Adherence to Isoniazid Preventive Therapy among children living in a high HIV and TB burden area of Southern Mozambique

Student: **Agnès Montoya M-Rimbau**

Supervisor: Alberto García-Basteiro
Area: Tuberculosis

ISGlobal

Universitat de Barcelona

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"Global health issues remind us – perhaps more than any other issue – that we are all children of the same extended family"

Kathleen Sebelius

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ABSTRACT

INTRODUCTION: Since 2006 (1), the World Health Organization (WHO) recommends daily treatment with isoniazid for 6 months for all healthy children aged under 5 years who are contacts of a smear-positive pulmonary tuberculosis (TB) case. However, it has been estimated that the implementation of this recommendation, known as Isoniazid Preventive Therapy (IPT), is low, especially in developing countries, which experience different obstacles when implementing the program.

SETTING: Manhiça Health Center, which is placed in a rural area with high prevalence of TB and HIV in Southern Mozambique, Southern Africa.

OBJECTIVE: To assess the coverage of IPT program among children ≤ 5 years old who had a household exposure to an adult pulmonary TB index case, and to study the factors influencing the initiation of IPT.

METHODS: Retrospective cross-sectional study based on routine surveillance data from January 2016 – March 2017. A statistical analysis was performed to determine the influence of some sociodemographic variables in the initiation of IPT. Adherence patterns were evaluated.

RESULTS: Of 136 child contacts (<6 years) of TB index patients, only 18 started IPT (coverage of 11.7%). Among those who started, 7 (38.9%) completed the full treatment, 5 (27.8%) did it partially (completes IPT collecting the 6 cycles of medication monthly but with a difference of +/- 10 days from the optimal date in at least one collection), and 6

(33.3%) did not complete. Living away from the health center and being older was associated with not initiating preventive treatment.

CONCLUSION: The coverage of the program is low and requires more attention to deal with the different factors and actors influencing the initiation of IPT, to reduce TB incidence in children. Community IPT given by field workers might be an intervention to consider to increase IPT access and coverage.

Keywords: IPT, tuberculosis, child contact, adherence, TB prevention

INTRODUCTION

According to the Global Tuberculosis Report 2018 (2) published annually by the World Health Organization (WHO), tuberculosis (TB) remains one of the 10 leading causes of death worldwide and the main cause due to a single infectious agent (above HIV/ AIDS). Millions of people continue to get sick and die of TB each year (1.3 million deaths [range 1.2-1.4] among HIV-negative people and additional 300 000 TB deaths [range 266 000-335 000] among HIV-positive people, in 2017).

TB is a contagious infectious disease caused by *Mycobacterium tuberculosis* (although it can be caused by other mycobacteria), which mainly affects the lungs, but can spread to extrapulmonary organs. The classic symptoms of pulmonary tuberculosis include chronic cough, fever, night sweats and weight loss (3,4).

The main route of transmission is by inhalation of infectious droplet nuclei containing viable bacilli, expelled by coughing, sneezing or talking by a person with active infection. Once in contact, if the individual's immune system fails to eliminate the infection, a granuloma (containing infected macrophages inside a phagosome) will be formed in the lung tissue (3,4).

The infection can progress to active disease, or on the other hand, the individual can continue harboring bacilli without symptoms (latent TB infection, which can progress to tuberculous disease early or after few years). It is estimated that approximately 25% of the world population has latent TB (5). Immunosuppressive drugs, HIV infection, malnutrition or ageing are some factors that can favour the progression of latent TB to active TB. In addition, active infection can spread to other organs through the lymphatic

system or the bloodstream (disseminated or miliary TB), leading to complications in central nervous system, cardiovascular system, etc.

The diagnosis is usually obtained through smear microscopy for acid-fast bacilli, mycobacterial culture or nucleic acid amplification tests, although they can also be complemented by the tuberculin skin test and radiographs, mainly thoracic.

With early diagnosis, TB is curable, and requires long treatments that combine antituberculous agents (such as isoniazid, rifampicin, pyrazinamide or ethambutol) (3,4). Currently, the advent of bacterial resistance to some of these drugs, mainly isoniazid and rifampin, is a major public health concern (2).

