HHS Public Access

Author manuscript

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2015 July 01.

Published in final edited form as:

Int J Tuberc Lung Dis. 2014 February ; 18(2): 198–204. doi:10.5588/ijtld.13.0314.

Modifiable risk factors associated with tuberculosis disease in children in Pune, India

J. Jubulis[*,†], **A. Kinikar**[‡], **M. Ithape**[§], **M. Khandave**[§], **S. Dixit**[‡], **S. Hotalkar**[§], **V. Kulkarni**[§], **V. Mave**[§], **N. Gupte**[§], **A. Kagal**[§], **S. Jain**[*], **R. Bharadwaj**[§], and **A. Gupta**[*]

[*]Johns Hopkins University, Baltimore, Maryland [†]Maine Medical Center, Portland, Maine, USA [‡]Byramji Jeejeebhoy Medical College (BJMC), Pune [§]BJMC Clinical Trials Unit, Pune, India

Abstract

SETTING—India accounts for the largest burden of tuberculosis (TB) worldwide, with 26% of the world's cases.

OBJECTIVE—To assess the association between novel modifiable risk factors and TB in Indian children.

DESIGN—Cases were children aged ≤5 years with confirmed/probable TB based on World Health Organization definitions (definition 1). Controls were healthy children aged ≤5 years. Logistic regression was performed to estimate the adjusted odds ratio (aOR) of being a TB case given exposure, including indoor air pollution (IAP; exposure to tobacco smoke and/or biomass fuels) and vitamin D deficiency. Cases were re-analyzed according to a new consensus research definition of pediatric TB (definition 2).

RESULTS—Sixty cases and 118 controls were enrolled. Both groups had high levels of vitamin D deficiency (55% vs. 50%, $P = 0.53$). In multivariable analysis, TB was associated with household TB exposure (aOR 25.41, 95%CI 7.03–91.81), household food insecurity (aOR 11.55, 95%CI 3.33–40.15) and IAP exposure (aOR 2.67, 95%CI 1.02–6.97), but not vitamin D deficiency (aOR 1.00, 95%CI 0.38–2.66). Use of definition 2 reduced the number of cases to 25. In multivariate analysis, TB exposure, household food insecurity and IAP remained associated with TB.

CONCLUSIONS—Household TB exposure, exposure to IAP and household food insecurity were independently associated with pediatric TB.

Keywords

pediatric tuberculosis; household food insecurity; indoor air pollution; vitamin D deficiency

Correspondence to: Jennifer Jubulis, Johns Hopkins University, Baltimore, MD 21218, USA. Tel: (+1) 207 662 5522. Fax: (+1) 207 662 5526. JUBULJ@mmc.org; Amita Gupta, Johns Hopkins University, Baltimore, MD 21218, USA. Tel: (+1) 410 502 2029. Fax: (+1) 443 287 6440. agupta25@jhmi.edu.

Conflict of interest: none declared.

TUBERCULOSIS (TB) remains widespread, with approximately 9 million new cases annually, of which at least 10% are children.[1,2] With the United Nations Millennium Development Goals and Stop TB Partnership targeting reduced childhood morbidity and improved TB control, a better understanding of risk factors in children is critical.[1,2]

In adults, several biologic risk factors for TB have been established.[1] Social factors are less clear; however, poverty and active tobacco smoking have been linked to TB.[1,3–7] Exposure to secondary smoke and/ or biomass cooking fuels (indoor air pollution [IAP]) is more controversial, with less evidence.[3,6,8–10] Malnutrition, in particular vitamin D deficiency, has also been associated with increased risk.[11–19]

In children, the above risk factors have not been well studied. One cross-sectional study of refugees in London found increased vitamin D deficiency in children with TB;[20] however, a recent study of refugees in Australia did not find this association.[21] IAP, which is typically defined as particulate matter from burning of solid fuels (coal, dung or wood), and which often also includes passive tobacco smoke, has been associated with respiratory infection in children.[22] However, the role of IAP in pediatric TB has not been well examined.

India has the greatest burden of TB worldwide, accounting for 26% of all cases. Approximately 10% of its population is aged <5 years.[23] Population prevalence of human immunodeficiency virus (HIV) infection (0.3%) is low; however, prevalence of IAP (70%), vitamin D deficiency (30–80%)[24] and household poverty (22%) is high.[23]

The objective of our study was to assess the strength of the association of the above risk factors with TB in children aged ≤5 years residing in Pune, India. Identifying modifiable risk factors will help inform prioritization for public health interventions aiming to reduce the burden of pediatric TB in India and other endemic settings.

