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Home humidity increased risk of tuberculosis in children living with adult active tuberculosis cases

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ABSTRACT

Indonesia is one of the countries with the largest number of tuberculosis (TB) cases in the world. Environmental factors play significant roles in infection and disease development in children living with adult active TB cases. The aim of this study was to explore the environmental factors affecting TB risk in children, including humidity and number of people living in the same house with the children. Using a cross-sectional study design, children living with active TB adults for at least 8 weeks were recruited. The subjects underwent clinical examination, tuberculin skin test (TST) and radiological investigations. Home visits were conducted three times daily, namely in the morning, at midday, and in the evening, to measure humidity by digital hygrometer and to observe home conditions. Of 56 index cases living with active TB adults in an urban low socio-economic setting, 64 contact TB children were recruited. These children were classified as class I with negative TST and no clinical signs, class II with positive TST and no clinical signs, and class III with both positive TST and clinical signs. There were 32 (50%) class I, 10 (15.6%) class II and 22 (34.3%) class III children. However, a sub-sample of 43 showed positive results for Mtb 16S rRNA, indicating that all children were infected. The humidity cut-off point was set at 75%, p=0.04 and EP 2.09 (CI= 1.32-3.29), signifying that children living in houses with a humidity higher than 75%, were twice more likely to be tuberculin positive. Environmental conditions playing a role in disease development were humidity and number of people living in the house.

Key words: Tuberculosis, home condition, humidity, children

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INTRODUCTION

Indonesia is one of the countries with the largest number of tuberculosis (TB) cases in the world, affecting people in the productive age range of 15-65 years. In endemic countries, TB in children accounts for 12-20% of all TB cases.[(1)] Children living with active TB parents, termed contact children, are infected by *Mycobacterium tuberculosis* (Mtb), the causative pathogen of TB. These contact children are at higher risk for infection and disease development, and as adults will constitute a reservoir of *M.tuberculosis* as well

as a source of infection for TB in the community.[2]

Adverse environmental conditions in the contact children's homes, such as high humidity and poor ventilation can increase the risk of TB. Moreover, a high population density in the house and a high number of household members further increase the infection rate from adult active TB cases, termed index cases, to children.[3] According to epidemiological data, areas with low socio-economic status have a high prevalence of TB. Whether children living with tuberculous adults will develop active TB depends both on the closeness of contact and the concentration of the Mtb agent in the sputum of index cases.

The aim of this study was to identify the home environmental conditions affecting the risk of TB infection in children living with adult active TB patients.

METHODS

Research design

An observational cross-sectional study was conducted from September 2009 to November 2009 at dr. Sutomo Hospital, Surabaya.

Research subjects

Children under 15 years of age who lived with adult open TB cases for at least 8 weeks consecutively were recruited into the study. Adult TB patients with positive smears who came to the pulmonology clinic at dr Sutomo Hospital were asked whether or not they were living with children under 15 years. Patients giving an affirmative answer were suggested to bring their children to the clinic for screening.

Sample size determination

Sample size was determined by the following formula:

$$n = \{N. Z^2_{1-\alpha/2} P (1-P)\} / \{(N-1) d^2 + Z^2_{1-\alpha/2} P (1-P)\}$$

where N = 140 (estimated monthly number of new sputum positive cases at the pulmonology clinic); α = 5%, therefore $Z^2_{1-\alpha/2} = (1.96)^2 = 3.84$; P = proportion of affected children among contact children; d = deviation from actual value = 12.5%.

The minimum sample was 50 TB patients, with all children living with them being included in the study sample. The subjects were selected by systematic random sampling.

Data collection

The children of the TB patients were asked to visit the clinic twice, the first visit being for blood collection, tuberculin tests and chest radiographs, while the second visit was for reading the tuberculin skin test (TST) results and collection of the stool samples brought by the children. Clinical and radiological examinations were conducted at the pediatric clinic, while TST results were examined by a physician. The homes of the children were visited three times. All observations, interviews and measurements were performed by trained field workers.

Diagnosis of tuberculosis

The diagnosis of tuberculosis was according to the WHO system as follows: Table 1[4]

Table 1. Description of tuberculosis class [4]

Class	Class type description
TB-0	No TB exposure. Not infected: no history of exposure, negative reaction to TST or negative in-vitro laboratory diagnostic tests.
TB-1	TB exposure. No evidence of infection: history of exposure and negative reaction to TST or negative in-vitro latent TB infection (LTBI) laboratory diagnostic tests.
TB-2	LTBI, no disease. Positive TST or positive in-vitro LTBI laboratory diagnostic tests, negative bacteriologic studies (if done) and no clinical and/or radiographic evidence of active TB.
TB-3	TB, clinically active. Laboratory, clinical, bacteriological, and/or radiographic evidence of current disease.

