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Prevalence and Risk Factors of LTBI at Madura Boarding School as a High-Risk Congregate Setting

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ABSTRACT

Introduction: Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (MTB), is a highly contagious airborne disease. High-risk environments with frequent close interactions contribute to the spread of TB. This study examined latent TB infection (LTBI) epidemiology in such settings to inform public health interventions and strategies to curb TB transmission in similar environments.

Methods: This cross-sectional observational study, conducted from January to August 2022 at two boarding schools in Bangkalan, involved 100 adolescents aged 10-18 years old tested for LTBI using interferon-gamma (IFN-γ) release assay (IGRA). Data were collected via questionnaires. Bivariate analysis was used to determine the correlation between LTBI prevalence and each research variable using Pearson correlation and odds ratio (OR). A p-value <0.05 was considered statistically significant.

Results: This study found that 30% of 100 adolescents in boarding schools had LTBI. Risk analysis showed a significant association between gender and LTBI, with males having a 1.02 times higher risk (p-value 0.000). Additionally, lower education levels were significantly associated with a 5.2 times higher risk of LTBI (p-value 0.021).

Conclusion: Boarding schools pose a TB transmission risk. Early LTBI screening is essential for TB eradication in Indonesia, and these findings emphasize the need to improve LTBI detection and prophylaxis therapy as a preventive measure against TB outbreaks.

Highlights:
1. Boarding school is a high-risk location for TB transmission. Therefore, stricter early prevention measures are required.
2. Gender and knowledge level were significantly related to LTBI, but there was no significant relationship between age and nutritional status.
3. Low level of knowledge was the highest risk factor compared to other factors, with a five times greater risk of contracting LTBI.

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Introduction

Latent tuberculosis infection (LTBI) refers to a state where an individual carries the *Mycobacterium tuberculosis* (MTB) bacteria but remains asymptomatic for active tuberculosis (TB), whether it affects the lungs or other organs like bones, kidneys, eyes, heart, or liver.[1] However, a positive outcome is obtained when testing for MTB using the tuberculin skin test (TST) or interferon-gamma (IFN-γ) release assay (IGRA).[2] The Global TB Report reported 7.1 million new TB cases worldwide in 2019.[3]

The World Health Organization (WHO) reported in 2016 that ¼ of the world's population (1.7 billion people) had been infected with MTB through TST and IGRA tests.[4] Indonesia is among the countries with a high burden of TB, currently ranking 3rd globally, with prevalence of 845,000 cases or 320 per 100,000 population and a death toll of 98,000 cases or 40 per 100,000 population.[5] Based on TB patient distribution data, West Java and East Java provinces have the highest number of TB patients. In fact, in 2018, the number of TB patients in East Java reached 20,535.[6]

Despite the decreasing rate of active TB reported cases in Indonesia, from 319 cases per 100,000 people in 2017 to 301 cases per 100,000 people in 2020, according to the assessment of WHO, approximately 30% of the global population carries LTBI, with approximately 5-10% of them experiencing the onset of active TB at some point during their lifetime.[7] Individuals with latent TB infection do not exhibit any symptoms of TB illness. The sole indication of LTBI is a positive response to TST or IGRA.[8]

The transmission of MTB occurs when an infected individual coughs or sneezes without properly covering their mouth and nose, releasing droplets into the air.[9] Transmission is usually direct, either through inhalation of airborne organisms in aerosols produced by sputum or exposure to infected secretions. It is important to recognize infection from disease. Infection involves seeding an outbreak with organisms that can or cannot cause clinically significant tissue damage. Most infections are contracted by direct person-to-person transmission of droplets from airborne organisms from an active case of a susceptible host.[1]

TB outbreaks tend to occur in institutional settings and have been documented in places like preschools, elementary schools, boarding schools, and universities.[10] Boarding schools, in particular, have an elevated risk of experiencing TB outbreaks due to the frequent congregation of adolescents in crowded conditions.[11] Adolescents residing in boarding schools are also reported to be at a heightened risk of TB transmission due to the cramped living conditions and inadequate ventilation.[12] A previous study approximated that 1.78 million adolescents and young adults between the ages of 10 and 24 years old developed TB globally in 2012.[13]