METHODS

Study setting and design

We conducted a prospective case-control study at Byramjee JeeJeeboy Medical College & Sassoon Hospital in Pune, India, a 1300-bed tertiary care public hospital center serving predominantly poor adults and children from urban and peri-urban areas.

Cases were children aged ≤5 years with confirmed or probable TB. Control patients were children aged ≤5 years attending immunization clinics at the same hospital without signs or symptoms suggestive of TB, another acute infection or malignancy.

Tuberculosis definitions

Cases were defined according to the World Health Organization and India's Revised National Tuberculosis Control Programme guidelines as confirmed or probable TB.[25] Confirmed TB cases were those with positive culture for *Mycobacterium tuberculosis*. Probable cases were those with clinical and radiographic findings consistent with TB, but negative acid-fast bacilli culture (definition 1). A second research definition (definition 2) was then retrospectively applied using new published guidelines for probable pulmonary TB

in pediatric patients.[26] Using this definition, definite cases were culture-positive for *M. tuberculosis*, while probable cases were defined as above, with two radiologists agreeing on chest radiograph (CXR) findings and follow-up data, including lack of response to antibiotics for pneumonia.

Data collection

Parents or guardians of study subjects completed a sociodemographic, health and nutrition questionnaire administered by trained study personnel, and children underwent a physical examination by a study physician. Individual and household factors were assessed, including household TB exposure, nutritional status (weight-for-age *Z* scores [WAZ]) and household food insecurity using standardized household food insecurity assessment scores (HFIAS).[27] IAP was assessed by asking if there were any tobacco smokers in the home and what primary cooking fuel was used. All study subjects had blood drawn for serum 25 hydroxyvitamin D levels. Cases underwent HIV testing.

Assessing vitamin D status

Serum for 25 hydroxyvitamin D testing was stored at −80°C and batch tested using the Diasorin Radioimmunoassay (Diasorin 25-hydroxy $D^{125}I$ RIA kit; Diasorin Corporation, Stillwater, MN, USA, 1994). Vitamin D categorizations were defined as deficiency ≤ 20 ng/ml and sufficiency > 20 ng/ml based on recommended definitions for vitamin D deficiency using this assay.[28]

Ethical approval and oversight

This study was approved by the ethical review committee of Byramji Jeejeebhoy Medical College, Pune, India, and the Institutional Review Boards of Pune and Johns Hopkins University, Baltimore, MD, USA. Written informed consent was provided by the parents or legal guardians of enrolled children. As the Johns Hopkins University Institutional Review Board (IRB) did not approve HIV testing in healthy children attending the immunization clinic, HIV status of controls was based on parent/guardian report.

Statistical analysis

We estimated that a sample size of 60 cases with 120 controls would provide 80% power to detect an odds ratio of 2 of being a case, based on vitamin D deficiency. Calculations were performed using STATA version 11 (Stata Corp, College Station, TX, USA). Vitamin D deficiency prevalence in children was assumed to be at least 30%,[24] based on previous studies.

Continuous variables were transformed into categorical variables based on clinical importance. WAZ scores were dichotomized to ≤–2 and >–2, corresponding to undernutrition standards. A composite variable for IAP was created including passive exposure to tobacco smoke and/or exposure to biomass fuels (wood, coal, animal dung). We also looked at passive exposure to tobacco and biomass fuel exposure as individual exposures. An HFIAS score of >1 was defined as household food insecurity. The χ^2 test was used to identify associations between categorical variables; Fisher's exact test was used when cell size was <5 observations. Univariable logistic regression analyses were performed

to assess differences in demographic and baseline health and nutrition characteristics between cases and controls. Multivariate analysis was then used to determine independent risk factors associated with TB cases. Variables were selected for evaluation in the multivariable model if $P < 0.20$ or if there was biological relevance. Model fitting and selection of best model was performed using stepwise regression and likelihood ratio testing. Two analyses were performed: the first using the a priori definition of definite/probable TB (definition 1), the second using the more stringent research definition of probable TB (definition 2).