One of the important gaps in relation to TB epidemics is found in prevention (2). Currently, prevention focuses on two main vulnerable populations: children aged under 5 years (due to their high rates of progression to active TB and disseminated forms of the disease (6)) and patients with HIV (since immune system is compromised and they are at higher risk of developing TB). The vaccination of children with the Bacillus Calmette-Guérin (BCG) vaccine against TB can be part of the national immunization programs according to the epidemiology of TB in the country (2). Treatment of latent TB infection (with different treatment options and regimens) is also recommended, especially in infants and children aged under 5 years who are household contacts of bacteriologically confirmed TB cases, people living with HIV, and clinical risk groups, including patients initiating anti-TNF treatment, receiving dialysis, or preparing for organ or hematological transplantation, and those with silicosis (2,4).

WHO recommends that all household or close contacts aged under 5 years who do not have active tuberculosis should, irrespective of their HIV status, receive isoniazid preventive therapy (IPT) at a dose of 10 mg/kg body weight for 6 months (1,6). However,

just 23% of the approximately 1.3 million children estimated to be eligible for preventive treatment were started on TB preventive treatment (2). Resource constrained populations are facing different barriers hindering implementation of the IPT program, such as supply problems, patient acceptance, concerns about amplifying resistance to isoniazid through IPT, poor patient adherence, treatment adverse events and lack of commitment of health managers (7).

Isoniazid, also known as isonicotinylhydrazide (INH), is a highly effective bactericidal antibiotic, which acts specifically on the bacteria that causes tuberculosis, *Mycobacterium Tuberculosis,* and other mycobacteria. It is believed that its primary action is the inhibition of the biosynthesis of mycolic acids, which are specific lipid components of the membrane of mycobacteria (8,9). For both oral and intramuscular administration, the drug is quickly absorbed and hepatically metabolized. It reaches therapeutic concentrations in serum, cerebrospinal fluid, and within caseous granulomas, and peak plasma concentrations are achieved within 1-2 hours (8–10).

The administration of isoniazid in children is safe and is approved by major regulatory agencies (8,9). INH was approved and marketed for the first time in 1952 (10) and is currently part of the World Health Organization's List of Essential Medicines (11), which specifies the most effective and safe medicines needed in a health system. The most common adverse event (AE) associated with INH is peripheral neuropathy (damage to the nerves of the peripheral nervous system, which can range from small debilitations and cramps -mainly in the lower limbs- to more severe manifestations in the motility or convulsions) (8–10). Peripheral neuropathy is dose-related, and occurs most often in malnourished patients and in those predisposed to neuritis (e.g. alcoholics and diabetics) (9). Another important AE is the increase of blood levels of liver enzymes that

can be asymptomatic or progress to more severe hepatic AEs. INH label of Food and Drug Administration (FDA, USA) carries a boxed warning for severe and sometimes fatal hepatitis, which is age-dependent (9). This hepatotoxicity is commonly enhanced when INH is associated with other anti-tuberculosis drugs and requires monitoring of patients at risk (8).

Generally, isoniazid is introduced orally and when that is not possible, it is administered intravenously (10). In monotherapy, the most widespread and distributed form of INH worldwide are tablets. There is a commercialized preparation of INH in oral solution (syrup) approved by the FDA (10), however it is not registered in the European Medicines Agency (EMA). In countries like Spain, for example, isoniazid syrups are compounding products formulated at the hospital level (12).

HYPOTHESIS AND OBJECTIVES

(1) To assess the coverage of IPT program among children ≤ 5 years old who had a household exposure to an adult pulmonary TB index case

(2) To determine possible risk factors (in children or households) that determine the uptake of IPT

(3) To assess the adherence among those starting IPT and the different patterns of adherence

The hypothesis on which the study is based is that the coverage of the program and its adherence is low. It is based on previous studies carried out in other Sub-Saharan African countries with characteristics and resources similar to Mozambique (7,13–16).

METHODOLOGY

STUDY SETTING

This study was conducted at the Manhiça District (165,000 inhabitants in 2014), Southern Mozambique, where the Centro de Investigação em Saúde de Manhiça (CISM) (17) is located, in the municipality of Manhiça. CISM is a research center which promotes and conducts biomedical research in priority health areas since 1996. It is located next to Manhiça District Hospital and Manhiça Health Center (primary care), where many of its studies are conducted. The center has a Health and Demographic Surveillance System (HDSS) since its opening in 1996, which allows studying the demographic characteristics of the district's population. The HDSS is in charge of the census update of the entire Manhiça district, which allows the development of an official list of the inhabitants, and also obtains other relevant information including sociodemographic data, economic data, health-related indicators (vaccination), etc. This census is updated through visits in all the houses every 6 months, through the daily information of births and deaths provided by the Manhiça District Hospital, and the weekly gathering of information at the community level (deaths, new homes, new residents, ...). In addition, the HDSS assigns an identification number (permanent identification [PermID]) to all the inhabitants at the time of entry to the census. This number will always be member specific, although the patient's information (such as the residence) may change. In these cases, all this information is also registered and encoded in the database.