The spread of MTB is not simply due to poor health conditions but to various factors. Social and economic problems greatly affect the spread of MTB. These problems affect the nutritional status of each individual, thereby affecting their sensitivity to TB infection.[14] Unfortunately, until now, there is no universally accepted standard for directly diagnosing LTBI in humans. However, WHO suggests that either the TST or IGRA test can be employed to determine the presence or absence of TB infection, aiding in identifying individuals with LTBI.[8] According to the LTBI examination algorithm and the administration of prophylaxis in the 2020 LTBI guideline in Indonesia, individuals with positive LTBI screening results may receive prophylaxis therapy and regular monitoring for active TB disease.[15]

Screening for LTBI can be conducted using the IGRA test in combination with an assessment of the individual's symptoms. There remains significant debate regarding the most suitable test for detecting LTBI.[16] The data concerning IGRA tests are evolving, and their reliability within certain patient populations is not as robust as that of the TST. IGRAs generally exhibit high specificity (93% to 99%) but somewhat lower sensitivity (between 70% and 90%). Despite the lower sensitivity, it is worth noting that there have been no false positive results for the IGRA test due to Bacillus Calmette-Guérin (BCG) vaccination.[17]

Based on previous studies conducted on family members of active TB patients, it was found that male samples with characteristics of productive age and normal BMI had a higher risk of LTBI.[18] Place of residence can be a risk of transmission of MTB. Inadequate living conditions, poor ventilation, and poor sunlight cause MTB to live long, increasing the transmission risk.[19]

High-risk congregational settings are seen as a potential source of MTB transmission. Boarding schools are particularly susceptible to outbreaks due to their overcrowded conditions and prolonged close interactions among students, both of which facilitate the spread of TB. Environmental factors and the efficacy of managing individual cases are key risk factors for the occurrence of outbreaks.[20] Given this context, this study examined the prevalence and risk factors of LTBI among boarding school residents.

Methods

This observational analytic study employed a cross-sectional method using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25 for Windows.[21] This study was conducted from January to August 2022 at Ar-Rohmani Al-Ushaqy Boarding School and Kramat Boarding School in Bangkalan. Blood samples for the IGRA test were collected simultaneously with questionnaire data collection. Whole blood samples of 3 ml were withdrawn for each research sample and placed into 3 different QuantiFERON-TB Gold Plus (QFT-Plus) blood collection tubes (control negative, TB antigen, control mitogen). These tubes were labeled and incubated upright at 37°C ± 1°C for 16-24 hours in an incubator.[22] Subsequently, the samples were

processed through centrifugation and interpreted with enzyme-linked immunosorbent assay (ELISA) at the Laboratory of Universitas Airlangga.

Population and Sample

The sample comprised 100 adolescents who underwent IGRA testing and met the inclusion criteria. Inclusion criteria encompassed individuals aged 10-18 years old, residing in boarding schools, and willing to participate as research subjects. Exclusion criteria included individuals with active TB, aged below 10 or over 18 years old, not residing in boarding schools.

Data Analysis

This observational analytic study used a cross-sectional method, utilizing IBM SPSS version 25 for Windows.[21] The data obtained from the study were normally distributed. Bivariate analysis was performed using Pearson correlation and odds ratio (OR) to find risk factors for each variable. This analysis was used to find the correlation between the prevalence of LTBI and each research variable as a detailed risk factor. The p-value of <0.05 was considered to be statistically significant.

Results

This study was conducted on 100 individuals out of 316 adolescents in 2 boarding schools in Madura with positive IGRA test results in January 2022. All samples met the inclusion criteria. The results, which include the number of occurrences, characteristics, and correlation of prevalence rates on risk factors, are presented in Table 1.

Table 1. LTBI sample prevalence

LTBI	n (%)
Positive	30
Negative	70

Source: Research data, processed

The data was obtained from the IGRA test and the completion of questionnaires regarding clinical symptoms of TB in adolescents at Ar-Rohmani Al-Ishaqy Boarding School and Kramat Boarding School in Bangkalan. Table 1 shows the prevalence of LTBI in the study sample, as high as 30%. This means a positive IGRA result was ⅓ of the adolescent population in boarding schools.

