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Obstacles Facing Tuberculosis Treatment in Children from a Developing Country: a Hospital-based Study

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Abstract **Background:** Despite availability of antituberculosis treatment and application of directly observed treatment short-course (DOTS) strategy, loss to follow-up in tuberculosis (TB) treatment is still a problem in controlling TB, especially in TB high-burden countries. **Methods:** This retrospective survey study to determine the magnitude and factors influencing loss to follow-up TB treatment was conducted on 1,350 documented clinically diagnosed TB cases registered in pediatric DOTS registry from January 2009 to June 2012. We interviewed the parents of 102 identified loss to follow-up TB treatment children. **Results:** Of the 102 (8.2%) children identified as loss to follow-up TB treatment, five children had completed TB treatment at the nearest public health facility, concluding loss to follow-up rate 7.8%. Survey obtained showed that the most common problems encountered are financial (22.7%), time clash of working parents (16.5%), and far dwelling (16.5%). Far dwelling (p = 0.027) and drug formulations (p = 0.001) are the significant factors influencing loss to follow patients. **Conclusions:** Our study found that children with far dwelling to the health facility in order to take TB treatment and different drug formula are the significant factors influencing loss to follow-up patients.

Keywords: *loss to follow-up TB treatment, children, DOTS strategy*

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1. Introduction

Tuberculosis (TB) remains a major cause of considerable morbidity and mortality among children in endemic countries [1]. In certain developing countries, the national control programme is still neglecting TB in children. However, there is increasing awareness of the fact that children carry a significant proportion of the global TB disease burden [2]. Childhood TB constitutes 20-40% of TB cases in high-burden countries [3].

Implementation of directly observed treatment short-course (DOTS) strategy for TB treatment resulted in improved global outcome [1,4,5,6,7]. However, effectiveness has been limited in areas where five components of DOTS are not fully implemented. This problems were reported in several developing countries [8,9,10]. The implementation is more difficult since poverty are prevalent in high burden developing countries [1], moreover DOTS implementation for TB in infants and children has been challenging, especially in supervising TB drugs.

In Indonesia, ranked as the fourth country with the largest number of TB cases in 2011 [11], TB is closely associated with poverty and malnutrition. Other reasons for low treatment success rate in developing countries are poor compliance and non-completion of treatment [3,12]. Loss to follow-up patients is one of the most important reasons for non-completion treatment [12,13]. Completion of TB treatment is essential as it reduces the risk of recurrent TB, prevent resistance, and reduces the risk of TB infection in communities [14].

World Health Organization (WHO) has revised the definition for reporting tuberculosis in 2013. Lost to follow-up patients, previously known as defaulted, was defined as a TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more [15].

This study was done in order to comprehend the obstacles toward an adequate completion of treatment by performing an active default tracing. Possible factors were collected and analyzed to find the determining factors of loss to follow-up TB treatment in Dr. Hasan Sadikin General Hospital DOTS clinic.

2. Methods

All pediatric patients diagnosed for either pulmonary or extra-pulmonary TB listed in our DOTS registry from January 2009 until June 2012 were included in this retrospective survey study. Our registry consisted of sex, age, type of TB, distance of the patient's dwelling to hospital (divided into Bandung city, Bandung district and outside Bandung district), payment methods, body weight, nutritional status, evaluation of treatment in a scheduled time and antituberculosis formulation. Payment methods

are divided into personal cost, government health insurance for the poor such as *Keluarga Miskin Daerah (Gakinda), Jaminan Kesehatan Masyarakat* (*Jamkesmas), Asuransi Kesehatan (Askes), Jaminan Sosial Tenaga Kerja (Jamsostek)* and other health insurance. *Gakinda* is health insurance paid by the district government for the poor, while *Jamkesmas* is paid by the central goverment. *Askes* is health insurance for goverment employees, while *Jamsostek* is given from companies for their workers. Other health insurance available are from other social group or insurance companies. Antituberculosis formulations consist of single drug formulations, combipact, or fixed dose combinations (FDCs) depending on pharmacy availability. Our study used WHO's revised definition for reporting tuberculosis [15]. Registry were searched carefully for any loss to follow-up patients.

