



# Prevalence of latent tuberculosis among refugee children in Malaysia

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## ABSTRACT

**Introduction:** Tuberculosis remains one of the top 10 major causes of global mortality, imposing social-economic and medical challenges in Malaysia. Refugees sheltered in Malaysia are a high-risk population but basic health checks upon their arrival, including tuberculosis screening, are not practised. This study aimed to identify the prevalence and risk factors of tuberculosis and latent tuberculosis infection (LTBI) among refugee children in Malaysia.

**Methods:** A cross-sectional study was performed in three refugee schools in the Klang Valley, Malaysia, using tuberculin skin tests or interferon- $\gamma$  release assays. Participants who tested positive were sent for further examination with chest radiography to confirm the tuberculosis diagnosis.

**Results:** From April 2018 to April 2019, we screened 430 refugee children with a median age of 13.0 years. Most of the children were born in Myanmar (n=274, 63.7%) and Pakistan (n=60, 14.0%). No children were diagnosed with active tuberculosis but 55 of the children (12.8%) were diagnosed with LTBI. Children with LTBI were generally older (OR 3.01, 95% CI 1.71–5.29; p<0.001) than those without LTBI infection. Sex, history of bacille Calmette–Guérin vaccination and country of birth were not associated with increased risk of LTBI.

**Conclusion:** The relatively high LTBI burden among refugee children in this study poses an indication of possible LTBI risk among this population nationwide, and thus would be an important group to target for preventive therapy. This provides a unique opportunity for researchers to further examine and implement well-structured preventive strategies in combating the endemic infectious disease in Malaysia.



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**The prevalence of latent tuberculosis infection among refugee children in Malaysia is considerably high. This provides further support for the local policy of screening all refugee children irrespective of age and country of birth.** <http://bit.ly/2NvNHLs>

**Cite this article as:** Wong YJ, Lee SWH. Prevalence of latent tuberculosis among refugee children in Malaysia. *ERJ Open Res* 2020; 6: 00254–2019 [<https://doi.org/10.1183/23120541.00254-2019>].



## Introduction

Tuberculosis is one of the major leading causes of mortality, with ~1.3 million deaths attributed to it in 2017 [1]. In order to achieve the targets of alleviating global social-economic and disease burden due to tuberculosis by 2035, as stated in the End TB Strategy, pragmatic intervention has been implemented in the prevention and treatment of the disease [2].

Malaysia, a developing country, was reported to have incidence of 92 tuberculosis cases per 100 000 population in 2018 [3]. While there has been a decline in the number of tuberculosis infections in Malaysia by 1.3% in 2018, this number is still staggering, with 25 837 cases recorded in 2018 alone [4]. As such, there is a need for a better understanding of the epidemiology and population dynamics of the disease. Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis infection [5, 6]. Almost one-third of the world's population is estimated to have LTBI, in which they do not have active TB disease but may develop it in the future [2, 7, 8]. If LTBI is left untreated, patients are susceptible to 5–10% lifetime risk of reactivation, with the majority developing tuberculosis disease within 5 years of initial infection [6, 7]. However, the risk is considerably greater in infected individuals who belong to specific high-risk populations as well as those with predisposing factors such as HIV, diabetes mellitus or immunocompromise [7, 9].

To date, there are limited data on LTBI among refugees seeking asylum in Malaysia. This is because routine or compulsory medical screening procedures for active tuberculosis or LTBI among refugees before and after their entry are not mandatory. The information is even more limited among children. We only identified two cross-sectional studies describing the prevalence of active tuberculosis among children in Malaysia. The latest available data show a 1.5% prevalence of active tuberculosis among children aged 0–14 years old living with tuberculosis patients in Kuala Lumpur [10]. Conversely, an earlier study in Kelantan, a northeastern state of Peninsular Malaysia, reported an 8.4% prevalence of active tuberculosis among paediatric patients [11]. The difference between these tuberculosis burdens could be attributed to differences in the methodology of the studies as well as the disparities in socioeconomic background of the communities. In view of the possibility of a high prevalence of active tuberculosis in settings with lower socioeconomic status, this study aimed to identify the prevalence of tuberculosis and LTBI among school-going refugee children in Malaysia, and risk factors for active tuberculosis infection in this group.

