

## ORIGINAL ARTICLE

# Factors Associated With Loss to Follow Up During Treatment of Latent Tuberculosis Infection in Children Under 5 Years of Age in Sabah, Malaysia

Sheila Miriam Mujin<sup>1</sup>, \*Richard Avoi<sup>1</sup> and Roddy Teo<sup>2</sup>

<sup>1</sup> Department of Public Health Medicine, Faculty of Medicine and Health Sciences, Universiti Malaysia Sabah, Jalan UMS, 88400, Kota Kinabalu, Sabah, Malaysia

<sup>2</sup> Sabah State Health Department, Tingkat 3, Rumah Persekutuan, Jalan Mat Salleh, 88590 Kota Kinabalu, Sabah, Malaysia

## ABSTRACT

**Introduction:** Loss to follow up remains one of the main problems in the treatment of latent tuberculosis infection (LTBI) in the state of Sabah, Malaysia. This study aims to identify the risk factors for loss to follow-up among LTBI treated TB contacts in children under 5 years of age, who did not complete 180 dosages of treatment within 6 to 9 months. **Methods:** This retrospective cohort study used anonymised data taken from the Malaysia national case-based TB registry (MyTB) between 2017 and 2019. To identify factors related with loss to follow-up, a logistic regression analysis was performed. **Results:** Of the 1334 treated LTBI cases, 10.4% were loss-to-follow-up. The mean age of study participants was 2.3 years, with 50.2% males. Factors associated with loss to follow-up include index-contact relationship i.e., Extended family (aOR = 1.82, 95% CI = 1.19, 2.77) and PTB index in whom the treatment outcome is loss to follow up (aOR = 4.84, 95% CI = 1.96, 11.95). Rural living was associated with less loss to follow (adjusted odds ratio (aOR) = 0.40, 95% confidence interval (CI) = 0.26, 0.61). **Conclusion:** Despite commendable efforts, the problem of loss to follow during LTBI treatment in children persisted. In spite of the inherent limitations of the study, the associated factors identified in this study can be used as a basis for future initiatives to strengthen LTBI management.

**Keywords:** Latent Tuberculosis Infection; Preventive therapy; Loss to follow up

### Corresponding Author:

Richard Avoi, MPH (Epidemiology)

Email: richard.avoi@ums.edu.my

Tel: +6017-8933977

maintained a high incidence rate of 144-201 TB cases per 100,000 population over the past decade (3). In 2018, TB cases under the age of 15 accounted for 3.8% of all TB cases in Sabah, of which 33.3% were under the age of 5 (3).

## INTRODUCTION

Tuberculosis (TB) remains a major public health problem worldwide. The World Health Organization (WHO) estimates that 13.7 million people worldwide have active tuberculosis, and approximately 1 million (11%) of these are children under the age of 15 years (1,2).

Malaysia has reported an estimated incidence of 92 new TB cases per 100 000 population in 2019 which placed Malaysia as an intermediate TB burden country (1). Tremendous effort had been made in the implementation of TB control strategies throughout the years, however, TB incidence is not declining in accordance with the milestones set by the global End TB Strategy. The state of Sabah, Malaysia, accounts for 20-30% of all TB cases in the country, which is significantly disproportionate to its population distribution of 10% of the country, and has always

Prophylactic treatment for latent tuberculosis infection (LTBI) is one of the critical components of the TB control program. Individuals with LTBI, a condition of sustained immune response to stimulation by Mycobacterium antigens with no evidence of active TB, and does not exhibit any signs and symptoms of TB but are at risk for developing TB disease (4). Hence, TB preventive treatment using 6 months Isoniazid therapy (6H) are given to children aged less than 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB (PTB) and who are found not to have active TB on appropriate clinical evaluation, even if LTBI testing is unavailable (4,5). TB exposure to the at-risk age group under 5 makes them very vulnerable to developing active TB, and treatment with 6H reduces the risk of them getting active TB by 60-90% (4). Thus, it is of utmost importance to have a complete course of prophylactic treatment not only to ensure favourable treatment

outcome but also to prevent future complications. The entire 6H course is given free of charge and is closely followed up and monitored in dedicated TB clinics. Yet, despite the initiated effort done, there still arise the issue of incomplete treatment, largely due to loss to follow up among those on LTBI treatment in the state of Sabah. Incomplete treatment reflects low adherence to treatment of LTBI, which reduces the TB prevention effort done (6). Loss to follow-up could be due to various factors. However, detailed studies on cases of loss to follow up in LTBI-treated children under five are still lacking, hence factors associated with loss to follow-up are not well understood in this state.