RESULTS

Study population

Of the 60 children with TB enrolled in the study between 1 August 2009 and 30 September 2011, 7 (12%) had definite TB and 53 (88%) had probable TB; 24 (45%) cases had a known household TB source case, for whom the mother was reported to be the source case for 11 (46%), the father for 9 (38%), a sibling for 2 (8%) and others for 2 (8%). Of the 118 controls, five (4%) reported a known household TB source case. Cases and controls did not differ by age (median 3 years, $P = 0.53$) or sex (57% vs. 59% males, $P = 0.82$; Table 1). Both cases and controls had a similarly high prevalence of vitamin D deficiency (33/60 [55%] cases and 59/118 [50%] controls, $P = 0.53$). Thirty-one (52%) cases were underweight compared to 45 (38%) controls ($P = 0.08$). Cases were also more likely to be HIV-infected than controls (9/60, 13% vs. 0/118, 0% reported). Of 51 cases who had complete data for both types of exposure to IAP, 28 (55%) reported exposure compared to 29/113 (26%) controls ($P < 0.001$). For individual components of IAP, cases were significantly more likely to be exposed to tobacco smoke (38% vs. 19%, $P = 0.009$) and biomass fuel (26% vs. 7%, $P < 0.001$). The study population overall had a low level of household food insecurity (HFIAS > 1, 4%), but cases had significantly higher household food insecurity than controls (16/60 [27%] vs. 5/118 [4%], $P < 0.001$).

Factors associated with TB

Univariate analysis showed no significant difference between cases and controls in age, sex, WAZ score, presence of bacilli Calmette-Guérin scar, household size or household monthly income. Vitamin D deficiency was also not associated with being a TB case (odds ratio [OR] 1.22, 95% confidence interval [CI] 0.66–2.28; Table 2). However, known household TB exposure (OR 21.93, 95%CI 7.05–68.27), household food insecurity (OR 8.22, 95%CI 2.84–23.80), exposure to IAP (OR 3.53, 95%CI 1.76–7.06), school, preschool or daycare attendance (OR 2.4, 95%CI 1.08–5.33) and reported presence of an HIV-positive person in the household (OR 3.56, 95%CI 1.30–9.73) were all associated with increased odds of being a TB case. In a multivariate model adjusting for age, sex, school attendance, exposure to IAP, household TB exposure, household food insecurity and vitamin D deficiency, household TB exposure (adjusted OR [aOR] 25.41, 95%CI 7.03–91.81), exposure to IAP (aOR 2.67, 95%CI 1.02–6.97) and household food insecurity (aOR 11.55, 95%CI 3.33–40.15) were independently associated with TB (Table 2). HIV infection in the child was not included in the final model, as HIV infection was not reported for any of the control subjects. In the sub-analysis, assessing exposure to biomass fuel and tobacco smoke

individually, the association with TB was attenuated due to the small sample size (biomass fuel exposure aOR 3.58, 95%CI 0.94–13.59; passive tobacco smoke exposure aOR 1.84, 95%CI 0.61–5.53), but approached significance (Table 2).

Retrospective application of a research definition for probable tuberculosis

Application of a newly published research definition for probable TB resulted in a substantial decrease in the number of cases from 60 to 25. This decrease was driven by inconsistencies on CXR, specifically related to disagreements over the diagnosis of hilar adenopathy. Patients with disagreement on hilar adenopathy according to the more strict second definition (definition 2) were therefore not included in the TB disease category (18 cases, 30%). Patients who improved without treatment or who responded to standard antimicrobials for community-acquired pneumonia were also excluded from the TB disease category in definition 2 (17 cases, 28%).

Household food insecurity remained more common in cases, occurring in 5/25 (20%) cases and 5/118 (4%) controls ($P = 0.001$). More exposure to IAP was also reported for cases (16 cases, 73%; 29 controls, 26%; $P < 0.001$; Table 1). Despite the decrease in case numbers and subsequent decrease in power, household TB exposure (aOR 34.75, 95%CI 5.16–233.97), exposure to IAP (aOR 7.18, 95%CI 1.84–27.93) and household food insecurity (aOR 9.33, 95%CI 1.43–60.96) remained independently associated with TB (Table 2). Furthermore, biomass fuel exposure assessed individually was also highly significantly associated with TB (7.86, 95%CI 1.39–44.54).