## Methods

### Study setting

This was a cross-sectional study conducted at three refugee learning centres located in the state of Selangor, Malaysia, from April 2018 to April 2019. These learning centres were primarily chosen from a neighbourhood that had a large proportion of the families that were likely to have emigrated from a highly tuberculosis-endemic country. All students who were enrolled in the learning centres were eligible for tuberculosis symptom screening. Screening was conducted in collaboration with a local hospital and community clinics. During the study, an investigator briefed the children on important information related to tuberculosis infection, disease and screening. Each child was provided with an informed consent form to bring home to their family together with additional information related to tuberculosis infection.

At initial screening, all eligible children, irrespective of symptoms, underwent clinical evaluation for tuberculosis by tuberculin skin test (TST) (Span Diagnostics, Surat, India) or interferon- $\gamma$  release assay (IGRA) (QuantiFERON-TB; Qiagen, Hilden, Germany). For each child, we specifically inquired regarding any symptoms related to tuberculosis including cough, fever, poor appetite and night sweats. TST was performed by a trained study nurse *via* intradermal injection of 0.1 mL two tuberculin purified protein derivative RT23 in the volar aspect of the forearm. Indurations were measured 72 h after administration and were considered positive if the indurations were  $\geq 10$  mm, regardless of bacille Calmette-Guérin (BCG) vaccination status. In all positive cases, chest radiography was performed in two views, lateral and anteroposterior, and interpreted by a blinded radiologist. Any child with a well-defined symptom was referred to undergo further sputum induction for subsequent investigation. Following screening and investigations, participants were classified as having either tuberculosis or LTBI, or being without tuberculosis infection. All children were evaluated again 6 months following the baseline assessment, and sent for sputum smear and culture if they developed symptoms of tuberculosis.

### Statistical analyses

All continuous variables are expressed as the mean with corresponding range while categorical variables are expressed as percentages. The prevalence of tuberculosis cases evaluated was compared using a  $\chi^2$ -test. We subsequently calculated the bivariate prevalence rate ratio and 95% confidence intervals using the Cochran-Mantel-Haenszel logit estimates. As age, history of vaccination, sex and country of birth with

high tuberculosis burden were risk factors for tuberculosis, we adjusted for these factors using logistic regression. We subsequently performed sensitivity analysis based upon different TST cut-off scores. Statistical analysis was performed in SPSS version 21.0 (IBM, Armonk, NY, USA).

