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Cigarette smoking among tuberculosis patients increases risk of transmission to child contacts

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SUMMARY

SETTING: Observational cohort study in Lima, Peru.
OBJECTIVE: To determine the association between exposure to a smoking tuberculosis (TB) case and latent tuberculous infection (LTBI).
METHOD: Between September 2009 and August 2012, we identified 2132 patients with drug-susceptible TB and their 2054 child household contacts. Data were collected on active and secondhand smoking status and other risk factors for infection specific to the index case, the household and the exposed contacts. Contacts underwent a tuberculin skin test (TST) to determine their tuberculous infection status at baseline, 6-month and 12-month follow-up. We estimated the association between exposure to a smoking index case and LTBI using a modified Poisson regression model.
RESULTS: The 21 children (age ⩽15 years) exposed to smoking index TB patients were more likely to be TST-positive at baseline (RR 2.64, 95%CI 1.78–3.91), by 6 months (RR 1.91, 95%CI 1.40–2.60) and by 12 months (RR 1.48, 95%CI 1.07–2.06), than those who were not exposed. TST positivity among children at these time points did not vary with secondhand smoke exposure.
CONCLUSIONS: TB patients who smoke may be more likely to transmit infection to their contacts. Interventions designed to reduce smoking among TB patients may minimise further spread of the disease.
KEY WORDS: tobacco use; tuberculous infection; household contacts; infectiousness

MULTIPLE STUDIES have demonstrated that children exposed to secondhand smoke (SHS) experience an increased risk of active tuberculosis (TB).[1–4] Some have also noted an increased risk of latent tuberculous infection (LTBI) among smoke-exposed children.[5–7] These studies infer that SHS exposure increases the risk of TB disease by reducing the ability to contain an early infection.[5–8] However, it is also possible that a smoker to whom a non-smoking household contact (HHC) was exposed was also the TB index case within the household. In this scenario, a TB patient who smokes during his/her illness might be more infectious than a non-smoking TB patient, and therefore might increase the risk of LTBI among contacts, regardless of their susceptibility. The only study to date that has examined the risk of LTBI among household contacts of smoking index cases reported an odds ratio (OR) of 1.5 for those exposed to an index case who smoked compared to one who did not.[9] However, because that study did not adjust for the smoking status of other household members, it is unclear whether the observed effect resulted from the increased susceptibility of smoke-exposed contacts or from the increased infectiousness of patients who smoked.

In the present study, we distinguish between these two possible mechanisms by assessing the risk of LTBI among children exposed to smoking index cases after adjusting for their exposure to any SHS, and we examine the roles of potential mediators of this effect.

METHODS

Study population

We conducted this study in a catchment area of Lima, Peru, of over 3.3 million inhabitants. The TB case notification rate was 96.1 per 100 000 population.[10] Between September 2009 and August 2012, we identified adult patients aged >15 years who were diagnosed with incident drug-susceptible pulmonary TB in 106 participating health centers. Suspect TB patients underwent an evaluation that included both smear microscopy and culture; those who were positive on either test were classified as index cases,

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while those who were negative on both tests were considered 'community controls'. Patients were initiated on directly observed therapy upon diagnosis, and we recorded whether an index case completed treatment during follow-up. Culture was repeated at 2 months. Within 1 month of the diagnosis of the index patient, a study nurse visited his/her household and invited exposed HHCs to participate in a 12-month longitudinal follow-up study for LTBI. Participants who did not report a previous positive tuberculin skin test (TST) result or TB diagnosis underwent baseline TST, and those with an induration size $\geqslant$10 mm were considered to have LTBI. Repeat TSTs were performed at 6 and 12 months for those who were TST-negative at the previous test. At baseline, 47.1% of children and 6.6% of adults were on isoniazid preventive therapy. We also assessed LTBI status among a subset of the HHCs of 'community controls', i.e., those patients with presumed TB who did not have microbiologically confirmed disease.

Data collection

We collected the following data from the index cases at baseline enrollment: age, sex, smoking status, alcohol intake, date of onset of cough, sputum smear status, and cavitary disease on chest radiography. As it was common for smokers in this setting to smoke only a single cigarette per day, we categorized participants as non-smokers, light smokers (1 cigarette/day), and moderate or heavy smokers (>1 cigarette/day). Smoking status was determined at baseline enrollment. We collected the following data for all exposed HHCs: age, sex, height, weight, self-reported bacille Calmette-Guérin (BCG) vaccine exposure, number of BCG vaccination scars, relation to index case, use of public transportation, and frequency of social and physical contacts, and the following data for adults only: smoking status, alcohol intake and occupation. For each household, we assessed the number of persons per room and type of housing.

Data analysis

We used a modified Poisson generalized estimating equation to evaluate the association between covariates and LTBI on a risk ratio (RR) scale. As we were concerned that the use of TST conversion among those who initially tested negative might lead to a survival cohort bias, we examined the associations of each potential predictor in both univariate age-adjusted and multivariate analyses using baseline TST status and infection at 6 and 12 months as outcomes. We considered the possibility that sputum smear status, duration of symptoms before diagnosis, cavitary disease, culture conversion at month 2, and default during follow-up might mediate the effect of the index case's smoking on LTBI. To examine this, we first assessed the association between index smoking status and these factors. Second, we compared the results of regression models with and without these variables, thereby measuring the magnitude of the direct effect of index case smoking that is not mediated by these factors. To ensure comparability of the results of three outcomes, we did not evaluate 2-month culture conversion or default in the multivariate model, as these would be expected to affect 6 and 12 month outcomes but not the baseline TST. Because we considered that adults were more likely to have had LTBI before exposure to the index case, we conducted separate analyses for children and adults. We chose 15 years of age as the cut-off to distinguish children from adults, on the basis of World Health Organization guidelines.[11]

The present study was approved by the human subjects committees of the Harvard School of Public Health (Boston, MA, USA) and the National Institute of Health in Lima, Peru.

RESULTS

Baseline, combined baseline and 6-month follow-up characteristics

We recruited 2131 index patients with incident drug-susceptible culture-positive TB and 6702 HHCs of the 1632 index cases who had at least one HHC (Appendix Table A.1*). The majority of the index cases (97.42%) reported being non-smokers, while 1.28% reported light smoking and 1.29% moderate to heavy smoking. After exclusion, baseline TST results were available for 5577 (83.21%) HHCs (Figure). The prevalence of LTBI in children and adults was respectively 27.89% and 53.84% at baseline, 37.82% and 70.10% at 6 months, and 47.76% and 79.37% at 12 months (Appendix Table A.2). The prevalence of TST positivity in community controls at baseline was 14.63% (115/786) in children and 41.92% (724/1 727) in adults.

Results of baseline data

After adjusting for possible confounders, we found that children were more likely to be TST-positive at baseline if they were exposed to an index patient who was a moderate or heavy smoker (RR 2.64, 95% confidence interval [CI] 1.78–3.91) or a heavy drinker (RR 1.36, 95%CI 1.00–1.85); were offspring of the index case (RR 1.72, 95%CI 1.33–2.24); or had more social contacts (RR if $\geqslant$1 times vs. 0 times per day 1.71, 95%CI 1.14–2.57). Children exposed to any SHS did not have an increased risk of LTBI (Tables 1 and A.5). When we repeated this analysis in

* The Appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2014/00000018/00000011/art00006

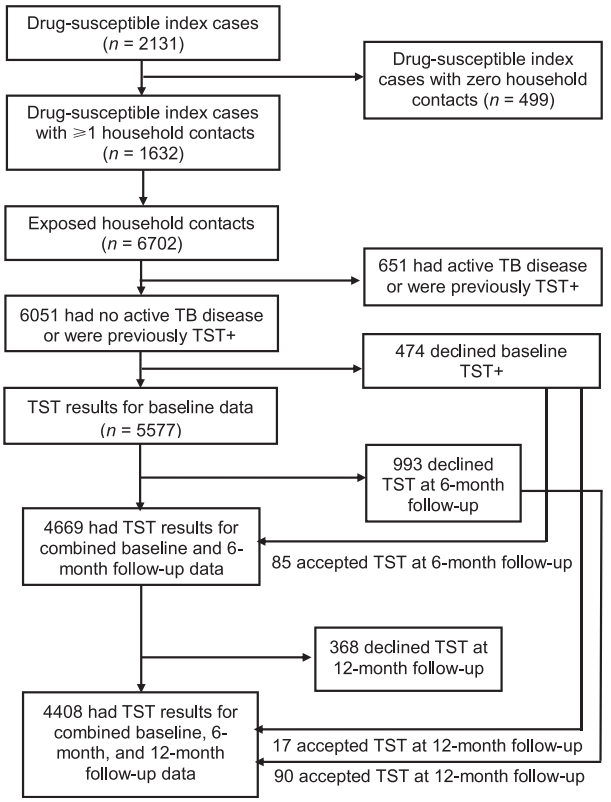

Figure Enrollment of baseline, combined baseline and 6-month follow-up data, and combined baseline, 6-month and 12-month follow-up data. TB = tuberculosis; TST = tuberculin skin test; + = positive.

adults, the RR for LTBI decreased from 2.64 to 1.35 among those exposed to an index case who smoked (Tables 2 and A.6).

Results of TST positivity by 6 months and 12 months

In a multivariate regression model, we found that children were more likely to be TST-positive by 6 months if they were exposed to an index case who was a moderate or heavy smoker (RR 1.91, 95%CI 1.40–2.60); had two BCG scars (RR 1.35, 95%CI 1.01–1.80); were offspring of the index case (RR 1.71; 95%CI 1.41–2.08); or had more daily social contacts (RR for ⩾1 vs. 0: 1.38 [95%CI 1.02–1.88]) (Tables 1 and A.5). The association between smoking among the index TB cases and TST positivity by 12 months was slightly attenuated compared to those at 6 months (Tables 2 and A.6). Exposure to any SHS did not increase the risk of TST positivity by 6 months or by 12 months (Tables 1, 2, A.5 and A.6). For adults, there was no significant difference in the risk of TST positivity between contacts of smoking index cases and contacts of non-smoking index cases by 6 months or by 12 months (Tables 2 and A.6).