Diagnosis of a child with TB is made by history of close contact of an adult suffering TB either positive or negative acid-fast bacilli combined with sign and symptoms such as persistent cough, weight loss or failure to thrive, persistent unexplained fever, enlargement of cervical lymph node, or bone swelling. Acid fast bacilli examination was not performed in our outpatient clinic. Chest radiograph and tuberculin skin test (TST) were performed to every child. Subsequently, the child can be diagnosed as clinically diagnosed TB, treated by our pediatric clinic and was given antituberculosis drugs by DOTS clinic. All antituberculosis drugs or forms could be taken in DOTS clinic according to the amount and dosage prescribed. No expense was charged for medication, visits to the doctor, chest radiograph or TST if the child is using any health insurance. Majority of our patients used the goverment health insurance. The child's visit to pediatric clinic consisted of a scheduled visit every 2 weeks during the intensive phase and every month during the continuation phase.

Ethical consideration was taken from parents while doing phone interview asking about their child condition. This study was approved by the Dr. Hasan Sadikin General Hospital Research and Ethics Commitee at Bandung, Indonesia. The parents who agreed to participate answered several questions regarding their child TB treatment compliance and whether their child were truly loss to follow-up patients or had continued treatment in another health facility. If they were truly loss to follow-up patients, parents were then asked reasons that hinders adequate TB treatment. If they continued their treatment in other health facility, parents were asked if they had completed TB treatment and whether they were given referral letter, the TB-9 form, from our DOTS clinic. We then checked the determining factors of the loss to follow-up TB treatment patients compared to non-loss to follow-up.

The data were collected, computerized and statistically analyzed. Results were presented as frequencies (n or %). Chi-squared test was used in comparing the results between the children who were loss to follow-up and not loss to follow-up. A p value of <0.05 was considered significant.

3. Results

The comparison between children loss to follow-up and not were done in order to search if any factors based on our registry that influenced loss to follow-up (Table 1).

Table 1. Characteristic data of children included in the registry from 1 January 2009 – 30 June 2012

Data included	Number of non-loss to follow-up TB treatment (total: 1253)	Number of loss to follow-up TB treatment (total: 97)
Sex		
Boys	679	54
Girls	574	43
Age (months)		
Median	60	72
≤12	170	11
13-60	468	35
61-120	439	35
>120	176	16
Type TB		
Pulmonary	1035	83
Extra pulmonary	218	14
Nutritional status		
Severely malnourished	81	12
Payment method		
Personal cost	283	17
Health insurance *Gakinda*	561	43
Health insurance *Jamkesmas*	256	32
Health insurance *Askes*	83	4
Health insurance *Jamsostek*	63	0
Other health insurance	7	0

Notes: Gakinda: Keluarga Miskin Daerah, Jamkesmas: Jaminan Kesehatan Masyarakat, Askes: Asuransi Kesehatan, Jamsostek: Jaminan Sosial Tenaga Kerja

Our study showed significant statistical differences for far dwelling ($p = 0.027$) and drugs formula availability ($p = 0.001$) between children identified as loss to follow-up and not (Table 2). Bandung city had the lowest percentage of loss to follow-up patients compared the other two locations. Our study also showed that combipact has the lowest percentage of loss to follow-up patients.

Table 2. Comparisons of children identified as loss to follow-up TB treatment and non-loss to follow-up TB treatment

Data	Number of non-loss to follow-up TB treatment (total cases: 1253)	Number of loss to follow-up TB treatment (total cases: 97)	%	p
Location of the patient's origin				
Bandung city	863	54	5.9	0.027
Bandung district	217	24	10	
Outside Bandung district	173	19	9.9	
Drug formula available				
Fixed dose combinations	543	57	9.5	0.001
Combipact	538	23	4.1	
Single drug formulations	172	17	9	

Table 3. Number of loss to follow-up TB treatment cases in DOTS Pediatric Clinic

No	Year	Number of cases	Before contacting parents		After contacting parents	
			Number of loss to follow-up TB cases	%	Number of loss to follow-up TB cases	%
1	2009	458	38	8.3	37	8.1
2	2010	388	23	5.9	23	5.9
3	2011	355	20	5.6	20	5.6
4	2012	149	21	14.1	17	11.4
Total		1350	102	8.5	97	7.8

The number of loss to follow-up TB patients each year in our hospital from previously defined periods are shown in Table 3. The number of identified loss to follow-up patients before contacting the parents were 102 children concluding loss to follow-up rate of 8.5%. After contacting parents by phone, it turns out that five patients had completed treatment in other health facilities but were not given the TB-9 form. This leads to only 97 children concluding a loss to follow-up rate of 7.8%. The reasons are financial problems encompassing 22 (22.7%) children, followed by time clash of working parents and time to go to the hospital encompassing 16 (16.5%) children and far dwelling encompassing 16 (16.5%) children. Table 4 depictured reasons of loss to follow-up TB treatment in children listed by parents that were contacted by phone. Only 14 (14.4%) children identified as loss to follow-up patients whose parent were not able to be contacted. The most frequent time loss to follow-up patients occured during the intensive phase (66%) (Table 5).

