Published in final edited form as:
Pediatr Infect Dis J. 2014 December ; 33(12): 1303–1306. doi:10.1097/INF.0000000000000506.

Increased Risk of *Mycobacterium Tuberculosis* Infection in Household Child Contacts Exposed to Passive Tobacco Smoke

Saranya Sridhar, MBBS, MS, DPhil, DFPH[*], **Nisha Karnani, BA**[*], **David W. Connell, MRCP**[*], **Kerry A. Millington, DPhil**[*], **Davinder Dosanjh, MD**[*], **Mustafa Bakir, MD**[†], **Ahmet Soysal, MD**[†], **Jonathan Deeks, DPhil**[‡], and **Ajit Lalvani, DM**[*]

[*]Tuberculosis Research Centre, Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College London, Norfolk Place, London

[†]Department of Paediatrics, Marmara University School of Medicine, Istanbul, Turkey

[‡]Department of Public Health, Epidemiology and Biostatistics, Public Health School of Health and Population Sciences, University of Birmingham, Edgbaston, United Kingdom

Abstract

Risk factors associated with *Mycobacterium tuberculosis* infection were investigated in a prospective cohort of household child tuberculosis contacts. A significantly increased risk of acquiring infection was associated with exposure to passive cigarette smoke, higher number of index cases, younger age and reduced household monthly income.

Keywords

childhood tuberculosis; infection; interferon-gamma release assay; smoking

An estimated, one third of the global population is infected with *Mycobacterium tuberculosis* (Mtb)1 with 8.6 million incident cases in 2012 alone.2 Individuals with latent tuberculosis infection, at risk of progression to active tuberculosis (TB), act as a significant reservoir of incident cases and are therefore a major target for TB control programs.3

Control of latent tuberculosis infection necessitates knowledge of biological and environmental risk factors that determine acquisition of infection to allow design and implementation of cost-effective interventions. While host characteristics such as age, exposure to an infectious case, bacillus Calmette–Guérin (BCG) vaccination and ethnicity have been well studied,4 data on environmental and socioeconomic determinants more amenable to intervention are more limited. Investigating these risk factors in children, who

Address for correspondence: Ajit Lalvani, MA, DM, FRCP, Tuberculosis Research Centre, Department of Respiratory Medicine, National Heart and Lung Institute, Imperial College London, 2 Norfolk Place, London W2 1PG, United Kingdom. a.lalvani@imperial.ac.uk.

Authors' contributions: S.S. and A.L. designed the research question. S.S., N.K., J.D. and A.L. analyzed the data. M.B., A.S., K.M., D.D. and A.L. completed the study and the experiments. S.S., N.K. and A.L. wrote the manuscript.

The authors have no conflicts of interest to disclose.

Ethical approval was granted by the IRB of Marmara University School of Medicine, Istanbul; The Turkish Ministry of Health, Ankara and the WHO Steering Committee on research involving human subjects, Geneva.

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are most susceptible to developing severe disseminated TB is therefore of public health importance.

Accurate diagnosis of Mtb infection is a barrier to investigating risk factors for Mtb infection. The challenges in identifying risk factors lie in distinguishing infection from progression to disease, use of the less specific tuberculin skin test (TST) rather than the interferon-gamma release assay (IGRA) and testing for Mtb infection at a single time point when using IGRAs with potential of misclassifying individuals who subsequently revert or convert their IGRA results at a later time point.5

We report a new analysis of a previously described child cohort of household TB contacts6,7 incorporating hitherto unavailable follow-up data. Use of a 2-time point IGRA screen offering a more robust diagnosis of Mtb infection, by excluding IGRA reverters and correctly classifying IGRA converters, is used to identify risk factors associated with acquisition of infection in children exposed to TB in the household.

Methods

Study Population

We used data from a Turkish cohort described previously7 in which childhood contacts of sputum smear-positive TB cases were recruited. All participants were tested with TST and an ex-vivo IFN-g ELISpot assay at the time of recruitment and a second ELIS-pot assay was repeated 6 months later. At enrollment, BCG vaccination status was assessed by the presence of a scar and demographic and socioeconomic information recorded. Details of the follow-up and incident cases have been previously published.6

Ex vivo IFN-g ELISPOT Assay

ELISpot was performed as described previously using ESAT-6 and CFP-10 peptides7 which is comparable to the commercially available T-Spot.TB IGRA. Responses were scored as positive if the test wells contained a mean of at least 5 spot-forming cells more than the mean of the negative control wells, and, additionally, this number was at least twice the mean of the negative control wells.

