Exposure

		Contacts Initiating Chemoprophylaxis		Contacts Not Initiating Chemoprophylaxis			
Estimate	Total	No. (%)[a]	No. (%) With Incident Tuberculosis[b]	No. (%)[a]	No. (%) With Incident Tuberculosis[b]	Absolute Risk Reduction, % (95% CI)	No. Treated to Prevent 1 Case (95% CI)
Crude estimate	7597	6001 (79)	22 (0.4)	1596 (21)	24 (1.5)	1.1 (.6–1.9)	88 (53–164)
Age-adjusted estimates							
Age (years)							
0–4	245	234 (96)	1 (0.4)	11 (4)	2 (18.2)	17.8 (4.6–47.3)	6 (2–22)
5–17	1049	968 (92)	1 (0.1)	81 (8)	2 (2.5)	2.4 (.5–8.5)	42 (12–195)
18–44	4119	3295 (80)	16 (0.5)	824 (20)	14 (1.7)	1.2 (.5–2.4)	82 (42–215)
45–64	1718	1215 (71)	3 (0.3)	503 (29)	2 (0.4)	0.2 (−.4 to 1.2)	664 (−246 to 83)[c]
≥65	466	289 (82)	1 (0.4)	177 (18)	4 (2.3)	1.9 (−.2 to 5.3)	52 (−532 to 19)[c]

Abbreviation: CI, confidence interval.

[a] Proportion of all contacts initiating or not initiating chemoprophylaxis.

[b] Proportion of contacts with incident tuberculosis among those initiating or not initiating chemoprophylaxis.

[c] When number needed to treat includes 0, the treatment effect is not significant.

improvements and technological advances in the diagnosis and treatment of LTBI. HIV-infected individuals and US-born contacts were less likely to initiate chemoprophylaxis in our cohort and because of their high risk of disease, targeted programmatic improvements in patient education and incentive programs could increase uptake of chemoprophylaxis and result in larger gains in tuberculosis prevention [28–30]. However, adding new initiatives to already financially constrained tuberculosis control programs may not be a feasible option. With regard to technological advances in LTBI diagnosis, the lower rates of progression from LTBI to active tuberculosis observed in non–US-born contacts highlight the limitations of using the TST to diagnose LTBI, because the TST can produce false-positive results for individuals who have received the BCG vaccine [31]. Interferon-γ release assays (IGRAs), a recent advancement in LTBI diagnosis, are not confounded by BCG vaccination [32–34]. As such, IGRAs may better prioritize chemoprophylaxis for those with greater risk of tuberculosis [35]. Also, uptake and completion of chemoprophylaxis may be higher when LTBI is diagnosed with IGRAs. Finally, the effectiveness of contact investigation would likely be enhanced if higher uptake and completion rates are attained through use of a shorter but equally effective chemoprophylaxis regimen. For example, an isoniazid and rifapentine regimen given once weekly for 3 weeks has recently been shown to be as effective as 9 months of isoniazid administered daily [36].

Our study has several limitations. This is a retrospective analysis using data collected for routine programmatic purposes. Many contacts had missing data for known tuberculosis risk factors, including HIV. Notably, HIV infection was not associated with incident tuberculosis in multivariate analysis of infected contacts, likely because of the large proportion with unknown HIV status. Also, we were unable to account for incident tuberculosis occurring among contacts who moved outside New York City during the follow-up period; this probably led to an underestimation of incident cases.

Our study also has considerable strengths. The NYC TB control program has the resources and infrastructure to evaluate this large number of contacts and maintain a data management system that permitted a robust analysis of programmatic data. Genotyping data provided assurance that the majority of active tuberculosis among contacts likely occurred from the exposure that prompted the contact investigation. To our knowledge, this is the largest cohort study to use tuberculosis control program data to examine the short- and long-term public health outcomes of contact investigation.

Contact investigation of tuberculosis cases requires substantial commitment of human resources, yet compelling data on the public health impact of this intervention are lacking. Our study provides evidence that contact investigation is a useful tool for early identification of active tuberculosis cases and for prevention of future cases. Tangible gains in tuberculosis prevention were achieved, despite modest chemoprophylaxis completion rates. Further, every tuberculosis case prevented among contacts can be considered a break in the chain of transmission, leading to prevention of not just 1 secondary case, but of a third generation of cases and so on, indicating that contact investigation plays an integral role toward tuberculosis elimination.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials

consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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