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Prevalence and risk factors of tuberculosis infection in orphanage children in Bali, Indonesia



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ABSTRACT

Background: Tuberculosis (TB) is an infectious disease that causes high morbidity and mortality worldwide. Indonesia ranks third in the most TB cases in 2020 globally. Orphanages are densely populated places with a high risk of transmission, but routine TB screening programs have yet to be carried out. This study aims to find the prevalence of tuberculosis infection and its risk factors in orphanage children.

Methods: This study used a cross-sectional approach. The data collected included age, gender, nutritional status, stunting, BCG scars, and abnormalities in physical examination. History, physical examination, and tuberculin test are the screening programs performed. All children with a positive tuberculin test as an induration of 10 mm 72 hours after the tuberculin

test underwent a chest X-ray.

Results: We conducted tuberculosis screening for 262 children in 15 orphanages in Denpasar and Badung from July to October 2022. There is no known history of contact with active TB sufferers. No active tuberculosis infection was detected. Latent tuberculosis infection (LTBI) occurred in 57 children (21.7%), 48 (84.2%) aged 10-17 years, 28 (49.1%) were male, 54 (94.7%) had normal nutritional status, 13 (22.8%) were stunted, and no BCG scars in 28 (49.1%). No BCG scar was a risk factor for LTBI with OR 2.29 (95% CI 1.06 - 4.97; p 0.03).

Conclusion: One-fifth of orphanage children suffer from LTBI, and no BCG scar was a risk factor for LTBI. TB screening should be done routinely and actively in the orphanage.

Keywords: Orphanage Children, Active TB Infection, Latent TB Infection, TB Screening, Tuberculin Test.

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INTRODUCTION

Tuberculosis (TB) remains a formidable infectious disease, exacting substantial global morbidity. The year 2020 witnessed a staggering 10 million TB cases, with a disquieting subset comprising 1.1 million afflicted children. Highlighting the severity, as per the World Health Organization (WHO), Indonesia ranked third globally in TB notifications in 2020, trailing behind India and China. The nation's TB-induced fatalities also attained an unsettling second position worldwide, escalating from 1.2 million in 2019 to an alarming 1.5 million in 2020.¹ The Indonesian Health Ministry's Tuberculosis dashboard underscores the gravity, outlining TB incidence rates of 22/10000 and 12/10000 among children aged below five years and 5-14 years, respectively. These rates culminated in a distressing

tally of 408127 TB-afflicted children aged 0-14 years across Indonesia.²

Further intensifying the concerns, Indonesia posted an average of 146 TB cases per 100000 individuals in 2021, with Bali, albeit among the provinces with the lowest notification rate at 69 per 100000, offering a limited glimpse into the broader TB landscape in other provinces.³ Tuberculosis transmission, predominantly through airborne droplets, elevates the risk within densely populated living environments, and orphanages squarely fall within this high-risk category. Previously, notably, a study from Pakistan reported an 8.3% TB incidence among orphanage children.⁴ Similarly, a historical study from Haiti indicated 13% and 44% TB infection rates in orphanages without and with active TB cases, respectively.⁵ However, these figures demand caution when extrapolated to different national

contexts. Strikingly, orphanages within Indonesia have not undergone systematic TB screening protocols, further underscoring the need to assess TB burdens within these institutions as a microcosm of broader transmission among the nation's children.

Based on those mentioned above, our study aims to discern the prevalence and risk factors associated with active and latent TB infection (LTBI) in children within orphanages situated in Bali.

METHODS

Study population and design

This cross-sectional observational study was conducted across orphanages in Bali's Denpasar and Badung regions. The orphanages were registered with the Bali Provincial Social Service. The study was carried out from July to October 2022.

Considerations were made to determine the sample size required for assessing the prevalence of tuberculosis infection within the orphanage, and an assumed prevalence of TB is 10% among children.⁶ This calculation incorporated a 5% margin of error to account for generalization while ensuring a precision level of 5%. As a result, a minimum of 138 orphanage children was deemed necessary.

Our hypothesis posits that latent TB infection in orphanage children is correlated with poor nutritional status, short stature, and the absence of BCG scars. A significant difference is a minimum of 25% in the proportions. Previous literature indicated that among children with latent TB infection, the prevalence of malnutrition and lack of BCG scars was 83.6% and 40%, respectively.⁷ For children without latent TB infection, the proportions of those with normal nutritional status and BCG scars were 20% and 13%, respectively.⁸ The statistical significance threshold was set at a type I error of 5% and a type II error of 20%. To adequately analyze the influence of these three risk factors in age- and sex-matched groups, the calculated minimum sample size for each group was determined to be 52.