Table 4. Reasons of loss to follow-up TB treatments in children

Year	Reasons (33 parents were able to be contacted)						Not able to be contacted	Total
	Alter- native Medi-cine	Financial Problems	No person to take the patient to the hospital	Bored to take medi-cation	Symptoms decli-ne	Far location of origin to the hospital		
2009	4	7	7	5	3	6	5	37
2010	0	8	3	1	2	4	5	23
2011	1	4	3	3	5	4	0	20
2012	2	3	3	0	3	2	4	17
Total	7	22	16	9	13	16	14	97
%	7.2	22.7	16.5	9.3	13.4	16.5	14.4	

Table 5. Time of loss to follow-up TB treatment in children registered in DOTS Pediatric Clinic

Time of loss to follow-up TB treatment		Number of cases	Percentage (%)
Intensive phase	First month	40	41
	Second month	24	25
Continuation phase	Third month	17	18
	Fourth month	16	16
Total		97	100

4. Discussions

This study is the first active tracing of loss to follow-up pediatric TB in our hospital. There were 1,350 registered TB cases in the 3.5 year period with 102 (8.5%) children registered as loss to follow-up based on the revised definition by WHO 2013 [15]. After contacting by phone to parents of identified loss to follow-up patients, only 97 (7.8%) children that were truly loss to follow-up patients (Table 1). Five other had completed treatment in other health facilities. Eventhough TB control programme in Indonesia has made acknowledgement of pediatric TB, however implementation still need a lot of improvements since TB control programme only included infants and children recently. The TB-9 form was not always given. The forms from our hospital are given to subsequent health institutions by the patients. Parents who are mostly low educated may not see the importance of it and fail to deliver the form causing an suboptimal reporting system in Indonesia.

Failure to complete treatment is universal, especially in developing countries [13,16]. Suboptimal antituberculosis blood level as consequence of incorrect dosage, or loss to follow-up TB treatment can lead to increased drug

resistance [3]. Tuberculosis treatment rarely fails in children. However, if it does, efforts should be taken to evaluate the causes [17]. Poor compliance and non-completion of treatment are the prominent reasons for low successful treatment in low-income countries [7,12]. This can occur in countries applying DOTS, if supervision for taking TB treatment is not complete [17].

A study of pediatric DOTS treatment in South Delhi, India over 10 years period showed loss to follow-up rates were 3% [4], which is lower than our study. Reasons may be multifactorial. DOTS components consist of political commitment, early case detection through quality-assurred diagnosis, standardized treatment with supervision and patient support, drug supply and management system, monitoring and evaluation [2]. Our pediatric DOTS clinic has not been able to apply all components of DOTS strategy. Supervision to children's treatment, consistent supply of drugs, and the routine used of FDCs was not able to be completed, particularly before 2012. Our loss to follow-up rate is lower than a study done in Brazil [8]. In 4 years period, loss to follow-up rate was 24.2% while Brazil did not used DOTS strategy. Another study in Malawi which did not apply DOTS strategy, showed loss to follow-up rate in children was 13% in one-year period [9]. Higher completion treatment was achieved by DOTS therapy. DOTS strategy have also been associated with decreased risk of death and less acquired drug resistance [5]. The importance of applying all DOTS strategy, especially supervising TB treatment was emphasized in a study done in Pakistan [10].

Our study is in agreement with the findings in Malawi that found poor outcomes and higher rates of TB in children aged less than 5 years [9]. The total children with TB aged <5 years in our study were 1158 (85%) with 81 children that were <5 years from the total 97 loss to follow-up children. Our study did not differentiate the children into less or more than 5 years in order to give a better perspective according to more specific age. Early studies have confirmed that young age is associated with increased TB susceptibility [9].

