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Level of Exposure to Childhood Tuberculosis in Household Contacts with Adult Pulmonary Tuberculosis

Tingkat Paparan terhadap Kejadian Tuberkulosis Anak yang Memiliki Kontak Serumah dengan Penderita Tuberkulosis Dewasa

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Abstract
Pulmonary tuberculosis (TB) in children is a neglected global health problem, with an increasing proportion of TB cases in Indonesia. Children with TB are most often impacted by TB transmission in the population at large, especially adult TB that exists in the child's household. This study aimed to find protective factors that can keep children healthy despite household adult TB contacts. This study reports on 132 respondents with a case-control study conducted at nine referred hospitals and several primary health care based on medical records in Special Region of Yogyakarta Province. The study lasted from January to December 2014, while the data analysis was used by both of bivariate (chi-square) and multivariate (multiple logistic regression) analysis. The study found that healthy houses, especially those with healthy bedrooms and fewer exposures to adult TB sufferer, influenced by confounder variables, protected children from TB even though they were exposed to adult TB in their environment. Longer periods of living together is not a risk factor for children to contract TB when living with adult TB patients at home. However, this risk increases with frequent exposure among children to adult TB patients at home.
Keywords: Children, exposure, household contact, tuberculosis

Abstrak
Tuberkulosis paru (TB) pada anak kian menjadi masalah kesehatan global yang masih terlupakan seiring dengan peningkatan proporsi TB di Indonesia. Penularan penyakit ini di populasi umum seringkali berdampak pada anak, terlebih ketika kontak TB terjadi di rumah tangga. Penelitian ini bertujuan untuk memperoleh faktor protektif sehingga anak tetap sehat meskipun memiliki kontak dengan penderita TB dewasa serumah. Penelitian ini dilakukan dengan pendekatan kasus-kontrol pada 132 responden anak yang berasal dari sembilan rumah sakit rujukan dan beberapa puskesmas di Provinsi Daerah Istimewa Yogyakarta. Penelitian dilakukan dalam periode Januari hingga Desember 2014 yang hasilnya dianalisis dengan uji bivariat (kai kuadrat) dan multivariat (regresi logistik ganda). Hasil penelitian menunjukkan bahwa rumah yang memenuhi syarat kesehatan, yakni ruang tidur yang sehat, serta paparan yang jarang diterima dari penderita TB dewasa mampu memproteksi anak agar tetap sehat meskipun tinggal serumah dengan penderita dewasa penyakit ini. Penelitian ini menyimpulkan bahwa lama tinggal bersama bukanlah faktor risiko penyakit TB pada anak. Hal ini karena meskipun lama tinggal bersama antara penderita TB dewasa dengan anak, namun apabila memiliki paparan yang jarang, hal ini pun tidak signifikan menjadikan anak untuk terkena TB.
Kata kunci: Anak-anak, paparan, kontak serumah, tuberculosis

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Introduction

The number of children with pulmonary tuberculosis (TB) is still an obstacle to predict and TB is difficult to diagnose in children.[1] Pulmonary TB control in children is also challenged by circumstances of limited resources, accompanied by the high burden of this disease. In fact, if the disease is undetected and untreated, the children would be at high risk for death.[2]

Although the Indonesian Ministry of Health through the Directorate General of Disease Control and Environmental Health, together with the Indonesian Paediatric Association have drafted a guideline for TB control in children in Indonesia, it is confirmed that Indonesia still has limited resources. Indonesian Paediatric Association led to the diagnosis of pulmonary TB in children through a scoring system.[3] This diagnostic tool is only effective when children are seen at healthcare facilities. For children not seen at healthcare facilities, pulmonary TB in children in Indonesia is still hard to determine.[4] This indicated that TB should not only be managed by territory in the various areas of Indonesia, but it should also be mandatory to focus on environment-based transmission of the disease.[5]

Childhood with pulmonary TB occurr in children when contact with adult pulmonary TB patient. Adult TB sufferers are the primary source of childhood TB occurrences due to children coming in contact with adult pulmonary TB patients. Risk of transmission increases when children live in the same house with a TB patient.[6] However, not all children who live in the same house with an adult with pulmonary TB get sick.[6] Several factors influence the risk and prevent some children from contracting pulmonary TB when in contact with an adult with pulmonary TB living in the same house.[7-9] This study was conducted to measure the level of exposure for reducing the risk of children contracting pulmonary TB when living in the same house with adult pulmonary tuberculosis patients.

