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Infection with tuberculosis in children under six who come into touch with smear-positive individuals

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Abstract
Introduction: Annually, tens of millions of children are being exposed to tuberculosis infection. Note that children are in higher risk of getting infection and sever types of the disease, detecting the factors associated with transmission of the tuberculosis infection and disease to the exposed children is necessary for disease prevention within the community.
Methods: In this retrospective cohort study, 50 children under 6 who were in close contact with 25 smear-positive pulmonary tuberculosis cases in Pondicherry, India, were investigated. Demographic, behavioral and clinical characteristics of children and index cases were collected and tuberculosis infection and disease were assessed using the WHO guidelines.
Results: Of 50 children exposed to the active cases, 12 (24%) were infected to tuberculosis but none of them had active disease. We also found significant associations of the history of diabetes mellitus in the index cases ($p = 0.043$) and large family size ($p = 0.026$) with the increased risk of infection among the exposed children.
Conclusion: Children under six which are in close contact with diabetic tuberculosis cases in large families are in higher risk of getting infection.

Keywords: Tuberculosis TB children TST LTBI latent TB infection

Introduction
Mycobacterium tuberculosis (MBT) is the most common infectious agent leading to mortality and morbidity and affects tens of millions of children each year [1]. Due to considerable delay in the diagnosis of active tuberculosis (TB) cases, the infection transmission continues within the community. It has shown that 30%- 50% of household contacts can lead to active infection which is more common in children in close contact with the adults TB cases [2]. Based on the surveys carried out by interferon-gamma release assay (IGRA), children are in higher risk of getting TB infection and disease. Moreover, they are more susceptible to disseminated forms of the disease such as miliary tuberculosis and TB meningitis leading to higher mortality [3]. Several factors are related to the transmission of the TB infection including the type of contact with the source of infection, environmental characteristics and host characteristics such as age and immunity [3, 4]. Considering the higher prevalence of tuberculosis infection and disease among the children in contact with the TB patients, investigating the source of infection and follow up of the household contacts is of great importance leading to better understanding and control of the disease [5-7].
WHO guidelines have emphasized on the preference of the prophylaxis treatment of children under 5 in household exposures to the active TB cases. More recent guidelines have generalized the mentioned prescriptions to the higher ages of children and even the adults in the high burden countries [8]. It seems that household contacts is one of the main causes of the infection transmission in the region. To be able to control the spread of the infection, early detection of the cases in the younger age groups as well as determining the associated factors of the infection transmission between children and other household members is necessary. Therefore, in the current study, all children under 6 with the close household exposure to the active TB cases were investigated regarding the evidences of any infection or disease as well as relevant associated factors.

Materials and Methods
Study design: All of the children under six who were in household close contacts with the active smear positive TB cases in Puducherry and Karaikal districts of Pondicherry province with the highest incidence rate of tuberculosis in India were retrospectively investigated.

It should be noted that families with TB cases without children under six years old age were not participated into the study. The sampling method was census. Therefore, there is no need to estimate the sample size. The protocol of the

Tuberculin skin test (TST)

Despite the challenges of the TST interpretation and the variability of its results, it is still being used as one of the main methods of TB infection/disease diagnosis in children [9]. According to the CDC (center for disease control and prevention), the TST induration size will be measured and interpreted after 48–72 h of intra-dermal injection. Any induration greater than or equal to five millimeters among children in close contact with active TB cases is considered positive [10]. A positive test without signs and symptoms of tuberculosis is introduced as latent TB infection (LTB) and should be received prophylactic anti-TB treatment [11].

Note that tuberculosis infection and disease among children can be seen with various signs and symptoms, they are usually misdiagnosed as the other disorders such as pneumonia, viral and bacterial infections, malnutrition and etc., which is one of the main challenges in the TB control system. TB infection and disease is diagnosed based on the history of exposure, clinical signs and symptoms, tuberculin skin test results, chest X ray and confirmation of the mycobacterium tuberculosis in the sputum smear and sputum culture. Due to the limited availability of sputum in younger children, negative sputum smear is one of the most diagnostic barriers in this age group [12, 13]. All required information were collected using the electronic files, interview with the patients and their family members and inspection of the children and active cases within a researcher-made checklist. Interpretation of the tuberculin skin tests and chest X-rays as well as physical examinations of the study subjects was performed by trained physicians.