Table 2. Correlation of LTBI prevalence to sex

	LTBI				Total		p-value	OR
	Positive		Negative					
	N	%	N	%	N	%		
Male	10	30.3	23	69.7	33	33		
							0.000	1.022
Female	20	29.85	47	70.15	67	67		

Source: Research data, processed

The data collected from 100 adolescents who underwent IGRA testing at Ar-Rohmani Al-Ishaqy Boarding School and Kramat Boarding School in Bangkalan as the sample revealed that there was a greater number of female participants compared to males. Males with positive LTBI were 10 from 33 samples (30.30%), and females with positive LTBI were 20 from 67 samples (29.85%). The analysis revealed a statistically significant association between sex and LTBI prevalence, with a p-value of 0.000, indicating a significant result. The OR was found to be 1.022, suggesting a slightly increased likelihood of LTBI in males compared to females.

Table 3. Correlation of LTBI prevalence to age

	LTBI				Total		p-value	OR
	Positive		Negative					
	N	%	N	%	N	%		
10-14	4	26.67	11	73.33	15	15		
							0.901	0.923
15-18	26	30.59	59	69.41	85	85		

Source: Research data, processed

Based on Table 3, there was a higher proportion of samples in the age range of 15-18 years old compared to those in the age range of 10-14 years old. The age range of 10-14 years old with LTBI positive was 4 from 15 samples (26.67%), and the age range of 15-18 years old with LTBI positive was 26 from 85 samples (30.59%). The correlation between LTBI prevalence and age was insignificant, with a p-value of 0.901. This high p-value indicated that there was no evidence to suggest a correlation between age and LTBI prevalence. The OR of 0.923 indicated that age did not substantially impact the odds of LTBI prevalence.

Table 4. Correlation of LTBI prevalence to education

	LTBI				Total		p-value	OR
	Positive		Negative					
	N	%	N	%	N	%		
Low	28	35.44	51	64.56	79	79		
							0.021	5.216
Moderate	2	9.52	19	90.48	21	21		

Source: Research data, processed

Regarding education levels, most of the samples had completed only low education, indicating a predominant basic educational background among them. Low education was 35.44%, and moderate was 9.52%. The correlation between LTBI prevalence and education level was statistically significant, with a p-value of 0.021. The OR of 5.216 indicated that individuals with a low level of education were significantly more likely to have LTBI compared to those with another level of education.

Table 5. Correlation of LTBI prevalence to nutritional status

	LTBI				Total		p-value	OR
	Positive		Negative					
	N	%	N	%	N	%		
Normal	6	12.5	42	87.5	48	48		
							0.0963	0.167
Obese	24	46.15	28	53.85	52	52		

Source: Research data, processed

None of the samples had low nutritional status, and most exhibited excess nutritional status. Normal nutritional status was 12.50%, and obese was 46.15%. The correlation between LTBI prevalence and nutritional status was not statistically significant, with a p-value of 0.0963. The OR of 0.167 suggested a protective effect, where individuals with a certain nutritional status were less likely to have LTBI compared to those with another nutritional status. However, given the non-significant p-value, this effect was not statistically conclusive.

Discussion

Based on the results of this study, 30% of the total samples tested positive for LTBI using the IGRA test. This study examined various risk factors, focusing on four main ones. Among these, two factors, gender and education level, were found to have a significant association with the occurrence of LTBI. However, age and nutritional status showed no significant relationship with LTBI incidence, with nutritional status suggesting a potential protective effect against LTBI. The prevalence of LTBI in this study indicated a relatively high prevalence, considering the WHO's estimate of LTBI incidence worldwide was 25%.[23]