Results of direct effects

We found that smoking index cases were more likely than non-smokers to remain culture-positive at 2 months (RR 3.11 95%CI 1.09–8.89) and to default from treatment (RR 2.23, 95%CI 1.18–4.22). We also found a positive association between the index case smoking and sputum smear positivity and treatment delay, although the results lack statistical significance (Table 3). When we adjusted for sputum smear positivity, treatment delay and cavitary disease, we found that the effect of the index case smoking on the child contact was slightly reduced compared to the marginal effect, by 10% at baseline (RR 2.64 vs. 2.38), 11% by 6 months (RR 1.91 vs. 1.70), and 7.5% by 12 months (RR 1.48 vs. 1.37) (Table 3, A.5).

DISCUSSION

Here, we have shown that among children aged <16 years, household exposure to TB patients who smoke resulted in twice the risk of LTBI compared to those exposed to non-smoking patients. While some of this effect was mediated by a higher bacillary load and/or sputum smear positivity among smokers, the effect of smoking remained significant even after adjusting for these factors. We also showed that culture conversion or default during follow-up may also mediate the effect of index case smoking on TB transmission. Because we measured the index case smoking and SHS statuses of HHCs simultaneously, we were able to distinguish between the effect of any SHS exposure and smoking in the index case and to demonstrate the role of smoking on transmission that was independent from the role of smoke exposure on susceptibility to infection.

In previous work, Singh et al. reported an OR of 2.68 for LTBI among children exposed to household cigarette smoke in India, but did not differentiate between exposure to any household smoke and to a TB patient who smoked.[6] Den Boon et al. reported that passive smoke exposure increased the risk of LTBI in children aged <15 years in South Africa[7] who had a household TB contact, but not in those without such a contact. Du Preez et al. also studied the impact of environmental smoke exposure on LTBI in South Africa, finding that the presence of ⩾2 household smokers increased the OR by 2.6-fold.[5] In contrast to these reports, we did not find an increased risk of LTBI in children or adults exposed to any SHS.

Three previous studies evaluated the impact of the smoking status of an index patient on LTBI among contacts. In one of these, the association was reported to be statistically significant, although the magnitude of the effect was not given.[12] A second study reported an unadjusted OR of LTBI among contacts of smoking index cases of 1.63; however, the effect was not significant after multivariate adjustment.[13] The last study reported an OR of 1.5 among contacts of smoking compared to non-smoking TB patients, but did not adjust for the smoking status of other household members.[9] It is therefore not clear whether

Table 1 Multivariate analysis in child contacts for characteristics associated with TST positivity

	Baseline ($n = 1790$)			Combined baseline and 6-month follow-up ($n = 1485$)			Combined baseline, 6-, and 12-month follow-up ($n = 1361$)		
	n (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)	*n* (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)	*n* (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)
Characteristic of household environment									
Household smoke exposure									
No	1606 (90)	1.00 (referent)	1.00 (referent)	1322 (89)	1.00 (referent)	1.00 (referent)	1213 (89)	1.00 (referent)	1.00 (referent)
Yes	184 (10)	1.00 (0.71–1.41)	0.93 (0.66–1.32)	163 (11)	1.07 (0.85–1.36)	1.01 (0.80–1.28)	148 (11)	1.02 (0.84–1.26)	0.97 (0.79–1.19)
Characteristics of TB index case									
Smoking status									
Non-smoker	1745 (97)	1.00 (referent)	1.00 (referent)	1453 (98)	1.00 (referent)	1.00 (referent)	1328 (98)	1.00 (referent)	1.00 (referent)
Light	20 (1)	1.67 (0.51–5.42)	1.41 (0.41–4.87)	11 (1)	1.02 (0.35–2.93)	0.95 (0.32–2.83)	11 (1)	0.70 (0.23–2.14)	0.69 (0.23–2.10)
Moderate or heavy	25 (1)	2.64 (1.78–3.91)	2.38 (1.60–3.55)	21 (1)	1.91 (1.40–2.60)	1.70 (1.27–2.28)	22 (2)	1.48 (1.07–2.06)	1.37 (1.02–1.95)
Alcohol use									
Non-drinker	1037 (58)	1.00 (referent)	1.00 (referent)	871 (59)	1.00 (referent)	1.00 (referent)	818 (60)	1.00 (referent)	1.00 (referent)
Light	581 (32)	0.78 (0.62–0.99)	0.80 (0.63–1.00)	467 (31)	0.88 (0.74–1.05)	0.91 (0.77–1.08)	412 (30)	0.99 (0.85–1.15)	1.01 (0.87–1.17)
Heavy	172 (10)	1.36 (1.00–1.85)	1.35 (1.00–1.81)	147 (10)	1.20 (0.95–1.51)	1.19 (0.94–1.49)	131 (10)	1.25 (1.02–1.52)	1.24 (1.02–1.51)
Sputum smear status									
Negative	415 (23)	—	1.00 (referent)	336 (23)	—	1.00 (referent)	295 (22)	—	1.00 (referent)
+	494 (28)	—	1.33 (0.96–1.84)	416 (28)	—	1.44 (1.10–1.87)	384 (28)	—	1.15 (0.92–1.43)
++	328 (18)	—	1.83 (1.31–2.56)	271 (18)	—	1.79 (1.37–2.34)	258 (19)	—	1.44 (1.16–1.79)
+++	553 (31)	—	1.74 (1.26–2.39)	462 (31)	—	1.82 (1.42–2.34)	424 (31)	—	1.48 (1.21–1.81)
Treatment delay, days									
0	131 (7)	—	1.00 (referent)	111 (7)	—	1.00 (referent)	96 (7)	—	1.00 (referent)
1–14	123 (7)	—	2.05 (1.05–4.03)	117 (8)	—	1.39 (0.84–2.31)	101 (7)	—	1.08 (0.70–1.65)
15–28	604 (34)	—	1.51 (0.82–2.78)	484 (33)	—	1.24 (0.81–1.91)	436 (32)	—	1.12 (0.80–1.59)
>28	932 (52)	—	2.07 (1.15–3.74)	773 (52)	—	1.53 (1.01–2.33)	728 (53)	—	1.26 (0.90–1.76)
Cavitary disease									
No	1521 (85)	—	1.00 (referent)	1223 (82)	—	1.00 (referent)	1114 (82)	—	1.00 (referent)
Yes	269 (15)	—	1.07 (0.86–1.34)	262 (18)	—	1.22 (1.03–1.43)	247 (18)	—	1.12 (0.97–1.29)

* Model with age, BCG scars, relation to index case, and number of social contacts per day of children contacts, household SHS exposure, type of housing, density of household, index case age, index case sex, index case smoking status, and index case alcohol intake.
† Model with age, BCG scars, relation to index case, and number of social contacts per day of children contacts, household SHS exposure, type of housing, density of household, and all covariates of TB index case.
TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; SHS = secondhand smoke.

Table 2 Multivariate analysis in adult contacts for characteristics associated with TST positivity

Characteristic of household environment	Baseline ($n = 3049$)			Combined baseline and 6-month follow-up ($n = 2587$)			Combined baseline, 6-, and 12-month follow-up ($n = 2482$)		
	n (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)	*n* (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)	*n* (%)	Final model* RR (95%CI)	Direct model† RR (95%CI)
Characteristic of household environment									
Household smoke exposure									
No	2659 (87)	1.00 (referent)	1.00 (referent)	2256 (87)	1.00 (referent)	1.00 (referent)	2164 (87)	1.00 (referent)	1.00 (referent)
Yes	390 (13)	1.10 (0.98–1.24)	1.08 (0.96–1.23)	331 (13)	1.05 (0.96–1.14)	1.04 (0.96–1.13)	318 (13)	1.04 (0.98–1.11)	1.03 (0.97–1.10)
Characteristics of TB index case									
Smoking status									
Non-smoker	2974 (98)	1.00 (referent)	1.00 (referent)	2525 (98)	1.00 (referent)	1.00 (referent)	2420 (98)	1.00 (referent)	1.00 (referent)
Light	29 (1)	0.93 (0.61–1.41)	0.90 (0.60–1.37)	21 (1)	0.84 (0.61–1.17)	0.84 (0.63–1.13)	22 (1)	0.91 (0.73–1.13)	0.90 (0.73–1.12)
Moderate or heavy	46 (2)	1.35 (1.04–1.75)	1.32 (1.02–1.71)	41 (2)	1.08 (0.92–1.28)	1.07 (0.92–1.26)	40 (2)	1.00 (0.86–1.16)	1.00 (0.85–1.15)
Alcohol use									
Non-drinker	1754 (58)	1.00 (referent)	1.00 (referent)	1512 (58)	1.00 (referent)	1.00 (referent)	1441 (58)	1.00 (referent)	1.00 (referent)
Light	961 (32)	0.96 (0.86–1.06)	0.95 (0.86–1.05)	823 (32)	0.99 (0.93–1.06)	0.99 (0.93–1.06)	792 (32)	1.01 (0.96–1.06)	1.01 (0.96–1.06)
Heavy	285 (10)	1.16 (1.01–1.34)	1.18 (1.02–1.35)	252 (10)	1.08 (0.99–1.18)	1.08 (0.99–1.18)	249 (10)	1.05 (0.97–1.12)	1.05 (0.98–1.13)
Sputum smear status									
Negative	712 (23)	—	1.00 (referent)	592 (23)	—	1.00 (referent)	564 (23)	—	1.00 (referent)
+	944 (31)	—	1.12 (0.99–1.27)	803 (31)	—	1.11 (1.02–1.21)	774 (31)	—	1.05 (0.98–1.11)
++	501 (16)	—	1.24 (1.08–1.44)	439 (17)	—	1.18 (1.08–1.30)	434 (17)	—	1.10 (1.03–1.18)
+++	892 (29)	—	1.16 (1.01–1.32)	753 (29)	—	1.12 (1.03–1.22)	710 (29)	—	1.10 (1.03–1.17)
Treatment delay, days									
0	315 (10)	—	1.00 (referent)	261 (10)	—	1.00 (referent)	245 (10)	—	1.00 (referent)
1–14	211 (7)	—	1.06 (0.83–1.34)	180 (7)	—	1.07 (0.92–1.25)	170 (7)	—	0.99 (0.87–1.12)
15–28	878 (29)	—	1.10 (0.90–1.34)	731 (28)	—	1.02 (0.91–1.15)	703 (28)	—	1.01 (0.93–1.10)
>28	1645 (54)	—	1.16 (0.96–1.40)	1415 (55)	—	1.03 (0.93–1.15)	1364 (55)	—	1.02 (0.94–1.10)
Cavitary disease									
No	2534 (83)	—	1.00 (referent)	2067 (80)	—	1.00 (referent)	1987 (80)	—	1.00 (referent)
Yes	515 (17)	—	0.96 (0.86–1.07)	520 (20)	—	0.96 (0.90–1.03)	504 (20)	—	0.97 (0.92–1.02)

* Model with age, BCG scars, relation to index case, smoking status, and alcohol intake of adult contacts, household SHS exposure, type of housing, density of household, index case sex, index case smoking status, and index case alcohol intake.
† Model with age, BCG scars, relation to index case, smoking status, and alcohol intake of adult contacts, household SHS exposure, type of housing, density of household, and all covariates of TB index case.
TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; SHS = secondhand smoke.

