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Mycobacterium tuberculosis Infection in Close Childhood Contacts of Adults with Pulmonary Tuberculosis is Increased by Secondhand Exposure to Tobacco

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Abstract. Tobacco use is a major risk factor for tuberculosis (TB). Secondhand smoke (SHS) is also a risk factor for TB and to a lesser extent, *Mycobacterium tuberculosis* infection without disease. We investigated the added risk of *M. tuberculosis* infection due to SHS exposure in childhood contacts of TB cases in The Gambia. Participants were childhood household contacts aged ≤ 14 years of newly diagnosed pulmonary TB (PTB) cases. The intensity of exposure to the case was categorized according to whether contacts slept in the same room, same house, or a different house as the case. Contacts were tested with an enzyme-linked immunospot interferon gamma release assay. In multivariate regression models, *M. tuberculosis* infection was associated with increasing exposure to a case (odds ratios [OR]: 3.9, 95% confidence interval [CI]: 2.11–71.4, $P < 0.001$]) and with male gender (OR: 1.5 [95% CI: 1.12–2.11], $P = 0.008$). Tobacco use caused a 3-fold increase in the odds of *M. tuberculosis* infection in children who slept closest to a case who smoked within the same home compared with a nonsmoking case (OR: 8.0 [95% CI: 2.74–23.29] versus 2.4 [95% CI: 1.17–4.92], $P < 0.001$). SHS exposure as an effect modifier appears to greatly increase the risk of *M. tuberculosis* infection in children exposed to PTB cases. Smoking cessation campaigns may be important for reducing transmission of *M. tuberculosis* to children within households.

INTRODUCTION

Tuberculosis (TB) remains a global health problem with 9.6 million incident cases and 1.5 million deaths in 2014 alone.[1] For more than two decades, one-third of the world's population was estimated to have *Mycobacterium tuberculosis* infection.[2,3] Even with the recent revision of this estimate to about a quarter of the global population,[4] this still constitutes a major reservoir of future active disease. With such a reservoir, it is important to investigate risk factors for *M. tuberculosis* infection such as tobacco use to guide development/implementation of interventions. This is particularly important in children who go on to carry their *M. tuberculosis* infection into adulthood where there is increasing incidence of pulmonary TB (PTB), tobacco, and alcohol use (lifestyle habits) and other comorbidities such as human immunodeficiency virus, type 2 diabetes, and chronic obstructive lung disease that may increase the risk of progression from *M. tuberculosis* infection to TB disease.

Tobacco use is a risk factor for respiratory diseases including active TB and *M. tuberculosis* infection.[5] Children with secondhand exposure to tobacco in household settings have been reported to be at an increased risk of *M. tuberculosis* infection based on tuberculin skin tests.[6–9] However, this association is still unclear and is less well studied with interferon gamma release assays (IGRAs).[10] In addition, other studies did not adjust for the intensity of TB exposure.

We hypothesized that secondhand exposure to smoke resulting from tobacco use by a TB case increases TB transmission and is associated with *M. tuberculosis* infection in their childhood household contacts. Therefore, we investigated the association between secondhand exposure to tobacco and *M. tuberculosis* infection in childhood contacts of newly diagnosed TB patients while adjusting for the TB exposure gradient within the home and smoking in other household contacts.

METHODS

This was a cross-sectional study conducted in the Greater Banjul Area, a mainly urban area around the capital of The Gambia with a population of 1,052,712 (2013 Population and Housing Census Preliminary Results, Gambia Bureau of Statistics).

We recruited index TB cases and their household contacts from major government chest clinics and the outpatients' clinic at the Medical Research Council Gambia Unit. Index cases were newly diagnosed with smear and culture positive PTB and aged ≥ 15 years. Household contacts were aged ≤ 14 years, lived in the same compound as the case for ≥ 3 months, had no history of TB treatment in the past year and did not develop TB within a month of recruitment/diagnosis of the index case. TB exposure was classified according to whether contacts slept in a different house on the same compound, the same house or room relative to the TB case.[11] Self-reported tobacco use was recorded for all participants.