Statistical analyses

STATA version 14 software was used for data description and analysis. Qualitative and quantitative variables were compared between groups using Chi square and T test/Mann Whitney U tests respectively. Investigating the factors associated with the TB infection, was used based on logistic regression models controlling the effect of potential confounders.

Results

Totally, during the study period, 25 smear positive pulmonary TB cases whose families included at least one under six-year-old children were diagnosed and registered in the study area. That included 13 families from Puducherry and 12 families from Karaikal districts. Most of them were female (72%). The youngest and oldest TB patients were 21 and 83 years old respectively with mean (SD) age of 55.4 (21.09). The smear positivity of the patients varied from 5.26% for 2+ to 50% for 1+. Most of them had abnormal chest X-ray (88%). Of the study families, 68% were rural residents. Among patients, 5 (20%) had history of diabetes mellitus. Investigating the family members showed that 50 children under six were in close contact with the TB cases, 27 of which were from Puducherry and 23 children were from Karaikal districts. The number of under six-year-old children in these families varied between 1 and 7 children. In other words, each patient in average was in house-hold contact with at least 3.04 children under six. Mean (SD) age of the exposed children was 2.87 (1.56) years varied between three months and 6 years. Of them, 31 (62%) were female. Mean (SD) TST induration size of the children was 2.7 (2.76) mm 12 (24%) of which were higher than 5 mm. Zero TST induration size was observed in most of the children (30%). Just two (4%) children had abnormal chest X-ray.

Frequency of rural residency among children with abnormal TST reaction was significantly lower than that of children with normal TST (25% vs 78.95% respectively, p = 0.001). Frequency of diabetic index cases among children with abnormal TST was significantly higher than that of children with normal TST (58% vs 10% respectively, $p<0.001$). Moreover, children with abnormal TST results compared to those with normal TST, were living in the families with larger sizes (mean number: 8±2.21 vs 4.16±2.51 respectively, $p<0.001$). No significant difference was observed between children with normal and abnormal TST regarding the frequencies of gender (p = 0.910), sputum smear positivity (p = 0.108), patient's pulmonary involvement (p = 0.092), cigarette smoking (p = 0.890) and opium addiction (p = 0.398) in the index cases, isolated room for the children (p = 0.495) and for the index case (p = 0.173) within the house, mean age of the index cases (p = 0.460), mean delay time in TB diagnosis (p = 0.082), mean duration of children stay in the house (p = 0.838), mean number of children living in each house (p = 0.134) and mean age of the children (p = 0.083) (Table 1). Table 2 shows that the odds ratios of children being infected was statistically significant for diabetic index case (p = 0.043) and living in contact with more than two members (p = 0.026). Other characteristics of the index and children had no significant associations with infection transmission.

Discussion

The present study was the first investigation of the TB household contacts in one of the regions with the highest prevalence of tuberculosis in India. Although one-fourth of the exposed children in this area were infected with TB, fortunately, none of them had evidences of active TB disease.

Lower rate of pathogenicity of tuberculosis among the exposed children in our study area can be due to good care and follow up of TB patients and their families in the PHC system of India particularly in the most prevalence areas. However, in contrast to the above-mentioned studies, the exposed family members in the current research were retrospectively followed up which may be another reason for the differences in the results.

Investigating the risk factors of TB infection transmission in the present study showed that if a smear positive TB patient was diabetic, the infection can be transferred to the exposed children easier than a non-diabetic index case. Similarly, Skowronski ´ *et al.* [16] and Harris *et al.* [17] reported that because both cellular and humoral immunity are affected during diabetes mellitus, these patients are in a higher risk of developing tuberculosis infection than the general population. They also have higher chance of transmitting the infection to the community.