Selection criteria and sampling technique

In this study, we included orphanage children within the age range of three months – 17 years. The exclusion criteria encompassed individuals currently undergoing immunosuppressant therapy and those previously diagnosed with tuberculosis. Additionally, orphanages with a documented history of tuberculosis among members within the preceding five years were also excluded. We use the age limit of 3 months as the lowest age limit by the minimum age limit for using the tuberculin test. The total number of orphanages registered with the Denpasar and Badung social services was 26, collectively housing 628 children. A cluster random sampling method based on the administrative areas of Denpasar and Badung was adopted to ensure representative sampling, considering that the locations of each orphanage are spread over a wide administrative area. This

approach was executed until the required minimum sample size was achieved.

Prior to participation, comprehensive tuberculosis counseling was provided to both orphanage caregivers and children. Securing informed consent involved obtaining permission from the orphanage management and every child aged 12 years or older. Consent from children below the age of 12 was sought through the orphanage administrator, acting as the authorized representative. This study was conducted by ethical guidelines and received approval from the relevant institutional review board.

Study variables

The study variables encompassed age, gender, nutritional status, stunted classification, presence of BCG scar, and tuberculosis status. 1) Age: was calculated from birth or stated in the family card until the examination, categorized into three groups: 0-5 years, 6-9 years, and 10-18 years. 2) Gender classification: was determined based on physical appearance and categorized as male and female. 3) Nutritional status: was assessed using specific criteria. For children aged 0-60 months, weight/length or height (good nutrition if in the range of -2SD to +1SD, malnutrition if <-2SD). For children aged 5-18 years, body mass index (BMI) was considered (good nutrition if in the range -2SD to +1SD, malnutrition if <-2SD). 4) Stunted classification: was based on the height for age graph, with classifies as normal if the length or height for age is from -2SD to +3SD and stunted if in the range <-2SD. Body weight was measured using a digital weight scale brand ABS. Height was measured using a stadiometer. 5) BCG scar: The presence or absence of a BCG scar was determined through direct visualization of the subject's right and left m. deltoid.

TB infection status is determined after all examination procedures were carried out according to the flow of TB diagnoses in children based on the 2016 Indonesia Child Tuberculosis Technical Guidelines.⁹ The flow consists of some parameters like a history of contact with active adolescent and adult TB patients (Score 3 if there is contact with an active TB sufferer with positive sputum results, score two if there

is a report of a household member or other close contact suffering from TB with unknown sputum results, and score 0 if there is no clear history of TB contact); tuberculin skin test result (Score 3 if the tuberculin test result is positive, and 0 if the tuberculin test result is negative); body weight or nutritional status (Score 2 if there is clinical severe malnutrition in the form of old man face, baggy pants, prominent rib or bodyweight/height <70% or bodyweight/age <60%, and score one if there is moderate malnutrition, namely bodyweight/height <90% or bodyweight/age <80%, score 0 if nutrition is good); fever without a clear cause for two weeks or more (Score 1 if there is a fever for >= two weeks, and 0 if there is no fever during that time); presence or absence of cough for two weeks or more (Score 1 if there is cough for >= two weeks, and 0 if there is no cough during that time); enlargement lymph nodes (Score 1 if there is an enlargement of colli, axillary or inguinal lymph nodes of >= 1 cm accompanied by an enlarged number of KGB > 1, and no pain, score 0 if there are no enlarged lymph nodes as described above); and chest X-ray results (Score 1, if there is a picture suggestive of tuberculosis like the presence of significant, infiltrates, enlarged hilar lymph nodes, and cavities, and score 0 if the chest x-ray picture is normal).

History of contact with active tuberculosis sufferers, weight loss in the last two months, fever, chronic cough, and bone or joint pain is determined by direct history taking of the subject. Symptoms of TB in the form of swollen lymph nodes were examined directly in the subject's cervical, axilla, and inguinal regions.

The tuberculin test was performed by injecting tuberculin reagent PPD 2 RT 0.1 mL subcutaneously 5-10 cm below the elbow on the volar part of the right forearm. If there is an infection on the skin in that area, we inject the reagent into the left arm. The interpretation of the tuberculin test results was carried out 72 hours after injection. Tuberculin test results are positive if there is an induration of >= 10 mm and negative if there is an induration of <10 mm. We performed chest X-rays on all children with a positive tuberculin test.

Based on these guidelines, a score >=

six is used as a benchmark for providing anti-tuberculosis therapy. Our research focuses on orphanages whose members have never been known to have TB contact. Hence, we declare the child has active TB if the tuberculin test results are positive, the chest X-ray is suggestive, and there are at least two of the TB symptoms according to the flow above; latent TB infection if only the tuberculin test results are positive while the chest X-ray is normal and the child has no symptoms; and not infected with TB if the tuberculin test result is negative.