To diagnose *M. tuberculosis* infection, contacts were tested with an interferon gamma (IFN-γ) enzyme-linked immunospot (ELISPOT) assay, a precursor to the commercial T-Spot.TB IGRA (Oxford Immunotec, Oxfordshire, United Kingdom).[11] Positive test wells were predefined as those with ≥ 8 spot-forming units/well/2×10^5 peripheral blood mononuclear cells more than negative control wells.[12] Logistic regression models were fitted to the ELISPOT results and adjusted for clustering by household, risk factors and likely confounders—age, gender,

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sleeping proximity to index case (TB exposure), smoking by other household contacts, BCG scar, frequency of smoking, alcohol use by TB cases; sputum smear grade, *M. tuberculosis* lineage (*M. tuberculosis* versus *M. africanum* by spoligotyping),[13] and severity of chest radiograph findings in TB case.

The Joint Gambia Government/Medical Research Council Ethics Committee approved this study. Written informed consent for study procedures was obtained from all adults, from the parent/guardian of every child < 18 years and assent was obtained for minors aged 15–17 years.

The Gambian TB program has a policy of TB preventive treatment of only under 5-year-old children.

RESULTS

There were 248 index TB cases with 718 household child contacts. The majority of index TB cases were male (71%, 176 of 248) with a median age of 21.5 years (interquartile range [IQR] 14–35 years) and only 34.7% (86 of 248) reported use of tobacco. Among child contacts, females accounted for 52.8% (379 of 718) and none of the children ≤ 14 years reported tobacco use.

As shown in Table 1, the odds of a positive ELISPOT test increased with the intensity of exposure but was unaffected by the smoking status of the TB case in the household. Fitting a logistic regression model to the ELISPOT result, adjusting for the child's age, sex, and allowing for household clustering, we found a significant interaction between smoking status of the TB case and sleeping proximity of the child to the TB case ($P = 0.024$). As shown in Table 1, children sleeping in the same room as the TB case are more likely ($P = 0.01$) to have a positive ELISPOT result if the TB case is a smoker compared with a nonsmoker (OR 7.98 versus OR 2.40).

Gender was an independent risk factor for *M. tuberculosis* infection. Frequency of smoking, alcohol use by TB cases and smoking by other household contacts had no effect (see Supplemental Table 1).

DISCUSSION

Our results confirm intensity of TB exposure is the most significant risk factor for *M. tuberculosis* infection within households as previously demonstrated.[14] The independent effects of age and gender on *M. tuberculosis* infection are also consistent with other studies in The Gambia.[15] We now find that secondhand exposure to tobacco use by a TB case acts as an effect modifier that may further increase the risk for *M. tuberculosis* infection in children.

Tobacco use by a TB case may exert a dual effect to increase the risk of TB transmission. First, the TB cases who smoke may be more infectious because they cough more,[6] have more severe pulmonary disease with cavity formation and miliary patterns[16] or have more time to transmit TB because their chronic cough leads to delayed presentation and diagnosis of TB.[6] Second, there is some evidence of damaging effects of secondhand tobacco exposure on respiratory immunity. These include decreased ciliary function, reduction in the numbers of IFN-γ and tumor necrosis factor alpha-producing macrophages, and other alterations in macrophage response and numbers.[17,18] Therefore, it is reasonable to expect a dose-response relationship with increasing exposure to the smoker within households increasing the incidence and intensity of these biologic mechanisms in their contacts.

In the largest review on the effect of secondhand tobacco exposure on *M. tuberculosis* infection in children, the authors found significant heterogeneity among the studies reviewed and that only a minority adjusted for relevant confounders.[19] Consequently, the initially apparent direct association between tobacco exposure and *M. tuberculosis* infection in childhood TB contacts disappeared on adjustment for all

TABLE 1
Tobacco use by index case and other risk factors for latent TB infection in childhood household contacts aged ≤ 15 years