DISCUSSION

Our study found two novel risk factors associated with TB disease in young children: exposure to IAP and household food insecurity. Moreover, when assessing the individual components of IAP using the most stringent definition of pediatric TB, biomass fuel exposure was identified as being highly independently associated with TB. This study also confirmed that close TB contact was a risk factor for TB disease. In contrast to studies among adult patients, we did not identify vitamin D deficiency as a risk factor for pediatric TB disease but noted that approximately half of all study subjects were vitamin D deficient.

Several studies have defined exposure to IAP as a composite of exposure to biomass fuel use and/or exposure to tobacco smoke in the home, and this is the definition used in our primary analysis.[3] Both of these variables have biologically plausible mechanisms for increasing risk of TB. Tobacco smoke alters T-cell responses, modulates mycobacterial containment and impairs macrophage cytokine responses.[3–7] Exposure to IAP generates particulate matter, carbon monoxide and other potentially toxic compounds such as polycyclic aromatic hydrocarbons.[3–7] Both interfere with mucociliary clearance, induce inflammation and reduce several antibiotic properties of lung macrophages, which in turn have been implicated as pathways for poor lung health.[3–7] It is known that exposure to IAP increases the risk of respiratory infection and asthma-related illnesses in children, with few studies assessing the role IAP plays in TB disease.[22,29–31] Two studies have found an association between tuberculin skin test positivity and passive tobacco exposure;[30,31] however, this is one of the first studies to demonstrate a strong epidemiological link between exposure to

IAP and pediatric TB disease. While this study was not powered to assess passive tobacco smoke exposure or biomass fuel exposure individually, tobacco exposure approached statistical significance, while biomass fuel exposure was highly independently associated with TB using the more stringent research definition of TB. In India, 25% of men and 3% of women smoke tobacco products and 70% of rural and 20% of urban Indians are exposed to biomass fuels.[23] Interventions reducing IAP through the use of safer household fuels, along with the reduction of exposure to tobacco, are thus likely to have a significant impact in reducing the risk of TB among children.

Another novel finding of our study was household food insecurity as a risk factor for TB in children aged <5 years, independent of nutritional status. Food security has been defined as 'having access to and being able to utilize food of sufficient quantity and quality at all times'.[32] Prevalence of household food insecurity in India is as high as 75%.[23] Food insecurity has been linked to adult acquisition of HIV;[32,33] however, studies of its relationship to other infections, including TB, are lacking. In this study, household food insecurity was significantly associated with increased risk of having TB, and food insecurity was not correlated with malnutrition or other socioeconomic descriptors such as monthly household income or household size.

It is unclear whether household food insecurity is a risk factor for TB or if it is a marker for other factors, such as poverty, that increase the risk of TB disease. In the model for HIV, insufficient quality and diversity of food can lead to micronutrient deficiencies which can affect disease acquisition, and food insecurity can lead to increased behavioral risks.[32] We do not know if this is also true for TB. However, interventions reducing household food insecurity, such as microfinance schemes and small business loans, merit further exploration.

Vitamin D deficiency is currently being investigated in association with respiratory infections, and specifically TB. Studies in adults have found that patients with TB have lower vitamin D levels than healthy controls,[19] and a cross-sectional study in refugee children had similar findings.[20] However, a recent study of refugee children found no difference in vitamin D levels between children with active TB, latent tuberculous infection or no TB.[21] Our study found a very high prevalence of vitamin D deficiency (52%), but found no association between vitamin D deficiency and TB disease in children aged <5 years.

Our study has some limitations. As this was a case-control study, we could only detect association, and not causation. It is therefore difficult, particularly in the category of vitamin D deficiency, to determine cause or effect of TB disease. However, unlike vitamin D levels, IAP and household food security will not be affected by acute disease and are thus less likely to be subject to reverse causation. Our study relied on self-reporting of HIV status for control children, which may have led to underestimation. However, we do not believe that this would have affected results, as HIV prevalence in this hospital is low (<2%), as in our results. We relied on questionnaire data without biomarkers for exposure to IAP; however, most epidemiological studies have relied on questionnaire data for such exposures. Finally, the definition of TB remains difficult in children. To counteract this, we analyzed data using

two definitions. While the use of the research definition attenuated study power, exposure to IAP and household food insecurity remained significant, strengthening the argument that these are true risk factors for pediatric TB.