Data analysis

Descriptive statistics were utilized for all characteristics, presented as proportions and percentages. For risk factor analysis, subjects were matched based on age and sex for hypothetical analysis. Bivariate analysis, employing chi-square, determined significant risk factors ($p < 0.05$). Multivariate analysis followed when multiple significant factors were identified. Results were presented as odds ratios (OR) with 95% confidence intervals and p-values. Data analysis was conducted using SPSS software version 29 (IBM Corp., USA).

RESULTS

A total of 262 subjects from 15 orphanages in Denpasar and Badung were enrolled. Among the cohort, 57 children (21.7%) exhibited latent TB infection. Notably, all children with positive tuberculin test results displayed normal chest radiographs, indicating the absence of active TB infection. The characteristics of orphanage children and those affected by latent TB infection are presented in Table 1 below.

Further analysis was performed on a subset of 56 subject pairs with and without latent TB infection matched by age and sex to investigate the hypothesis concerning the role of nutritional status, stunting, and BCG scar as risk factors for latent TB infection. The absence of BCG scar emerged as a significant risk factor for latent TB infection in orphanage children, with an odds ratio (OR) of 2.29 (95% CI 1.06 - 4.97) and a p-value of 0.03. Detailed results of the comprehensive analysis are provided in Table 2.

Table 1. The characteristics of children in orphanages without TB infection and those suffering from latent TB infection

Characteristic	No TB infection (n=205)	Latent TB infection (n=57)
Age, n (%)		
≤ 5 y.o	3 (1.50)	2 (3.50)
> 5 – 10 y.o	48 (23.40)	7 (12.30)
> 10 y.o	154 (75.10)	48 (84.20)
Sex, male, n (%)	107 (52.20)	28 (49.10)
Nutritional status, n (%)		
Moderate malnutrition	20 (9.80)	3 (5.30)
Stunted	52 (25.40)	13 (22.80)
No BCG scar, n (%)	67 (32.70)	28 (49.10)
TB symptoms, n (%)		
Decreased body weight	2 (0.90)	2 (3.50)
Fever with unknown cause	2 (0.90)	0 (0.00)
Cough ≥ 2 weeks	5 (2.40)	1 (1.70)
Lymphadenopathy	2 (0.90)	6 (10.50)
Skeletal symptoms	0 (0.00)	0 (0.00)

Table 2. Analysis of risk factors for latent TB infection in orphanage children

Risk factors	OR (95%CI)	p
Moderate malnutrition	0.47 (0.11 – 1.98)	0.30
Stunting	0.76 (0.32 – 1.77)	0.52
No BCG-scar	2.29 (1.06 – 4.97)	0.03*

*Statistically significant if p-value less than 0.05

DISCUSSION

Tuberculosis remains a significant global health concern, yet reported TB case notifications in Indonesia often fall below the actual prevalence, creating a gap between reported and true cases.⁶ This discrepancy can lead to insufficient resource allocation for TB diagnosis and treatment facilities, emphasizing the need for accurate case reporting. The primary mode of *M. tuberculosis* transmission through droplets underscores the increased risk in densely populated environments. Orphanages, with their close living quarters, exemplify such settings. Surprisingly, despite this heightened vulnerability, studies investigating TB incidence in orphanages are notably sparse both on a global and national scale. The lack of routine TB screening programs in orphanages across many developing nations, including Indonesia, further accentuates this gap in addressing TB transmission.¹⁰

Our findings revealed no active TB infection but a prevalence of latent TB infection among orphanage children, affecting approximately one-fifth of the cohort. Latent TB infection is characterized by the presence of *M. tuberculosis* without

clinical manifestations, and its significance lies in its dual nature. Firstly, 5-15% of latent TB infections may progress to active TB disease.¹⁰ Secondly, latent TB infection offers a crucial time for preventive interventions, halting disease progression, with a significant 60-90% estimated protective effect.¹¹

One of the studies on the incidence of TB in orphanages was quite old, namely in 2013. This study found the incidence of latent TB in 542 orphanages in North Pakistan at 8.3%.⁴ The difference in results with our study was due to differences in the method of diagnosis, in which the study used serum TB antibodies and PCR. These examination methods do not yet exist in Indonesia and are currently not recommended by WHO to diagnose tuberculosis in children.¹²

