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Original Article

Occurence and risk factors of tuberculosis infection in orphanage children in Bali

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Abstract

Background Tuberculosis (TB) is an infectious disease that is still a common threat worldwide, especially in pediatric populations. TB transmission occurs particularly when the transmitter has no obvious manifestation of the disease. There is a higher incidence of TB infection in children than in the general population, especially in high risk populations such as children in orphanages. However, the incidence of TB infection in orphaned children in Indonesia, including Bali, is unknown.

Objective To describe the incidence and risk factors for TB infection in children in orphanages in Bali.

Methods This case-control study was conducted in 12 orphanages in Bali. Subjects were divided into a case group comprised of children with TB infection, and a control group comprised of those without TB infection. TB infection was diagnosed by positive tuberculin test without clinically confirmed TB.

Results A total of 175 children were recruited as subjects. There were 49 (28.0%) children with TB infection. Bivariate analysis revealed significant associations between density, humidity, ventilation/room area ratio, and area of origin with TB infection. Multivariate analysis showed that ventilation/room area ratio and room humidity of ≥73% were independently positive correlated with TB infection. Natural lighting and BCG scar were not significantly different between groups.

Conclusion The occurence of TB infection in children residing in orphanages in Bali is high (28%). The risk factors identified independently are lower ventilation and higher room humidity.

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Keywords: *tuberculosis; tuberculin test; orphanages; risk factors*

Tuberculosis (TB) is an infectious disease that continues to pose a hazard to all nations, particularly developing countries such as Indonesia. An estimated 1.7 billion people worldwide are infected with tuberculosis, and around 35% of TB cases occur in Southeast Asia.[1] Children and young adolescents, aged less than 15 years, account for 11% of the global TB population.[1] Twelve out of 10,000 children ages 5 to 14 in Indonesia had tuberculosis in 2021, as did 22 out of 10,000 children ages 0 to 4. The Bali Provincial Health Office reported an incidence rate of tuberculosis in 2018 of 12,391 cases, including 4,114 new cases and 206 cases occurring in children aged 0-14 years, or around 5%.[2]

Diagnosis of tuberculosis in children poses a challenge. Atypical symptoms are caused by the latent nature of *Mycobacterium tuberculosis* (MTB) and the relatively large incidence of extrapulmonary TB in children (25-30%).[3] Children can be infected

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with MTB bacteria without developing tuberculosis (hence, referred to as TB infection) due to the interplay between MTB bacteria and a robust immune system.[4] According to earlier studies, 5 to 10% of patients with TB infection develop TB illness within five years. Those who are immunocompromised, malnourished, or on immunosuppressive treatments, such as chemotherapy or steroids are at a greater risk.1 TB in children is associated with high morbidity and mortality, particularly in those under 2 years of age, immunocompromised, and with comorbidities.[5]

Children residing in orphanages are at particularly high risk for TB transmission,[6] due to the high residential density, inadequate sunlight, and high humidity, all of which are risk factors for the occurrence of TB.[7] A high population density increases the likelihood of interaction or contact with TB-infected individuals.[8] The prevalence of tuberculosis among orphans in underdeveloped nations with a high prevalence of TB is 1,123 per 100,000.[9] In a study in India, 38% of orphanage-dwelling children had positive tuberculin test results, although only 10 children were confirmed to have TB.[10] A 2018 study of orphanages in Myanmar revealed that 19.2% of children tested positive for tuberculosis. Chest X-rays revealed that 1.2% of children had indications of a primary tuberculosis complex.[11] Data on TB infection in children residing in Indonesian orphanages, particularly in Bali, are not available due to the lack of study on the topic. In Indonesia, tuberculosis screening in orphanages has become necessary for these reasons.

Tuberculosis is still a leading cause of morbidity and mortality in children around the world, but its elimination has received less attention. Estimates of TB infection among children in orphanages lag behind those of TB-affected children. To better understand the severity of the problem and prevent transmission, morbidity, and death from tuberculosis, it is crucial to have accurate statistics on the prevalence or infection of TB in orphanages. The paucity of studies and understanding about the burden of TB among orphanages in Indonesia, particularly in Bali, prompted us to conduct this study to screen for TB in order to determine the occurence and risk factors for TB infection among children residing in orphanages.