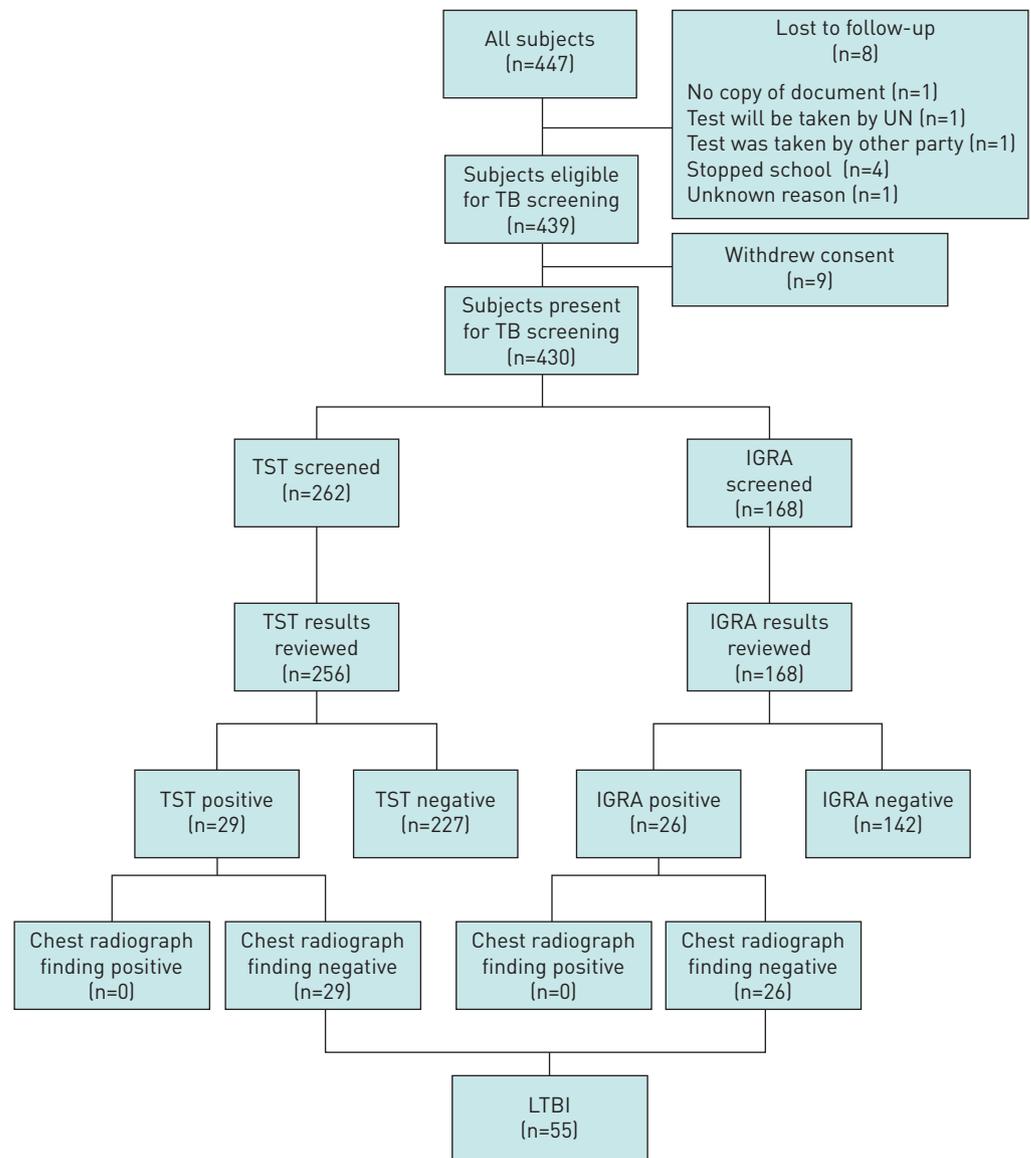
#### Ethics consideration

Written informed consent was obtained from the immediate caretakers before inclusion. The study was approved by Monash Human Research Ethics Committee (2018-11694-16157).

## Results

### Study population

Between April 2018 to April 2019, 447 children aged 4–18 years were recruited to participate in this study and were screened for tuberculosis. 430 children were included in the final analysis, with 17 children excluded as eight were lost to follow-up and nine withdrew consent (figure 1). Children who were lost to follow-up had defaulted appointment sessions to review the measurement of TST induration, which was scheduled 72 h after the administration of tuberculin purified protein derivative. Several attempts had been taken to contact the children who missed the follow-up appointment but eight of them could not be reached. Hence, the results of measurement could not be obtained.



**FIGURE 1** Flowchart showing the results of screening procedures in refugee schools, Malaysia. UN: United Nations Refugee Agency; TB: tuberculosis; TST: tuberculin skin test; IGRA: interferon- $\gamma$  release assay; LTBI: latent TB infection.

The demographics and characteristics of participants are presented based upon the World Health Organization (WHO) tuberculosis burden country lists [12, 13] (table 1). There were 430 children who underwent TB screening, using either TST (n=262) or IGRA (n=168). Most of the children were aged between 6 and 12 years of age (62%), had been previously vaccinated with BCG (66%), with an almost equal proportion of males and females. The children mostly originated from high tuberculosis burden countries including Bangladesh, Cambodia, India, Indonesia, Liberia, Myanmar and Pakistan, and had mean age of 11 years. None of the children had a history of being treated for tuberculosis or any symptoms suggestive of tuberculosis (including prolonged cough and night sweats).