Table 3 Association between index case smoking status and potential mediators

			RR (95%CI)
Smear status at baseline			
	Negative	Positive	
Non-smoker	512	1514	1.40 (0.72–2.71)
Smoker	11	46	
Duration of coughing before diagnosis			
	⩽14 days	>15 days	
Non-smoker	341	1658	1.69 (0.73–3.95)
Smoker	6	50	
Presence of cavitary disease			
	No	Yes	
Non-smoker	1589	406	0.95 (0.41–2.16)
Smoker	29	7	
Culture conversion at month 2			
	Negative	Positive	
Non-smoker	1758	81	3.11 (1.09–8.89)
Smoker	46	4	
Complete treatment			
	Yes	Default	
Non-smoker	1816	210	2.23 (1.18–4.22)
Smoker	45	12	

Note: sample size varies according to different missing values across covariates. RR = risk ratio; CI = confidence interval

the effect was due to an increase in the index case's infectiousness or to increased susceptibility among the contacts exposed to SHS.

Four possible mechanisms may explain the increased infectiousness of a TB patient who smokes. First, smokers cough far more frequently than non-smokers, with healthy smokers coughing on average 5.3 times an hour compared to 0.7 times for non-smokers.[14] Loudon reported that cough frequency predicted household TB transmission.[15] Second, chronic coughers may also be slow to recognize symptoms of respiratory infection and thus to seek care, thereby possibly exposing their contacts to infection for a longer period of time.[16,17] Third, smoking index cases may be more likely to remain culture-positive at 2 months and to continue to transmit TB after diagnosis. Although this mechanism would not be expected to have an impact on baseline LTBI in our study, it may help explain the continued increased risk of LTBI over the subsequent 6 or 12 months. Fourth, cigarette smoke may alter the local immune response of the lung in TB patients, promoting increased growth of the bacilli and/or the destruction of lung tissue.[18]

Shang et al. reported an increase in bacillary load in the lung and in the number and size of lung infiltrates in *Mycobacterium tuberculosis* infected mice exposed to smoke.[19] Tissue damage resulting from TB is believed to be due, in part, to the expression of host metalloproteinases (MMPs), which can break down the extracellular matrix of the lung.[20,21] The MMP 1 promoter is a direct target of cigarette smoke in lung epithelial cells.[22,23] In one recent study, MMP expression correlated with TB-induced lung tissue damage, implicating disregulated protease activity in this pathology.[24] Although our epidemiological data do not provide evidence in support of an association between smoking status and cavitary disease, these pathological and molecular biological data raise the possibility that smoke exposure further exacerbates the breakdown in pulmonary extracellular matrix induced by TB, leading to the destructive lesions most likely to be associated with productive cough and aerosol-mediated bacillary spread.

We found that the effect of index case smoking on LTBI in adult contacts is much smaller than in child contacts. One possible explanation for this is that there is more non-differential misclassification of infection in adults than in children. Of note, among community controls, 41.9% of adults were TST-positive at baseline in contrast to 14.6% of the children. This result suggests that more adults than children may have been infected before exposure to the index case; the impact of index-case-specific factors will therefore be lower in this group.

Our research has several limitations. First, we cannot rule out the possibility that smokers represent a unique population and that there might be other uncontrolled factors that explain the elevated risk of LTBI in HCCs. Second, in our study cohort, average cigarette consumption among smokers was 3.97 cigarettes per day, much lower than the numbers reported in two previous studies that investigated the relationship between SHS and risk of LTBI in South Africa.[5,7,25] If the impact of smoking on infectiousness were dose-dependent, we would expect smoking index patients to have an even greater impact on household transmission of TB in settings where it is common for smokers to smoke more than in Lima. Third, we collected self-reported smoking status at the time when the case was diagnosed. One previous study found that a significant proportion of TB patients quit smoking before TB diagnosis as their symptoms worsen,[26] while others have noted that self-reported smoking can underestimate actual exposure. Both of these two factors may lead to non-differential misclassification of exposure and bias our results toward null effect.

CONCLUSION

Our study demonstrates that smoking among index TB patients may facilitate the spread of infection. Given that close contacts of TB index cases are at high risk of infection, both index cases and their close contacts should be advised to quit smoking. A recent cluster randomized controlled trial in Pakistan showed that behavioral support alone or in combination with bupropion is effective in achieving smoking abstinence in TB suspects.[27] Targeted interventions for smoking cessation in populations

with a high TB burden may therefore play an important role in TB control.

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References

1 Chiang C Y, Slama K, Enarson D A. Associations between tobacco and tuberculosis. Int J Tuberc Lung Dis 2007; 11: 258–262.
2 Lin H H, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLOS MED 2007; 4: e20.
3 Patra S, Sharma S, Behera D. Passive smoking, indoor air pollution and childhood tuberculosis: a case control study. Indian J Tuberc 2012; 59: 151–155.
4 Ramachandran R, Indu P S, Anish T S, Nair S, Lawrence T, Rajasi R S. Determinants of childhood tuberculosis—a case control study among children registered under revised National Tuberculosis Control Programme in a district of South India. Indian J Tuberc 2011; 58: 204–207.
5 du Preez K, Mandalakas A M, Kirchner H L, et al. Environmental tobacco smoke exposure increases *Mycobacterium tuberculosis* infection risk in children. Int J Tuberc Lung Dis 2011; 15: 1490–1496.
6 Singh M, Mynak M L, Kumar L, Mathew J L, Jindal S K. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. Arch Dis Child 2005; 90: 624–628.
7 den Boon S, Verver S, Marais B J, et al. Association between passive smoking and infection with *Mycobacterium tuberculosis* in children. Pediatrics 2007; 119: 734–739.
8 Janson C. The effect of passive smoking on respiratory health in children and adults. Int J Tuberc Lung Dis 2004; 8: 510–516.
9 Godoy P, Calya J A, Carmona G, et al. Smoking in tuberculosis patients increases the risk of infection in their contacts. Int J Tuberc Lung Dis 2013; 17: 771–776.
10 Ministerio de la Salud. Plan Estratégico Multisectorial de la Respuesta Nacional a la Tuberculosis en el Perú, 2009–2018. Lima, peru: MINSA, 2009. ftp://ftp2.minsa.gob.pe/descargas/dgsp/ESN-tuberculosis/Material de Difusion/Notas de Prensa/PEM_TB_06marzo_2009.pdf. Accessed August 2014.
11 Centers for Disease Control and Prevention. TB in children in the United States. Atlanta, GA, USA: CDC, 2012. http://www.cdc.gov/tb/topic/populations/TBinChildren/default.htm Accessed August 2014.
12 Gerald L B, Tang S, Bruce F, et al. A decision tree for tuberculosis contact investigation. Am J Respir Crit Care Med 2002; 166: 1122–1127.
13 Aissa K, Madhi F, Ronsin N, et al. Evaluation of a model for efficient screening of tuberculosis contact subjects. Am J Respir Crit Care Med 2008; 177: 1041–1047.
14 Sumner H, Woodcock A, Kolsum U, et al. Predictors of objective cough frequency in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013; 187: 943–949.
15 Loudon R G. Smoking and cough frequency. Am Rev Respir Dis 1976; 114: 1033–1036.
16 Bam T S, Enarson D A, Hinderaker S G, Bam D S. Longer delay in accessing treatment among current smokers with new sputum smear-positive tuberculosis in Nepal. Int J Tuberc Lung Dis 2012; 16: 822–827.
17 Storla D G, Yimer S, Bjune G A. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 2008; 8: 15.
18 Stämpfli M R, Anderson G P. How cigarette smoke skews immune responses to promote infection, lung disease and cancer. Nat Rev Immunol 2009; 9: 377–384.
19 Shang S, Ordway D, Henao-Tamayo M, et al. Cigarette smoke increases susceptibility to tuberculosis—evidence from in vivo and in vitro models. J Infect Dis 2011; 203: 1240–1248.
20 Elkington P T, Ugarte-Gil C A, Friedland J S. Matrix metalloproteinases in tuberculosis. Eur Respir J 2011; 38: 456–464.
21 Sheen P, O'Kane C M, Chaudhary K, et al. High MMP-9 activity characterises pleural tuberculosis correlating with granuloma formation. Eur Respir J 2009; 33: 134–141.
22 Elkington P T, Friedland J S. Matrix metalloproteinases in destructive pulmonary pathology. Thorax 2006; 61: 259–266.
23 Mercer B, Brinckerhoff C, D'Armiento J. Activation of the MMP-1 promoter by cigarette smoke in human small airway epithelial cells requires ERK MAP kinase signaling: differential response of the 1G and 2G promoter sequences. Proc Am Thorac Soc 2006; 3: 477.
24 Elkington P, Shiomi T, Breen R, et al. MMP-1 drives immunopathology in human tuberculosis and transgenic mice. J Clin Invest 2011; 121: 1827–1833.
25 van Walbeek C. Recent trends in smoking prevalence in South Africa—some evidence from AMPS data. S Afr Med J 2002; 92: 468–472.
26 Lam C, Martinson N, Hepp L, et al. Prevalence of tobacco smoking in adults with tuberculosis in South Africa. Int J Tuberc Lung Dis 2013; 17: 1354–1357.
27 Siddiqi K, Khan A, Ahmad M, et al. Action to stop smoking in suspected tuberculosis (ASSIST) in Pakistan: a cluster randomized, controlled trial. Ann Intern Med 2013; 158: 667–675.

APPENDIX

ADDITIONAL ONLINE METHODS

Data collection

We collected the following data from index cases at the time of diagnosis: age, sex, smoking status, alcohol intake, time from onset of cough to diagnosis, sputum smear and culture status, and the presence of cavitary disease on chest radiography. Directly observed therapy was initiated at the time of diagnosis and smear and culture were repeated after 2 months of anti-tuberculosis treatment. We collected the following data for exposed household contacts: age, sex, height, weight, self-reported bacille Calmette-Guérin (BCG) vaccine exposure, number of BCG vaccination scars, relation to index case, use of public transportation, and frequency of social and physical contacts. We also collected smoking status, alcohol intake and occupation for adult contacts. For each household, we assessed the number of individuals per room, the type of housing, and presence of household tobacco smoke.

