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Original Article

Risk factors of tuberculosis in children with adult household tuberculosis contact

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Abstract

Background Since children are more likely than adults to become infected with *Mycobacterium tuberculosis* or suffer from tuberculosis (TB), it is important to identify the risk factors of TB in children with adult household TB contacts.

Objective To identify the risk factors of TB in children with adult household TB contacts.

Methods This cross-sectional study was conducted at the Pediatric Respirology Inpatient Ward and Outpatient Clinic at Dr. Soetomo Hospital, Surabaya, East Java, Indonesia, using medical records of hospitalized patients from 2010 to 2018. Patients were children below 18 years of age who had a history of adult TB household contact(s). We analyzed age at TB diagnosis, nutritional status, BCG vaccination status, and HIV status as possible risk factors of TB.

Results A total of 367 children with adult household TB contacts were included in our study. Age of <5 years (OR 8.38; 95%CI 3.78 to 18.21; P<0.001), severe malnutrition (OR 8.88; 95%CI 1.19 to 66.27, P<0.05), absence of BCG scar (OR 2.96; 95%CI 1.32 to 6.62, P<0.05), and positive HIV status (OR 6.72; 95%CI 1.72-38.49, P<0.05) were risk factors for contracting active TB.

Conclusion Age of <5 years, severe malnutrition, absence of BCG scar, and positive HIV status are significant risk factors for active TB in children with adult household TB contacts. **[Paediatr Indones. 2024;64:287-92; DOI: 10.14238/pi64.4.2024.287-92].**

Keywords: *tuberculosis; household contact; risk factor*

Tuberculosis (TB) is a communicable disease and a worldwide cause of illness and, potentially, death. Childhood TB remains a serious problem because of difficulties in diagnosing tuberculosis in children. However, tuberculosis can be cured and prevented. Data showed that around 85% patients with TB have been successfully treated with a 6-month therapeutic regimen.[1]

The results of studies on children with pulmonary TB infection and disease and adult household TB contacts have been disparate, as countries' epidemiological practices vary, as do the characteristics of the index cases and the criteria used to determine TB infection and illness.[2] The *World Health Organization* (WHO) estimated that 4 million children aged below 5 years have TB household contacts, but only 29% of them receive TB preventive therapy (TPT).[1]

It is important to be aware of TB risk factors in children with adult household TB contacts, as children

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are at higher risk for TB infection and disease. Younger age, undernutrition, and absence of BCG vaccination have been identified elsewhere as risk factors for transmission of infection in children.[3,4] However, there have been few studies in Indonesian children with adult household TB contacts. Knowledge of the risk factors will assist stakeholders to plan effective disease control strategies and guide national TB program recommendations. Thus, we aimed to identify risk factors of TB in children with adult household TB contacts.

Methods

This cross-sectional, analytic, observational study was done using medical record data of children hospitalized between January 1, 2010, and December 31, 2018. Inclusion criteria was children below 18 years of age who had a history of adult TB household contact(s). Diagnoses of latent TB infection and TB disease were based on the *Technical Guidance for Management and Therapy of Pediatric Tuberculosis* published by the *Indonesian Ministry of Health*.[5] Subjects were classified as 'non-active TB' if their diagnosis was TB-exposed or latent TB infection (LTBI), and as 'active TB' if their diagnosis was pulmonary or extrapulmonary TB (e.g. TB meningitis, TB lymphadenitis, pleural TB, scrofuloderma, bone/joint TB, abdominal TB, or disseminated TB).

Patients with incomplete medical records were excluded. We collected data on the patients' gender, age, nutritional status, BCG status, HIV status, as well as comorbidities (neoplasm, thalassemia, asthma, Down syndrome, and others). Age was classified as ≤5 years or > 5years. Nutritional status was determined using the WHO z-score[6] for children aged ≤5 years and the *CDC Growth Chart*[7] for those aged >5 years. Children were considered well-nourished if weight-for-height z-score was <-2 according to the *WHO Growth Chart*[6] (for children ≤5 years) or if weight was <90% of ideal weight for height according to the *CDC Growth Chart*[7] (for children >5 years). Malnutrition was further classified as moderate (z-score <-2 but >-3 on the *WHO Growth Chart* for children ≤5 years or weight <90% but >70% of ideal weight for height on the *CDC Growth Chart* for children >5 years) and severe (z-score <-3 on the *WHO Growth Chart* for children ≤5 years or weight <70% of ideal weight for height on the *CDC Growth Chart* for children >5 years).[6,7]

This study was approved by the Dr. Soetomo Hospital Research Ethics Committee. Informed consent was not required due to the study's retrospective design.