Mozambique is one of the countries included in the 3 high-burden country lists for TB, TB/HIV and MDR (multidrug-resistant)-TB. A prospective community-based study conducted in 2015 in Manhiça District reported a minimum community-based incidence

rate of TB (confirmed plus probable cases) of 470 of 100,000 person-year (95% confidence interval: 343–629 of 100,000). HIV co-infection was present in 44% of the TB cases (18).

STUDY DEFINITIONS

- **Pulmonary TB case:** any patient who presents with cough and eliminate tuberculosis bacilli in the air (whether or not they have positive bacilloscopy results) (4) in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment (19).

- **TB contacts:** any children $\leq$ 5 years old who shared the household with a pulmonary TB case (definition above) at the time of index case diagnosis.

- **Isoniazid preventive therapy:** prophylactic course of isoniazid monotherapy at a dose of 10 mg/kg body weight given to children $\leq$ 5 years old who were TB contacts (definition above). IPT is given daily for 6 months, on self-administered basis (specifically, in the context of the study it is usually administered by the mother). It is dispensed at the health center monthly through a follow-up doctor's visit.

- **Coverage of IPT program:** number of children $\leq$ 5 years who were TB contacts (definition above) that were notified and treated with IPT in a given year, divided by the estimated number of children $\leq$ 5 years who were TB contacts (definition

above) in the same year, expressed as a percentage. It provides an indication of the effectiveness of the program in finding and treating TB contacts.

- **Adherence:** extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment (20). Our study will consider 3 patterns of adherence:

  - **Full adherence:** the patient completes IPT (collects the 6 cycles of medication monthly) according to the prescribed pattern. Difference less than +/- 10 days from the optimal date in all doses
  - **Partial adherence:** the patient completes IPT (collects the 6 cycles of medication monthly) but with a difference more than +/- 10 days from the optimal date in at least one collection
  - **Incomplete adherence:** the patient does not complete IPT (collects 5 or less cycles of monthly medication)

STUDY DESIGN

This is a cross sectional analytical design with retrospectively-collected data based on routine surveillance data which is part of the *Programa Nacional de Controlo da Tuberculose* (PNCT, the National TB Control Program) at Manhiça Health Center, and the Health and Demographic Surveillance System.

The study population is limited to those adult cases and children contacts who are entitled to receive health care and treatment at the Manhiça District Hospital and Health Center.

The year of the study is 2016, including adult TB cases diagnosed during 2016, and TB contacts until March 2017 (assuming that some contacts could have started the treatment up to three months later than the diagnosis of the TB case).

DATA COLLECTION AND ANALYSIS

The personal and clinical information was initially entered and worked in Excel (version 16.25) to later be imported into R program to proceed with statistical analysis.

As mentioned above, obtaining coverage of the IPT program was based on a percentage:

$$\text{COVERAGE} = \frac{\text{nº of children} \leq 5 \text{ years old who were TB contacts and started IPT during the period studied}}{\text{estimated nº of children} \leq 5 \text{ years old who were TB contacts during the period studied}} \cdot 100$$

Therefore, the numerator was the number of child contacts who began IPT during 2016 or January-March 2017.