In conclusion, we found two important modifiable risk factors associated with TB disease in young children: IAP and household food insecurity. Interventions reducing IAP, particularly reducing adult tobacco use and household biomass exposure, as well as improving food security, will likely have a significant impact on the risk of childhood disease.

Acknowledgments

The authors thank D Persaud, K Sik Kim, W-T Yang and R Warlick for editorial support. They also thank their study team and the families who participated in this study. This work was supported by the Indo-US Indian Council for Medical Research and the National Institutes of Child Health Diseases, the US National Institutes of Health (Grant 1R03HD0610509 01 [RB and SJ]); the National Institutes of Allergy and Infectious Diseases, National Institute of Health Clinical Trials Unit (Grant 5U01A106977 [AG]), Bethesda, MD, USA; Johns Hopkins Center for Global Health Faculty Grant, Baltimore, MD, USA (SJ); Gilead Foundation, Foster City, CA, USA (AG); Ujala Foundation, New Delhi, India (AG); and BD, Sparks, MD, USA, for donation of MGIT tubes.

References

1. Lönnroth K, Castro KG, Chakaya JM, et al. Tuberculosis control and elimination 2010–50: cure, care and social development. Lancet. 2010; 375:1814–1829. [PubMed: 20488524]
2. Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald PR, Starke JR. Childhood pulmonary tuberculosis: old wisdom and new challenges. Am J Respir Crit Care Med. 2006; 173:1078–1090. [PubMed: 16484674]
3. Lin HH, Ezzati M, Murray M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. PLOS Med. 2007; 4:e20. [PubMed: 17227135]
4. Shang S, Ordway D, Heneo-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. [PubMed: 21357942]
5. van Zyl Smit RN, Pai M, Yew WW, et al. Global lung health: the colliding epidemics of tuberculosis, tobacco smoking, HIV and COPD. Eur Respir J. 2010; 35:27–33. [PubMed: 20044459]
6. Prasad R, Suryakant, Garg R, Singhal S, Dawar R, Agarwal GG. A case control study of tobacco smoking and tuberculosis in India. Ann Thorac Med. 2009; 4:208–210. [PubMed: 19881167]
7. Gupta KB, Gupta R. Association between smoking and tuberculosis. Indian J Tuberc. 2003; 50:5–8.
8. Kolappan C, Subramani R. Association between biomass fuel and pulmonary tuberculosis: a nested case-control study. Thorax. 2009; 64:705–708. [PubMed: 19359267]
9. Lakshmi PV, Virdi NK, Thakur JS, Smith KR, Bates MN, Kumar R. Biomass fuel and risk of tuberculosis: a case-control study from northern India. J Epidemiol Community Health. 2012; 66:457–461. [PubMed: 21118950]
10. Mishra VK, Retherford RD, Smith KR. Biomass cooking fuels and prevalence of tuberculosis in India. Int J Infect Dis. 1999; 3:119–129. [PubMed: 10460922]
11. Cegielski JP, McMurray DN. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis. 2004; 8:286–298. [PubMed: 15139466]
12. Lönnroth K, Williams BG, Cegelski P, Dye C. A consistent log-linear relationship between tuberculosis incidence and body mass index. Int J Epidemiol. 2010; 39:149–155. [PubMed: 19820104]
13. Semba RD, Darnton-Hill I, de Pee S. Addressing tuberculosis in the context of malnutrition and HIV coinfection. Food Nutr Bull. 2010; 31:S345–364.