Data categorization

As it was common for smokers in this setting to smoke only a single cigarette per day, we categorized participants as non-smokers, light smokers (1 cigarette/day), and moderate or heavy smokers (>1 cigarette/day). We also categorized participants as non-drinkers, light drinkers (<40 g or 3 alcoholic drinks/day), and heavy drinkers ($\geqslant 40$ g or 3 drinks/day).[1] We categorized sputum smear status as negative (0–10 acid-fast bacilli [AFB]/100 fields), + (10–99 AFB/100 fields), ++ (1–5 AFB/50 fields), and +++ (>1 AFB/10 fields). The time to treatment for index cases was measured as the number of days of reported cough before to tuberculosis (TB) diagnosis. Nutritional status was based on World Health Organization body mass index *Z*-score tables, where those with a *Z*-score $\leqslant 2$ were considered underweight, and those with a *Z*-score >2 overweight.[2] We assessed the frequency of social and physical contact by asking participants to enumerate the number of persons with whom they had conversations lasting more than 5 min and with whom they had any physical contact on the previous day, respectively. We classified adult contacts as having frequent occupational contact if they were bus drivers or fare collectors, street vendors, waitpersons, or worked at a prison.

Data analysis

Risk of tuberculous infection of household contacts

To account for clustered data from participants in the same household, we used a modified Poisson generalized estimating equation to evaluate the association between covariates and tuberculous infection on a risk ratio scale. We specified an exchangeable correlation structure for observations within the same household, and used empirical standard error estimates to obtain robust statistical inference.[3] We examined the associations of each measured potential predictor of tuberculous infection of child contacts in an age-adjusted analysis using both baseline tuberculin skin test (TST) status and infection at 6 months and 12 months as outcomes. We then constructed a multivariable regression including characteristics that we expected would modify the risk of tuberculous infection; these included sex, smoking status, and alcohol use of the index case, household cigarette smoke exposure, and density of the household. We also included child contact (age $\leqslant 15$ years) characteristics that may modify secondhand smoke exposure: relation to index case, frequency of public transportation use, number of social contacts per day, and number of physical contacts per day if they had $P \leqslant 0.1$ in the initial age-adjusted model and $P < 0.1$ in the multivariate model. To reduce the effect of false-positive TSTs induced by BCG vaccination, we also included the number of self-reported BCG scars in the multivariate model. As we considered that sputum smear status, duration of symptoms, and presence of cavitary disease might mediate the effect of the index case's smoking on the child contact's tuberculous infection, we did not include these variables in the final adjusted model. Because we were also interested in measuring the magnitude of the direct effect of index-case smoking that is not mediated by these factors, we performed a regression analysis including mediators under the assumption that upon adjusting for observed covariates, no unobserved confounding remained for the joint effects of index-case smoking and the three mediators on child contacts' tuberculous infection. We also assumed that index case smoking did not confound the relationship between these mediators and the child contacts' tuberculous infection status. We conducted a separate analysis for contacts aged >15 years.

References

1 Rehm J, Samokhvalov A V, Neuman M G, et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. BMC Public Health 2009; 9: 450.

2 World Health Organization. Child growth standards. Geneva, Switzerland: WHO, 2014. http://www.who.int/childgrowth/standards/bmi_for_age/en/index.html. Accessed August 2014.

3 Zeger S L, Liang K Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986; 42: 121–130.

Table A.1 Baseline characteristics of household contacts stratified by index case smoking status

Variables	Persons, *n* (%)			
	Non-smoker (*n* = 5788, 97.42%)	Light smoker (*n* = 76, 1.28%)	Moderate or heavy smoker (*n* = 77, 1.29%)	Total (*n* = 5941)
Characteristics of household contacts				
Sex				
Female	3203 (55)	32 (42)	42 (55)	3277 (55)
Male	2585 (45)	44 (58)	35 (45)	2664 (45)
Age, years				
0–15	2150 (37)	27 (36)	27 (35)	2204 (37)
16–30	1545 (27)	29 (38)	20 (26)	1594 (27)
31–45	942 (16)	10 (13)	9 (12)	961 (16)
46–60	734 (13)	7 (9)	10 (13)	751 (13)
>60	417 (7)	3 (4)	11 (14)	431 (7)
BCG vaccination				
No	188 (3)	4 (5)	2 (3)	194 (3)
Yes	5238 (90)	71 (93)	72 (94)	5381 (91)
Missing	362 (6)	1 (1)	3 (4)	366 (6)
BCG scars				
0	821 (14)	11 (14)	11 (14)	843 (14)
1	3766 (65)	44 (58)	52 (68)	3862 (65)
2	952 (16)	20 (26)	12 (16)	984 (17)
⩾3	249 (4)	1 (1)	2 (3)	252 (4)
Smoking status				
Non-smoker	5392 (93)	64 (84)	74 (96)	5530 (93)
Light	192 (3)	5 (7)	3 (4)	200 (3)
Moderate or heavy	164 (3)	6 (8)	0 (0)	170 (3)
Missing	40 (1)	1 (1)	0 (0)	41 (1)
Diabetes mellitus				
No	5644 (98)	76 (100)	75 (97)	5795 (98)
Yes	100 (2)	0 (0)	2 (3)	102 (2)
Missing	44 (1)	0 (0)	0 (0)	44 (1)
Drinking				
Non-drinker	4280 (74)	49 (64)	55 (71)	4384 (74)
Light	1134 (20)	19 (25)	16 (21)	1169 (20)
Heavy	275 (5)	5 (7)	5 (6)	285 (5)
Missing	99 (2)	3 (4)	1 (1)	103 (2)
Relation to TB case				
Child	1106 (19)	12 (16)	12 (16)	1130 (19)
Parent	814 (14)	10 (13)	15 (19)	839 (14)
Sibling	1160 (20)	18 (24)	14 (18)	1192 (20)
Spouse	447 (8)	3 (4)	7 (9)	457 (8)
Other relationship*	2131 (37)	19 (25)	27 (35)	2177 (37)
Missing	130 (2)	14 (18)	2 (3)	146 (2)
Nutritional status†				
Normal weight	5184 (90)	69 (91)	67 (87)	5320 (90)
Underweight	74 (1)	1 (1)	2 (3)	77 (1)
Overweight	530 (9)	6 (8)	8 (10)	544 (9)
History of incarceration				
No	5632 (97)	69 (91)	77 (100)	5778 (97)
Yes	37 (1)	7 (9)	0 (0)	44 (1)
Missing	119 (2)	0 (0)	0 (0)	119 (2)
Frequency of public transportation use, days/week				
Never	1571 (27)	33 (43)	17 (22)	1621 (27)
1–3	1844 (32)	22 (29)	27 (35)	1893 (32)
4–7	2254 (39)	20 (26)	33 (43)	2307 (39)
Missing	119 (2)	1 (1)	0 (0)	120 (2)
Number of social contacts per day				
0	298 (5)	7 (9)	7 (9)	312 (5)
1–7	4062 (70)	51 (67)	51 (66)	4164 (70)
⩾8	1304 (23)	18 (24)	19 (25)	1341 (23)
Missing	124 (2)	0 (0)	0 (0)	124 (2)
Number of physical contacts per day				
0	694 (12)	7 (9)	9 (12)	710 (12)
1–7	4323 (75)	55 (72)	59 (77)	4437 (75)
⩾8	652 (11)	12 (16)	9 (12)	673 (11)
Missing	119 (2)	2 (3)	0 (0)	121 (2)

Table A.1 (continued)

Variables	Persons, *n* (%)			
	Non-smoker (*n* = 5788, 97.42%)	Light smoker (*n* = 76, 1.28%)	Moderate or heavy smoker (*n* = 77, 1.29%)	Total (*n* = 5941)
Job with frequent social contact				
No	3064 (53)	41 (54)	39 (51)	3144 (53)
Yes	2723 (47)	35 (46)	38 (49)	2796 (47)
Missing	1 (0)	0 (0)	0 (0)	1 (0)
Student				
No	3866 (67)	54 (71)	54 (70)	3974 (67)
Yes	1919 (33)	22 (29)	23 (30)	1964 (33)
Missing	3 (0)	0 (0)	0 (0)	3 (0)
Characteristics of household environment				
Household smoke exposure				
No	5088 (88)	56 (74)	52 (68)	5196 (87)
Yes	687 (12)	18 (24)	25 (32)	730 (12)
Missing	13 (0)	2 (3)	0 (0)	15 (0)
Type of housing				
House	4234 (73)	59 (78)	52 (68)	4345 (73)
Apartment	959 (17)	11 (14)	14 (18)	984 (17)
Substandard housing	552 (10)	6 (8)	11 (14)	569 (10)
Missing	43 (1)	0 (0)	0 (0)	43 (1)
Density, median, persons/room	2.67	2.29	4	2.67
Characteristics of TB index case				
Sex				
Male	2447 (42)	16 (21)	13 (17)	2476 (42)
Female	3341 (58)	60 (79)	64 (83)	3465 (58)
Age, years				
15–30	3442 (59)	57 (75)	30 (39)	3529 (59)
31–45	1098 (19)	1 (1)	45 (58)	1144 (19)
46–60	587 (10)	16 (21)	2 (3)	605 (10)
>60	661 (11)	2 (3)	0 (0)	663 (11)
Drinking				
Non-drinker	3259 (56)	3 (4)	15 (19)	3277 (55)
Light	1771 (31)	49 (64)	48 (62)	1868 (31)
Heavy	541 (9)	15 (20)	14 (18)	570 (10)
Missing	217 (4)	9 (12)	0 (0)	226 (4)
Sputum smear status				
Negative	1347 (23)	15 (20)	6 (8)	1368 (23)
+	1692 (29)	22 (29)	29 (38)	1743 (29)
++	980 (17)	16 (21)	6 (8)	1002 (17)
+++	1769 (31)	23 (30)	36 (47)	1828 (31)
Treatment delay, days				
0	545 (9)	10 (13)	2 (3)	557 (9)
1–14	408 (7)	0 (0)	0 (0)	408 (7)
15–28	1718 (30)	17 (22)	21 (27)	1756 (30)
>28	3053 (53)	49 (64)	52 (68)	3154 (53)
Missing	64 (1)	0 (0)	2 (3)	66 (1)
Cavitary disease				
No	4588 (80)	75 (99)	58 (75)	4721 (79)
Yes	1117 (19)	1 (1)	17 (22)	1135 (20)
Missing	83 (1)	0 (0)	2 (3)	85 (1)

* Includes relative other than child, parents, sibling, spouse and non-relative.
† Defined by body mass index *Z*-score from World Health Organization; *Z*-score <2 was defined as underweight; >2 was defined as overweight.
BCG = bacille Calmette-Guérin; TB = tuberculosis.