#### Active tuberculosis and LTBI

Of the 430 children screened, 55 had positive TST (n=29) or IGRA (n=26) results. All 55 children were referred for further medical assessment and chest radiographic investigations showed negative findings for active tuberculosis. Overall, the prevalence of LTBI among the children was 12.8% (55 out of 430). The median age of children was 13 years, (range 3–17 years) with 31 (56%) boys. Children born in countries with high tuberculosis burden had a 2.5-fold higher risk of being diagnosed with LTBI. These children were from Myanmar (n=44, 80%), Pakistan, (n=5, 9%) and Indonesia (n=2, 4%).

Children with LTBI were generally older (median age 13 *versus* 11 years) than those without infection. The median induration of TST was 2.0 mm (range 0–20 mm). Regression analysis suggested that older children had a significantly higher risk of developing LTBI (OR 3.01, 95% CI 1.71–5.29;  $p < 0.001$ ). However, other variables such as sex, BCG vaccination status and country of origin were not significantly associated with an increased risk of LTBI (table 2).

#### Sensitivity analysis

We also examined the impact of using different TST cut-off values on the prevalence of LTBI in our cohort of children. Using a lower cut-off value of  $\geq 5$  mm, a total of 70 children will be diagnosed with LTBI. Conversely, using a higher cut-off value of  $\geq 15$  mm, only two of the children were potential LTBI patients.

TABLE 1 Characteristics of participants for tuberculosis (TB) screening

Variables	All participants	TST	IGRA	Absentees
<b>Children</b>	447	262	168	17
<b>Age range years</b>				
≤5	14 (3.13%)	12 (85.71%)	1 (7.14%)	1 (7.14%)
6–12	278 (62.19%)	174 (62.59%)	95 (34.17%)	9 (3.24%)
13–18	155 (34.68%)	76 (49.03%)	72 (46.45%)	7 (4.52%)
<b>Sex</b>				
Male	245 (54.81%)	148 (60.41%)	83 (33.88%)	14 (5.71%)
Female	202 (45.19%)	114 (56.44%)	85 (42.08%)	3 (1.49%)
<b>BCG status</b>				
Vaccinated	285 (66.28%)	184 (64.56%)	101 (35.44%)	
Not vaccinated	145 (33.72%)	78 (53.79%)	67 (46.21%)	
<b>TB burden region</b>				
High	373 (86.74%)	224 (60.05%)	149 (39.95%)	
Bangladesh	3 (0.70%)	2 (66.67%)	1 (33.33%)	
Cambodia	3 (0.70%)	0	3 (100%)	
India	4 (0.93%)	4 (100%)	0	
Indonesia	24 (5.58%)	3 (12.50%)	21 (87.50%)	
Liberia	2 (0.47%)	2 (100%)	0	
Myanmar	274 (63.72%)	169 (61.68%)	105 (38.32%)	
Pakistan	60 (13.95%)	44 (73.33%)	16 (26.67%)	
The Philippines	3 (0.70%)	0	3 (100%)	
Intermediate	57 (13.26%)	38 (66.67%)	19 (33.33%)	
Iran	1 (0.23%)	1 (100%)	0	
Malaysia	32 (7.44%)	25 (78.13%)	7 (21.87%)	
Sri Lanka	23 (5.35%)	12 (52.17%)	11 (47.93%)	
UAE	1 (0.23%)	0	1 (100%)	

TST: tuberculin skin test; IGRA: interferon- $\gamma$  release assay; BCG: bacille Calmette–Guérin; UAE: United Arab Emirates.