14. van Lettow M, Fawzi WW, Semba RD. Triple trouble: the role of malnutrition in tuberculosis and human immunodeficiency virus co-infection. Nutr Rev. 2003; 61:81–90. [PubMed: 12723640]
15. Korthals Altes H, Kremer K, Erkens C, van Soolingen D, Wallinga J. Tuberculosis seasonality in the Netherlands differs between natives and non-natives: a role for vitamin D deficiency? Int J Tuberc Lung Dis. 2012; 16:639–644. [PubMed: 22410705]
16. Liu PT, Stenger S, Tang DH, Modlin RL. Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. J Immunol. 2007; 179:2060–2063. [PubMed: 17675463]
17. Martineau AR, Wilkinson RJ, Wilkinson KA, et al. A single dose of vitamin D enhances immunity to mycobacteria. Am J Respir Crit Care Med. 2007; 176:208–213. [PubMed: 17463418]
18. Wejse C, Gomes VF, Rabna P, et al. Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med. 2009; 179:843–850. [PubMed: 19179490]
19. Wejse C, Olesen R, Rabna P, et al. Serum 25-hydroxyvitamin D in a West African population of tuberculosis patients and unmatched healthy controls. Am J Clin Nutr. 2007; 86:1376–1383. [PubMed: 17991649]
20. Williams B, Williams AJ, Anderson ST. Vitamin D deficiency and insufficiency in children with tuberculosis. Pediatr Infect Dis J. 2008; 27:941–942. [PubMed: 18776821]
21. Gray K, Wood N, Gunasakera H, et al. Vitamin D and tuberculosis status in refugee children. Pediatr Infect Dis J. 2012; 31:521–523. [PubMed: 22189532]
22. Kodgule R, Salvi S. Exposure to biomass smoke as a cause for airway disease in women and children. Curr Opin Allergy Clin Immunol. 2012; 12:82–90. [PubMed: 22157154]
23. International Institute for Population Sciences. Nutrition in India National Family Health Survey 3, India, 2005–2006. Mumbai, India: IIPS; 2007. http://www.rchiips.org/NFHS/volume_1.shtml [Accessed October 2013]
24. Harinarayan CV, Joshi SR. Vitamin D status in India—its implications and remedial measures. J Assoc Physicians India. 2009; 57:40–48. [PubMed: 19753759]
25. Amdeka YK. Consensus statement on childhood tuberculosis. Working Group on Tuberculosis, Indian Academy of Pediatrics. Indian J Pediatr. 2010; 47:41–55.
26. Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definition for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. J Infect Dis. 2012; 205 (Suppl 2):S199–S208. [PubMed: 22448023]
27. Swindale A, Bilinsky P. Development of a universally applicable household food insecurity measurement tool: process, current status, and outstanding issues. J Nutr. 2006; 136 (Suppl): 1449S–1452S. [PubMed: 16614442]
28. Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008; 122:398–417. [PubMed: 18676559]
29. Smith KR. National burden of disease in India from indoor air pollution. Proc Natl Acad Sci USA. 2000; 97:13286–13293. [PubMed: 11087870]
30. du Preez K, Mandalakas AM, Kirchner HL, et al. Environmental tobacco smoke exposure increases *Mycobacterium tuberculosis* infection risk in children. Int J Tuberc Lung Dis. 2011; 15:1490–1496. [PubMed: 22008762]
31. den Boon S, Verver S, Marais B, et al. Association between passive smoking and *Mycobacterium tuberculosis* infection in children. Pediatrics. 2007; 119:734–739. [PubMed: 17403844]
32. Tsai AC, Hung KJ, Weiser SD. Is food insecurity associated with HIV risk? Cross-sectional evidence from sexually active women in Brazil. PLOS Med. 2012; 9:e1001203. [PubMed: 22505852]
33. Bloem MW, Saadeh R. The role of nutrition and food insecurity in HIV and tuberculosis infections and the implications for interventions in resource-limited settings. Foreword Food Nutr Bull. 2010; 31 (Suppl):S289–S291.

Table 1

Child, maternal and household factors among probable and definite TB cases and healthy controls associated with TB disease in children aged ≤5 years, Pune, India