Various studies were done on factors contributing to the completion of LTBI treatment. Nevertheless, results varied between countries and were conducted mainly in developed and low-TB burden countries, with few studies conducted in countries that are integrating BCG vaccination into their national TB programs. Furthermore, there are limited studies on the same among the paediatric age group, particularly under 5 years old. Loss to follow up reflects low adherence to LTBI treatment, thus undermining TB prevention efforts (Li et al., 2010). Therefore, this study aims to determine the proportion of loss to follow up in LTBI treated individuals and its associated factors, particularly among children under 5 years of age. Considering the demographic background and geographical topography of the state, socio-demographic factors and economic status, among others, were included in this study. With the insight gained, tailored interventions could be proposed to improve treatment outcome, thus strengthen LTBI treatment management. In return, this could further consolidate the programmatic management to control and prevent TB, targeting TB in children particularly. By successfully treating the so-called reservoir of TB infection, the development of active TB cases could be reduced, hence minimizing disease transmission in the community. The management and treatment of LTBI along with the management of active TB is a powerful strategy in reducing TB incidence towards achieving the goals of the End TB strategy.

## MATERIALS AND METHODS

### Study Design

This is a retrospective cohort study conducted in the Malaysian state of Sabah, which is located in the northern part of Borneo Island. The study population was close contacts of smear positive PTB, under 5 years old who were on LTBI treatment. Data was extracted from two different databases i.e the LTBI registry and the Malaysian TB National Information System (myTB). At the time of study, the LTBI registry database under the TB/Leprosy Control Unit of the Sabah State Health Department includes children, mainly under 5 years

old, who were close contact of an active PTB case and was given prophylactic treatment i.e., 6H, with or without additional testing done. Exclusion of active TB disease was done based on either symptoms and or Tuberculin skin testing with or without chest radiography. The LTBI registry database was started in 2017, therefore for this study, all close contacts of sputum smear positive PTB indexes aged under 5 years who were prophylactically treated with 6H, regardless of LTBI testing done, were extracted from the LTBI registry from the year 2017 till 2019. Close contacts in whom the index case was sputum smear negative PTB and or bacteriologically proven to have drug resistant PTB (DRTB) were excluded. In regard to the corresponding PTB index, in whom the identified close contact is related too, case information including treatment outcome was obtained from the Malaysian TB National Information System (myTB). The myTB database is a web-based national TB registry under the Ministry of Health, which includes the notification, registration, investigation, and treatment, including outcome of TB cases of all types throughout the country. The sample size was calculated using the formula for difference in proportions i.e., to ensure the number of samples were adequate to determine the significant effect in this study (7). The effect size i.e., difference in proportion was set at 9% and pooled prevalence of 17.5%. With a statistical significance level of 1.96 and a power of 80%, the required sample size for this study equated to 560 contacts.

### Definition

The independent variables that were investigated in this study were variables that were recorded in the LTBI registry database. The sociodemographic variables were expressed as the age of PTB contacts during the commencement of LTBI treatment expressed in years i.e. 0 years for those less than 1 year old. The household income was categorized in accordance with the Malaysian income classification by household, where B40 refers to those with income ranging from less to RM2,500 up to RM 4,849 i.e. low income, whereas M40 ranged from RM4850 to RM10,959 i.e. average or middle income. The variable of PTB index-contact relationship refers to the type of familial or social relationship between the PTB index and the corresponding PTB contact in which LTBI treatment was started, whereas the related PTB index treatment outcome was the treatment outcome of the corresponding PTB index, in whom the contact that was started on LTBI treatment was related to. Loss to follow up refers to the treatment outcome of smear positive PTB contacts under 5 years old on 6H who did not complete 180 dosages of treatment within 6 months or 9 months of an extended treatment period. Names and identifiers of the patients in the registry were anonymized and kept confidential.

