

# Initiation and adherence to Isoniazid Preventive Therapy in children under 5 years of age in Manhiça, Southern Mozambique

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## **ABSTRACT**

The WHO recommends preventive treatment for all pediatric contacts of a TB case, but coverage remains low in many high TB burden countries. We aimed to assess the coverage and adherence of the isoniazid preventive therapy (IPT) program among children under 5 years of age with household exposure to an adult pulmonary TB case in the Manhiça Health Center catchment area, and to identify possible risk factors that limit the uptake of IPT. The estimated IPT coverage was 11.7%. Distance to the health center and lower age of the children, hindered IPT initiation. Among patients who started treatment, 12/18 (69.9%) were adherent to the 6-month treatment.

## **INTRODUCTION**

Tuberculosis (TB) remains a major cause of ill health globally, with more than 10 million people estimated to fall ill with TB every year[1]. The World Health Organization (WHO) currently recommends that all pediatric contacts of a TB case aged 15 years or under who do not have TB symptoms should, receive a course of preventive therapy (PT). PT reduces the risk of developing active TB about 93% of children under 5 and in 59% of children aged  $\leq 15$  years [2-3]. The most frequent PT regimen in high burden settings is isoniazid for at least 6 months [4]. There is considerable variation among high TB burden countries in the coverage of TB preventive treatment, ranging from  $<25\%$  to  $\geq 90\%$ [1]. Resource constrained populations are facing numerous barriers that hinder the implementation of the IPT program, such as medication stockouts, patient acceptance, concerns about amplifying resistance to isoniazid through IPT, poor treatment adherence, treatment adverse events and lack of political will.[5-6] Previous studies carried out in Sub-Saharan African countries have shown that the coverage of IPT and its adherence remains low [6-8]. This study aims to estimate the coverage and adherence of IPT in Manhiça, Mozambique among children under 5 years of age and identify associated risk factors that may influence them.

## **MATERIALS AND METHODS**

This study was conducted in the Manhiça District in Southern Mozambique with a population of 201,845 habitants as of 2019. This district is serviced by the Manhiça District Hospital, the Xinavane Rural Hospital and 14 peripheral health care units, including the Manhiça Health Center. At the time of the study, the National Tuberculosis Control Program (NTP) in Mozambique was recommending 6-month isoniazid (6H) for all children under 5 who are contacts to a pulmonary TB case.

The study had a cross sectional analytical design with retrospectively-collected data based on three data sources; a) Registry of TB cases starting treatment at the NTP office in the district, b) IPT registry books from the Manhiça Health Center, and b) CISM's Health and Demographic Surveillance System (HDSS) [9]. The HDSS oversees the census update of the entire Manhiça district, and obtains other relevant information including sociodemographic data, economic data, health-related indicators, etc. In addition, the HDSS assigns an identification number (permanent identification [PermlD]) to all the inhabitants at the time of entry to the census.

Data from TB cases starting treatment from January to December 2016 was collected, from which pediatric contacts under 5 years of age starting IPT were identified, and those who were registered through March 2017 were included in the study (assuming that some pediatric contacts could have started the treatment up to three months later than the diagnosis of the TB case). From the name and age of TB patients registered in the NTP treatment initiation book, we conducted probabilistic record linkage in order to identify them in the HDSS database. This allowed us to identify eligible contacts under 5 years. We then manually verified the number of contacts that were registered in the IPT registry book. For the purpose of this study, we estimated IPT coverage as the number of children  $\leq 5$  years old who were household contacts of a TB case who were registered in the IPT book divided by the estimated number of children  $\leq 5$  years who were TB contacts as per CISM's HDSS, expressed as a percentage. This provides an indication of the effectiveness of the program in finding and treating TB contacts.

Bivariate and multivariate analyses were performed using R software [10]. Those variables with a statistical significance level of less than  $p=0.2$  in the bivariate analysis were included in the multivariable logistic regression analysis obtaining the adjusted odds ratio (aOR) and the 95% confidence intervals.

Finally, IPT treatment adherence was defined as a dichotomous variable where compliance was defined as completing at least 167 doses of preventive treatment

within a period of 8 months after the first dose [11], and treatment non-compliance pattern was defined as not meeting the previous definition.

The protocol was submitted and approved by the CISM's Internal Scientific Committee and the CIBS's Institutional Bioethics Committee (CIBS-CISM).

## **RESULTS**

In this study, 448 TB cases starting treatment in 2016 were identified as members of the HDSS area, representing 44.4% (448/1009) of those starting treatment that year in the district). Of those, 164 cases were registered as having Manhica Health Center as their reference health facility, and were linked to 154 pediatric contacts under 5 years of age who were eligible for IPT according to the NTP guidelines. Of these contacts, 75 (48.7%) were female and 79 (51.3%) were male with a median age of 3.1 years. Around 98.0 % had their parents alive and the median distance between Manhiça Health Centre and the household was 16.6 km.