		Definition 1*			Definition 2†		
Characteristic	**Total‡**	**Cases (*n* = 60) *n* (%)**	**Controls (*n* = 118) *n* (%)**	***P* value**	**Cases (*n* = 25) *n* (%)**	**Controls (*n* = 118) *n* (%)**	***P* value**
Child							
Age, years, median [IQR]	3 [1.5–3.8]	3 [1.4–4]	3 [1.6–3.7]	0.779	2.3 [1–3.5]	3 [1.6–3.7]	0.278
Age, months							
≤12	29	11 (18)	18 (15)	0.599	10 (40)	18 (15)	0.005
>12	149	49 (82)	100 (85)		15 (60)	100 (85)	
Sex							
Male	103 (58)	34 (57)	69 (59)	0.817	14 (56)	69 (59)	0.846
Female	75 (42)	26 (43)	49 (41)		11 (44)	49 (41)	
Weight-for-age *Z* score							
>–2	102 (57)	29 (48)	73 (62)	0.084	15 (60)	73 (62)	0.001
≤–2	76 (43)	31 (52)	45 (38)		10 (40)	45 (38)	
BCG scar present							
No	25 (14)	9 (15)	16 (14)	0.794	3 (12)	16 (14)	0.823
Yes	153 (86)	51 (85)	102 (86)		22 (88)	102 (86)	
HIV status§							
Negative	169 (95)	51 (85)	118 (100)	<0.001	19 (76)	118 (100)	<0.001
Positive	9 (5)	9 (15)	0		6 (24)	0	
Tobacco smoke exposure							
No	124 (76)	29 (62)	95 (81)	0.009	11 (55)	94 (81)	0.010
Yes	40 (24)	18 (38)	22 (19)		9 (45)	22 (19)	
Biomass fuel exposure							
No	148 (87)	42 (74)	106 (93)	<0.001	14 (58)	106 (93)	<0.001
Yes	23 (17)	15 (26)	8 (7)		10 (42)	8 (7)	
Exposure to indoor air pollution¶							
No	107 (65)	23 (45)	84 (74)	<0.001	6 (27)	84 (74)	<0.001
Yes	57 (35)	28 (55)	29 (26)		16 (73)	29 (26)	

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2015 July 01.

Characteristic	Total[‡]	Definition 1[*] Cases (*n* = 60) *n* (%)	Definition 1[*] Controls (*n* = 118) *n* (%)	Definition 1[*] *P* value	Definition 2[†] Cases (*n* = 25) *n* (%)	Definition 2[†] Controls (*n* = 118) *n* (%)	Definition 2[†] *P* value
Vitamin D deficient[#]							
No	86 (48)	27 (45)	59 (50)	0.528	12 (48)	59 (50)	0.826
Yes	92 (52)	33 (55)	59 (50)		13 (52)	59 (50)	
Attends school							
No	146 (83)	43 (74)	103 (87)	0.029	21 (88)	103 (87)	0.966
Yes	30 (17)	15 (26)	15 (13)		3 (12)	15 (13)	
Household TB exposure							
No	135 (83)	29 (55)	106 (96)	<0.001	12 (67)	106 (96)	<0.001
Yes	28 (17)	24 (45)	4 (4)		6 (33)	4 (4)	
Maternal and household							
Maternal education							
≥4th grade	133 (76)	39 (67)	94 (80)	0.071	14 (58)	94 (80)	0.027
<4th grade	43 (24)	19 (33)	24 (20)		10 (42)	24 (20)	
Household income, INR[**]							
≥5000	79 (45)	29 (52)	50 (42)	0.244	9 (39)	50 (42)	0.749
<5000	95 (55)	27 (48)	68 (58)		14 (61)	68 (58)	
HIV-positive person in home[††]							
No	160 (90)	49 (82)	111 (94)	0.009	20 (80)	111 (94)	0.022
Yes	18 (10)	11 (18)	7 (6)		5 (20)	7 (6)	
House size, m^2							
>46.5	148 (86)	47 (87)	101 (86)	0.420	22 (96)	101 (86)	0.182
≤46.5	24 (14)	7 (13)	17 (14)		1 (4)	17 (14)	
HFIAS score[‡‡]							
<1	113 (96)	44 (73)	113 (96)	<0.001	20 (80)	113 (96)	0.005
≥1	5 (4)	16 (27)	5 (4)		5 (20)	5 (4)	

[*] Confirmed TB cases consisted of those with positive AFB smear and/or culture; probable cases were those with known TB contacts, clinical and CXR findings consistent with TB, but AFB smear or culture negative.

[†] Included no response to antibiotics at 2 weeks and two CXR readings. Cases decreased from 60 to 25 primarily due to initial over-classification of hilar lymphadenopathy on CXR.

[‡] Numbers of individual columns may not add up to number of cases/controls due to some non-responses.

[§] HIV status confirmed by testing in cases and self-report in controls.

[¶] Indoor air pollution created as a composite of passive tobacco smoke exposure and/or biomass cooking fuel exposure.

[#] Vitamin D measured as serum 25 hydroxyvitamin D using Diasorin Radioimmunoassay; deficiency <20 ng/ml.

[**] Household income obtained by self-report in INR (<100 US dollars/month).

[††] Household contact with HIV obtained by self-report only.

[‡‡] HFIAS score using standardized questionnaire. Score >1 indicates some degree of household food insecurity.