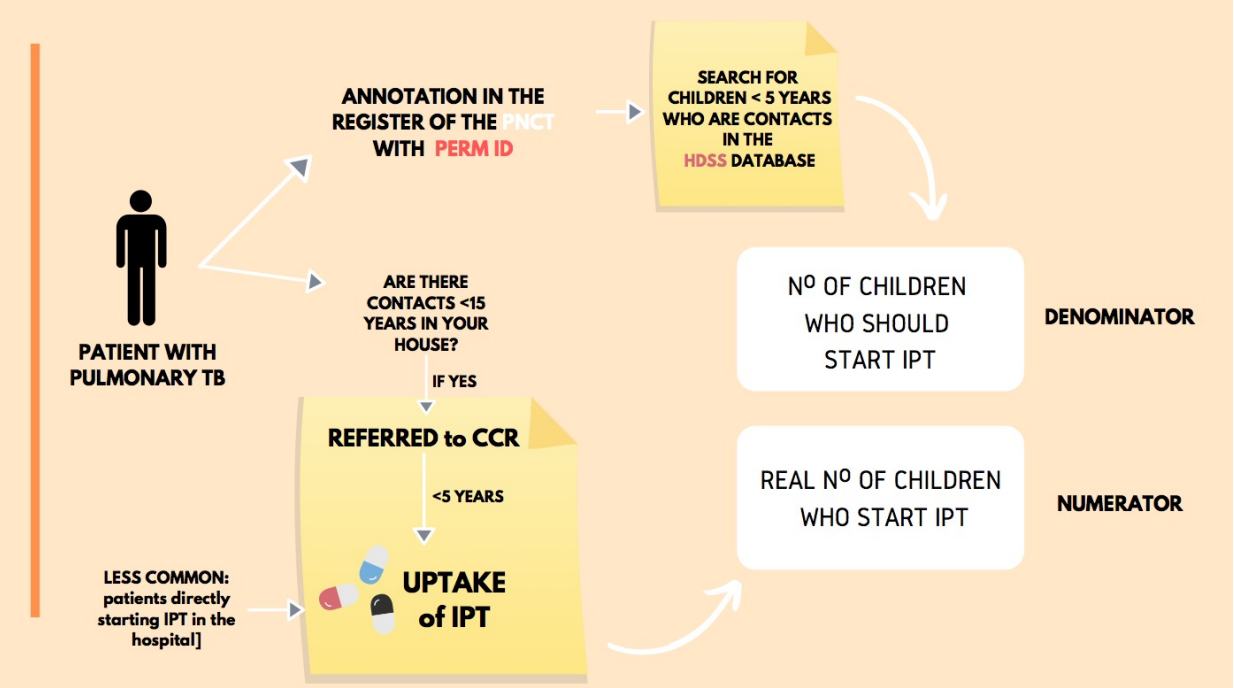
According to national guidelines (4), when a patient is diagnosed with TB, it is registered in PNCT books (Figure 1). The patient (index case) is asked if he has contacts, and children under 15 years of age are referred to the Consulta da Criança em Risco (CCR), which is the pediatric unit in the health center in charge of the cases of providing IPT. Once in CCR, children under 5 years of age begin treatment with IPT for 6 months if TB disease is ruled out and there is no other contraindication, and are scheduled for follow-up on a monthly basis. At the beginning of 2016, those who were treated in CCR were registered in the IPT book and the CCR registry. From March 2016, the registration of these cases was unified only in one CCR book, that contains personal and clinical data about the child and its IPT follow-up. On the other hand, there is another possible way

to start IPT, although it less common: some children who are followed up by the hospital pediatric service for some other condition (for example, because they are HIV positive) are registered in the hospital's IPT pediatric book.

Accordingly, the numerator of our division was composed of all children $\leq$ 5 years that were registered in the mentioned books of IPT or CCR because they were TB contacts.

On the other hand, the denominator was an estimate made from the sociodemographic data of HDSS. The total number of estimated contacts was obtained by extracting data from children $\leq$ 5 years who lived in the same house as a TB case at the time of diagnosis of that case. The adult-contact relationship was made using the PermID that identifies the TB case in the PNCT's book, and the information of its household in the HDSS database. The extraction of this data was done automatically by computer systems, while the search of subjects between the two lists (children seen in CCR vs. children who should have been seen) was done manually.

Figure 1. Diagram of the data collected to estimate the coverage of IPT program



For all those cases in which a child started IPT in the CCR of Manhiça Health Center but did not appear in the contacts list that correspond to its catchment area, if their registration/household was in the database they were included (in other words, they really should have gone to another health center but they went to Manhiça Health Center). Accordingly, all children ≤ 5 years old from the same house were included in the study as contacts, in order to avoid a selection bias. This same requirement was applied to those children who were registered in the IPT book of the pediatric unit of the district hospital. Its 95% confidence intervals (CI) were also calculated.

The variable that refers to the distance between the household and the health center was obtained by means of the coordinates registered in the database, calculating the distance in a straight line between the two geographical points.

The influence of the sociodemographic variables on the initiation or not of IPT, was studied with R software, executed with R Studio (Version 1.1.463) and its "Rcmdr" package (see Appendix 1). The proportions for categorical variables were compared by elaborating contingency tables and obtaining the crude odds ratio (cOR) and the 95% confidence intervals.

