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Effectiveness of isoniazid preventive therapy (IPT) and risk factors for IPT failure in children below 5 years of age who are household contacts of smear positive adult patients with tuberculosis

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Abstract

Introduction: Childhood tuberculosis (TB) is yet a major problem in developing countries. Isoniazid preventive therapy (IPT) is recommended for children below 5 years of age who are household contacts of smear positive adult TB patients.

Objectives: To assess effectiveness of the six month IPT therapy and the risk factors for IPT failure in children less than 5 years old who are household contacts of smear positive adult TB patients.

Method: **A** prospective longitudinal cohort study was carried out in the Surabaya Public Health Centre from January to June 2019 in children below 5 years of age who were household contacts of smear positive adult TB patients and who were given isoniazid for 6 months. Bivariate analysis using Chi-Square test and multivariate analysis were used. p <0.05 was considered significant.

Results: Ninety one children below 5 years of age met the inclusion criteria and were included in study. Efficacy of IPT was 95.5%. In multivariate analysis, the risk factors associated with IPT failure were child contacts living in house without ventilation (p = 0.007) and incomplete IPT (p = 0.007).

Conclusions: Efficacy of IPT in reducing the incidence of TB in children below 5 years of age who were household contacts of smear positive adult TB patients was 95.5%. Low adherence to completion of therapy and unavailability of house ventilation were associated with IPT failure.

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Introduction

Tuberculosis (TB) in children accounts for 11% of TB globally[1] and most get infected through close household contact with an adult TB patient[2]. 'End TB' strategy targets in Indonesia are increasing case finding and providing isoniazid preventive therapy (IPT) to children in close contact with adult TB patients[3]. Operational matters are reported to be the main factor of IPT programme outcome[4]. There is a lack of studies about effectiveness of IPT and factors which contribute to IPT failure in Indonesia.

Objectives

To assess the effectiveness of the six month IPT therapy and the risk factors for IPT failure in children less than 5 years old who are household contacts of smear positive adult TB patients.

Method

A prospective longitudinal cohort study was conducted in the Surabaya Public Health Centre from January to June 2019.

***Inclusion criteria*:** 1) Children under 5 years old, 2) in close contact or living at home with positive smear adult TB patients, diagnosed at least 1 month ago, 3) who had no symptom or sign of TB disease[5], 4) parents signed the informed consent.

Exclusion criteria: children who already received treatment for TB.

For each subject isoniazid (INH) 10 mg/kg/day was given once daily for 6 months. Regular follow up was conducted monthly to evaluate symptoms/signs of TB disease and INH side effects. Subjects who could not be followed up due to any reason were dropped from the study. Nutritional status was evaluated based on Indonesia Paediatric Nutrition Care nutritional status[6].

At the end of the study, effectiveness was calculated based on the number of subjects who did not develop TB disease. It was considered as IPT failure if the subjects developed TB disease, and/ or was lost to follow up (subjects who did not take IPT for 1 month in a row or more) or died during observation period.

Ethical issues: Study was approved by the Ethical Committee of Faculty of Medicine Universitas Airlangga Surabaya, Indonesia (No 319/ EC/ KEPK/

FKUA/2018). Written informed consent was obtained from the parents of the children participating in the study.

Statistical analysis: Data collected were analysed using Chi-square. Relative Risk was calculated on risk factors with a p value <0.05. Risk factors with a p value <0.25 were further analysed using logistic regression. All analyses were done using SPSS 21.

Results

There were 91 subjects included in study. Figure 1 shows sample recruitment. Table 1 describes characteristics of subjects.