Table A.2 Sample size and prevalence of TST positivity among child and adult contacts at baseline, 6-month, and 12-month follow-up

	Sample size, *n*		Prevalence of TST positivity, %	
	Child contacts	Adult contacts	Child contacts	Adult contacts
Baseline	2054	3523	27.89	53.84
6-month follow-up	1692	2977	37.82	70.10
12-month follow-up	1543	2865	47.76	79.37

TST = tuberculin skin test.

Table A.3 Age-adjusted univariate analysis in child contacts aged ⩽15 years for characteristics associated with TST positivity

	Baseline ($n = 2054$)*		Combined baseline and 6-month follow-up ($n = 1692$)*		Combined baseline, 6-, and 12-month follow-up ($n = 1543$)*	
Variables	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)
Characteristic of household contacts						
Sex						
Female	1005 (49)	1.00 (referent)	836 (49)	1.00 (referent)	762 (49)	1.00 (referent)
Male	1049 (51)	0.97 (0.84–1.11)	856 (51)	0.98 (0.88–1.09)	781 (51)	0.99 (0.91–1.08)
BCG vaccination†						
No	57 (3)	1.00 (referent)	44 (3)	1.00 (referent)	41 (3)	1.00 (referent)
Yes	1952 (97)	0.96 (0.62–1.48)	1617 (97)	0.94 (0.68–1.30)	1474 (97)	1.05 (0.78–1.39)
BCG scars‡						
0	387 (19)	1.01 (0.84–1.22)	319 (19)	0.96 (0.82–1.11)	295 (19)	0.87 (0.76–1.00)
1	1618 (79)	1.02 (0.84–1.23)	1328 (78)	1.00 (referent)	1203 (78)	1.00 (referent)
2	47 (2)	1.13 (0.75–1.70)	43 (3)	1.24 (0.94–1.64)	43 (3)	1.06 (0.82–1.36)
Relation to index						
Child	689 (35)	1.78 (1.41–2.25)	569 (35)	1.70 (1.43–2.03)	531 (36)	1.59 (1.38–1.85)
Sibling	371 (19)	1.32 (1.01–1.73)	315 (19)	1.23 (1.00–1.51)	287 (19)	1.11 (0.93–1.32)
Other relationship§	929 (47)	1.00 (referent)	750 (46)	1.00 (referent)	676 (45)	1.00 (referent)
Nutritional status¶						
Normal	1499 (73)	1.00 (referent)	1233 (73)	1.00 (referent)	1122 (73)	1.00 (referent)
Underweight	62 (3)	0.99 (0.64–1.55)	53 (3)	0.84 (0.59–1.22)	44 (3)	0.89 (0.66–1.20)
Overweight	493 (24)	1.32 (1.12–1.55)	406 (24)	1.10 (0.97–1.25)	377 (24)	1.08 (0.97–1.20)
Frequency of public transportation use (days/week)						
0	853 (42)	1.00 (referent)	696 (42)	1.00 (referent)	646 (42)	1.00 (referent)
1–3	677 (34)	1.02 (0.85–1.23)	550 (33)	1.03 (0.90–1.18)	498 (33)	1.08 (0.96–1.21)
4–7	487 (24)	1.04 (0.85–1.27)	417 (25)	1.04 (0.89–1.21)	377 (25)	1.08 (0.94–1.23)
Number of social contacts (times/day)						
0	170 (8)	1.00 (referent)	136 (8)	1.00 (referent)	120 (8)	1.00 (referent)
⩾1	1840 (92)	1.48 (1.01–2.17)	1520 (92)	1.29 (0.97–1.72)	1395 (92)	1.09 (0.87–1.35)
Number of physical contacts (times/day)						
0	158 (8)	1.00 (referent)	131 (8)	1.00 (referent)	119 (8)	1.00 (referent)
1–7	1625 (81)	0.87 (0.68–1.12)	1342 (81)	0.94 (0.78–1.14)	1228 (81)	0.97 (0.82–1.15)
⩾8	234 (12)	0.81 (0.59–1.11)	190 (11)	0.90 (0.71–1.14)	174 (11)	0.89 (0.73–1.10)
Student						
No	696 (34)	1.00 (referent)	547 (32)	1.00 (referent)	493 (32)	1.00 (referent)
Yes	1356 (66)	0.94 (0.76–1.16)	1144 (68)	0.94 (0.81–1.09)	1049 (68)	0.93 (0.82–1.05)
Characteristic of household environment						
Household smoke exposure						
No	1837 (90)	1.00 (referent)	1504 (89)	1.00 (referent)	1372 (89)	1.00 (referent)
Yes	209 (10)	1.09 (0.81–1.46)	181 (11)	1.05 (0.85–1.31)	164 (11)	1.04 (0.88–1.24)
Type of housing						
House	1515 (74)	1.00 (referent)	1269 (75)	1.00 (referent)	1157 (75)	1.00 (referent)
Apartment	330 (16)	1.11 (0.86–1.42)	258 (15)	1.22 (1.02–1.46)	244 (16)	1.18 (1.01–1.37)
Substandard housing	199 (10)	1.34 (1.01–1.79)	156 (9)	1.09 (0.86–1.39)	134 (9)	1.30 (1.08–1.56)
Density, persons/room						
Continuous	—	1.01 (0.97–1.05)	—	1.01 (0.98–1.04)	—	1.00 (0.98–1.03)
Characteristics of TB index case						
Sex						
Female	959 (47)	1.00 (referent)	817 (48)	1.00 (referent)	751 (49)	1.00 (referent)
Male	1095 (53)	0.80 (0.66–0.96)	875 (52)	0.93 (0.81–1.08)	792 (51)	0.94 (0.83–1.07)
Smoking status						
Non-smoker	1973 (97)	1.00 (referent)	1641 (98)	1.00 (referent)	1491 (97)	1.00 (referent)
Light	27 (1)	1.45 (0.57–3.64)	16 (1)	1.41 (0.75–2.67)	16 (1)	1.05 (0.54–2.03)
Moderate or heavy	27 (1)	2.00 (1.32–3.01)	22 (1)	1.82 (1.38–2.39)	23 (2)	1.47 (1.11–1.95)
Alcohol use						
Non-drinker	1125 (57)	1.00 (referent)	932 (57)	1.00 (referent)	872 (59)	1.00 (referent)
Light	649 (33)	0.82 (0.65–1.02)	524 (32)	0.92 (0.78–1.09)	461 (31)	1.00 (0.86–1.15)
Heavy	200 (10)	1.35 (1.01–1.81)	172 (11)	1.22 (0.97–1.52)	150 (10)	1.25 (1.04–1.51)
Sputum smear status						
Negative	463 (23)	1.00 (referent)	364 (22)	1.00 (referent)	317 (21)	1.00 (referent)
+	574 (28)	1.55 (1.11–2.15)	486 (29)	1.52 (1.18–1.97)	442 (29)	1.25 (1.01–1.54)
++	368 (18)	2.03 (1.45–2.83)	301 (18)	1.87 (1.44–2.43)	287 (19)	1.48 (1.20–1.84)
+++	649 (32)	2.06 (1.51–2.82)	541 (32)	2.03 (1.60–2.58)	497 (32)	1.63 (1.34–1.98)

Table A.3 (continued)

	Baseline ($n = 2054$)*		Combined baseline and 6-month follow-up ($n = 1692$)*		Combined baseline, 6-, and 12-month follow-up ($n = 1543$)*	
Variables	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)
Treatment delay, days						
0	153 (8)	1.00 (referent)	126 (8)	1.00 (referent)	105 (7)	1.00 (referent)
1–14	135 (7)	2.42 (1.22–4.80)	128 (8)	1.78 (1.07–2.95)	111 (7)	1.19 (0.78–1.83)
15–28	675 (33)	1.97 (1.07–3.63)	530 (32)	1.82 (1.18–2.80)	476 (31)	1.36 (0.96–1.94)
>28	1069 (53)	2.93 (1.62–5.32)	895 (53)	2.24 (1.46–3.42)	840 (55)	1.55 (1.10–2.18)
Cavitary disease						
No	1641 (81)	1.00 (referent)	1368 (78)	1.00 (referent)	1245 (82)	1.00 (referent)
Yes	382 (19)	1.24 (0.99–1.54)	300 (22)	1.31 (1.11–1.54)	277 (18)	1.23 (1.07–1.41)

* Sample size varies according to different missing values across covariates.
† Two children with number of scars = 3 were excluded.
‡ One child with spouse relation with the index case was removed.
§ Includes relatives other than child, parent, sibling, and spouse and non-relative.
¶ Defined by body mass index *Z*-score from World Health Organization; *Z*-score <2 was defined as underweight; >2 was defined as overweight.
RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; TB = tuberculosis.