Methods

This observational-analytic study utilizing a case-control design between March and August 2022. Children under the age of 18 who provided written informed consent filled in by the orphanage administrator as the legal guardian form were included. Those who had prior infections and/or TB treatment were excluded. Subjects were included by consecutive sampling. Tuberculosis (TB) scoring was a method used to assess a child's TB diagnosis. The parameters encompassed in this study consisted of the examination of TB contact history, tuberculin test results, body weight and nutritional status, fever of unknown aetiology, presence of enlarged lymph nodes (colli, axillary, inguinal), swollen bones and joints in the hip and knee, as well as a chest X-ray.[12] A TB grade of 6 indicates the presence of symptoms associated with TB illness.[13]

The tuberculin test entailed the administration of 0.1 mL of tuberculin through an intradermal injection on the inner surface of the forearm. The measurement of the reaction was conducted in millimetres of induration, which refered to the presence of a palpable, elevated, hardened region or swelling, within a time frame of 48 to 72 hours following injection. The measurement of the indurated area should be conducted perpendicular to the long axis of the forearm, excluding any presence of erythema. Induration more than or equal 10 mm indicated positive and under 10 mm indicated negative test.[14]

The categorization of height against age was determined by the growth guidelines established by the *World Health Organisation* (WHO), which offer percentiles and z-scores for children between the ages of 0 and 5 years. The *World Health Organisation* (WHO) suggests use cut-off values of +/- 2 z-scores, which approximately align with the 2nd and 98th percentiles, as a means of identifying individuals exhibiting unhealthy growth patterns. The growth charts provided by the UK-WHO for children and adolescents aged 2-18 years offer valuable insights into the initiation and advancement of puberty, as well as a BMI centile lookup.[15]

Age, sex, height for age, body mass index (BMI) for age, TB contact history, BCG immunization status, tuberculin test results, presence of prolonged fever,

chronic cough, enlarged lymph nodes, swelling of bones and joints, chest x-ray results, total TB score, history of chronic disease, place of origin, number of children per room, ventilation/room area ratio, occupancy density, humidity, and room lighting were evaluated. Subjects underwent history-taking, and physical examinations.

Room lighting was defined as the level of light that entered a room, as measured by a photometer in 4 different quadrants of the room for 24 hours, then averaged and expressed in lux units. The minimum requirement of room lighting was 60 lux. Humidity measurements were carried out with hygrometer by hanging the tool at a height of 1.25-2 meters, leaving it for 24 hours, then reading the output.

Factors potentially associated with TB were analyzed by Chi-square test. Variables with P values < 0.25 in the bivariate analysis were subjected to multivariate logistic regression test. This study was approved by the Research and Development Unit (R&D) of the Faculty of Medicine, Udayana University/Prof. IGNG Ngoerah Hospital. The Bali Province Investment and One Stop Service Office provided permits to conduct our study in local Bali orphanages.

Results

This case-control study was conducted in 12 orphanages in Bali. One researcher conducted the history-taking, physical examinations, and tuberculin tests to ensure reliability and consistency of measurements. Participants were divided into two groups, case and control, using consecutive sampling. Of 175 children, three were excluded because they were absent when the tuberculin results were read. Thus, 49 (28.0%) children with positive tuberculin test results (though none were clinically confirmed to have TB disease) were diagnosed with TB infection and classified as the case group. The control group comprised 126 (72.0%) children declared free of tuberculosis because their tuberculin test results were negative (**Figure 1**). Every child with TB infection received preventative treatment (TPT).