Method

A case-control study was conducted with 66 cases and 66 controls collected by proportional random sampling of a childhood TB database for nine referred hospitals. Controls were selected in each of several health centers based on medical records where the same cases were found. Samples were gathered using a minimum sample size for a case control study conducted by WHO.[10,11] It added 10% to prevent sample inadequacy and ensure relevance regarding outlier or normal distribution requirements.

The dependent variable (the pulmonary TB status of children who lived in the same house with an adult pulmonary TB sufferer) was collected by the secondary data (medical records of the hospital and public health center), while the independent variables were obtained by the primary data (questionnaire). The subjects of this study were children (aged <14 years old) who shared a house with an adult pulmonary TB sufferer in the Special Region of Yogyakarta Province. The primary data obtained by the instrument of the study were already examined by validity and reliability tests. The instrument consisted of a questionnaire of the WHO manual to track the pulmonary TB contact and the questionnaire of National Basic Health Research (Basic Health Research, 2013) to measure the independent variables in this study.[12,13] The data on the contact status of adult pulmonary TB and that of child pulmonary TB were obtained by screening, and contact was investigated.[13]

Cases defined as children's pulmonary TB (positive childhood TB diagnosed using scoring system that generated by pediatric in eight referral children hospitals at Special Region of Yogyakarta Province) that had contact with adult pulmonary TB sufferer through living in a shared house were obtained from children's pulmonary TB incidence records of the hospital. Cases recorded to have a positive pulmonary TB children had been traced, and the tracing showed that an adult pulmonary TB sufferer lived in the same home as the children. However, cases recorded to have a negative impact (adult TB was not found) were not reported. Adult pulmonary TB in this study was indicated as a TB patient who was being treated or had already recovered from TB, who lived in a home with children aged 0-14 years old. Controls were traced as the healthy children. Children older than five years old can suffer pulmonary TB after one year of primary infection by an adult pulmonary TB sufferer, whereas those under five years old only need a shorter time or several weeks.[8,14,15]

Controls are described as healthy children (negative pulmonary TB) who are delivered by an adult pulmonary TB sufferer. They were gathered by screening the results from the medical records of the same hospital that were obtained by health professionals.

Data collection was different in the cases and controls group and was performed to prevent selection bias. Cases and controls were strictly defined by children of pulmonary TB status as a positive and negative impact (outcome) that both of them were exposed by adult pulmonary TB contact who lived at the same house. To maintain comparability between the cases and the controls group, the possible confounding variable was identified. Variables that influenced the status of children's pulmonary TB were turned into independent variables. Multiple logistic regression analysis was used to calculate the strongest correlation (OR) from the value of the resulting standardized beta.

The enter method of multiple logistic regression was used to enable the predictor model to describe the pro-

Table 1. Baseline and Screening of Bivariate Analysis

Variable	Category	Case (n = 66)		Controls (n = 66)		β	Wald	SE	OR	p Value
		n	%	n	%					
Level of exposure										
Exposure intensity	Full day	37	56.1	18	27.3	Ref	10.995	Ref	Ref	0.004
	Only at night	14	21.2	21	31.8	1.126	6.288	0.449	3.083	
	Only at daylight	15	22.7	27	40.9	1.308	9.189	0.432	3.700	
Sleep status	Shared bed	30	45.5	30	45.5	Ref	0.000	Ref	Ref	1.000*
	Shared bedroom only	36	54.5	36	54.5	0.00		0.350	1.00	
Weaning status	In weaning	7	10.6	7	10.6	Ref	0.518	Ref	Ref	0.772*
	Kindergarten (unweaning)	12	18.2	9	13.6	-0.288	0.172	0.693	0.750	
	In school	47	71.2	50	75.8	0.062	0.012	0.572	1.064	
Relatives status	Blood relation	34	51.5	40	60.6	Ref	1.104	Ref	Ref	0.293*
	Family outside	32	48.5	26	39.4	-0.370		0.352	0.691	
Child condition										
Nutritional status	Poor nutrition	5	7.60	7	10.6	Ref	8.056	Ref	Ref	0.045
	Less nutrition	8	12.1	6	9,10	-0.624	0.614	0.797	0.536	
	Normal nutrition	48	72.7	36	54.5	-0.624	0.995	0.626	0.536	
	Overnutrition	5	7.60	17	25.8	0.887	1.309	0.776	2.429	
Age (numeric)						NA	NA	NA	NA	0.058
Sex	Male	38	57.6	28	42.4	Ref	3.007	Ref	Ref	0.083
	Female	28	42.4	38	57.6	0.611		0.352	1.842	

Notes:
n = Number of Sample; SE = Standard Error; OR = Odds Ratio

tective factor of pulmonary TB status of children who lived with an adult pulmonary TB sufferer in the same house. This method was used by entering all variables that passed the screening test. Variables were excluded one by one from the greatest until the smallest p value with the desired significance, but the changing of OR that was not allowed (> 10%) in each predictor variable was also considered.