Table A.4 Age-adjusted univariate analysis in adult contacts aged >15 years for characteristics associated with TST positivity

	Baseline (n = 3523)*		Combined baseline and 6-month follow-up (n = 2977)*		Combined baseline, 6-, and 12-month follow-up (n = 2865)*	
Variables	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)
Characteristic of household contacts						
Sex						
Female	2086 (59)	1.00 (referent)	1800 (60)	1.00 (referent)	1748 (61)	1.00 (referent)
Male	1437 (41)	0.98 (0.91–1.05)	1177 (40)	1.04 (0.99–1.08)	1117 (39)	1.06 (1.02–1.10)
BCG vaccination						
No	122 (4)	1.00 (referent)	106 (4)	1.00 (referent)	101 (4)	1.00 (referent)
Yes	3107(96)	1.06 (0.86–1.29)	2631 (96)	1.12 (0.97–1.29)	2528 (96)	1.09 (0.95–1.25)
BCG scars						
0	395 (11)	0.91 (0.80–1.04)	327 (11)	0.89 (0.82–0.98)	314 (11)	0.91 (0.84–0.98)
1	2021 (57)	1.00 (referent)	1698 (57)	1.00 (referent)	1622 (57)	1.00 (referent)
2	870 (25)	1.08 (1.00–1.18)	745 (25)	1.06 (1.01–1.12)	722 (25)	1.08 (1.03–1.12)
⩾3	237 (7)	1.22 (1.08–1.38)	207 (7)	1.10 (1.02–1.19)	207 (7)	1.07 (1.01–1.14)
Diabetes mellitus						
No	3387 (97)	1.00 (referent)	2862 (97)	1.00 (referent)	2748 (97)	1.00 (referent)
Yes	99 (3)	1.05 (0.87–1.26)	83 (3)	1.04 (0.91–1.19)	85 (3)	0.96 (0.85–1.08)
Smoking status						
Non-smoker	3145 (90)	1.00 (referent)	2666 (90)	1.00 (referent)	2566 (91)	1.00 (referent)
Light	187 (5)	1.24 (1.08–1.42)	159 (5)	1.10 (1.01–1.19)	153 (5)	1.07 (1.00–1.14)
Moderate or heavy	153 (4)	1.10 (0.95–1.27)	122 (4)	1.08 (0.99–1.17)	116 (4)	1.08 (1.00–1.16)
Drinking						
Non-drinker	2086 (61)	1.00 (referent)	1790 (62)	1.00 (referent)	1718 (62)	1.00 (referent)
Light	1075 (31)	1.04 (0.96–1.12)	890 (31)	1.06 (1.00–1.11)	858 (31)	1.04 (1.00–1.09)
Heavy	271 (8)	1.11 (0.97–1.27)	221 (8)	1.10 (1.01–1.19)	213 (8)	1.10 (1.02–1.18)
Relation to index						
Child	364 (11)	1.19 (1.02–1.39)	312 (11)	1.07 (0.96–1.18)	311 (11)	1.02 (0.94–1.11)
Parent	787 (23)	1.15 (1.01–1.30)	699 (24)	1.05 (0.98–1.13)	682 (24)	1.04 (0.98–1.10)
Sibling	776 (22)	1.11 (0.98–1.25)	649 (22)	1.00 (0.93–1.08)	621 (22)	1.01 (0.95–1.07)
Spouse	419 (12)	1.33 (1.18–1.50)	366 (13)	1.14 (1.06–1.23)	355 (13)	1.11 (1.05–1.18)
Other relationship†	1105 (32)	1.00 (referent)	888 (30)	1.00 (referent)	838 (30)	1.00 (referent)
Nutritional status‡						
Normal	3489 (99)	1.00 (referent)	2950 (99)	1.00 (referent)	2837 (99)	1.00 (referent)
Underweight	9 (0)	1.25 (0.85–1.83)	7 (0)	1.10 (0.86–1.41)	7 (0)	1.20 (1.08–1.34)
Overweight	25 (1)	0.78 (0.45–1.34)	20 (1)	0.90 (0.64–1.26)	21 (1)	0.90 (0.67–1.21)
History of incarceration						
No	3424 (99)	1.00 (referent)	2899 (99)	1.00 (referent)	2786 (99)	1.00 (referent)
Yes	38 (1)	1.27 (0.98–1.65)	32 (1)	1.17 (1.03–1.32)	31 (1)	1.11 (0.98–1.26)
Frequency of public transportation use, days/week						
0	668 (19)	1.00 (referent)	546 (19)	1.00 (referent)	524 (19)	1.00 (referent)
1–3	1104 (32)	0.98 (0.88–1.08)	938 (32)	0.97 (0.90–1.04)	907 (32)	0.95 (0.89–1.00)
4–7	1690 (49)	0.95 (0.87–1.05)	1445 (49)	0.95 (0.89–1.01)	1385 (49)	0.95 (0.90–1.00)
Number of social contacts, times/day						
0	115 (3)	1.00 (referent)	93 (3)	1.00 (referent)	94 (3)	1.00 (referent)
⩾1	3349 (97)	0.915 (0.77–1.09)	2838 (97)	0.92 (0.82–1.04)	2723 (97)	0.90 (0.82–0.99)
Number of physical contacts, times/day						
0	505 (15)	1.00 (referent)	420 (14)	1.00 (referent)	412 (15)	1.00 (referent)
1–7	2548 (74)	0.98 (0.89–1.08)	2172 (74)	0.96 (0.90–1.01)	2085 (74)	0.99 (0.94–1.03)
⩾8	408 (12)	1.02 (0.90–1.17)	336 (11)	1.02 (0.94–1.11)	318 (11)	1.03 (0.96–1.10)
Job with frequent social contact						
No	1832 (52)	1.00 (referent)	1537 (52)	1.00 (referent)	1485 (52)	1.00 (referent)
Yes	1691 (48)	1.01 (0.94–1.09)	1440 (48)	1.00 (0.95–1.05)	1380 (48)	1.00 (0.96–1.04)
Student						
No	3014 (86)	1.00 (referent)	2549 (86)	1.00 (referent)	2469 (86)	1.00 (referent)
Yes	508 (14)	0.75 (0.66–0.86)	427 (14)	0.79 (0.73–0.87)	395 (14)	0.83 (0.77–0.89)
Characteristic of household environment						
Household smoke exposure						
No	3042 (87)	1.00 (referent)	2581 (87)	1.00 (referent)	2483 (87)	1.00 (referent)
Yes	474 (13)	1.09 (0.97–1.21)	392 (13)	1.04 (0.96–1.13)	378 (13)	1.04 (0.97–1.10)
Type of housing						
House	2611 (75)	1.00 (referent)	2197 (74)	1.00 (referent)	2105 (74)	1.00 (referent)
Apartment	569 (16)	1.15 (1.03–1.28)	489 (17)	1.09 (1.02–1.17)	478 (17)	1.06 (1.01–1.12)
Substandard housing	314 (9)	1.27 (1.12–1.43)	269 (9)	1.15 (1.06–1.24)	261 (9)	1.10 (1.03–1.16)

Table A.4 (continued)

	Baseline ($n = 3523$)*		Combined baseline and 6-month follow-up ($n = 2977$)*		Combined baseline, 6-, and 12-month follow-up ($n = 2865$)*	
Variables	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)	*n* (%)	RR (95%CI)
Density, persons/room						
Continuous	—	0.99 (0.98–1.00)	—	1.00 (0.99–1.00)	—	0.99 (0.99–1.00)
Characteristics of TB-infected household case						
Sex						
Female	1348 (38)	1.00 (referent)	1138 (38)	1.00 (referent)	1101 (38)	1.00 (referent)
Male	2175 (62)	1.04 (0.96–1.14)	1839 (62)	1.01 (0.95–1.06)	1764 (62)	0.99 (0.95–1.03)
Smoking status						
Non-smoker	3354 (97)	1.00 (referent)	2838 (97)	1.00 (referent)	2731 (97)	1.00 (referent)
Light	45 (1)	0.86 (0.56–1.32)	31 (1)	0.93 (0.71–1.21)	31 (1)	1.01 (0.83–1.22)
Moderate or heavy	49 (1)	1.39 (1.13–1.73)	44 (2)	1.09 (0.94–1.26)	43 (2)	1.00 (0.87–1.16)
Alcohol use						
Non-drinker	1971 (58)	1.00 (referent)	1676 (58)	1.00 (referent)	1600 (58)	1.00 (referent)
Light	1080 (32)	0.98 (0.89–1.08)	897 (31)	1.00 (0.94–1.06)	862 (31)	1.01 (0.97–1.06)
Heavy	341 (10)	1.23 (1.08–1.40)	303 (11)	1.08 (1.00–1.17)	297 (11)	1.06 (0.99–1.13)
Sputum smear status						
Negative	808 (23)	1.00 (referent)	672 (23)	1.00 (referent)	644 (22)	1.00 (referent)
+	1053 (30)	1.10 (0.97–1.24)	898 (30)	1.10 (1.02–1.19)	861 (30)	1.05 (0.99–1.12)
++	596 (17)	1.21 (1.05–1.38)	512 (17)	1.13 (1.04–1.23)	504 (18)	1.07 (1.00–1.15)
+++	1066 (30)	1.18 (1.04–1.33)	895 (30)	1.13 (1.05–1.22)	856 (30)	1.11 (1.04–1.17)
Treatment delay, days						
0	364 (10)	1.00 (referent)	304 (10)	1.00 (referent)	286 (10)	1.00 (referent)
1–14	227 (7)	1.09 (0.86–1.38)	195 (7)	1.08 (0.93–1.25)	185 (7)	0.97 (0.86–1.09)
15–28	978 (28)	1.14 (0.95–1.37)	816 (28)	1.06 (0.95–1.19)	785 (28)	1.02 (0.94–1.11)
>28	1904 (55)	1.19 (1.00–1.42)	1620 (55)	1.07 (0.97–1.19)	1568 (56)	1.03 (0.95–1.11)
Cavitary disease						
No	2812 (80)	1.00 (referent)	2361 (80)	1.00 (referent)	2265 (80)	1.00 (referent)
Yes	670 (20)	0.973 (0.87–1.08)	586 (20)	0.99 (0.93–1.06)	569 (20)	0.99 (0.97–1.09)

* Sample size varies according to different missing values across covariates.
† Includes relatives other than child, parent, sibling, and spouse and non-relative
‡ Defined by body mass index *Z*-score from World Health Organization; *Z*-score <2 was defined as underweight; >2 was defined as overweight.
TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; TB = tuberculosis.