For continuous variables, the evaluation of their association with the initiation or not of IPT was executed by means of a logistic regression analysis, obtaining also the cOR and the 95% confidence intervals.

Those variables with a statistical significance level of less than p = 0.02 in the bivariate analysis were included in the multivariable logistic regression analysis obtaining the adjusted odds ratio (aOR) and the 95% confidence intervals.

Ultimately, adherence was based on a percentage and included the patients who initiated IPT during the period studied. We only studied the adherence of those subjects that were included in the IPT coverage analysis (who started IPT), since they were registered in the HDSS database. The type of adherence observed was classified in three categories previously mentioned (full/partial/incomplete adherence), and the percentages were calculated and presented with the corresponding 95% CI.

$$\text{ADHERENCE} = \frac{\text{nº of children} \leq 5 \text{ years old who took "X" doses of IPT}}{\text{TOTAL nº of children} \leq 5 \text{ years old who started IPT}}$$

ETHICAL ISSUES

The retrospective nature of the study, using routine clinical data, implied that an informed consent from participants was not required. The protocol was submitted and approved by the CISM's Internal Scientific Committee. Given that the use of data included in this study has been granted by the NTP for another project (TB REACH), an amendment (which includes the ethical coverage for this specific analysis) is currently under consideration by the National Bioethics Committee. Databases were password protected and only available for researchers involved in the analysis. After the masterfile was created by CISM data managers, to proceed with the analysis, the information that could identify the participants (name, address) was erased to preserve participant's confidentiality. The entire study was developed under the considerations of the International Ethical Guidelines For Health-related Research Involving Humans published by The Council for International Organizations of Medical Sciences (CIOMS) and the basic principles of The Declaration of Helsinki which was promulgated by the World Medical Association.

RESULTS

During the study period, 71 children were seen and registered in the book of CCR or IPT book of CCR because they were contacts of a TB case (Table 1). Of these, 18 were correctly identified in the HDSS database, and could be included in the study. No child registered in the pediatric IPT book could be included in the analysis (Table 1).

Table 1. Summary of subjects included/excluded in the analysis

Number of children seen in CCR who started IPT	**71**
Number of children who started IPT included in the analysis	**18/71**
Cases of TB in the district of Manhiça identified with PermID ▪ Having Manhiça Health Center as reference health center	**448** 164/448
Number of TB contacts in the district of Manhiça ▪ Having Manhiça Health Center as reference health center	**361** 132/361
Number of TB contacts included in the analysis	**154**
Number of children in the IPT registry of pediatrics included in the analysis	**0**

On the other hand, the list of estimated contacts indicated that 154 contacts should have been treated, obtaining a coverage of 11.7 of IPT (Table 2) in 2016 corresponding to Manhiça Health Center.

Of all contacts included in the study, 75 (48.7%) were female (Table 3) and the median age was 3.1 years. Of all children starting treatment, 11 (61.1%) were female (Table 2 and 3) and the median age was 2.0 years.

Table 2. Coverage of IPT program in Manhiça Health Center in 2016

IPT initiation	n	%	95% CI
YES	18	11.7%	(7.5 - 17.7)
NO	136	88.3%	(81.9 - 92.7)

The bivariate analysis showed a statistically significant association between living away from the health center and not starting ITP (cOR=1.25 [95% CI 1.13-1.46], p<0.001 / aOR=1.25 [95% CI 1.12-1.50], p=0.0015), and also between being older and not starting IPT (cOR=1.52 [95% CI 1.10-2.19], p=0.016 / aOR=1.71 [95% CI 1.19-2.61], p=0.006). This association was also observed in the multivariate logistic regression analysis (Table 3). The median distance between Manhiça Health Centre and the household was 16.63 km. The influence of having or not having the mother alive, unlike the father, could not be evaluated statistically (Table 3).