Table 1: Shows number of negative TST (%) and positive TST (%)

Characteristics of participants		Number of Negative TST (%)	Number of Positive TST (%)	P-value
Patient gender	Male	12 (31.58)	4 (33.33)	0.910
	Female	26 (68.43)	8 (66.67)	
Smear positivity	1–9 bacillus	5 (13.16)	0 (0)	0.108
	1+	19 (50)	3 (25)	
	2+	2 (5.26)	2 (16.67)	
	3+	12 (31.58)	7 (58.33)	
Patient's CXR	Normal	10 (26.32)	0 (0)	0.092
	Abnormal	28 (73.68)	12 (100)	
Residence area	Urban	8 (21.05)	9 (75)	0.001
	Rural	30 (78.95)	3 (25)	
History of diabetes	No	34 (89.47)	5 (41.67)	<0.001
	Yes	4 (10.53)	7 (58.33)	
Cigarette smoking	No	31 (81.58)	10 (83.33)	0.890
	Yes	7 (18.42)	2 (16.67)	
Opium addiction	No	31 (81.58)	10 (83.33)	0.398
	Yes	7 (18.42)	2 (16.67)	
Children gender	Male	15 (39.47)	4 (33.33)	0.702
	Female	23 (60.53)	8 (66.67)	
Separate room for children	No	10 (26.32)	2 (16.67)	0.495
	Yes	28 (73.68)	10 (83.33)	
Separate room for patient	No	30 (78.95)	12 (100)	0.173
	Yes	8 (21.05)	0 (0)	
Patient's age(year)	Mean (SD)	55.97 (19.82)	60.17 (20.92)	0.460
Children age (year)	Mean (SD)	3.09 (1.52)	2.19 (1.56)	0.083
Delay in diagnosis (days)	Mean (SD)	35.29 (29.29)	46.92 (29.67)	0.082
Family size (persons)	Mean (SD)	4.16 (2.51)	8 (2.21)	<0.001
Number of children in house (persons)	Mean (SD)	2.89 (2.14)	1.38 (3.5)	0.134
Duration of children stay in house (days)	Mean (SD)	20.10 (5.62)	20.67 (5.07)	0.138

TST: tuberculin skin test, SD: standard deviation.

Table 2: Adjusted odds ratios for getting infection based on different factors

Abnormal TST	Adjusted odds ratio	P-value
Diabetic index case	21.48	0.043
Family size	1.76	0.026
Living in rural area	1.36	0.808
Delay in TB diagnosis	0.99	0.828
Children age	0.37	0.060
CXR	Omitted at multivariable model	

In the current study, the children in close contact to TB cases in large families had higher risk of getting infection. However, other demographic, behavioral and clinical characteristics of the index cases as well as the exposed children had no effect on the infection transmission. Conversely, Gessner *et al*. showed that the involvement of the upper lobe of the left lung was significantly associated with developing infection in the exposed individuals [18]. Similar to our findings, Lienhardt *et al*. found the family size of the patients as a risk factor for infection transmission, but in contrast to our results, they reported that the duration of coughing, children's age as well as their nutritional status were also associated with this transmission [19].

In a study carried out by PerezVelez, the age and duration of being exposed as well as the severity of disease (Smear positivity index) in the index case, were introduced as effective factors of getting infection by the in-contact children [20]. HIV status of the index case was also reported as a risk factor for transmission of the infection in some researches [21]. This factor was also investigated in the current study, but none of the index cases were HIV positive. Our study was some limitations such as the small sample size leading to limited investigation of all factors associated in the infection transmission such as HIV status of the TB cases.

However, we tried to carry out the study in the areas with the most incidence rate of tuberculosis in India. In addition, the best method for investigating the close contacts is prospective designs, but our study subjects were retrospectively followed approximately-two years after being exposed with the index cases. However, we know that the highest rate of transmission is the first 2–4 weeks of the anti-TB treatment and it should be noted that all of the index patients in this study received effective treatment immediately after diagnosis.

Conclusion

In conclusion, our study emphasizes on preventive measures as the best method for limiting the infection transmission to the household close contacts. According to our results, such preventive measures should be taken into account especially in the large family sizes with TB patients and those who have history of diabetes mellitus.

Declaration of Competing Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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