### Data analysis

The data in this study were presented as descriptive and inferential statistics. Logistic regression was used to test the relationship between the independent and dependent variables. Univariable analysis was performed to identify crude association between the dependent and independent variables. Variables that were chosen for multivariable analysis were chosen considering statistical significance ( $p$  value  $< 0.05$ ), science, and experience. Multicollinearity testing was performed by checking Variance Inflation Factor. The interaction between variables i.e. citizenship and corresponding index outcome, and citizenship and household income, were tested using Wald test and Omnibus test. Hosmer-Lemeshow test was applied to ensure model fitness. The age of the study participants was analysed as continuous data, and the rest of the variables as categorical data. Between study commencement and completion, data were transferred into Microsoft excel for the study database, and the data analysis was done by using Statistical Package for Social Sciences (SPSS) V26.

### Ethical Approval

The ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC),

**Table I : Characteristics of Study Respondents**

Variables	n (%)
Age (Years), Mean (SD)	2.34 (1.58)
Gender	
Male	525 (50.2)
Female	521 (49.8)
Citizenship	
Malaysian	701 (67)
Non-Malaysian	345 (33)
Residence	
Urban	248 (23.7)
Rural	798 (76.3)
Household Income	
B40	1036 (99)
M40	10 (1.0)
Index-Contact Relationship	
Nuclear Family	631 (60.3)
Extended Family	376 (35.9)
Others	39 (3.7)
PTB Index Treatment Outcome	
Complete treatment	974 (93.1)
Incomplete treatment	47 (4.5)
Loss to follow up	25 (2.4)

Ministry of Health Malaysia (Ref. No: KKM/NIHSEC/P21 – 409 (4)), and the Medical Research Ethics Committee of University Malaysia Sabah (Ref. No.: UMS/FPSK6.9/100-6/1/95).

## RESULTS

### Study Profile

Between 2017 and 2019, 1,334 close contacts under 5 years old were registered and given prophylactic treatment for LTBI in the state of Sabah. Of these, 288 cases were excluded, consisting of 17 duplicate cases, 172 cases were close contacts of sputum smear negative PTB, 2 cases with DRTB contacts, and 97 cases contained incomplete information or no details of their respective index cases.

### Characteristics of Study Participants

The mean age of the respondents was 2.35 years, with a standard deviation of 1.58. There were 50.2% males and 49.8% females. The majority were locals (67%), and most of them lived in rural areas (76.3%). Almost all respondents were from the B40 household group (99%). Most of those who were started on LTBI treatment have a familial relationship with the index cases. The characteristics of the study respondents in this research were summarized in Table I.

### Loss to follow up

From 2017 to 2018, the proportion of PTB contacts under 5 years old on LTBI treatment in Sabah increased from 5.5% (9 cases) to 15.4% (55 cases), respectively, with a slight decline to 8.6 % (45 cases) in 2019. From 2017 to 2019, the cumulative proportion of loss to follow up is 10.4%.

### Factors Associated with Loss to Follow up

Table II shows the factors associated with loss to follow up among PTB contacts under 5 years old on LTBI treatment.