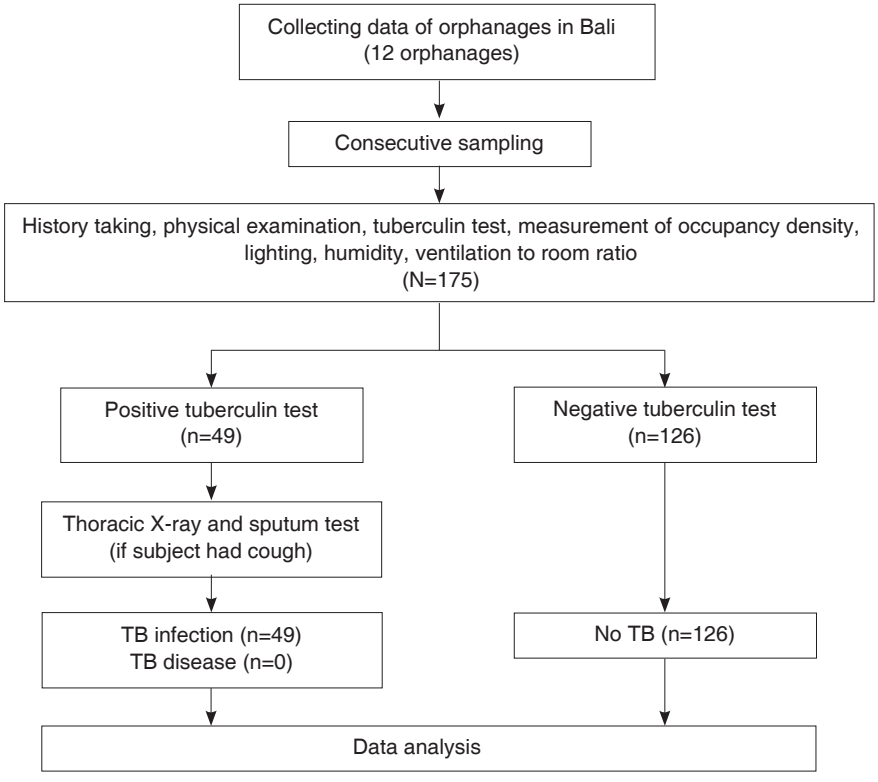

Figure 1. Study flow chart

None of the subjects underwent sputum testing because none had a clinical cough. Subjects with positive tuberculin test results underwent antero-posterior and lateral chest x-ray examinations, which revealed only one child with fibrosis (without other clinical symptoms) and 48 other children with no evidence of pulmonary tuberculosis or lymph node enlargement. The child with fibrosis on chest X-ray did not exhibit clinical symptoms of TB, so he was diagnosed with TB infection rather than TB disease. The current treatment was based on TB scoring, without investigations (sputum examination or tuberculin). The child had a negative tuberculin test, indicating that the child was unlikely to have ever been infected with tuberculosis, hence, he was not considered to be a TB contact at the associated orphanage. There was no known history of TB contacts between caregivers and orphanage residents, nor among other close connections, such as instructors or classmates, in other orphanages.

Subject's characteristics are listed in **Table 1**. The case group consisted of 23 (46.1%) males and 26 (53.1%) females. The median age and number of children per room were the same for both groups: 15 years and 4, respectively, in the case and control groups. One child out of 49 in the case group was under the age of five years, while the other subjects were over the age of five years. In addition, the median humidity in the two groups was nearly identical: 75 (range 65-84)% and 73 (range 63-85)%, respectively, in the case and control groups. The median occupancy density for both groups was 4.95 square meters per person. The ventilation-to-room size ratio was similar between the two groups: 16.67 (2.86 to 44.64) for the case group and 19.19 (2.50 to 44.64) for the control group. The nutritional status of children in this study was determined using the height-to-age and BMI-to-age ratios (U).

Bivariate analysis with Chi-square test revealed significant relationships between TB infection and occupancy density, humidity, ventilation/room area ratio, and place of origin. Children who lived in homes with a density of less than 8 m^2/person, greater than 73% humidity, less than 10% ventilation/room area ratio, and originating outside Bali were at higher risk of TB infection by 2.79, 3.66, 2.41, and 2.29 times, respectively (**Table 2**).

All independent variables with $P<0.25$ in bivariate analysis (**Table 2**) were further analyzed by multivariate logistic regression test (**Table 3**). Two

Table 1. Subjects' characteristics

Characteristics	TB infection (n=49)	No TB infection (n=126)
Median age (range), years	15.00 (4.00 – 18.00)	15.00 (6.00 – 17.00)
Sex, n (%)		
Male	23 (46.9)	65 (51.6)
Female	26 (53.1)	61 (48.4)
Median number of children/room (range)	4.00 (2.00 – 16.00)	4.00 (1.00 – 18.00)
Median room humidity (range), %	75.00 (65.00 – 84.00)	73.00 (63.00 – 85.00)
Median density (range), m2/person	4.95 (1.44-10.44)	4.95 (1.44-40.00)
Median lighting (range), lux	40.00 (10.00 – 96.00)	79.5 (40.00 – 265.00)
Median ventilation/room area ratio (range)	16.67 (2.86-44.64)	19.19 (2.50-44.64)
Mean height-to-age Z score (SD)	-1.18 (0.83)	-1.03 (1.01)
Height-to-age, n (%)		
Very short	1 (2.1)	2 (1.6)
Short	8 (16.3)	16 (12.7)
Normal	40 (81.6)	108 (85.7)
Median BMI-to-age Z score,(range)	-0.04 (-2.53 - 3.08)	0.10 (-3.11 - 2.89)
BMI-to-age, n (%)		
Severely thin	0	1 (0.8)
Thin	1 (2.0)	7 (5.5)
Normal	40 (81.6)	94 (74.6)
Overweight	4 (8.2)	18 (14.3)
Obese	4 (8.2)	6 (4.8)

variables maintained their statistical significance as positively associated with TB infection, namely, the <10% ventilation/room area ratio (OR=2.7; P=0.011) and less than 73% room humidity (OR=3.9; P=0.001).