Statistical Analysis

The primary outcome for this analysis is TB infection assessed by IGRA results at baseline and 6-month follow-up time point. Individuals with TB infection were defined as those with either persistent positive IGRA result (at baseline and 6-months) or IGRA converters (IGRA negative at baseline and IGRA positive at 6 months). Those without TB infection were defined by persistent negative IGRA (at baseline and 6-months). Individuals with an IGRA reversion (IGRA positive at baseline and IGRA negative at 6 months) were excluded as the clinical and biological significance of an IGRA reversion is uncertain. Descriptive statistics were used to describe characteristics of the 2 groups in each analysis, TB infection versus no TB infection, including frequencies (percentages) and means with standard deviations. Where relevant, the Fisher exact test or the χ^2 test were used to compare proportions and the independent groups' *t* test was used to compare means between the 2 groups. A

multivariable logistic regression model was built to investigate the effect of different risk factors on TB infection and progression to active disease. Before fitting the main model, univariable logistic regression models were used to investigate the association between variables and IGRA reversion. A model was then fitted containing variables associated with TB infection on univariate regression ($P < 0.2$) along with age and sex (irrespective of their P value) and stepwise backward selection was conducted to remove variables 1 at a time based on Wald statistics. An overall P value of 0.05 was considered to be statistically significant. Statistical analyses were undertaken using Stata version 11 (StataCorp, College Station, TX).

Results

There were 714 children with available IGRA results at baseline and the 6-month follow-up time point. As defined above, 341 (47.76%) children were classified as infected with Mtb, which comprised 273 children with a persistent positive IGRA and 68 IGRA converters. Three hundred and seventy-three (52.24%) individuals had a persistent negative IGRA and were defined as not being infected with Mtb. The median age of the cohort was 7.5 years (range 1 month to 16 years).

Univariate analysis of host, environmental and socioeconomic risk factors for Mtb infection (Table 1) showed a significant association ($P < 0.05$) with age, number of index patients in the household, having a smoker in the household, monthly household income and mother's education.

Independent risk factors for TB infection, after fitting a multivariate model, were age, BCG status, number of index patients in the household, having a smoker in the household and monthly household income (Table 1). A smoker in the household [odds ratio (OR): 1.52, 95% confidence interval (CI): 1.09–2.12) increased risk of acquiring TB infection in child contacts while a household monthly income ≥US$75 decreased risk of infection (OR: 0.55, 95% CI: 0.38–0.79). Children were more likely to be infected with increasing age, for every 1 year increase in age the risk of acquiring infection increased by 6% (OR: 1.06, 95% CI: 1.03–1.10), and exposure to more than 1 index case in the household (OR: 6.42, 95% CI: 2.09–19.74), whereas children with a BCG scar were 20% less likely to become infected (OR: 0.67, 95% CI: 0.46–0.99).

Discussion

There is growing public health concern of the impact of smoking on the TB epidemic. While several meta-analyses have confirmed the increased risk of TB infection and disease in active smokers,8,9 data on the association of passive smoking and risk of Mtb infection is sparse. Our cohort study of child household contacts of smear positive pulmonary TB revealed second-hand tobacco smoke to increase the risk of acquiring Mtb infection after controlling for other risk factors associated with Mtb infection.

Unlike adults in whom disentangling the independent effects of active and passive smoking is difficult, children who do not smoke offer an ideal setting in which to assess the effect of passive smoking on Mtb infection. Children in contact with an infectious case were at a 52%

increased risk of acquiring Mtb infection when exposed to a smoker in the household [adjusted odds ratio (aOR) 1.52]. This effect independent of age, sex, socioeconomic status and the amount of exposure to infection is similar to the risk of Mtb infection associated with active smoking obtained by several meta-analyses (aOR ~1.5).8,9 The magnitude of effect in our study is similar to that obtained by Godoy et al10 in over 7000 contacts across different age groups in Catalonia (aOR: 1.52) but, lower than an unadjusted estimate by Singh et al.11 in Indian child household contacts (OR: 2.68) and lower than that reported by den Boon et al12 from a cross-sectional survey of the general population in South Africa (aOR: 4.60). The lower estimate in our study is probably a result of using the IGRA assay to diagnose infection, which has greater accuracy in children than the TST used in previous reports.13,14 However, other reasons such as the manner of recording exposure to passive smoking and study design and sample size may also account for the difference in estimates. One other study used IGRAs to diagnose Mtb infection but did not find any association between exposure to tobacco smoke and acquiring Mtb infection in child contacts.15 Our study, unlike previous studies, used a combination of IGRA results at baseline and a follow-up time point to generate a more robust system to diagnose Mtb infection. This minimizes the potential for misclassification of individuals who subsequently converted or reverted their IGRA results, thus enabling identification of hitherto unrecognized risk factors.

Passive tobacco smoking has been implicated in increasing risk of clinical disease and our finding, for the first time reports an association between passive tobacco smoking and acquisition of TB infection diagnosed using IGRA. If future studies were to show increased risk of progression from infection to active disease, it would implicate passive tobacco smoking in every stage of the natural history of TB.