	N = 718			IGRA positive result			
	n (%)	Odds ratio*	95% CI	*P* value	Odds ratio†	95% CI	*P* value
Exposure gradient to TB case							
Different house	183 (25.5)	1			1		
Different room	372 (51.8)	1.97	1.19–3.25	0.008	2.01	1.20–3.40	0.008
Same room	163 (22.7)	3.48	1.98–6.12	< 0.005	3.88	2.11–7.14	< 0.005
Smoking status of TB case							
No	460 (64.1)	1			1		
Yes	258 (35.9)	0.77	0.50–1.19	0.240	0.99	0.63–1.57	0.980
Exposure + ## smoking interactions							
Different house + nonsmoking case	78 (10.9)	1			1		
Different house + smoking case	105 (14.6)	0.60	0.29–1.24	0.172	0.58	0.25–1.34	0.202
Different room + nonsmoking case	247 (34.4)	1.57	0.88–2.80	0.127	1.60	0.81–3.13	0.175
Different room + smoking case	125 (17.4)	1.36	0.71–2.58	0.352	1.35	0.62–2.96	0.452
Same room + nonsmoking case	135 (18.8)	2.20	1.18–4.09	0.013	2.40	1.17–4.92	0.017
Same room + smoking case	28 (3.9)	6.56	2.54–16.90	< 0.005	7.98	2.74–23.29	< 0.005
Age, years							
Median (interquartile range)	7 (4–11)	1.02	0.98–1.06	0.910	1.04	1.0–1.09	0.036
Gender							
Female	379 (52.8)	1			1		
Male	339 (47.2)	1.41	1.03–1.94	0.034	1.53	1.12–2.11	0.008

CI = confidence interval; IGRA = interferon gamma release assay; TB = tuberculosis.

* Univariate regression models, unadjusted.

† Multivariable regression models including interaction terms (##) and adjusted for clustering by household and confounders—age, gender, sleeping proximity, smoking status of other household contacts, BCG scar, sputum smear grade, *Mycobacterium tuberculosis* lineage, and severity of chest radiograph findings in TB case. Only significant results are shown.

confounding variables. This is consistent with our findings in this study.

That our study allowed for an examination of the independent effect of smoking in TB cases adjusted for TB exposure gradient and smoking by other household members is the key strength of this study. Although we did not test for cotinine to confirm the self-reported tobacco use data we obtained, the prevalence of tobacco use we found among TB cases in this study is consistent with earlier reports on adults in the same urban setting.[20] Because the older children (14–18 years old) are not represented in our sample, it is possible we underestimated their use of tobacco in our adjustment for other smokers in households given the findings of Maassen and others regarding initiation of smoking in this age group.[21] Although children typically acquire *M. tuberculosis* infection and subsequent active disease from close adult contacts, this may not always be within their own households so it is possible some of the *M. tuberculosis* infection seen here was not acquired from the index case. The linear relationship between sleeping exposure to the TB case and *M. tuberculosis* infection among contacts in this study and earlier reports,[11,22] reinforces sleeping exposure as a reliable measure of closeness of contact with a TB case. We did not observe increased risk of *M. tuberculosis* infection from SHS exposure from other household members, nor did we see increased risk with increasing numbers of cigarettes smoked. These and the fact that there were relatively few ($N = 28$) contacts exposed to a smoking index case in the highest exposure category, suggest some caution is needed and confirmation in other studies would be helpful. Our inability to assess the role of socioeconomic status on our results is also a limitation. The limitation may be mitigated by the fact that our study area is known to have the highest burden of active TB and *M. tuberculosis* infection in the whole country.[15,23]

Our findings from this study are of public health importance because approximately 50% of the world's children experience secondhand tobacco exposure in their homes and many of them in settings like ours with poor tobacco regulation and high TB burden.[23–25] This does not include the additional risk of third-hand smoke contamination caused by secondhand tobacco exposure in homes and other locations.[26,27] Our study contributes to the body of evidence on the association between secondhand tobacco exposure and *M. tuberculosis* infection in children exposed to TB cases. In addition, these results provide further evidence to support smoking cessation campaigns as part of TB control efforts and specifically as an intervention to reduce TB transmission to children within households.

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Disclaimer: Due to ethical restrictions related to protecting patient confidentiality, data cannot be made publicly available. Data will be made available from the MRC Gambia Unit and Institutional Data Access Committee to researchers who meet the criteria for access to confidential data. Interested researchers can contact the Head of Data Management, Mr. Bai Lamin Dondeh (bdondeh@mrc.gm).

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