Discussion

Tuberculosis is more prevalent among youngsters residing in orphanages. It has been shown that the prevalence of this condition exceeds initial expectations and is higher among the overall paediatric population. The occurrence of TB orphanages can be likened to an iceberg phenomenon. Children in orphanages were treated for TB at younger ages, had more advanced stage of the disease, and were malnourished. Prior to the introduction of ART, the incidence of tuberculosis was higher in orphanages. The prevalence of MDR-TB ranged from 3.5 - 5.5%.[16] Studies on TB in orphanages and Islamic boarding schools in Russia showed them to be at significantly higher risk of contracting tuberculosis than their peers. The incidence of primary infection and illness was 8.5% and 1.8% more prevalent from the primary infection and the diseases, respectively.[17]

One sign of the high rate of TB infection, particularly among orphanage-dwelling children, is the occupancy density. The risk of infectious diseases transmission is higher when people are in close proximity to one another, particularly in diseases transferred by minute droplets, such as tuberculosis. Occupancy density leads to an increased risk of TB infection.[15] Similarly, we found a substantial correlation between higher occupancy density and TB infection risk, as children residing in homes with

Table 2. Bivariate analysis of possible risk factors for TB infection

Risk factor	Case (n=49)	Control (n=126)	OR (95%CI)	P value
Occupancy density, n(%)				
<8 m^2/person	42 (85.7)	86 (68.3)	2.79 (1.15 to 6.75)	0.02
≥8 m^2/person	7 (14.3)	40 (31.7)		
Lighting				
<60 lux	32 (65.3)	62 (49.2)	1.94 (0.98 to 3.85)	0.06
≥60 lux	17 (34.7)	64 (50.8)		
Humidity				
≥73%	39 (79.6)	65 (51.6)	3.66 (1.68 to 7.97)	<0.01
<73%	10 (20.4)	61 (48.4)		
Ventilation area/room ratio				
<10%	20 (40.8)	28 (22.2)	2.41 (1.19 to 4.90)	0.01
≥10%	29 (59.2)	98 (77.8)		
BCG scar				
No	20 (40.8)	38 (30.2)	1.60 (0.81 to 3.17)	0.18
Yes	29 (59.2)	88 (69.8)		
Origin				
Outside Bali	27 (55.1)	44 (34.9)	2.29 (1.17 to 4.48)	0.02
Bali	22 (44.9)	82 (65.1)		

Table 3. Multivariate logistic regression analysis

Risk factors	Coefficient	S.E.	Wald	df	OR	95% CI	P value
Ventilation/room area ratio <10%	0.988	0.386	6.546	1	2.686	1.260 to 5.725	0.011
Room humidity ≥73%	1.365	0.409	11.158	1	3.917	1.758 to 8.727	0.001
Origin non bali	0.534	0.406	1.732	1	1.706	0.770 to 3.782	0.187
Lighting < 60 lux	0.565	0.378	2.227	1	1.759	0.838 to 3.692	0.133
Occupancy density < 8 m^2 / person	0.749	0.477	2.467	1	2.114	0.831 to 5.381	0.111
No BCG scar	0.710	0.380	3.496	1	2.034	0.966 to 4.281	0.061

a density of less than 8 m^2/person were 2.79 times more likely to contract TB than children residing in homes with a density of greater than 8 m^2/person.[8] Yustikarini *et al.*[16] noted a significant association between occupancy density and the incidence of pulmonary tuberculosis (OR 9.14; 95%CI 1.90 to 43.0; P=0.002). Our results were consistent with their findings.

Direct and artificial lighting must have an intensity of at least 60 lux and illuminate the entire room without dazzling. This is due to the ultraviolet (UV) can killed the *Mycobacterium tuberculosis* and prevent the transmission.[18] The inadequate amount of lighting was associated with tuberculosis transmission (OR 3.218; 95%CI 1.248 to 8.028; P=0.024).[18] The lack of a significant association in our study may have been due to our control group having more dwellings with unsatisfactory lighting conditions than the case group, despite the fact that practically all respondents in the case group lived in houses with inadequate lighting. Since so many subjects experienced inadequate lighting, we could not determine a significant association.