Loss to follow-up patients were not influenced by the type of TB in our study. The results is in concordance with previous study in India [6]. However, this is not the same with the study conducted in Malawi that found lower treatment completion in pediatric extra-pulmonary TB [9]. In present study, the incidence of loss to follow-up mainly occured during the intensive phase (65%) (Table 5). This also happened in the study of pediatric TB treatment in India [4], Brazil [8], and Kenya [13]. Our study is in accordance with a systematic review about timing of default TB treatment of adults in developing countries that stated loss to follow-up usually happen at the intensive phase [12].

From contact to parents with loss to follow-up pediatric TB treatment, it was found that financial burden was the most reason mentioned (Table 4). Previous study conducted in Kenya also concluded that low income was independently assosiated with default [13]. The second most common was nobody to take the children to the hospital that may be caused by occupational comitment of parents that clash with the time taking their children to the hospital. In India, due to this same problem, they extended the centre hours outside school and working hours proving improved adherence and contributed to low default rate [4]. The third most reason was far dwelling to the hospital.

Our goverment has given insurance for the poor, however cost to the hospital or expenses need during the trip are from personal money of the patient. Like other high burden countries, many children with TB in Indonesia can access health services only through limited referral hospitals located in the cities [1]. The burden of transport to the city may be high. Bandung is surrounded by mountains making transportation fee for some a burden.

We identified the significant factor affecting loss to follow-up TB treatment was far location from patient's dwelling to the hospital dan drug preparation (Table 2). In Malawi, poor treatment outcomes in children occured with smear negative pulmonary TB and extra-pulmonary TB [9]. Previous study in India showed that problems related to DOTS treatment in children were due to occupational commitments of parents, dependency on parents, prolonged treatment and ignorance [4]. Another study in India with 676 adults concluded that higher loss to follow-up rate were associated with irregular treatment, male, history of previous treatment, and alcoholism [18]. A study in Kenya with 945 loss to follow-up patients concluded that inadequate knowledge on tuberculosis, herbal medication use, low income, alcohol abuse, previous default, co-infection with HIV were independently associated with loss to follow-up [13]. This study showed that risk factors for the loss to follow-up rate in children are not the same as adults and may differ between countries.

Drug formula has proved to influence the rate of loss to follow-up TB patients in pediatric DOTS ($p = 0.001$) (Table 2). World Health Organization (WHO) now has recently made child friendly drug formulations available to developing countries, including Indonesia. Pediatric FDCs tablets are available for free consistently in our clinic since 2012. Like many developing countries, problems of non-availability was once a problem in our hospital and drug formula was given based on availability. The benefits of certain drug formula was noted in India [4]. However, our study showed that combipact has the lowest percentage of loss to follow-up patients in our study. This can occur since combipact was available in our clinic before FDCs. Since 2012, FDCs were given consistently to our patients, however, the percentage of loss to follow-up patients also increased. This may be due to regulation of Indonesian government starting at the end of 2011, that every referral to a province hospital like our hospital need referral letter from other district health centers. The policy has made parents seeking medical treatment in district health centers causing the biggest proportion of loss to follow-up occured in 2012 than any other year. Meanwhile at that time, pediatric FDCs just started consistently available. This may be bias why combipact showed the lowest portion of loss to follow-up. Our government policy was made to overcome transportation problems that could be an obstacle for compliance. This study proved far dwelling to the hospital is a significant factor influencing loss to follow-up TB treatment.

Some limitations encountered were that we did not do any home visits. However, this study was able to give us insights for the main reason of loss to follow-up. These data may have been suboptimal due to a retrospective study. It must be noticed that the pediatric DOTS clinic

should further improve in reporting and recording systems. Attempts to refine are still being done. Pediatric FDCs was not available consistently initially so this may be bias in our study. Another limitation is that DOTS strategy in our hospital is not fully implemented, particulary direct face to face supervision.

5. Conclusions

Different reasons of loss to follow-up treatment appear in pediatric TB treatment that need to be noticed in order to overcome the challenges in DOTS strategy in Indonesia. Eventhough the government policy has tried to overcome problems encountered with various health insurance for the poor, other reasons still need to be solved. Problems encountered in our hospital found far dwelling to the health facility in order to take TB treatment and drug formula are the significant factors influencing loss to follow-up patients.

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Competing Interests

The authors declare that they have no competing interests.

Author's Contribution

HMN has contributed to conception and design of the study, acquisition of data, analysis interpretation of data, and revising the article. NW has contributed to acquisition of data, analysis interpretation of data, and revising the article. All authors read and approved the final manuscript.

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