Statistical analysis was done using *IBM SPSS version 23* (*IBM*, Armonk, New York). We analyzed the association between each risk factor and TB using the chi-square test and logistic regression test. Results with P values of <0.05 were considered to be statistically significant.

Results

During the eight-year study period, a total of 1,338 pediatric patients with adult household TB contacts met our inclusion criteria. However, 971 patients were excluded due to incomplete data, leaving 367 patients for analysis. Most subjects were male (55.9%), well-nourished (71.4%), aged >5 years (64.3%), HIV-negative (91.6%), and without comorbidities (96.5%). A BCG scar was also present in most children (80.9%) (**Table 1**). A total of 277 patients were classified as active TB disease, while the remaining 90 had non-active TB. Bivariate analysis revealed that age of <5 years, absence of BCG scar, positive HIV status, and normal nutritional status were significant risk factors for TB disease (**Table 2**).

Amongst patients with malnutrition, we further analyzed the risk of active TB in those with moderate vs. severe malnutrition. The odds of active TB in children with severe malnutrition was 32.87-fold that of children with moderate malnutrition (**Table 3**).

All risk factors were entered into a multivariate analysis using logistic regression. Age of ≤5 years, absence of BCG scar, and positive HIV status retained statistical significance (**Table 4**).

Discussion

In our study, children with household TB contacts were more likely to have active TB than non-active TB. Preventive therapy using chemoprophylaxis is the main intervention to lower the risk of progression to

Table 1. Subjects' characteristics

Characteristics	N=367
Gender, n (%)	
Male	205 (55.9)
Female	162 (44.1)
Nutritional status, n (%)	
Malnutrition	
Moderate malnutrition	64 (17.4)
Severe malnutrition	36 (9.81)
Overweight	3 (0.82)
Obesity	2 (0.54)
Normal	262 (71.4)
Age, n (%)	
≤ 5 years	131 (35.7)
> 5 years	236 (64.3)
BCG status, n (%)	
Scar negative	70 (19.1)
Scar positive	297 (80.9)
HIV status, n (%)	
Positive	31 (8.4)
Negative	336 (91.6)
Comorbidities, n (%)	
Yes	13 (3.5)
Oncology disease	3 (0.8)
Thalassemia	2 (0.5)
Asthma	3 (0.8)
Down syndrome	3 (0.8)
Congenital heart disease	1 (0.3)
Nephrotic syndrome	1 (0.3)
No	354 (96.5)
Diagnosis, n (%)	
Non-active TB	
Exposed to TB	53 (14.4)
Latent TB infection	37 (10.1)
Active TB	
Pulmonary TB	180 (49.0)
Miliary TB	27 (7.4)
Extrapulmonary TB	95 (25.9)
Meningitis TB	14 (3.8)
Lymphadenitis TB	39 (10.6)
Pleural TB	2 (0.5)
Scrofuloderma	2 (0.5)
Bone/joint TB	27 (7.4)
Abdominal TB	4 (1.1)
Disseminated TB	7 (1.9)
Pulmonary + extrapulmonary TB	2 (0.5)

active TB in exposed children. Prevention, control, and BCG vaccination can provide protection from severe forms of childhood tuberculosis. A previous study reported that most subjects with active TB had no history of prophylactic anti-TB treatment and no BCG scar.[8] There was a global increase in people receiving tuberculosis preventive therapy from 1.0 million in 2015 to 3.6 million in 2019. However, in 2020, this number had declined by 21% to 2.8 million.[1] The decrease resulted from the disruption of health services due to the COVID-19 pandemic. The same disruption also caused an estimated 25% reduction in global BCG coverage.[9] The target BCG coverage for the 2018-2022 period was 30 million, but only 29% of that target was achieved, with a combined total of 8.7 million vaccinated.[10]

A meta-analysis in 2017 involving 1.27 million children aged under 5 years showed that tuberculosis preventive therapy is still underutilized in children worldwide. To help eliminate tuberculosis infection clusters and reach the "End TB Strategy" targets, improvements must be made.[8] In an Iranian study, 230 children who had household contact with TB index cases underwent testing using *QuantiFERON-TB Gold Plus*. The test showed that 104 (45.2%) of these children had LTBI. These results suggests that children exposed to household TB contacts have a high prevalence of LTBI.[10]