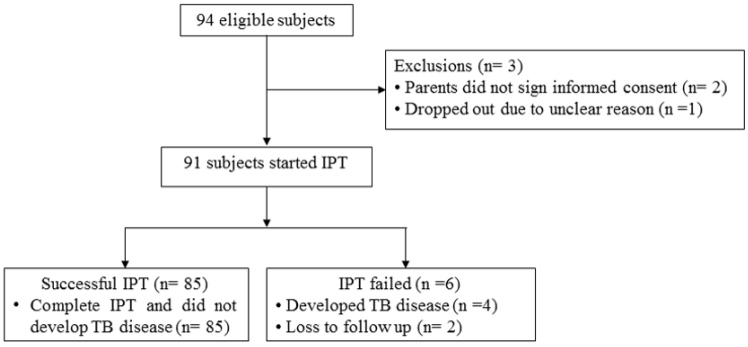

Figure 1: Sample recruitment

Table 1: Characteristics of Subjects *(n=91)*

Characteristic	Categories	Number (%)
Sex	Male Female	40 (44.6) 51 (55.4)
Age (years)	< 1 1 – 2 >2 - <5	20 (22.0) 29 (31.9) 42 (46.2)
Nutritional status	Normal Malnutrition	85 (93.4) 06 (06.6)
BCG scar	Yes No	85 (93.4) 06 (06.6)
Tuberculin test	Positive Negative Unavailable	07 (07.7) 25 (27.5) 59 (64.8)
IHC visits	Routinely every month Not routinely every month	54 (59.3) 37 (40.7)
House ventilation	No ventilation ≥ 1 ventilation	09 (09.9) 82 (90.1)
Distance to IHC	≤ 1 km > 1 km	55 (60.4) 36 (39.6)
Adult TB source		
Relationship with subject	Parent Grandmother/grandfather Sibling Other	57 (62.6) 28 (30.8) 02 (02.2) 04 (04.4)
Anti-TB drug treatment	In treatment	91 (100.0)
Location	In the same house Close contact but different house	59 (64.8) 32 (35.2)
Isoniazid preventive therapy (IPT)		
Adherence to IPT completion	Incomplete Complete	09 (09.9) 82 (90.1)
Result of IPT	Successful (did not develop TB) Unsuccessful (developed TB) Loss to follow up	85 (93.4) 04 (04.4) 02 (02.2)
The reason for stopping IPT	Did not stop IPT Parents refused to continue IPT	89 (97.8) 02 (02.2)
Symptoms and signs of TB in child		
Symptoms of TB	Cough > 2 weeks Fever > 2 weeks	02 (02.2) 02 (02.2)
Signs of TB	Body temperature > 38ºC Respiratory signs	02 (02.2) 02 (02.2)

At the end of the six month study period, there were 4 subjects who developed TB. Therefore, the effectiveness of IPT to prevent TB disease was 95.5%.

Table 2 shows the bivariate analysis of risk factors of IPT failure. There were 8 risk factors associated significantly with IPT failure ($p < 0.05$). These were age, nutritional status, BCG scar, tuberculin test, Integrated Healthcare Centre (IHC) visits, availability of house ventilation, the distance to IHC and adherence to IPT completion (Table 2).

Table 2: ***Bivariate analysis of risk factors of isoniazid preventive therapy (IPT) failure***

Variable	Result of IPT			p	RR
	Successful n (%)	Failed n (%)	Total n (%)		
Sex					
Male	36 (90.0)	04 (10.0)	40 (100.0)	0.399	-
Female	49 (96.1)	02 (03.9)	51 (100.0)		
Age (years)					
< 1	20 (100.0)	0 (0)	20 (100.0)		
1-2	24 (82.8)	05 (17.2)	29 (100.0)	0.023*	-
> 2 - < 5	41 (97.6)	01 (2.4)	42 (100.0)		
Nutritional status					
Normal	82 (96.5)	03 (03.5)	85 (100.0)	0.003*	14.2
Malnutrition	03 (50.0)	03 (50.0)	06 (100.0)		
BCG scar					
Yes	81 (95.3)	04 (04.7)	85 (100.0)	0.049*	7.5
No	04 (66.7)	02 (33.3)	06 (100.0)		
Tuberculin test					
Positive	04 (57.1)	03 (42.9)	07 (100.0)		
Negative	25 (100.0)	0 (0)	25 (100.0)	0.003*	-
Unavailable	56 (94.9)	03 (05.1)	59 (100.0)		
IHC visits					
Routinely every month	54 (100.0)	0 (0)	54 (100.0)	0.003*	-
Not routinely every month	31 (83.8)	06 (16.2)	37 (100.0)		
House ventilation availability					
None	05 (55.6)	04 (44.4)	09 (100.0)	0.001*	18.2
≥ 1 ventilation	80 (97.6)	02 (02.4)	82 (100.0)		
Distance to IHC					
≤ 1 km	55 (100.0)	0 (0)	55 (100.0)	0.003*	-
> 1 km	30 (83.3)	06 (16.7)	36 (100.0)		
Adult TB source					
Relationship with subject					
Parent	54 (94.7)	03 (05.3)	57 (100.0)		
Grandmother/grandfather	25 (89.3)	03 (10.7)	28 (100.0)	0.600	-
Sibling	02 (100.0)	0 (0)	02 (100.0)		
Other	04 (100.0)	0 (0)	04 (100.0)		
Location					
In the same house	55 (93.2)	04 (06.8)	59 (100.0)	1.000	-
Close contact but different house	30 (93.8)	02 (06.3)	32 (100.0)		
Adherence to IPT completion					
Complete	80 (97.6)	02 (02.4)	82 (100.0)	0.001*	18.2
Incomplete	05 (55.6)	04 (44.4)	09 (100.0)		

**significant*

Table 3 shows the multivariate analysis of risk factors of IPT failure. In multivariate analysis house ventilation availability and adherence to IPT completion were significantly associated with IPT failure