TABLE 2 Proportion of latent tuberculosis infection (LTBI) and its associated factors among refugee children in Malaysia

Variables	Children			Univariate		Multivariate	
	Reviewed (n=424)	LTBI (n=55)	p-value	OR (95% CI)	p-value	aOR (95% CI)	p-value
<b>Age range years</b>							
≤5	13 (3.1%)	2 (15.4%)	<0.001	1 (referent)		1 (referent)	
6–12	265 (62.5%)	19 (7.2%)					
13–18	146 (34.4%)	34 (23.3%)		3.11 (1.77–5.46)	<0.001	3.01 (1.71–5.29)	<0.001
<b>Sex</b>							
Male	227 (53.5%)	31 (13.7%)	0.65	1.14 (0.64–2.02)	0.65	1.12 (0.62–2.02)	0.71
Female	197 (46.5%)	24 (12.2%)		1 (referent)		1 (referent)	
<b>BCG status</b>							
Vaccinated	280 (66.0%)	31 (11.1%)	0.10	0.62 (0.35–1.11)	0.11	0.67 (0.37–1.21)	0.18
Not vaccinated	144 (34.0%)	24 (16.7%)		1 (referent)		1 (referent)	
<b>TB burden region</b>							
High	367 (86.6%)	52 (14.2%)	0.06	2.97 (0.90–9.86)	0.08	2.67 (0.79–8.98)	0.11
Intermediate	57 (13.4%)	3 (5.3%)		1 (referent)		1 (referent)	

aOR: adjusted OR; BCG: bacille Calmette–Guérin; TB: tuberculosis.

## Discussion

The increasing transmission and incidence of tuberculosis has often been associated with refugee communities. As they flee their countries of birth to escape war, violence and persecution, they encounter all forms of stress from lack of basic needs for living to psychosocial distress, predisposing them to immune deficiency; thus, they are more prone to infectious disease [14]. For example, when millions of Syrians had to seek refuge in the neighbouring countries due to war, a notable increase in tuberculosis and LTBI cases was reported in countries bordering Syria, where extensive dissemination of tuberculosis was found among refugee population and local [15].

In this study, we detected that nearly one (12.8%) in every eight refugee children in learning centres in Malaysia had LTBI. None of the children were diagnosed with active tuberculosis. The prevalence of LTBI found in this study was higher than in two studies that both reported a figure of only 6% LTBI prevalence among refugee children arriving at Germany and the USA [16, 17]. In addition to refugee children, one of the studies also included immigrants in the screening process for tuberculosis and LTBI, yielding an overall number of 67334 children being examined with 12% prevalence of LTBI in total [17]. The prevalence of LTBI was found to be higher among older individuals, which is expected given the longer time period and potential for exposure to individuals having tuberculosis [5, 18, 19]. Our study also did not find any significant differences in LTBI prevalence between sexes, as noted in other high-risk populations, and in concordance with the study by TAYLOR *et al.* [17] showing an identical percentage of males and females with LTBI. Studies involving children with LTBI found a higher proportion of males diagnosed with LTBI in China and Peru; those authors hypothesised that males could have spent more time socialising and interacting where the risk originated [18–20]. Our findings also suggest that children vaccinated with BCG have a 33% lower likelihood of developing LTBI (OR 0.67, 95% CI 0.37–1.21;  $p=0.18$ ), albeit being nonsignificant. A study that investigated the effectiveness of BCG vaccination against LTBI indicated a lower prevalence of LTBI in BCG-vaccinated adult contacts of tuberculosis screened using IGRA. The vaccine effectiveness was reported to be 30% [21]. These results could be an indication of protective effect of BCG vaccination against LTBI. Similarly, our findings suggest that there was an association between LTBI and country of birth with high tuberculosis burden. Taken together, our study provides strong support for the policy of screening all refugee children regardless of age and country of birth. Since this is the first initiative to screen refugee children for tuberculosis and LTBI in Malaysia, the high prevalence of LTBI in the small communities of refugee participants from our study could serve as an alarm and pointer to expand the screening process for more extensive coverage of the tuberculosis preventive programme through policy improvement.