Infant immune systems are less mature than those of adults. Infants have fewer macrophages, neutrophils, and dendritic cells and less robust immune function than adults, which leads to a 5-to-10-fold risk of developing active TB.[11] A previous study reported that BCG vaccination in the first year of life induced a strong release of T-helper 1 CD4 and CD8 cells, reducing the likelihood to develop TB disease in this vulnerable age group.[12]

We noted a significant association between severe malnutrition and the risk of active TB. Similarly, an Indian study found that inadequate dietary intake was a significant risk factor for TB incidence in children (P=0.001).[13] Gene signatures that predict TB risk are associated with undernutrition, and an increased immune response to infection is observed with the administration of nutritional supplements. Available evidence suggests that gene expression and immune function are affected by malnutrition, a predisposing factor to TB progression.[14,15]

We also discovered that HIV-positive status was a significant risk factor for active TB. In contrast, a previous study found no significant association between the HIV status of children or their parents and TB.[16] Children and adolescents with HIV are more susceptible to developing active tuberculosis, due to the depletion of CD4 T-cells that results in the suppression of cell-mediated immunity. TB-specific CD4 T-cell depletion often occurs in

Table 2. Bivariate analysis of risk factors of TB in children with adult household TB contacts (N=367)

Variables	Active TB (n=277)	Not Active TB (n=90)	OR	95%CI	P value
Age, n (%)					
> 5years	154 (55.6)	82 (91.1)	ref.		
≤ 5years	123 (44.4)	8 (8.9)	8.19	3.81 to 17.57	<0.001
BCG scar, n (%)					
Scar positive	216 (78.0)	81 (90.0)	ref.		
Scar negative	61 (22.0)	9 (10.0)	2.54	1.21 to 5.35	0.012
HIV status, n (%)					
Negative	248 (89.5)	88 (97.8)	ref.		
Positive	29 (10.5)	2 (2.2)	5.14	1.20 to 22.01	0.015
Nutritional status, n (%)					
Normal	209 (75.5)	53 (58.9)	ref.		
Malnutrition	68 (24.5)	37 (41.1)	8.88	1.19 to 66.27	0.003

ref.=reference group

Table 3. Bivariate analysis of nutritional status as a risk factor of TB in children with adult household contacts (N=100)

Variables	Active TB (n=68)	Not Active TB (n=32)	OR	95%CI	P value
Degree of malnutrition, n (%)					
Moderate	33 (48.5)	31 (96.9)	ref.		
Severe	35 (51.5)	1 (3.1)	32.87	4.24 to 254.72	<0.001

ref.=reference group

Table 4. Multivariate analysis of risk factors of TB in children with adult household contact

Risk factors	OR	95%CI	P value
Age ≤ 5 years	8.38	3.78 to 18.21	<0.001*
No BCG scar	2.96	1.32 to 6.62	0.008*
Positive HIV status	6.72	1.72 to 38.49	0.012*

*P<0.05 statistically significant

the peripheral blood and lungs, resulting in the generation of granulomas and damage in lung tissue, facilitating infection of the lungs by *Mycobacterium tuberculosis*.[17-20] Hence, the implementation of early antiretroviral treatment, thus increasing CD4 T-cells and repairing the immune system, along with widespread TB preventive treatment, has led to a decline in the incidence of HIV-associated tuberculosis in children and adolescents.[21]

This study had several limitations, including the use of secondary data from medical records. The large number of patients with incomplete medical record data that had to be excluded from the study may have led to information bias. In addition, there were no data on the duration of exposure to household contacts and no data on the results of bacteriological examinations of index cases, both of which could have made our findings more robust. Moreover, BCG vaccination status was obtained only from the presence or absence of BCG scars as recorded in the medical records, since parental recall was unreliable and proof of vaccination was often not provided.

In conclusion, age of <5 years, severe malnutrition, absence of BCG scar, and HIV-positive status are significant risk factors for TB in children with adult household contacts. Recognizing potential risk factors for TB in children who have adult TB household contacts should lead healthcare providers to consider TB screening in such high-risk children. As such, a diagnosis of TB can be established early and patients can receive early, comprehensive therapy to reduce morbidity and mortality.

Conflict of interest

None declared.

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