In addition to room temperature and the amount of sunshine that enters a room, indoor air humidity is a determining factor of air quality. Humidity is a potential risk factor for tuberculosis infection because the lack of sunlight entering the home creates a dark and humid environment in which microbes, including TB-causing bacteria, can survive for days to months. Mycobacterium can survive in the air for one to two hours, especially in humid and dark environments.[19] Bivariate and multivariate analyses revealed significant associations between air humidity and the probability of tuberculosis infection. Children living in houses with relative humidity of less than 73% were 3,917 times more likely to contract TB (OR 3.917; 95%CI 1.758 to 8.727; P=0.009).[13]

There is a relationship between indoor air humidity and ventilation. Children residing in houses with ventilation/room ratios less than 10% were 2.68 times more likely to contract tuberculosis than children residing in homes with ventilation/room ratios > 10%. A previous study reported that inadequate ventilation increased the risk of TB by 7.8 times.[20] Moreover, another study also noted that dwellings with inadequate ventilation increased the risk of TB infection (OR 3.717; 95%CI 1.581 to 8.738; P=0.004).[18]

BCG vaccine is 60-80% effective in reducing the occurrence of TB in children. Geographic location affects the efficiency of the BCG vaccine. The BCG strain administered also impacts the vaccine efficacy. On the other hand, the efficacy of BCG vaccination is declining in developing countries as a result of the emergence of new strains of Mycobacterium tuberculosis.[21] Moreover, BCG vaccination was not associated with the occurrence of tuberculosis in children.[16] In contrast, a study found a positive correlation between BCG immunization and the incidence of pulmonary tuberculosis in children in Sukabumi, West Java, Indonesia.[22] Similar to the abovementioned study, Kartasasmita *et al.*[23] asserted that immunizing newborns with BCG can provide protection against tuberculosis. Variations in study findings may have been due to our use of the presence or absence of BCG scars as a proxy, as not all BCG immunizations result in scarring on the child's arm. Immunization statuses of our subjects were unknown, therefore, we used the BCG scar as sign of their immunization status.

A child's place of origin was significantly associated with prevalence of tuberculosis in our bivariate analysis, but significance was not retained in the multivariate analysis. A person's exposure to tuberculosis is determined by the number of individuals with the disease in their immediate vicinity. The greater the number of instances of tuberculosis case in an area, the greater the risk of infection exposure.[24] Children from outside Bali were 2.29 times (bivariate analysis) more likely to contract tuberculosis than children from Bali. According to the *Indonesian Ministry of Health* profile data, multiple provinces have high incidences of tuberculosis, but Bali was not even among the top five provinces in Indonesia with high prevalences of TB in children aged 5-14 years. Those top 5 provinces were West Java (20,194 cases), Central Java (7,062 cases), East Java (5,401 cases), DKI Jakarta (5,242 cases), and Banten (3,123 cases).[25]

There were several limitations in in our study. First, because the data came from children in orphanages, it was difficult to gather information on their individual health histories, such as diabetes mellitus status, HIV, TB contact history, and immunization status, because often children arrive

at the orphanages with little known about their background. Second, we could not identify sources of transmission in the TB-infected children because their contact history was unclear. Third, a causal relationship between an orphanage environment and TB prevalence could not be determined due to the sampling being conducted at one time. Fourth, use of the Mantoux test as a diagnostic instrument might have produced false-positive or false-negative results. Some individuals may react to the Mantoux test despite not being infected with M. tuberculosis. False positive reactions may be due to mycobacterial illness other than tuberculosis, past BCG vaccination, wrong interpretation of the reaction, or improper use of antigens. False negative Mantoux results can be due to a variety of reasons, including skin anergy (the inability to react to skin tests due to a weakened immune system), recent TB infection (within 8-10 weeks of exposure), or severe TB infection.[14]

Despite the aforesaid limitations, this is the first study in Bali to explore the risk factors for tuberculosis among orphanage-dwelling children. In addition, history-taking, measurement of tuberculin test results, and physical examination were objectively assessed by a single trained observer using a single calibrated measuring apparatus, so as to ensure good validity and reliability.

Our findings suggest that attention to and protection from TB can be improved for orphanage-dwelling children, in terms of health services, such as screening for infectious and chronic diseases (HIV and diabetes) that can have a substantial impact on children's health. Our study can also serve as a basis to inform the government and private parties who construct orphanages to pay greater attention to the environmental conditions, especially humidity and ventilation, as well as proper health examinations of children, in order to limit the spread of disease.

In conclusion, the occurrence of tuberculosis infection among orphanage children in Bali remains high. Children living in residential areas with high population density (less than 8 m^2/person), high humidity (greater than 73%), and a low ventilation/room ratio (10%), as well as origin outside of Bali, increase the incidence of tuberculosis in orphanages in Bali in bivariate analysis. However, only ventilation and relative humidity of indoor air are significant, positive, independent risk factors for TB.

Conflict of interest

None declared.

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