The IGRA test used in this study was the QFT-Plus test, which boasted a sensitivity of 98.9% and a specificity of 98.09%. This QFT-Plus test assesses the cell-mediated immune response to peptide antigens that stimulate mycobacterial proteins. The QFT-Plus test uses whole blood samples to measure IFN-γ response to antigens (ESAT-6, CFP-10, and TB7.7) via the ELISA method. The QFT-Plus test involves three specialized blood tubes (negative control, TB antigen, mitogen control), each requiring 1 mL of blood. In this study, competent nurses collected blood samples under a pediatric specialist's supervision. After incubation, the samples were sent to the Laboratory of Universitas Airlangga for further processing, including centrifugation to separate the plasma and analysis by ELISA. The results were then interpreted as positive, negative, or intermediate.[22]

The questionnaire used in this study was adapted from one previously utilized in other research and modified to fit the study's specific needs. Participants completed the questionnaire independently, with guidance from the authors. Before data collection began, a brief session was held to explain how to fill out the questionnaire. During the process, participants were allowed to ask for clarification on any questions. Data from the questionnaire and IGRA results were then compiled and analyzed using IBM SPSS version 25 for Windows.[21]

The transmission of TB can be affected by various factors beyond external influences, such as internal variables like gender, age, level of education, and nutritional status. The significant rise in LTBI cases in Africa and Southeast Asia, including Indonesia, demonstrates a more substantial increase among adolescents compared to other regions.[24] The prevalence of LTBI varies across age groups. The likelihood of LTBI is higher among younger age groups, attributed to their less developed immune systems and reduced capacity to combat infections.[1] Young children face a heightened risk of developing LTBI, with studies indicating a risk of 10% to 20% for those under five years old.[25]

This study shows similar findings to a study conducted by Laycock, explaining that a significant increase in the estimated number of TB cases between early adolescence and young adulthood was consistent with historical observations.[11] The highest number of cases in this study occurred in the 20-24 age group, with the second-highest age group being 15-19 years old.[26] Adolescents, aged 10 to just before turning 18, are alternatively defined as individuals growing into adulthood, encompassing mental, emotional, social, and physical maturity. In this context, adolescents are vulnerable to contracting TB due to their developing immune system, which is not yet fully mature.[27]

Social behavior plays a role as well, as adolescents often engage in social activities such as gathering with friends or interacting with many people at school, which increases the risk of TB transmission.[25] Environmental conditions are also a factor, as adolescents find themselves in less hygienic environments while exploring new experiences. Additionally, their food consumption patterns may involve purchasing food from outside their homes, the cleanliness of which may be unknown.[9] Middle schools were more likely to transmit TB from index cases than high schools. This could be attributed to the observation that at higher levels of education, physical proximity among students tends to decrease, thus diminishing the transmission risk.[28]

A previous study explained that in terms of quantity, more males suffer from pulmonary TB compared to females.[9] The likelihood of experiencing pulmonary TB is nearly the same in terms of quality, as evidenced by OR analysis. Males have a 1.7 times higher risk of contracting pulmonary TB than females, which shows a similar finding from this study where males have a slightly higher risk of LTBI. Nevertheless, gender is not a primary risk factor for the occurrence of pulmonary TB because the active role of females outside the home, such as in work, social activities, religious activities, and social gatherings, has increased contact with individuals suffering from pulmonary TB.[29]

Additionally, when a male has pulmonary TB, the female around him (family) also has the potential to be infected because the transmission of pulmonary TB occurs through the air when the patient coughs, sneezes, or talks, releasing bacteria in the form of droplets (sputum particles). In this case, there are several potential factors explaining why females may experience a higher prevalence of TB cases. Biologically, females have certain hormones like estrogen that can influence the immune response to TB. In addition to biological factors, the population of Indonesia is predominantly composed of females, leading to increased interactions among females.[30]

Individual factors are not only based on gender and age, but education can influence a person's knowledge of a disease. The level of a person's formal education influences a person's mindset to continue to develop and learn, including in terms of TB. This is because a high level of education can easily absorb various information about TB.[31] Health-related education can play a role in changing

the behavior of individuals, groups, and communities following health values. Behavioral changes are expected to be able to maintain and improve health, prevent the risk of illness, protect themselves from the threat of disease, and actively participate in the public health movement. Therefore, behavior change is the result of education related to health.[32]