Table A.5 Multivariate analysis in child contacts for characteristics associated with TST positivity

	Baseline ($n = 1790$)			Combined baseline and 6-month follow-up ($n = 1485$)			Combined baseline, 6- and 12-month follow-up ($n = 1361$)		
	Final model*		Direct model†	Final model*		Direct model†	Final model*		Direct model†
Variables	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)
Characteristic of household contacts									
BCG scars‡									
0	331 (18)	0.91 (0.74–1.13)	0.91 (0.74–1.13)	277 (19)	0.88 (0.75–1.04)	0.88 (0.75–1.04)	257 (19)	0.82 (0.71–0.95)	0.83 (0.71–0.96)
1	1419 (79)	1.00 (referent)	1.00 (referent)	1173 (79)	1.00 (referent)	1.00 (referent)	1068 (78)	1.00 (referent)	1.00 (referent)
2	40 (2)	1.22 (0.82–1.83)	1.23 (0.83–1.82)	35	1.36 (1.02–1.80)	1.36 (1.02–1.80)	36 (3)	1.14 (0.87–1.48)	1.13 (0.88–1.46)
Relation to index§									
Child	625 (35)	1.72 (1.33–2.23)	1.73 (1.35–2.23)	522 (35)	1.70 (1.41–2.06)	1.70 (1.41–2.06)	488 (36)	1.58 (1.34–1.86)	1.58 (1.34–1.85)
Sibling	328 (18)	1.28 (0.97–1.69)	1.29 (0.99–1.69)	282 (19)	1.25 (1.01–1.54)	1.25 (1.01–1.54)	257 (19)	1.07 (0.89–1.29)	1.09 (0.91–1.30)
Other relationship¶	837 (47)	1.00 (referent)	1.00 (referent)	681 (46)	1.00 (referent)	1.00 (referent)	616 (45)	1.00 (referent)	1.00 (referent)
Number of social contacts, times/day									
0	155 (9)	1.00 (referent)	1.00 (referent)	126 (8)	1.00 (referent)	1.00 (referent)	112 (8)	1.00 (referent)	1.00 (referent)
⩾1	1635 (91)	1.71 (1.14–2.57)	1.72 (1.16–2.57)	1359 (92)	1.36 (1.01–1.84)	1.36 (1.01–1.84)	1249 (92)	1.12 (0.89–1.41)	1.11 (0.88–1.39)
Characteristic of household environment									
Household smoke exposure									
No	1606 (90)	1.00 (referent)	1.00 (referent)	1322 (89)	1.00 (referent)	1.00 (referent)	1213 (89)	1.00 (referent)	1.00 (referent)
Yes	184 (10)	1.00 (0.71–1.41)	0.93 (0.66–1.32)	163 (11)	1.01 (0.80–1.28)	1.01 (0.80–1.28)	148 (11)	1.03 (0.84–1.26)	0.97 (0.79–1.19)
Type of housing									
House	1312 (73)	1.00 (referent)	1.00 (referent)	1108 (75)	1.00 (referent)	1.00 (referent)	1017 (75)	1.00 (referent)	1.00 (referent)
Apartment	302 (17)	1.00 (0.77–1.29)	0.99 (0.77–1.28)	238 (16)	1.16 (0.96–1.39)	1.12 (0.94–1.35)	224 (16)	1.13 (0.97–1.33)	1.10 (0.94–1.29)
Substandard housing	176 (10)	1.35 (1.00–1.82)	1.35 (1.02–1.78)	139 (9)	1.05 (0.81–1.36)	1.03 (0.81–1.31)	120 (9)	1.23 (1.01–1.51)	1.20 (0.99–1.46)
Density, persons/room									
Continuous	—	1.01 (0.97–1.05)	1.00 (0.97–1.05)	—	1.02 (0.99–1.05)	1.01 (0.99–1.04)	—	1.00 (0.97–1.03)	1.00 (0.97–1.03)
Characteristics of tuberculosis index case									
Sex									
Female	855 (48)	1.00 (referent)	1.00 (referent)	727 (49)	1.00 (referent)	1.00 (referent)	674 (50)	1.00 (referent)	1.00 (referent)
Male	935 (52)	0.84 (0.68–1.04)	0.83 (0.68–1.02)	758 (51)	0.98 (0.84–1.15)	0.97 (0.83–1.13)	687 (50)	0.98 (0.85–1.12)	0.97 (0.85–1.11)
Smoking status									
Non-smoker	1745 (97)	1.00 (referent)	1.00 (referent)	1453 (98)	1.00 (referent)	1.00 (referent)	1328 (98)	1.00 (referent)	1.00 (referent)
Light	20 (1)	1.67 (0.51–5.41)	1.41 (0.41–4.87)	11 (1)	1.01 (0.35–2.92)	0.95 (0.32–2.83)	11 (1)	0.70 (0.23–2.15)	0.69 (0.23–2.10)
Moderate or heavy	25 (1)	2.64 (1.78–3.91)	2.38 (1.60–3.55)	21 (1)	1.91 (1.40–2.61)	1.70 (1.27–2.28)	22 (2)	1.48 (1.07–2.06)	1.37 (1.02–1.85)
Alcohol use									
Non-drinker	1037 (58)	1.00 (referent)	1.00 (referent)	871 (59)	1.00 (referent)	1.00 (referent)	818 (60)	1.00 (referent)	1.00 (referent)
Light	581 (32)	0.78 (0.62–0.99)	0.80 (0.63–1.00)	467 (31)	0.88 (0.74–1.05)	0.91 (0.77–1.08)	412 (30)	0.99 (0.85–1.15)	1.01 (0.87–1.17)
Heavy	172 (10)	1.36 (1.00–1.85)	1.35 (1.00–1.81)	147 (10)	1.20 (0.95–1.51)	1.19 (0.94–1.49)	131 (10)	1.25 (1.03–1.52)	1.24 (1.02–1.51)
Sputum smear status									
Negative	415 (23)	—	1.00 (referent)	336 (23)	—	1.00 (referent)	295 (22)	—	1.00 (referent)
+	494 (28)	—	1.33 (0.96–1.84)	416 (28)	—	1.44 (1.10–1.87)	384 (28)	—	1.15 (0.92–1.43)
++	328 (18)	—	1.83 (1.31–2.56)	271 (18)	—	1.79 (1.37–2.34)	258 (19)	—	1.44 (1.16–1.79)
+++	553 (31)	—	1.74 (1.26–2.39)	462 (31)	—	1.82 (1.42–2.34)	424 (31)	—	1.48 (1.21–1.81)

Table A.5 (continued)

	Baseline ($n = 1790$)			Combined baseline and 6-month follow-up ($n = 1485$)			Combined baseline, 6- and 12-month follow-up ($n = 1361$)		
	Final model*		Direct model†	Final model*		Direct model†	Final model*		Direct model†
Variables	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)
Treatment delay, days									
0	131 (7)	—	1.00 (referent)	111 (7)	—	1.00 (referent)	96 (7)	—	1.00 (referent)
1–14	123 (7)	—	2.05 (1.05–4.03)	117 (8)	—	1.39 (0.84–2.31)	101 (7)	—	1.08 (0.70–1.65)
15–28	604 (34)	—	1.51 (0.82–2.78)	484 (33)	—	1.24 (0.81–1.91)	436 (32)	—	1.12 (0.80–1.59)
>28	932 (52)	—	2.07 (1.15–3.74)	773 (52)	—	1.53 (1.01–2.33)	728 (53)	—	1.26 (0.90–1.76)
Cavitary disease									
No	1452 (81)	—	1.00 (referent)	1223 (82)	—	1.00 (referent)	1114 (82)	—	1.00 (referent)
Yes	338 (19)	—	1.07 (0.86–1.34)	262 (18)	—	1.22 (1.03–1.43)	247 (18)	—	1.12 (0.97–1.29)

* Model with age, BCG scars, relation to index case, and number of social contacts per day of children contacts, household SHS exposure, type of housing, density of household, index case age, index case sex, index case smoking status, and index case alcohol intake.
† Model with age, BCG scars, relation to index case, and number of social contacts per day of children contacts, household SHS exposure, type of housing, density of household, and all covariates of TB index case.
‡ One child with number of scars = 3 was excluded.
§ Includes relatives other than child, parents, sibling, and spouse and non-relatives
¶ One child with spouse relation with the index case was removed.
TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; TB = tuberculosis; SHS = secondhand smoke.

Table A.6 Multivariate analysis in adult contacts for characteristics associated with TST positivity