There was a significant association seen between the area of residency, index-contact relationship, and the index treatment outcome, with loss to follow up among contacts on LTBI treatment under 5 years old. Those who are residing in the rural area showed 60% lower odd (AOR 0.40, 95% CI: 0.26, 0.61) of becoming loss to follow up compared to those staying in the urban area. 13.3% children were loss to follow up, when the corresponding index were from their non-nuclear or extended family i.e., grandparents, uncles, aunts or cousins, with an increase odd of 1.58 (AOR 1.82, 95% CI: 1.19, 2.77) compared to those in whom index case are within the nuclear family i.e., father, mother, siblings. There is also nearly a five-fold increase odd (AOR 4.84, 95% CI: 1.96, 11.95) of becoming loss to follow up among contacts on LTBI treatment in whom their respective PTB index was also loss to follow up, compared to those

**Table II : Factors Associated with Loss to Follow up among PTB contacts under 5 years old on LTBI treatment using logistic regression**

Variables	Completed treatment n (%)	Loss to follow up n (%)	Simple logistic regression		Multiple logistic regression	
			Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (Years)	937 (89.6)	109 (10.4)	0.90 (0.80, 1.03)	0.119	0.91 (0.79, 1.03)	0.135
Citizenship						
Malaysian	632 (90.2)	69 (9.8)	1		1	
Non-Malaysian	305 (88.4)	40 (11.6)	1.20 (0.80, 1.82)	0.384	1.21 (0.79, 1.85)	0.387
Residence						
Urban	204 (82.3)	44 (17.7)	1		1	
Rural	733 (91.9)	65 (8.1)	0.41 (0.27, 0.62)	<0.001	0.40 (0.26, 0.61)	<0.001
Household Income						
B40	1036 (89.7)	929 (10.3)	0.46 (0.10, 2.20)	0.331	-	-
M40	8 (80)	2 (20)	1			
Index-Contact Relationship						
Nuclear Family	575 (91.1)	56 (8.9)	1		1	
Extended Family	326 (86.7)	50 (13.3)	1.58 (1.05, 2.36)	0.028	1.82 (1.19, 2.77)	0.005
*Others	36 (92.3)	3 (7.7)	0.86 (0.23, 2.87)	0.801	1.39 (0.41, 4.82)	0.601
PTB Index Treatment Outcome						
Complete treatment	878 (90.1)	96 (9.9)	1		1	
Incomplete treatment	42 (89.4)	5 (10.6)	1.09 (0.42, 2.82)	0.861	0.95 (0.36, 2.53)	0.924
Loss to follow up	17 (68)	8 (32)	4.30 (1.81,10.24)	0.001	4.84 (1.96,11.95)	0.001

\*Others include caretaker, classmates and neighbour

Hosmer-Lemeshow test ( $p = 0.606$ ), was applied to check the model fitness

in whom PTB index had successfully completed their treatment. The associations and general magnitude of effect did not change in the univariable and multivariable analysis.

## DISCUSSION

The overall rate of loss to follow up in this study was 10.4%. Loss to follow up among those who were on chemoprophylactic anti-TB are not uncommon. A research done in Indonesia reported 51% children < 5 years of age, did not return to the clinic after the first month of medication prescription (8). A study done in TB endemic settings in South Africa found 27 – 69% children who showed poor adherence to LTBI treatment (9). Another study done in Brazil reported 53% among household contacts who were initiated with LTBI treatment were loss to follow up (10).

Taking into consideration the barriers to health care accessibility, including distance and logistical issues that the rural area might face, the initial hypothesis of this study postulated that staying in urban areas is less likely to result in loss to follow up (11). Studies reported that having to travel to public health service,

and considering those residing in rural areas took longer time to reach the health facility due to longer distance and transportation issues, which will incur higher cost of transportation, were known to be associated with higher early non-adherence and complicate LTBI treatment (12,13). This study, in contrary observed those who live in rural areas are less likely to be lost to follow up than those who live in urban areas. A plausible explanation could be the delegation of continuity of care for TB contacts from the main TB clinic to the nearest rural health clinic. The practice of continuation and personalized care at the rural health clinic contributed to the country's improved health care services and outcomes (11). Spicer et al. (2013) reported that those treated at an offsite, neighbourhood clinic were more likely to complete treatment compared to those treated at the main hospital clinic, allowing the children to be followed up at the health facility closer to where they live, hence promoting adherence to treatment (14). Thus, continuation of anti-TB prophylaxis could be delegated to the nearest health clinic. In addition, another study reported that patient-provider interaction is one of the main predictors of patient satisfaction and consequently adherence to treatment, and found that the interactions

were more satisfactory in the rural health care facilities, which could be due to higher workload in the urban health care facilities as a result of higher prevalence of TB in the area (15). It is imperative that health care providers are well-trained and should be knowledgeable in the care and management of LTBI.