Note: Our study subjects were contact children, therefore we did not have TB class 0.

Tuberculin test

Purified Protein Derivative (Biofarma, Bandung) was used for TST. Results were examined after 72 hours, the presence of an induration of >10 mm in diameter indicating a positive TST, regardless of age and BCG status.

Measurements

Each adult patient's house was visited and observed, the humidity of the house being measured by means of a digital hygrometer, and expressed as the percentage of water in the air. A dwelling is considered to be healthy at a humidity of 40-60%.[5] The cut-off point in our study was set at a humidity of 75%, which was higher than recommended in the reference,[5] because all dwellings housed TB patients.

The numbers of bacilli found in index cases is very important, because it is a measure of both the degree of infectivity of the patient and the severity of the disease. The International Union Against Tuberculosis and Lung Disease (IUATLD) recommends the following grading scale of smear microscopy results (Table 2).[6]

M. tuberculosis 16S rRNA was measured on PBMC by means of a commercial kit (Cobas Amplicor Roche), exactly as written in the manufacture's protocol. Sensitivity and specificity of the kit, as compared to bacterial culture, was 80.2 % and 96.6%, respectively.

Ethical clearance

Ethical clearance of the study protocol was granted by the Ethical Committee of dr Sutomo Hospital.

Statistical analysis

Data were analyzed using SPSS version 13. The prevalence exposure rates of several environmental factors, viz. humidity, ventilation, number of people living in the same house, and genetic proximity (relatedness) of index case, were compared between tuberculin skin test (TST) results. For ordinal data, Mann-Whitney and Kruskal-Wallis tests were used for comparison between groups. The level of significance was set at 0.05.

RESULTS

A total of 73 children under 15 years of age who were living with 56 adult smear-positive cases were examined. Most of them came from households of low economic status. The mean age of the children was 6.8 ± 3.5 years (range 1 year to 15 years), with a slight excess of males (39 or 53%) over females (34 or 47%). Most of the homes were crowded, with 5 ± 1 persons (range 3–9) per dwelling and calculated mean density per 10 m^2 of 2 ± 1 persons (range 0.15 – 10) (Table 3).

Table 2. IUATLD-recommended grading of sputum smear microscopy results[6]

Acid fast bacilli (AFB) counts	Recording/reporting
No AFB in at least 100 fields	0/negative
1 to 9 AFB in 100 fields*	Actual AFB counts†
10 to 99 AFB in 100 fields‡	+
1 to 10 AFB per field in at least 50 fields†	++
> 10 AFB per field in at least 20 fields‡	+++

*A finding of 1 to 3 bacilli in 100 fields does not correlate well with culture positivity. The interpretation of the significance of this result should be left to the national tuberculosis program (NTP) and not to the microscopist. It is recommended that a new smear be prepared from the same sputum specimen and be re-examined.
†The reporting of actual acid fast bacilli (AFB) counts is recommended to allow a competent authority to determine whether the number fits the TB case definition of the NTP.
‡In practice most microscopists read a few fields and confirm the finding by a quick visual scan of the remaining fields.

Table 3. Distribution of housing density, proximity to index cases, smoking and chronic cough of household members (n= 73)

Variable indicator	n (%)
Housing density *	
Number of people living in the same house	5 ± 1
Density per 10 m^2	2 ± 1
Proximity to index cases	
Genetic proximity:	
Parents	54 (78)
Non-parents	19 (22)
Sharing the same room:	
Yes	57 (67)
No	16 (23)
Duration of contacts (weeks) *	40 ± 46.9
AFB** index case :	
Positive 1	37 (51)
Positive 2	27 (37)
Positive 3	9 (12)
Smoking and chronic cough	
Smoking household member :	
One	36 (49)
More than one	5 (6.8)
None	32 (42.2)
Chronic cough in other household members :	
Yes	9 (12)
No	64 (88)

* Mean ± SD; **AFB=acid fast bacilli

Although 9 children had clinical TB, their TB class was undetermined, because of negative TST results. Based on the IGRA/ ELISPOT results, only 71 children could be tested. In addition, there were 8 children with clinical TB but negative IGRA/ELISPOT test results, who were therefore also not categorized as to TB class.

Regarding the genetic proximity of the children to the index cases, in 54 children (78%) the index cases were their parents (first degree relatives), while 19 children (22%) had non-parents as index cases. Most of the children (57 or 67%) shared bedrooms with their index case and only 16 (23%) did not. The majority of the children had also long-standing contact with their index case, with a mean duration of 40 weeks (range 8–208 weeks). As to the concentration of acid-fast bacilli (AFB) in the sputum of index cases, 37 adults (51%) were positive 1(+), 27 (37%) were positive 2 (++), and 9 adults (12%) positive 3 (+++). A total of 36 children (49%) had one smoking household member, 5 children (6.8%) had more than one smoker in the household and 32 (43%) had none (Table 4).