Independent of passive smoking, a higher household monthly income, BCG scar and younger age were associated with a reduced risk of infection while exposure to more than 1 TB case in the household increased risk of Mtb infection among child contacts in our study. This corroborates our previous analysis from this child contact cohort which only used baseline IGRA results to diagnose Mtb infection, highlighting the strength of the association of these risk factors.7

Our study has certain limitations. Although active smoking in Turkish children during the time of our study was uncommon, we did not specifically collect this information and therefore cannot rule out the effect of active smoking on TB infection. Similarly, the contribution of indoor air pollution was not measured. Although we recorded exposure to passive smoking, we did not record which household member smoked or their smoking habits. Thus, we were unable to distinguish the independent contributions of passive smoke from the index case from that of other household members or report a dose–response relationship that has previously been shown.16 Future studies will need to undertake such analysis to identify the most appropriate target groups if smoking cessation interventions were to be incorporated into TB control strategies.

Our finding, adding to the small body of evidence, of an association between passive tobacco smoke and an increased risk of Mtb infection in children has vital public health implications. With an estimated 700 million children worldwide, approximately 40% of all

children exposed to second-hand tobacco smoke at home17 and 80% of global smokers in countries with the highest TB burden and the least stringent tobacco control, our study has found new evidence to support the incorporation of smoking cessation strategies into TB control programs.

Acknowledgements

This study was funded by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the Wellcome Trust. A.L. is a Wellcome Senior Research Fellow in Clinical Science. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Table 1
Risk Factors for Mtb Infection in Child Contacts

	Uninfected*	Infected*	Unadjusted		Adjusted†	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Host risk factors						
Sex‡						
Female	175 (50.87%)	169 (49.13%)	1			
Male	198 (53.66%)	171 (46.34%)	0.89 (0.67–1.20)	0.457		
Median age in months (interquartile range)	84(38–126)	98 (56.5–140)	1.06 (1.03–1.10)	0.001	1.06 (1.03–1.10)	0.001
BCG vaccination‡						
0	63 (45.32%)	76 (54.68%)	1		1	
≥1	310 (54.01%)	264 (45.99%)	0.71 (0.49–1.02)	0.067	0.67 (0.46–0.99)	0.046
Environmental risk factors						
Number of index patients in household‡						
1	369 (53.48%)	321 (46.52%)	1		1	
>1	4 (17.39%)	19 (82.61%)	5.46 (1.84–16.22)	0.002	6.42 (2.09–19.74)	0.001
Smoker in the household						
No	138 (58.97%)	96 (41.03%)	1		1	
Yes	235 (48.96%)	245 (51.04%)	1.5 (1.09–2.06)	0.012	1.52 (1.09–2.12)	0.014
Socioeconomic risk factors						
Monthly income ‡						
<75 US$	66 (38.60%)	105 (61.40%)	1		1	
≤75 US$	306 (56.46%)	236 (43.54%)	0.49 (0.34–0.69)	<0.001	0.55 (0.38–0.79)	0.001
Mother’s profession						
Routine/manual	11 (47.83%)	12 (52.17%)	1.01 (0.77–1.32)	0.930		
Intermediate occupations	2 (100.00%)	0 (0.00%)				
Managerial/professional	7 (70.00%)	3 (30.00%)				
Other	353 (51.99%)	326 (40.01%)				
Father’s profession						
Unemployed	49 (46.67%)	56 (53.33%)	0.89 (0.73–1.07)	0.206		
Routine/manual	279 (52.74%)	250 (47.26%)				
Intermediate occupations	14 (50.00%)	14 (50.00%)				
Managerial/professional	19 (63.33%)	11 (36.67%)				
Other	12 (54.55%)	10 (45.45%)				
Mother’s education						
No education or primary school	316 (51.13%)	302 (48.87%)	1			
Intermediate/high school/university	57 (59.38%)	39 (40.63%)	0.62 (0.43–0.89)	0.010		
Father’s education§						
No education or primary school	260 (50.29%)	257 (49.71%)	1			
Intermediate/high school/university	111 (57.81%)	81 (42.19%)	0.74 (0.53–1.03)	0.075		

	Uninfected*	Infected*	Unadjusted		Adjusted†	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value
Attends school						
No	170 (55.37%)	137 (44.63%)	1			
Yes	203 (49.88%)	204 (50.12%)	1.25 (0.93–1.68)	0.146		
Mobile phone ownership						
No	129 (48.31%)	138 (51.69%)	1			
Yes	244 (54.59%)	203 (45.41%)	0.78 (0.57–1.05)	0.105		

*Mtb infection was defined by a combination of IGRA results at baseline and the 6-month follow-up time point. Individuals with TB infection were defined as either a positive IGRA result at baseline and 6 months or those with IGRA negative at baseline and IGRA positive at 6 months (IGRA converters). Mtb Uninfected was defined as negative IGRA at baseline and 6 months

†Estimated by stepwise logistic regression with Mtb infection as dependent variable with sex, age, BCG, number of index cases in household, smoker in the household, monthly income, mother's education, father's education, school attendance and mobile phone ownership as independent variables.

‡Data available for 713 of 714 individuals with IGRA results.

§Data available for 709 of 714 individuals with IGRA results.

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