Variables in this study consisted of childhood TB status (positive TB as case and negative TB as control) who sharing a house with an adult pulmonary TB sufferer as dependent variable. Whilst primary independent variables were varied of level of exposure between children and their adult TB sufferer household contacts, in this case, it measured by several variables that namely exposure intensity, sleep status, weaning status, and relatives status. It also evaluated child condition that composed by three variables that namely nutrition status, age, and sex.

Informed consent from the respondents was obtained in written form. The ethical approval of the study was obtained from the Expert Commission on Research and Research Ethics of the Public Health Faculty of The University of Indonesia, Number: 87/H2.F10/PPM. 00.02/2014.

Results

All variables of the children's condition, namely, nutritional status (p value = 0.045), age (p value = 0.058), and sex of children (p value = 0.083), were used in the multivariate analysis. The level of exposure was reflected by five variables. Limited exposure intensity was found to protect childhood TB significantly (p value = 0.004). Although sleep status (p value = 1.00), weaning status (p value = 0.772), and blood relatives (p value = 0.293) were variables that were assessed insignificantly, further analysis (multivariate) should be conducted since these variables also play important roles in affecting childhood TB incidence substantially.

The interaction test was performed on each variable that showed a tendency to influence the final result. After the covariated variable was obtained, and the results indicated that no significant interaction existed between exposure intensity and length of stay and exposure intensity and blood relationship (relative relationship). This result means the protective factor of childhood TB prevention consisted of limited exposure intensity when an adult TB household existed. However, indirect predictors measured by blood relatives and age were also important.

Discussion

Blood relatives of the adult pulmonary TB sufferer who shared the same house with children showed no significant correlation with the child pulmonary TB incidence. They also showed no correlation to sleep and weaning status of the children who lived in the same house with the adult pulmonary TB patient. However, all variables in the exposure level were considered substantial.[8,16,17] Thus, these variables were used for multivariate analysis.

Nutritional status, which was measured by weight and height in this study, was not significant or was not a pro-

Table 2. Multivariate Analysis of Childhood Tuberculosis Prevention Model

Variable	Category	Bivariable Analysis			Multivariable Analysis					
		Crude OR	95% CI	p Value	β	Standard Error	Wald	Adjusted OR	95% CI	p Value
The level of exposure										
Exposure intensity	Full day	Referral	Referral	0.004	Referral	Referral	11.811	Referral	Referral	0.003
	Only night time	3.083	1.279-7.434	0.012	2.340	0.846	7.644	10.379	1.976-54.513	0.006
	Sometime	3.700	1.588-8.622	0.002	2.895	0.962	9.048	18.085	2.742-119.286	0.003
	Child	Referral	Referral	0.691	Referral	Referral	0.122	Referral	Referral	0.727
Status of relative relation	Relative /family	0.691	0,346-1,378		-0.299	0.857		0.741	0.139-3.979	
Child condition										
Age	Numeric	1.008	1.000-1.017	0.060	0.008	0.008	1.093	1.008	0.993-1.023	0.296

Notes:
OR = Odds Ratio; CI = Confidence Interval

tective variable when controlled by other predictors in the protective model of the pulmonary TB status of children who shared the same house with an adult pulmonary TB sufferer. However, nutritional status indirectly correlated with the predictive model and was significant in the bivariate analysis. This result indicates children's immune system prevented them from suffering pulmonary TB when they shared a house with an adult pulmonary TB sufferer. Good nutritional status and other factors also influenced this condition. The nutritional status of the children showed a more likely minimum proportion in maintaining the children's health to avoid pulmonary TB when they were exposed to primary TB infection (by sharing a house with an adult pulmonary TB sufferer).

Incidence of children's pulmonary TB was determined by the reactivation of latent TB infection or primary infection that was obtained by contact with an adult pulmonary TB sufferer.[8] The components of the immune system, such as cytokine, gamma interferon level (IFN-γ) in the blood, and interleukin (IL-10), to combat *Mycobacterium tuberculosis sp.* (MTB) could be used to diagnose the absence of TB infection in the body.[18]

The immune system of children can be measured by the intake status related to the nutrition status of children. Even though the relevance of chronic disease exposure such as pulmonary TB that had directly affects children's nutrition status, predicting it as the measuring association is still difficult.