As Malaysia is not a signatory to the 1951 UN Refugee Convention, it only serves as a transitional place for refugees while they are waiting to be resettled in another country. As such, no refugee camps exist in Malaysia, with refugees having to live with the local communities. However, the refugees often face discrimination as they have limited access to subsidised health service, education and employment. The majority of these refugees live in urban settings, having to bear with overcrowded conditions without basic provision of water and sanitation as well as scarcity of food, increasing the risk of tuberculosis infection,

tuberculosis reactivation and disease transmission [22, 23]. Additionally, the current national tuberculosis policy in Malaysia primarily focuses on active tuberculosis case finding; hence, LTBI is not clinically diagnosed and treated, which could be a challenge for diagnosis and treatment of LTBI to be practised among healthcare providers, not only when screening refugees, but also local [23]. Nevertheless, the findings obtained from this study can be useful evidence to prompt consideration for management of LTBI to be implemented as complementary care on top of tuberculosis for local and refugee children.

Children are particularly vulnerable to developing more severe manifestations of tuberculous diseases; therefore, those diagnosed with LTBI should be treated [24, 25]. They are potential medium of infective disease transmission as they have weaker immune systems, constant active tuberculosis contact and long times spent in high tuberculosis burden regions that could contribute to the activation of the bacteria to infective tuberculosis anytime in their life [24]. Hence, tuberculosis will be continuously progressive unless treatment can be initiated promptly for LTBI upon diagnosis before it becomes infective and causes casualties [7]. Unfortunately, tuberculosis preventive therapy is underimplemented in many high-burden countries, including Malaysia, and only 13% of children eligible for preventive therapy received treatment in 2016 [26]. A more concerted effort to target children and adolescents with LTBI is needed, in supporting the WHO's End TB Strategy to eliminate the global tuberculosis epidemic by 2035. This could include mandatory screening of all children and adolescents in countries with high tuberculosis burden and offering preventive therapy. This will ultimately help to eliminate tuberculosis seedbeds for future cases of active tuberculosis.

This study has some important limitations that warrant further discussion. Firstly, the study was limited by its sample size, which may limit the precision in determining the prevalence in the cohort of refugees as well as factors related to LTBI positivity. Secondly, the comparability between both tests was not assessed. The TST, while an easily available and relatively low-cost test, has a high false-positive rate even among those who may not be infected with *M. tuberculosis*, due to cross reactivity of infection with nontuberculosis mycobacteria as well as previous BCG vaccination [27, 28]. In addition, the TST requires the participant to return for a follow-up between 48 and 72 h later, and in this study, ~1.4% had defaulted on their appointment. Finally, we relied on patient self-reported history, as accurate medical records were often unavailable among the cohort of refugees.

Despite the breadth of evidence available, most of the current policy worldwide, including in Malaysia, focuses only on the detection and screening of active tuberculosis. Nevertheless, case-finding and treatment approaches alone would be insufficient. Prioritising LTBI management requires integrated effort from the public health division together with political will for implementable strategies to be formulated in order to control the risk of tuberculosis infection in line with the End TB Strategy [29]. Evidence of the effectiveness of preventive therapy is available, and this study provides further support for a programmatic screening and treatment of LTBI to support a comprehensive and epidemiologically sound strategy for tuberculosis elimination.

### Conclusion

The global refugee crisis has led to an influx of refugees from high tuberculosis burden regions into Malaysia. As such, there is a need for targeted programmatic screening of refugees in Malaysia with a focus on implementing a comprehensive epidemic control strategy that would reduce new tuberculosis cases to elimination targets. However, the challenges on financial resources are undeniable. Therefore, as an initiative to achieve the milestones of WHO End TB Strategy, further studies and research are needed to evaluate the significance in terms of cost-effectiveness of tuberculosis screening and treatment for both tuberculosis and LTBI, ensuring integrated medical care is provided to alleviate the catastrophic costs incurred in managing tuberculosis.

**Acknowledgements:** We wish to thank the staff and administrators of the various refugee learning centres for their participation in this study as well as members of staff in Sentosa Medical Centre (Kuala Lumpur, Malaysia) for providing support to this study.

**Conflict of interest:** Y.J. Wong has nothing to disclose. S.W.H. Lee has nothing to disclose.

**Support statement:** This study was funded by an unrestricted research grant from Global Asia in the 21st Century Platform, Monash University Malaysia (GA-HW-17-S02) and the Monash-Warwick Alliance Accelerator Grant (2110580).

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