Table 3. Bivariate and multivariate analysis of predictor factors for not starting treatment with IPT

RISK FACTORS	TOTAL ANALYSED	IPT INITIATION, n (%)		Crude OR	95% CI	p value	Adjusted OR	95% CI	p value
		YES	NO						
CHILDREN									
Sex	**154**								
Female	75	11 (7.1)	64 (41.6)	Ref.					
Male	79	7 (4.5)	72 (46.8)	1.76	(0.58 - 5.70)	0.32			
Age (years)	**154**	18 (11.7)	136 (88.3)	1.52	(1.10 - 2.19)	0.016	1.71	(1.19 - 2.61)	0.006
Father alive	**138**								
YES	136	16 (11.6)	120 (86.9)	Ref.					
NO	2	1 (0.7)	1 (0.7)	0.14	(0.001 - 11.12)	0.23			
Mother alive	**139**								
YES	136	17 (12.2)	119 (85.6)						
NO	3	0 (0.0)	3 (2.2)						
HOUSEHOLD									
Distance to the Manhiça Health Center (kms)	**153**	18 (11.8)	135 (88.2)	1.25	(1.13 - 1.46)	< 0.001	1.25	(1.12 - 1.50)	0.0015
TB INDEX CASE									
Sex	**121**								
Female	72	7 (5.8)	65 (53.7)	Ref.					
Male	49	9 (7.4)	40 (33.1)	0.48	(0.14 - 1.58)	0.18	0.40	(0.10 - 1.43)	0.17
Age (years)	**121**	16 (13.2)	105 (86.8)	1.01	(0.97 - 1.05)	0.79			
Ability to read and write	**118**								
YES	85	13 (11.0)	72 (61.0)	Ref.					
NO	33	2 (1.7)	31 (26.3)	2.78	(0.58 - 26.83)	0.23			
education reached (courses 1-12)	**108**	16 (13.9)	95 (86.1)	0.89	(0.67- 1.24)	0.45			

Regarding the adherence (Table 4), of all subjects who had a full adherence, 7 (100%) were female. Of all subjects who had a partial adherence, 3 (50%) were female. Of those subjects who did not complete treatment, 5 (100%) were male.

Table 4. Adherence patterns among patients who initiated IPT included in the statistical analysis

ADHERENCE	n	%	95% CI
FULL	7	38.9%	(18.3 – 63.9)
PARTIAL	5	27.8%	(10.7-53.6)
INCOMPLETE	6	33.3%	(14.4-58.9)

Full adherence: *the patient completes IPT (collects the 6 cycles of medication monthly) according to the prescribed pattern. Difference less than +/- 10 days from the optimal date in all doses*
Partial adherence: *the patient completes IPT (collects the 6 cycles of medication monthly) but with a difference of +/- 10 days from the optimal date in at least one collection*
Incomplete adherence: *the patient does not complete IPT (collects 5 or less cycles of monthly medication)*

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 and its determining factors.

IPT COVERAGE AND ADHERENCE

The study showed a rather low program coverage of 11.7%, which indicates that the implementation of this recommendation of WHO and PNCT is suboptimal.

If we look at the adherence, we see that once they are included in the IPT program, the number of children who complete treatment is only moderate, so it could suggest that the ones who initiated IPT were still unaware of the importance of it.

Obtaining both coverage and adherence results implies that the main gap could be a low referral of contacts to the health center to start treatment, or that this referral was not effective enough. Once a case of pulmonary tuberculosis is diagnosed, he/she is asked about his contacts, especially those under 5 years of age, to be referred to the CCR. However, after the recommendation there is no other measure that connects children with the health system.

According to the literature, there are many factors that explain why parents do not bring their children to the CCR to receive IPT (in many cases the same factors that condition adherence), including the choice of other types of therapies, such as alternative / traditional care and natural remedies (21), or even because they have a different understanding on disease transmission or prevention strategies, which in many cases is stigmatized (22,23). Childhood TB is considered "The Hidden Epidemic" (24): there is an

underdiagnosis influenced by the fact that symptomatology in some cases is different from that of adults (less specific), and infected children present fewer bacteria in the lungs, which makes the diagnosis more complicated and causes them to have less disease transmissive capacity. In some cases, this may cause the parents to be unaware of the illness and consequently do not understand the purpose of the treatment (21,25). Misinformation is also closely related to another type of reason that contributes to children not initiating IPT: the preventive nature of the program. IPT program implies that the drug is administered to healthy children (15), and this significantly reduces the perception of risk and the need to take the treatment (25). And on the other hand, the fear of the adverse effects caused by the treatment with antituberculous drugs, creates rejection to it (7,22,25), especially when the treated population is children, since it turns it into a more delicate debate.

Despite that, our study shows a statistically significant association between the age of the contact and the beginning of the treatment: for every 1 year increase of the child, there is a 71% increase of the possibility of not starting IPT (OR = 1.71 [1.19 - 2.6)], p = 0.006). We believe that this association may be due to the greater dependence and vulnerability of children of lesser age, which can influence and increase parents' fears about children's health and their commitment to follow the recommendations.