	Baseline ($n = 3049$)			Combined baseline and 6-month follow-up ($n = 2587$)			Combined baseline, 6-, and 12-month follow-up ($n = 2482$)		
	Final model*		Direct model†	Final model*		Direct model†	Final model*		Direct model†
Variables	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)
Characteristic of household contacts									
BCG scars									
0	341 (11)	0.90 (0.77–1.04)	0.89 (0.77–1.04)	278 (11)	0.90 (0.81–0.99)	0.90 (0.81–0.99)	267 (11)	0.89 (0.82–0.97)	0.89 (0.82–0.97)
1	1758 (58)	1.00 (referent)	1.00 (referent)	1488 (58)	1.00 (referent)	1.00 (referent)	1416 (57)	1.00 (referent)	1.00 (referent)
2	745 (24)	1.09 (0.99–1.19)	1.09 (0.99–1.19)	642 (25)	1.06 (1.00–1.12)	1.06 (1.00–1.12)	622 (25)	1.07 (1.02–1.11)	1.06 (1.02–1.11)
⩾3	205 (7)	1.23 (1.07–1.40)	1.23 (1.08–1.41)	179 (7)	1.11 (1.02–1.20)	1.11 (1.02–1.20)	177 (7)	1.07 (1.00–1.14)	1.07 (1.00–1.14)
Smoking status									
Non-smoker	2776 (91)	1.00 (referent)	1.00 (referent)	2359 (91)	1.00 (referent)	1.00 (referent)	2264 (91)	1.00 (referent)	1.00 (referent)
Light	156 (5)	1.23 (1.05–1.43)	1.24 (1.06–1.45)	135 (5)	1.09 (0.99–1.19)	1.09 (0.99–1.19)	130 (5)	1.06 (0.99–1.14)	1.07 (1.00–1.14)
Moderate or heavy	117 (4)	1.09 (0.91–1.30)	1.09 (0.91–1.31)	93 (4)	1.09 (0.98–1.20)	1.09 (0.98–1.20)	88 (4)	1.07 (0.98–1.17)	1.07 (0.98–1.17)
Drinking									
Non-drinker	1872 (61)	1.00 (referent)	1.00 (referent)	1605 (62)	1.00 (referent)	1.00 (referent)	1537 (62)	1.00 (referent)	1.00 (referent)
Light	942 (31)	1.02 (0.94–1.11)	1.03 (0.94–1.12)	788 (30)	1.04 (0.99–1.10)	1.04 (0.98–1.10)	758 (31)	1.03 (0.99–1.08)	1.03 (0.99–1.08)
Heavy	235 (8)	1.06 (0.91–1.23)	1.05 (0.90–1.21)	194 (7)	1.04 (0.95–1.15)	1.03 (0.94–1.13)	187 (8)	1.05 (0.97–1.13)	1.04 (0.97–1.12)
Relation to index									
Child	317 (10)	1.14 (0.96–1.35)	1.14 (0.96–1.35)	273 (11)	1.02 (0.9–1.140)	1.00 (0.89–1.13)	269 (11)	0.99 (0.90–1.09)	0.98 (0.90–1.08)
Parent	711 (23)	1.24 (1.09–1.41)	1.25 (1.10–1.43)	636 (25)	1.09 (1.01–1.17)	1.09 (1.01–1.17)	620 (25)	1.06 (0.99–1.12)	1.06 (1.00–1.13)
Sibling	687 (23)	1.12 (0.99–1.28)	1.12 (0.99–1.28)	577 (22)	1.00 (0.92–1.09)	1.00 (0.92–1.09)	550 (22)	1.01 (0.95–1.08)	1.01 (0.95–1.08)
Spouse	378 (12)	1.29 (1.13–1.47)	1.29 (1.13–1.47)	328 (13)	1.12 (1.04–1.22)	1.12 (1.03–1.21)	318 (13)	1.11 (1.04–1.18)	1.10 (1.04–1.17)
Other relationship‡	956 (31)	1.00 (referent)	1.00 (referent)	773 (30)	1.00 (referent)	1.00 (referent)	725 (29)	1.00 (referent)	1.00 (referent)
Characteristic of household environment									
Household smoke exposure									
No	2659 (87)	1.00 (referent)	1.00 (referent)	2256 (87)	1.00 (referent)	1.00 (referent)	2164 (87)	1.00 (referent)	1.00 (referent)
Yes	390 (13)	1.10 (0.98–1.24)	1.08 (0.96–1.23)	331 (13)	1.05 (0.96–1.14)	1.04 (0.96–1.13)	318 (13)	1.04 (0.98–1.11)	1.03 (0.97–1.10)
Type of housing									
House	2278 (75)	1.00 (referent)	1.00 (referent)	1924 (74)	1.00 (referent)	1.00 (referent)	1836 (74)	1.00 (referent)	1.00 (referent)
Apartment	500 (16)	1.2 (1.07–1.35)	1.19 (1.06–1.33)	432 (17)	1.12 (1.04–1.20)	1.12 (1.04–1.20)	424 (17)	1.08 (1.02–1.14)	1.07 (1.01–1.13)
Substandard housing	271 (9)	1.32 (1.16–1.5)	1.32 (1.17–1.50)	231 (9)	1.18 (1.09–1.28)	1.19 (1.10–1.29)	222 (9)	1.13 (1.07–1.20)	1.13 (1.06–1.20)
Density									
Continuous	—	0.99 (0.99–1)	0.99 (0.99–1)	—	0.99 (0.99–1.00)	0.99 (0.99–1.00)	—	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Characteristics of tuberculosis index case									
Sex									
Female	1202 (39)	1.00 (referent)	1.00 (referent)	1016 (39)	1.00 (referent)	1.00 (referent)	979 (39)	1.00 (referent)	1.00 (referent)
Male	1847 (61)	1.02 (0.92–1.12)	1.01 (0.92–1.11)	1571 (61)	1.00 (0.94–1.06)	0.99 (0.93–1.05)	1503 (61)	0.98 (0.93–1.02)	1.01 (0.92–1.12)
Smoking status									
Non-smoker	2974 (98)	1.00 (referent)	1.00 (referent)	2525 (98)	1.00 (referent)	1.00 (referent)	2420 (98)	1.00 (referent)	1.00 (referent)
Light	29 (1)	0.93 (0.61–1.41)	0.90 (0.60–1.37)	21 (1)	0.84 (0.61–1.17)	0.84 (0.63–1.13)	22 (1)	0.91 (0.73–1.13)	0.90 (0.73–1.12)
Moderate or heavy	46 (2)	1.35 (1.04–1.75)	1.32 (1.02–1.71)	41 (2)	1.08 (0.92–1.28)	1.07 (0.92–1.26)	40 (2)	1.00 (0.86–1.16)	1.00 (0.85–1.15)

Table A.6 (continued)

	Baseline ($n = 3049$)			Combined baseline and 6-month follow-up ($n = 2587$)			Combined baseline, 6-, and 12-month follow-up ($n = 2482$)		
	Final model*		Direct model†	Final model*		Direct model†	Final model*		Direct model†
Variables	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)	*n* (%)	RR (95%CI)	RR (95%CI)
Alcohol use									
Non-drinker	1754 (58)	1.00 (referent)	1.00 (referent)	1512 (58)	1.00 (referent)	1.00 (referent)	1441 (58)	1.00 (referent)	1.00 (referent)
Light	961 (32)	0.96 (0.86–1.06)	0.95 (0.86–1.05)	823 (32)	0.99 (0.93–1.06)	0.99 (0.93–1.06)	792 (32)	1.01 (0.96–1.06)	1.01 (0.96–1.06)
Heavy	285 (10)	1.16 (1.01–1.34)	1.18 (1.02–1.35)	252 (10)	1.08 (0.99–1.18)	1.08 (0.99–1.18)	249 (10)	1.05 (0.97–1.12)	1.05 (0.98–1.13)
Sputum smear status									
Negative	712 (23)	—	1.00 (referent)	592 (23)	—	1.00 (referent)	564 (23)	—	1.00 (referent)
+	944 (31)	—	1.12 (0.99–1.27)	803 (31)	—	1.11 (1.02–1.21)	774 (31)	—	1.05 (0.98–1.11)
++	501 (16)	—	1.24 (1.08–1.44)	439 (17)	—	1.18 (1.08–1.30)	434 (17)	—	1.10 (1.03–1.18)
+++	892 (29)	—	1.16 (1.01–1.32)	753 (29)	—	1.12 (1.03–1.22)	710 (29)	—	1.10 (1.03–1.17)
Treatment delay, days									
0	315 (10)	—	1.00 (referent)	261 (10)	—	1.00 (referent)	245 (10)	—	1.00 (referent)
1–14	211 (7)	—	1.06 (0.83–1.34)	180 (7)	—	1.07 (0.92–1.25)	170 (7)	—	0.99 (0.87–1.12)
15–28	878 (29)	—	1.10 (0.90–1.34)	731 (28)	—	1.02 (0.91–1.15)	703 (28)	—	1.01 (0.93–1.10)
>28	1645 (54)	—	1.16 (0.96–1.40)	1415 (55)	—	1.03 (0.93–1.15)	1364 (55)	—	1.02 (0.94–1.10)
Cavitary disease									
No	2453 (80)	—	1.00 (referent)	2067 (80)	—	1.00 (referent)	1987 (80)	—	1.00 (referent)
Yes	596 (20)	—	0.96 (0.86–1.07)	520 (20)	—	0.96 (0.90–1.03)	504 (20)	—	0.97 (0.92–1.02)

* Model with age, BCG scars, relation to index case, smoking status, and alcohol intake of adult contacts, household SHS exposure, type of housing, density of household, index case sex, index case smoking status, and index case alcohol intake.
† Model with age, BCG scars, relation to index case, smoking status, and alcohol intake of adult contacts, household SHS exposure, type of housing, density of household, and all covariates of tuberculosis index case.
‡ Includes relatives other than child, parents, sibling, and spouse and non-relatives.
TST = tuberculin skin test; RR = risk ratio; CI = confidence interval; BCG = bacille Calmette-Guérin; TB = tuberculosis; SHS = secondhand smoke.

RESUME

CONTEXTE : Etude d'observation de cohorte à Lima, Pérou.

OBJECTIF : Déterminer l'association entre l'exposition à un patient tuberculeux qui fume et une infection tuberculeuse latente (LTBI).

MÉTHODES : Entre septembre 2009 et août 2012, nous avons identifié 2 132 patients atteints de tuberculose (TB) pharmacosensible et leurs 2 054 enfants contacts domestiques. Des données ont été recueillies sur le statut de fumeur actif ou passif et les autres facteurs de risque d'infection spécifiques au cas index, au foyer et aux autres contacts exposés. Les contacts ont eu un test cutané à la tuberculine (TST) afin de déterminer leur statut initial en matière de TB et leur statut lors du suivi à 6 mois et 12 mois. Nous avons estimé l'association entre l'exposition à un cas index fumeur et LTBI grâce au modèle de régression de Poisson modifié.

RÉSULTATS : Les 21 enfants âges de ⩽15 ans exposés à un patient index tuberculeux et fumeur avaient plus souvent un TST positif au départ (RR 2,64 ; IC95% 1,78–3,91), à 6 mois (RR 1,91 ; IC95% 1,40–2,60) et à 12 mois (RR 1,48 ; IC95% 1,07–2,06) que ceux qui n'étaient pas exposés à la fumée. Par contre, la positivité du TST aux mêmes dates parmi les enfants exposés au tabagisme passif ne variait pas.

CONCLUSIONS : Les patients tuberculeux qui fument semblent avoir plus de risques de transmettre leur infection à leurs contacts. Les interventions visant à réduire le tabagisme chez les patients tuberculeux pourraient diminuer l'expansion ultérieure de la maladie.

RESUMEN

MARCO DE REFERENCIA: Estudio de observación de cohortes realizado en Lima, Perú.

OBJETIVO: Determinar la asociación entre la exposición a un caso de tuberculosis (TB) en un fumador y la transmisión de la infección tuberculosa latente (LTBI).

MÉTODO: De septiembre del 2009 a agosto del 2012 se detectaron 2 132 pacientes con TB normosensible y 2 054 contactos domiciliarios pediátricos. Se recogieron datos sobre el tabaquismo activo y pasivo y otros factores de riesgo de infección específicos del caso inicial, del domicilio y de los contactos expuestos. Se practicó a los contactos la prueba cutánea de la tuberculina (TST) a fin de definir su estado frente a la infección tuberculosa al comienzo del estudio, a los 6 meses y a los 12 meses de seguimiento. Se calculó la correlación entre la exposición a un caso inicial en un fumador y la LTBI mediante un modelo de regresión de Poisson modificado.

RESULTADOS: Los 21 niños de ⩽15 años de edad expuestos al caso inicial de un fumador exhibieron una mayor probabilidad de obtener un resultado positivo de la TST al comienzo (riesgo relativo [RR] 2,64; IC95% 1,78–3,91), a los 6 meses (RR 1,91; IC95% 1,40–2,60) y a los 12 meses de seguimiento (RR 1,48; IC95% 1,07–2,06), que los niños sin exposición. La exposición pasiva al humo de tabaco no modificó la positividad de la TST en los niños en los mismos tiempos de evaluación.

CONCLUSIÓN: Los pacientes tuberculosos que fuman tal vez transmiten con mayor facilidad la infección a sus contactos. Las intervenciones encaminadas a disminuir el tabaquismo en los pacientes que padecen TB pueden disminuir la propagación de la enfermedad.