Our study highlighted an intriguing age-based susceptibility pattern, where 84.2% of orphanage children with latent TB infection were more than ten years of age. Early to middle adolescents have a higher risk of developing TB than the younger age group due to a shift in immune patterns to Th1 dominance, hormonal changes, and changes in lifestyle to increased socialized and outside home activities.^{12,13} The fact that most of the

orphanage children in this study were in their teens highlights the importance of TB screening in this population. Our study unveiled the absence of BCG scars as a significant risk factor for latent TB infection in orphanage children. This observation resonates with a prior study at Cipto Mangunkusumo Hospital, which correlated absent BCG scars with higher extrapulmonary TB incidence.¹⁴

BCG vaccination is a vaccine that is routinely given to all babies up to 2 months of age in Indonesia. BCG scar, a local reaction typically occurring within 4-8 weeks post-vaccination, is a valuable indicator of BCG vaccination status. Although variations exist, most BCG-vaccinated infants exhibit scar formation, which underlines the importance of correct vaccination technique and strain. An exciting study by Dhanawade SS et al. reported that BCG scars formed in 91.4% and positive TST with a size of 6.01 ± 3.224 3 months post-vaccination in 71.4% of 70 babies who received the BCG vaccine.¹⁵ We can conclude two things from this study: the development of BCG scars and positive TST reactions with size <10 mm in most babies who receive the BCG vaccine. Funch KM et al. reported that the main factors for non-forming BCG scars in children with the BCG vaccine were the vaccination technique and vaccine strain. Regarding the vaccination technique, the BCG vaccine should be given intracutaneously with a wheal diameter above three mm.¹⁶ Achieving a wheal with a diameter of >3 mm requires skill from the injector and the person holding the baby. Meanwhile, the strain of BCG vaccine microorganisms most often associated with the absence of scar formation is the Moscow strain currently used in Indonesia. This contradicts our previous study, which found no significant difference in scar tissue formation and tuberculin conversion between the Moscow strain and the Pasteur strain three months post-vaccination involving 220 infants (63.1% vs. 66.6%, p 0.57 and 24.5% vs. 29.1%, p 0.25 respectively).¹⁷

Repeating the BCG vaccine to children without BCG scars is not yet recommended in Indonesia. We cannot confirm whether children without BCG scars in this study have never received the BCG vaccine, considering that these children no longer

have parents. Until now, the absence of a BCG scar was thought not to mean no immunity against M.Tb. Several older and newer studies on the effectiveness of repeated BCG vaccines have used a variety of subject approaches. Some give BCG re-vaccination to subjects without BCG scars; some use a negative tuberculin test as a benchmark. There needs to be uniformity in managing children without BCG scars. They did not get an increase in the protective effect against tuberculosis in subjects who received repeated BCG vaccinations compared to those who did not.¹⁸⁻²¹ The results of our study do require further validation from studies in different populations. However, they can also be used as a consideration in making decisions about administering the BCG vaccine again when dealing with children without BCG scars in population groups such as children in orphanages.^{22,23}

Malnutrition has long been considered a risk factor for TB, but in reality, it has been challenging to prove. Contrary to the longstanding notion of malnutrition as a TB risk factor, our study did not establish a significant association between poor nutritional status and short stature with TB infection. Since 3/4 of the orphans in the age range are teenagers aged ten years and over, comparing the nutritional status of orphanage children with the nutritional status of Indonesian youth, in general, is not excessive. Malnutrition occurs in 8.1 - 8.7%, while stunting occurs in 25.7 - 26.9% of Indonesian youth. This figure is not much different from what we found for the children in the orphanages in this study, likewise with stunting, which in common sense can be a risk factor for TB.^{24,25}

The weakness of our study is the weakness of the tuberculin test in determining TB infection. However, the tuberculin test is still the WHO's recommendation and is a cost-effective tool for TB infection screening programs in large populations. Another limitation of this study is that it was carried out at one time, affecting the quality of risk factor causality.

CONCLUSION

In summary, latent TB infection was prevalent in one-fifth of orphanage children in Bali, with the absence of a BCG

scar emerging as a noteworthy risk factor. Our study underscores the imperative for active tuberculosis screening in Indonesian orphanages and raises the question of re-administering BCG vaccines to those lacking BCG scars and unclear vaccination history. The findings advocate for targeted interventions within this vulnerable population to mitigate latent TB infection and its potential progression to active disease.

CONFLICT OF INTEREST

None declared.

ETHICAL CONSIDERATION

This study was completed after all orphanage administrators and children had agreed to participate in the study voluntarily and had been given information. Their data were kept confidential. The study was carried out after receiving ethical approval from the Faculty of Medicine Ethics Committee, Udayana University – RSUP Prof. Dr. IGNG Ngoerah Hospital (No 1882/UN14.2.2.VII.14/LT/2022).

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AUTHOR CONTRIBUTION

All authors contributed significantly to this work, and all are in agreement with the contents of this article.

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