There are also other factors that limit the initiation of IPT related to the treatment itself: the lack of pediatric formulations (population of 0-5 years cannot swallow tablets or capsules in its vast majority) (22) and the long duration of treatment (daily dose for 6 months) (15,22). Recent literature suggest that isoniazid in syrup form shows benefits over tablet form when providing IPT in children, both in efficacy and safety (26).

It has not been evaluated in this study, but in some cases patients may be receiving treatment with antiretrovirals, which in total means a very high number of daily pills (7). In our case, the treatment involves moving once a month to the health center, which for some families may involve high economic cost and a long time (15,22) due to the long distances they have to travel. As we have reflected statistically, for each extra kilometer from the household to the health center, increases by 25% the possibility of not starting the treatment (OR = 1.25 [1.12 - 1.50], p <0.001).

Finally, in a context such as that of Manhiça and Mozambique, the shortage of isoniazid could be common (7,15,22,25), since stock-outs of essential health products is a fairly common problem (27) faced by healthcare systems in developing countries. In recent years, stockouts were reported (communication made by health personnel), but it was not possible to check if they occurred during the study period of this analysis.

In spite of all the factors mentioned, we assume that once the patient is enrolled in the IPT programme, the adherence is moderate, since 2/3 of the people who initiate the treatment went to collect the 6 monthly cycles of treatment. However, half of these patients finished the treatment before/after the recommended 6-month period. Within the subgroup of children who initiated IPT, we also detect a much higher compliance among the female sex. Even so, a study with a greater number of patients who started IPT would be convenient to perform a more complete evaluation of IPT adherence patterns.

LIMITATIONS

Our study had several limitations, especially those related to obtaining subjects who entered the study. On the one hand, the retrospective nature of the study limited the

obtaining of some variables that were initially considered to be possibly associated with the initiation or non-initiation of IPT (see Future Prospects of Research).

Another important aspect to be highlighted is the significant number of patients who actually started IPT during the study period (n = 72; registered in CCR book) and who could not enter the study (n = 54) since they were not identified as members of the HDSS database, and therefore we were not able to establish a link between them and the index case or their household. In addition, the list of estimated contacts was also generated only from those adults who had PermID in our database, so at that point we also lost subjects without permID or whose permID could not be identified.

We also suppose that some patients were not included in the study due to the different names used by patients (lack of official registration), handwriting errors on the names and the matching variables (all the books were registered manually and later digitized by different personnel) and the impossibility of verification on those without a perfect matching.

The lack of coincidence between the list of contacts and the list of TB patients is mainly associated with two factors: on the one hand, Manhiça Health Centre is located next to the hospital that in practice represents the district's reference hospital of Manhiça. That means that not only people who are entitled to receive treatment there due to the location of their homes go to this hospital for medical care, but it receives people from all over the district. Since colonial times, labor migration of men to South Africa is quite common, especially among the inhabitants of southern Mozambique and in rural areas who aim to work in mining, mainly promoted for reasons of family and economic responsibility (28,29). It is also increasingly common to migrate to more urbanized areas. All of these migratory movements affect the family nucleus, the care of children, the

family economy, and significantly impede the demographic monitoring of the population. Another possible scenario is one in which the index case and the child do not start treatment in the same health unit, and this factor, like the others, leads to an underestimation of the coverage.

It is also important to note that the distance between the health center and the households was measured by coordinates, in a straight line, so that distances traveled on foot are greater, and we can assume variability.

The methodology of the study was also limiting since only those children who lived at the time an adult was diagnosed with TB were considered as contacts. However, there are other collectives that may be susceptible to receiving IPT, since the contact definition includes "any children under 5 years old who share the same environment for a prolonged period of time (8 or more hours/day) with a pulmonary TB case", which is also applicable for other children who share the same house including children from domestic employees, but also for people who live in barracks, or who share other environments such as communities, schools or health units (4). In this case, due to the inclusion criteria in which only the children who lived at the same moment in the index case were included, there is a possibility that the denominator of the coverage was greater, and as a consequence the coverage could be higher too.

In relation to adherence, the health workers recorded whether the child finished treatment or not based on the monthly collection of treatment at the center. However, we do not have the verification that these children actually took the medication daily.