Several studies have described that viewing the correlation between nutrition status and TB from a methodological standpoint was challenging, because TB exposure itself may influence children's nutrition status.[19-22] This temporary correlation was indicated by pulmonary TB that also causes weight loss, and this disease was also changing the macro and micro nutrients at specific periods. The type of study was measured to perform an appropriate consideration.[21] A case control or cross-sectional study is believed to result in unestablished association and overestimation compared with the cohort or nested case control study that results in a reliable estimation of the association of the pulmonary TB incidence to the children's nutrition status.[21,22]

A meta-analysis study found that nutrition status played a protective role for pulmonary TB incidence.[21] Poor nutrition status has been a steady risk factor in TB in the last decade, and it was analyzed further in the present study with two main findings. First, quantification in logarithmic form was showed fair association of the BMI status consistently in various study and population that was studied. Second, dosage response correlation occurred in BMI status >25 kg/m^2. This result shows that obesity or being overweight was a preventive factor for pulmonary TB incidence.[22]

Nutritional status, age, and sex of children were significantly correlated (p value < 0,05). Thus, these three variables could be used in multivariate analysis (p value < 0,25). The BCG immunization status of the children was related to children's pulmonary TB incidence,[23] but one variable failed the candidate test (p value = 0,333 > 0,25). This variable was excluded in the multivariate analysis because the variance of the data was not balanced or almost all study samples already received BCG immunization (97%).

Housing condition, especially the condition of the bedroom, significantly affected the risk of pulmonary TB transmission to children who shared a house with an adult pulmonary TB patient.[24] However, transmission risk did not directly mean that children's TB was caused by sleeping in the same room with an adult pulmonary TB sufferer. The transmission of TB to children in a nuclear family (composed of father, mother, and children) with adult pulmonary TB was uncertain.[25-27]

Children who share a house with an adult pulmonary TB sufferer will directly suffer from TB in a shorter period (< 6 months). Generally, the immune system of children is still developing. Thus, children, especially under five, are vulnerable to TB after direct exposure to MTB infection.[28] Staying longer with an adult pulmonary TB sufferer did not significantly ascertain whether the children suffered from TB. The children who lived with an adult pulmonary TB sufferer in a longer period but had limited exposure intensity remained healthy or did not suffer from pulmonary TB.[29]

The exposure indicator of children could be explained by exposure intensity that was partially observed. The exposure intensity of the adult pulmonary TB sufferer was measured by spending time in a shared room every day. The result showed rare exposure (sometimes) with an adult pulmonary TB sufferer protected the children and allowed them to remain healthy.[27]

The predictor in the exposure level indicated that children's pulmonary TB was caused by an adult pulmonary TB sufferer who shared a house with the children. In several scenarios, the children might be at risk through an adult pulmonary TB population outside their house, such as from contact with a neighbor and at school. Many reports on transmission through public transportation are also available.[30,31] Moreover, this also happened by insufficient or limited health accessibility of adult TB perception for their children health assessment.[32] However, the risk increases when the transmission source is in the house, and children experience a high exposure intensity.[27,33]

Since the case control design had potential of differential misclassification bias,[34] the results of the study were affected by the inability to perform an anonymous investigation (blinding) that tends to assess poor on cases and good on controls. However, this bias was controlled by training and rechecking of the questionnaire when the data had been collected. Moreover, this study had limitations in assessing the effects of natural history/incidence order risk/protective factors. The final result showed that the confounding variable could affect the main variable. In ecological bias, the inability to determine the independent variable (aggregate or individual variable) might cause measurement bias, which was considered to influence the same level of confounding variable.[35,36] However, multivariable analysis was conducted to reduce/adjust the influence of the independent variables that correlated or interacted with one another.

Generalizing the external validity of the study in other settings is not yet optimal. However, the study presented the risk/protection of the pulmonary TB status of children who shared a house with an adult pulmonary TB sufferer in Indonesian areas as a general characteristic based on density and population pyramid of the regency/municipality in the Special Region of Yogyakarta Province province.

Conclusion

This study shows that exposure intensity of children to an adult pulmonary TB is the main cause of childhood TB incidence. Rare exposure intensity is the greatest factor that reduces the transmission risk compared to the often exposure intensity when the children live in shared house with adult pulmonary TB. Further study needs to explore housing and environment with good sunlight and children nutrition especially in early age child, in order to prove that children remain healthy when they have shared house with adult active pulmonary TB sufferer.

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