In total, 18 pediatric contacts were correctly identified in the IPT registry book of the Manhiça Health Centre as having initiated IPT, indicating an IPT coverage of 11.7%. Eleven (61.1%) were female and 7 (39.9%) were male, with a median age of 2.0 years. Twelve children (66.7%) were adherent to the entire 6-month course of IPT, while 6 (33.3%) did not complete treatment adequately.

The odds of children initiating IPT who lived close to the Manhica Health Center was 1.3 times higher than the odds of those living further away, with a median distance of 2.4 km in the group who started IPT compared to 17.4 km in the group that did not start. Additionally, females had an odds for IPT initiation 1.8 times higher than men. Sex of the TB index case also seemed to impact IPT uptake. Pediatric contacts of a male index case were less likely to initiate treatment (OR: 0.40 95% CI: 0-10-1.43)), although this finding was not statistically significant. **Table 1** shows the results of

bivariate and multivariate analysis of predictor factors for not starting treatment with IPT.

## **DISCUSSION**

Although studies of adherence to TB treatment in Mozambique have been done previously, to our knowledge this is the first study that focuses on the evaluation of IPT adherence in children under 5 who are TB contacts in the country.

Although the sample size is limited, this study shows that the coverage of the IPT program in Manhica is low at 11.7%, which highlights some important implementation gaps of the NTP PT recommendations. In particular, this study points to a major gap in referrals of pediatric household contacts to the health center once a case of TB has been diagnosed. There is a need to implement solutions to increase referrals of pediatric contacts to the health center in Manhica, such as contact investigations, improving patient education, and decentralizing TB contact screening and the provision of medication. The data also show that the long distances that patients have to travel to the health center and the older age of the contacts may hinder the initiation of IPT.

This study was limited by the low sample size, given that only a small percentage of cases starting treatment in the Manhica Health Centre could be matched with the HDSS database. The IPT coverage should represent the minimum estimate, since some patients might have not been identified due to handwriting errors on the IPT registry, children starting IPT elsewhere or the possibility that some children might have not been living in the district (potential outdated information in the HDSS database). The retrospective nature of the study limited the ability to clarify such errors.

Additional research is needed to assess barriers to care and the capacity of peripheral health centers in initiating IPT in all children who are eligible. Continuous monitoring of PT coverage should be incorporated to main indicators of TB control in order to assess

whether this lifesaving strategy is being implemented effectively and further understand potential barriers.

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## **TABLES AND FIGURES**

TABLE 1. Bivariate and multivariate analysis of predictor factors for not starting treatment with IPT

RISK FACTORS	TOTAL ANALYSED	IPT INITIATION, n (%)		Bivariate analyses			Multivariate analyses		
		YES	NO	Crude OR	95% CI	p value	Adjusted OR	95% CI	p value
<b>CHILDREN</b>									
<b>Sex</b>	<b>154</b>								
Female	75	11 (7.1)	64 (41.6)	<b>Ref.</b>					
Male	79	7 (4.5)	72 (46.8)	1.76	(0.58 - 5.70)	0.32			
<b>Age (years)</b>	<b>154</b>	18 (11.7)	136 (88.3)	1.52	(1.10 - 2.19)	0.02	1.71	(1.19 - 2.61)	< 0.01
<b>Father alive</b>	<b>138</b>								
YES	136	16 (11.6)	120 (86.9)	<b>Ref.</b>					
NO	2	1 (0.7)	1 (0.7)	0.14	(0.001 - 11.12)	0.23			
<b>Mother alive</b>	<b>139</b>								
YES	136	17 (12.2)	119 (85.6)						
NO	3	0 (0.0)	3 (2.2)						
<b>HOUSEHOLD</b>									
<b>Distance to the Manhiça Health Center (kms)</b>	<b>153</b>	18 (11.8)	135 (88.2)	1.25	(1.13 - 1.46)	< 0.001	1.25	(1.12 - 1.50)	< 0.01
<b>TB INDEX CASE</b>									
<b>Sex</b>	<b>121</b>								
Female	72	7 (5.8)	65 (53.7)	<b>Ref.</b>					
Male	49	9 (7.4)	40 (33.1)	0.48	(0.14 - 1.58)	0.18	0.40	(0.10 - 1.43)	0.17
<b>Age (years)</b>	<b>121</b>	16 (13.2)	105 (86.8)	1.01	(0.97 - 1.05)	0.79			
<b>Ability to read and write</b>	<b>118</b>								
YES	85	13 (11.0)	72 (61.0)	<b>Ref.</b>					
NO	33	2 (1.7)	31 (26.3)	2.78	(0.58 - 26.83)	0.23			
<b>Maximum level of education reached (courses 1-12)</b>	<b>108</b>	16 (13.9)	95 (86.1)	0.89	(0.67 - 1.24)	0.45			

CI: confidence interval; IPT: isoniazid preventive therapy; kms: kilometres; OR: odds ratio; Ref: reference; TB: tuberculosis.