Table 3: ***Multivariate analysis of risk factors of isoniazid preventive therapy (IPT) failure***

Variable	B	P
House ventilation availability None ≥ 1 ventilation (ref)	3.424	0.007*#
Adherence to IPT completion Incomplete Complete	3.424	0.007*#

**p < 0.05 was considered statistically significant*

#Logistic regression test was used

Discussion

Most of the subjects included in this study completed IPT for 6 months and did not develop TB. A study in South Africa about starting IPT in those who were in close contact with adult TB patients reported that only around 9% of them succeeded in completing IPT[7]. A lack of information and education about TB disease transmission and development could be the main reason for ITP failure. Other factors for IPT failure are described by health professionals, such as uncertain INH supply, difficulties in reaching health facilities, insufficient knowledge and training for health professionals, and poor monitoring[8].

In this study, there were 4 subjects who developed TB disease. Therefore, the effectiveness of IPT in preventing TB disease was 95.5%. This is in line with a previous study in Indonesia that reported that none of their subject developed TB after starting IPT[9]. A study in Rwanda[10] found that IPT reached 88% effectiveness and compliance. They also stated that parents, comorbidity, overcrowded family and healthcare providers are the determinants of effectiveness and compliance in completing IPT.

Our study found that age is a significant risk factor associated with IPT failure. A study in Kenya reported that younger age (<1 year old) was not significantly associated with IPT failure[4]. BCG vaccine has been reported to induce the release of strong type-CD4 Th1 and CD8 in the first year of life. Therefore, children under 1 year old who already receive BCG vaccine rarely develop TB[11]. Older children tend to have more interaction with adults in their daily lives and are more vulnerable to be infected both in their houses or society[12].

This study found that half the subjects who failed IPT were having malnutrition. Malnutrition is associated with IPT failure and increases the risk of IPT failure up to 14 times. It is in line with a previous study reporting that children with malnutrition are 2-5 times as likely to have TB[13]. Malnutrition is related to immunosuppression that makes children vulnerable to mycobacterial invasion and disease development[14] and is the most important predisposing factor for TB in areas with limited resources[15].

BCG scar is significantly related to IPT failure and children who do not have the BCG scar are 7 times more likely to fail IPT. BCG vaccine has the ability to protect children from TB, especially in younger children[16] with success rate up to 88%[17,18]. Moreover, a study conducted in Peru found that BCG scar was a sensitive indicator for vaccination status until the age of 3 years[19].

Our study found that a positive tuberculin test is significantly associated with IPT failure. This is in line with a previous study that reported positive tuberculin test was related to IPT failure[4]. Positive tuberculin test indicates TB infection and not TB disease and in children under 5 years old, a positive tuberculin test determines TB infection and is a risk factor for developing TB disease[20]. Furthermore, a previous study found that tuberculin test result is an important risk factor for developing TB disease in children with TB contact[21].

This study found that non-availability of house ventilation is associated with IPT failure. It is in accordance with a previous study in Nigeria describing that insufficient ventilation and an overcrowded family in a house would increase the risk factor of TB disease development. House ventilation itself is related to mycobacterium spread[22]. Inadequate house ventilation leads to bad quality of air, increases mycobacterium transmission, and increases humidity with less sunlight. Those will indeed increase the risk of TB disease development[23,24].

Living far from the Integrated Healthcare Centre (IHC) and infrequent IHC visits are significant risk factors of IPT failure. This is supported by a previous study in India[25]. A study in Indonesia evaluated compliance of IPT. They reported that there were various risk factors that could reduce compliance of IPT. Difficult access and a great distance to health facilities that lead to high travel expense is often a major problem[26]. Hence, providing health facilities that are close to their residences with easier access is mandatory. Then, information and education about IPT can be more easily accepted[25,26].

Adherence to IPT completion represents its compliance. Only 9.9% subjects in this study did not complete IPT. There was better compliance compared with a previous Indonesian study where 74.4% of children under five who participated in the IPT programme had low compliance[26]. Another study in Indonesia also reported that only 49.5% of their subjects completed IPT for 6 months. Drug regimens, factors related to caregivers, support and social access were the main obstacles[27].

This study evaluated the side effects of IPT. We found most of subjects experienced no side effects. Around seven percent of them experienced side effects, such as loss of appetite, nausea, and tingling sensation. However, all subjects who failed IPT did not experience any side effect. Experiencing side effects of IPT was not a significant risk factor of IPT failure. This is in line with a previous study in Kenya which reported that IPT side effects were not significantly associated with IPT failure[4].

Conclusions

Efficacy of IPT in reducing the incidence of TB disease in children below 5 years of age who were household contacts of smear positive adult TB patients was 95.5%. Low adherence to completion of therapy and unavailability of house ventilation were significantly associated with IPT failure.

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