One of the important factors that enables the participation in TB contact screening and subsequent contact management including initiation of LTBI care and management is the relationship to TB index case, where close relatives were known to have higher odds in continued participation in contact management (16). In this study, it is notable that the index-contact relationship has a significant association with loss to follow up, which differs from other studies where no significant association was observed (8,10). The contacts that were started on LTBI treatment in whom the index case are their parents or siblings are least likely to become lost to follow up, and a higher risk in becoming loss to follow up are seen in whom the index case is their extended family or non-familial relationship. The tight-knit nature of a nuclear family provides a positive network and supportive environment that enhances health and medication adherence (17). When the index case is outside the nuclear family, the guardian of the contacts on isoniazid preventive therapy (IPT) may not be as vigilant as they do not have the active disease themselves, and considering those who have LTBI exhibits no symptoms, convincing guardians for the need and benefits of treatment can be challenging (18). This should alert health providers to emphasize treatment adherence during counselling, especially when index cases are from non-nuclear family or has no familial relationships.

There are almost no studies that have mentioned and discussed the association between the treatment outcome of the TB index and the outcome of contacts on LTBI treatment. In this study, those in whom the index case was loss to follow up, have four times higher odd of also becoming loss to follow up. This is especially true when the index and contacts have a familial relationship. Most of the time, the cases of loss to follow in this state are unreachable and are lost for the continuation of treatment. This could be due to stigma, safety, security, or work-related reasons. Because children under the age of five are highly dependent on their guardians, who are also index TB cases, the guardian's treatment outcome has a direct impact on the treatment completion of the contacts on IPT. Therefore, efforts to improve the treatment outcome of the index case will have a direct impact on the treatment outcome of contacts receiving LTBI treatment.

Surprisingly, citizenship was not significantly associated with loss to follow up, contrary to the findings of other studies. Still, non-locals have been found to be at a higher risk of being loss to follow up which is similar to other studies, where higher rates of incomplete treatment of LTBI among foreign-born were observed (19–21). The lack of association of household income in this study, and the observance where children from lower socio-economic background were less likely to become loss to follow up, could be due to the smaller population of higher income i.e., M40 that were studied, which may not be representative of the population and could limit statistical comparison to be done.

This study is not without its limitations. Being a retrospective study that relies on secondary data, this study focuses only on the socio-demographic and economic characteristics of the contacts, their relationship with the corresponding index TB cases and the treatment outcome of the same. Other potential risk factors were not explored such as patient factors, caregiver factor, and health care provider factors which include but are not limited to health and service accessibility, barriers related to medication, health service experience, knowledge, and belief of disease (8,15,22,23). Furthermore, not all information may be captured, and some information may be periodically missing, hence these inherent limitations may affect the accuracy of the results of this study. Notably, the narrow confidence interval in this study could be due to less variability within the sample which could lead to more consistent estimates of the population parameter, however the generalizability of the findings to represent the larger population may be lessened by the sample size.

## CONCLUSION

In conclusion, while efforts to strengthen LTBI management are commendable, there is also a problem of loss to follow-up, which can significantly impede an effective TB control program in this state. This study outlines the factors associated with loss of follow-up including residential area, index case-to-contact relationship, and TB Index treatment outcome. In spite of the inherent limitations of the study, the knowledge gained in this study can be helpful in developing future initiatives to further strengthen the programmatic management of LTBI. The findings of this study indicate that improving the treatment completion rate required the implementation of pertinent health education and promotional strategies which should be directed towards both the index case and exposed contacts. Moreover, it is imperative to provide training and necessary resources for effective management of LTBI to competent prescribing physicians and healthcare personnel.

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