A previous study showed that knowledge about pulmonary TB disease significantly prevented increased MTB transmissions from one individual to another. Individual education levels can influence low levels of knowledge about pulmonary TB.[33] This study is consistent with the study conducted by Matakanye (2021), which explained that there was a significant correlation between knowledge and the family's role in preventing pulmonary TB.[34]

The ease of accessing information is positively influenced by the level of education, with higher education facilitating better information access. Family members primarily receive information from healthcare professionals, and some obtain information from the Internet. Education plays a crucial role in shaping one's learning process, and a higher level of education makes it easier for individuals to comprehend and absorb information. Improved knowledge levels are associated with more positive attitudes and behaviors, while lower levels of knowledge are linked to negative behaviors.[35]

Another factor that can influence TB transmission is nutritional status. Nutritional status is the health status that balances nutritional needs and nutrient intake. It is categorized into underweight, normal, and obesity. Obesity is excessive fat accumulation due to an imbalance between energy intake and expenditure. In other words, it describes a condition in which someone has an excessively overweight body with a high fat content.[36] The results of this study are not in line with those of the study conducted by Hussien (2019), which reported a high prevalence of nutritional deficiencies.[37] Furthermore, nutritional support for nutritional assessment and diet counseling is necessary for better treatment outcomes and an effective TB management program. This is because nutritional status is correlated with the immune system.[37]

This study found nutritional status has a protective effect on LTBI. The decrease in TB risk associated with an increase in BMI has primarily been observed in pulmonary TB and not in cases of extrapulmonary disease. When assessing the impact of body mass index (BMI) on overall mortality and mortality from specific causes, a similar inverse relationship between obesity and TB has been noted on a global and regional scale. While the exact mechanism behind this inverse relationship between obesity and TB is not yet fully understood, it has been suggested that nutritional factors and related adiposity could affect the ability of the immune system to combat TB and other infections.[38]

Experimental infection models have demonstrated the role of cytokine-mediated innate immunity in protecting the host against MTB infection. This highlights the crucial role of IFN-γ, tumor necrosis factor-α (TNF-α), and interleukins (ILs) in controlling infections. Adipocytes and immune cells within adipose tissue release higher levels of these inflammatory mediators, which can impact insulin sensitivity, inflammation, and innate and adaptive immune responses.[38]

This study found that 30% of the samples tested positive for LTBI, exceeding the WHO estimate of 25% for LTBI prevalence worldwide. This difference suggests that the population under study may face a higher risk, possibly influenced by specific risk factors that elevate LTBI prevalence in boarding schools. This aligns with a previous study indicating that school, prison, and boarding environments carry higher risks of MTB transmission than other settings.[39]

The discovery of positive LTBI cases indicates the potential presence of MTB transmission within boarding environments. While transmission can occur inside and outside these settings, efforts should focus on identifying sources of exposure within boarding environments to intervene and break the transmission chain. Another study showed that individuals with positive LTBI have a 5-10% chance of developing active TB within two years of exposure.[23] In line with Indonesian LTBI guidelines, preventive measures include administering TB prophylactic therapy tailored to each case's characteristics. Commonly used therapies include isoniazid and rifampicin for three months, with monitoring for active TB symptoms, both pulmonary and extrapulmonary, during and after treatment.[15]

Strength and Limitations

The strength of this study was that all the samples were obtained based on examinations conducted independently. However, due to budget constraints in conducting IGRA tests, not all individuals within the population could undergo examination.

Conclusion

The study indicated that boarding schools pose a risk for LTBI transmission. No correlation was found between age or nutritional status and LTBI prevalence. To address positive LTBI results, participants may receive prophylactic therapy according to Indonesian guidelines. The findings suggested exposure to MTB from within and outside the boarding school, highlighting the need for early prevention measures. Further studies should be conducted with a larger sample size across a wider range of boarding schools to obtain accurate results.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Health Research, Universitas Airlangga, Surabaya (No. 267/EC/KEPK/FKUA/2021) on 14-02-2022.

Authors' Contributions

Conceived the study, designed the study, gathered, analyzed, and interpreted the data, created tables, and wrote the manuscript: MA. Reviewing and revising the manuscript: RA, PL. All authors contributed and approved the final version of the manuscript.

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