TB = tuberculosis; IQR = interquartile range; BCG = bacille Calmette-Guérin; HIV = human immunodeficiency virus; INR = Indian rupee; HFIAS = Household Food Insecurity Access Score; AFB = acid-fast bacilli; CXR = chest radiograph.

Table 2

Univariate and multivariate analysis of child, maternal and household factors among probable and definite TB cases and healthy controls associated with TB disease in children aged ≤5 years, Pune, India

	Definition 1*		
Characteristic	**Univariate OR (95%CI)**	**Multivariate OR (95%CI)**	**Definition 2† Multivariate OR (95%CI)**
Child			
Sex			
Male	Reference		
Female	1.08 (0.57–2.02)	‡	‡
Nutritional status			
WAZ >–2	Reference		
WAZ ≤–2	1.73 (0.93–3.25)	‡	‡
Age < 12 months			
No	Reference	Reference	Reference
Yes	1.25 (0.55–2.84)	2.01 (0.61–6.70)	6.73 (1.69–26.84)
BCG scar present			
No	Reference		
Yes	0.89 (0.37–2.14)	‡	‡
Household TB exposure			
No	Reference	Reference	Reference
Yes	21.93 (7.05–68.26)	25.41 (7.03–91.81)	34.75 (5.16–233.97)
Exposure to indoor air pollution§			
No	Reference	Reference	Reference
Yes	3.53 (1.76–7.06)	2.67 (1.02–6.97)	7.18 (1.84–27.93)
Tobacco smoke exposure§			
No	*Reference*	*Reference*	*Reference*
Yes	*2.68 (1.27–5.67)*	*1.84 (0.61–5.53)*	*2.88 (0.67–12.39)*
Biomass fuel exposure§			
No	*Reference*	*Reference*	*Reference*
Yes	*4.73 (1.87–11.99)*	*3.58 (0.94–13.59)*	*7.86 (1.39–44.54)*
Vitamin D deficient (<20 ng/ml)			
No	Reference	Reference	Reference
Yes	1.22 (0.66–2.28)	1.00 (0.38–2.66)	0.53 (0.13–2.07)
School attendance			
No	Reference	Reference	Reference
Yes	2.40 (1.08–5.33)	1.85 (0.51–6.67)	0.76 (0.06–9.51)
Maternal and household			
Maternal education <4th grade			
No	Reference		
Yes	1.91 (0.94–3.87)	‡	‡
Household income <5000 INR/month			

	Definition 1*		
Characteristic	**Univariate OR (95%CI)**	**Multivariate OR (95%CI)**	**Definition 2† Multivariate OR (95%CI)**
No	Reference		
Yes	0.68 (0.36–1.30)	‡	‡
HIV-positive person in home			
No	Reference		
Yes	3.56 (1.30–9.73)	‡	‡
House size ≤46.5 m^2			
No	Reference		
Yes	1.13 (0.44–2.91)	‡	‡
HFIAS >1			
No	Reference	Reference	Reference
Yes	8.22 (2.84–23.80)	11.55 (3.33–40.15)	9.33 (1.43–60.96)

*Confirmed TB cases were those with positive AFB smear and/or culture; probable cases were those with known TB contacts, clinical and radiographic findings consistent with TB, but AFB smear or culture negative.

†Included no response to antibiotics at 2 weeks and 2 CXR readings. Cases decreased from 60 to 25 primarily due to initial over classification of hilar lymphadenopathy on CXR.

‡Not included in model due to $P > 0.20$, or excluded via stepwise regression; HIV-positive children not included in model as no control patients were HIV-positive.

§Indoor air pollution was analysed as a composite of passive tobacco smoke exposure and/or biomass cooking fuel exposure. We also assessed each of these individually in univariable and multivariable analyses as shown above in italics. Using the same variables in the main multivariable model that assessed indoor air pollution as a composite outcome, biomass fuel exposure as an individual exposure reached statistical significance at $P < 0.05$ using definition 2, and showed a strong trend using definition 1.

TB = tuberculosis; OR = odds ratio; CI = confidence interval; WAZ = weight-for-age *Z* score; BCG = bacille Calmette-Guérin; INR = Indian rupee; HIV = human immunodeficiency virus; HFIAS = Household Food Insecurity Access Score; AFB = acid-fast bacilli; CXR = chest radiograph.