Children with parents as index case had significantly different TST results and TB class compared to those with non-parents as index case. This difference was not apparent for geographic proximity to index case, bacterial density and presence of BCG scar. (Table 5). In our study, Mtb 16S rRNA were found in all 43 sub-samples.

Table 4. Social status and housing conditions of respondents (n = 73)

Variables	n (%)
Social status	
House ownership :	
Owned by respondent	31 (42)
Owned by family of spouse	27 (37)
Rented	15 (20)
Productive person in household :	
Parents	63 (86)
Others	10 (14)
Food consumption per day (in thousand *rupiah*) *	20.8 ± 8
Housing conditions and environment :	
Size of dwelling*	55.4 ± 54.6
Building material :	
Concrete wall	67 (91.8)
Board	6 (8.2)
Special room for children :	
Yes	20 (27.4)
No	53 (72.6)
Humidity (%)*	73.0 ± 10.0
Ventilation :	
Good	14 (19.2 %)
Poor	59 (80.8 %)
Illumination :	
Dark	30 (40)
Light	43 (60)

* Mean ± SD

Table 5. Distribution of risk factors according to TB class (n=64)

Variables	TB class			p
	Class 1 (n=32)	Class 2 (n=10)	Class 3 (n=22)	
Humidity (%)	66.7 ± 12.1	76.1 ± 18.3	74.5 ± 11.9	0.03*†
Illumination				
Light	17	8	16	0.172
Dark	15	2	6	
Ventilation				
≤ 20%	24	9	17	0.558
> 20%	8	1	5	
Size of house#	52.5 (9-30)	24.5 (6-90)	46.0 (9-216)	0.397
Number of people living in the same house	47.7 ± 1.0	5.0 ± 0.8	5.6 ± 1.4	0.018*
Genetic proximity:				
Parent	19	10	20	0.011*
Non-parent	13	0	2	
Proximity to index case				
Sharing of bed room:				
Yes	22	9	18	0.275
No	10	1	4	
Duration of contact (weeks)	33.8 (41.5)	40 (50.1)	43.7 (56.1)	0.754
BCG scar				
Present	19	6	15	0.791
Absent	13	4	7	
Bacterial density of index case				
Positive 1	15	6	10	0.441
Positive 2	11	4	9	
Positive 3	6	0	3	

* significant; #median (min-max)
Continuous data tested by t test/Anova and Mann-Whitney/Kruskal-Wallis when not normally distributed. Nominal data tested by X^2

The environmental variables yielding significant differences were the number of people living in the same house and the humidity, both according to TB class and tuberculin test results, while size of the house and illumination were not significantly different. The humidity cut-off point was set at 75%, p=0.04 and exposure prevalence (EP) was 2.09 (CI: 1.32-3.29), indicating that children living in dwellings with a humidity more than 75%, were twice more likely to be tuberculin positive. The high cut-off point of 60% as minimum criterion of a healthy dwelling was chosen considering that all dwellings housed TB patients (Table 6).

Table 6. Exposure prevalence for risk factors associated with tuberculin skin test

Variable	Tuberculin skin test		Exposure prevalence (95% C.I.)
	Negative (n=32)	Positive (n=32)	
Humidity			2.09 (1.32-3.29)
<75%	34	14	
>75%	7	18	
Index case			4.59 (1.24- 17.01)
Parents	19	30	
Non-parents	13	2	

DISCUSSION

TB was diagnosed by detecting the mycobacterium in sputum, gastric lavage, or blood. Since infection is defined as colonization of the host by the agent,[7] and the 16S rRNA subsample was taken randomly, we may conclude that all children were infected. This study showed for the first time that living in the same house with active TB patients for at least 8 weeks, was sufficient for children to get infected.

Most adult cases are secondarily infected, either through reinfection or reactivation. Children may get primary infection from adults and the disease manifestations are more severe. As adults they in turn may become a source of infection to others.[8] In general, this may be the reason why tuberculosis in children is more apparent, systemic, and has broad clinical manifestations, whereas in adults with their mature immune response, there are already memory T cells against Mtb, resulting in a protective immune response and a more contained pulmonary TB. Unfortunately, the TB bacilli, however contained, are still living in the host macrophages, waiting for the host immunity to wane. Therefore, in an endemic country setting like Indonesia there will always be the threat of a new upsurge of pulmonary TB cases, originating from the reservoir of adults who contracted TB in childhood. In addition, the increasing number of patients with HIV/AIDS and/or diabetes mellitus may result in a TB pandemic as new emerging disease.

Prospective studies have shown the TB prevalence in HHC children in Colombia and Senegal to be 1.6%[9] and 1.5%,[10] respectively, in contrast with a non-endemic area in the UK, where the morbidity risk in school contacts was only 1.5%.[11] The discrepancy with our study might be due to the diagnostic criteria used. Diagnosis of TB in these studies was based on the results of bacterial culture and smear examination, while our study was based on Mtb 16S rRNA and clinical signs and symptoms. Our study results support the prevailing opinion that bacterial cultures or smears are capable of detecting only a small proportion of child TB cases.

The children in this study came from the same social class**.** We found that there were significantly more positive TSTs in children with parents as index cases, as compared to children with other persons as index cases (p=0.031). However, sharing the same bed-room and index case bacterial density did not lead to significantly different TST results. These findings are similar to those of other studies, where it was found that first degree genetic proximity (parents) had an odds ratio of 3.15 times that of third/fifth degree proximity, which was similar to our three- or four-fold exposure prevalence.[3]

The number of people living in the household showed a significant difference between TB class 1 and TB class 3. In this study, groups who were developing disease tended to have larger households than those with negative TST results. In Gambia, on the contrary, among children under five years old, a higher risk of TST positivity was found in the smaller households, which was caused by a more intensive contact between TB parents and their childen.[3] In Laos, however, no difference was found between the number of persons living with children with latent TB infection (LTBI children) and non-LTBI children.[13] The risk of TB infection is presumably influenced by the pattern of child care and local endemicity. In Indonesia, where the society is communal, there are more people in one house and more people attending the children, so the probability for contacts is higher. The situation is different in Laos, where the study was conducted in a rural area with a low density of people, thus no variability was found in the number of people living in a house between TST result groups.

The presence of a BCG scar in the present study was essentially similar between TST-positive and TST-negative groups, being consistent with the results in Gambia and

Laos.[3,12] Apparently, a successful BCG vaccination, as indicated by the presence of a scar, is not correlated with cellular immune response to Mtb infection. A low effectiveness of BCG vaccination could be due to co-infection with helminths,[13] although in all 50 fecal samples examined, no evidence of helminths was found. Before the BCG era, TB disease in children was mostly non-pulmonary.[14] Along with the fact that infection is systemic, BCG vaccine seems to protect the body from disease developing in other organs, but to be of no influence on the spreading process itself.

That tuberculosis is correlated with humidity and other environmental factors, was shown in a Russian study finding an increased incidence rate associated with high relative humidity, low ambient temperature and severe air pollution.[15] In Indonesia, one case control study on children showed an eight-fold higher odds ratio (OR) in cases from homes with a higher humidity,[16] in comparison to an OR of 1.7 in adult cases, with a humidity cut-off of 70%,[17] suggesting that humidity has a higher impact on children than adults. This research used different approach than Nurhidayah did; by given the exposure index case clear. The humidity factor here represents the condition where successful transmission happened. This was also the reason why we chose the higher cut-off point of 75%, instead of the standard 60% humidity for a healthy environment,[5] considering that all houses already had TB patients.

An in vitro study on cytokine production by human cell lines found that the fungal species *Stachybotrys chantarum* stimulated IL-6 production.[18] In this connection, it should be emphasized that mycobacteria are also found in proportional numbers with fungi in moisture-damaged building materials.[19] The present study found that home humidity differed significantly between TB classes as well as between TST groups, so that humidity might a play role in host responses to TB infection and development of disease. As suggested by Sun et al., humidity shifts the Th1-Th2 balance, resulting in disease development.[20]

Another environmental factor, namely altitude, was shown in a Peruvian study to affect TST positivity, where the prevalence of positive TST results was lower at higher altitudes (+/- 6%), in comparison to TST results at sea level (+/- 30%).[21] Similar reults were also found in Vietnam.[22] Our study, which was conducted in Surabaya, just 5 meters above sea level, found a proportion of 50% positive TST results. These findings support the opinion that the humid and warm air near sea level may be important for mycobacterial transmission.

Since the Indonesian national guidelines for children with TB prescribe mandatory preventive drugs for children living with TB patients,[22] the observations in this study could only made before diagnosis. For this reason, we chose a cross-sectional design for this study. However, an inherent weakness of this design is that it cannot determine cause-and-effect relationships, all variables being observed at the same time. A one-way relationship between independent and dependent variable cannot be determined with certainty. That was why, we substituted odds ratio, with exposure prevalence.

CONCLUSIONS

Housing conditions that play a significant role in the host reaction to tuberculosis are humidity and household size, i.e. the number of persons living in a household. On the other hand, presence of BCG scars, sharing bedrooms, and mycobacterial density of index cases, presumably play less important roles. In the risk approach to child TB those factors should be included on the scoring system available. Appropriate housing conditions and the optimal number of persons living in a household should be taken into consideration for a long term TB national program.

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