FUTURE PROSPECTS OF RESEARCH

As mentioned above, some variables related to the initiation of IPT could not be included in the study due to lack of data. However, the following variables could be included in future studies since they were determinant in previous projects and we believe that in the context of this study they can be influential:

- Of children: history of BCG, history of other diseases (e.g. asthma), nutritional status, symptomatology and HIV status or coinfection
- Of index case: relation to child contact, sputum result, symptomatology, socioeconomic status, HIV coinfection and adherence to antiretroviral treatment
- Of the household: number of people living in the house, number of children under 5 years old living in the house, death in the household in previous years

We believe it would be important to continue investigating the status of the implementation of the IPT program in the region through prospective studies that allow greater and better data collection, and the performance of qualitative studies including both health personnel and patients (mainly index cases and parents of children) to detect the weaknesses of the program and the social determinants influencing it.

It would be interesting to evaluate interventions that bring IPT closer to those who receive it to see if IPT coverages are increased. A possible strategy would be community-based directly observed therapy (CB DOT), in which community health workers are trained to increase awareness, detection, and treatment of TB and bring services directly to the homes of those at risk for infection (30).

Replicating this study including all the district could also reduce the limitations related to displacement within the district.

CONCLUSIONS

Our study shows that the coverage of the IPT program is low at 11.7%, which evidences certain weaknesses of the IPT implementation. Given that 2/3 of the patients who started taking IPT collected all the 6 cycles of treatment in the health center, we believe that the adherence is moderate. That is why we trust that one of the main concerns for the program is the lack of referral of children contacts to the health center once a case of TB has been diagnosed. The study shows how the long distances that patients have to travel to the health center, and an older age of the children, negatively influence the initiation of IPT.

We believe that implementing solutions to some of the shortcomings of the program, such as an active search for contacts, more education, bring the treatment dispensation to the community, or the replacement of tablets by pediatric formulations, can be a great support to improve the implementation and coverage of the program. Further research is needed to detect other factors that influence the implementation of the program, and to increase its efficiency to prevent infant morbidity and mortality associated with tuberculosis.

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AVAILABLE RESOURCES AND WORK PLAN

This work has been carried out entirely by the student with the support and guidance of the supervisor, which has facilitated the obtaining of data through the CISM staff, who have also given support to solve some questions related with the study.

Initially, the approach was made in Barcelona between the student and the supervisor. During April 2019 the student traveled to Manhiça to extract the data and surround herself with experts and professionals in the field. In addition, the student was able to acquire knowledge about the operation of the research center, the hospital, the health care protocols, and the collection of data. The National TB Control Program (Programa Nacional de Controlo da Tuberculose [PNCT]) at Manhiça Health Center and its staff were also visited to extract data and their subsequent validation. The records of the medical visits (IPT books of the CCR and pediatrics) were digitized manually by the student. The rest of variables were extracted from the database by CISM data managers and other staff. The statistical analysis has been carried out by the student and supported by the biostatistics team of ISGlobal. Finally, the writing and results were validated by the supervisor.

BENEFITS OF RESEARCH

One of the main benefits of this study is that it expands the current knowledge of the application of the IPT program in a real population. It can help to understand some of the gaps of the program. As it reflects and justifies with data a poor program coverage,

it is expected that the study could help to promote a change to reinforce and improve it, and thus ensure a greater coverage of children to protect them from childhood TB. The project reveals problems for which a strategy has not been considered, and it is expected that they can be debated and considered for the future. Finally, it opens up new possible lines of research, such as some factors that affect the initiation of IPT.

The degree of internal and external validity can be explained by the reasons mentioned in the limitations of the study (See Limitations).

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APPENDICES

Appendix 1. Example of R code used for statistical analysis

```
#clean workspace
rm(list = ls())

#open R commander
library(Rcmdr)

#open file
Dataset <- readXL("/Users/agnesmontoyarimbau/Desktop/LLISTA ANALISI.xlsx",
                  rownames=FALSE, header=TRUE, na="", sheet="PER ANÀLISI (sense noms A B)",
                  stringsAsFactors=TRUE)
#DATA SUMMARY
summary(Dataset[,c("inicia.IPT", "genderKID")])

#RUN CONTINGENCY TABLE AND ANALYSIS (categorical variables)
library(abind, pos=17)
local({
  .Table <- xtabs(~inicia.IPT+genderKID, data=Dataset)
  cat("\nFrequency table:\n")
  print(.Table)
  cat("\nTotal percentages:\n")
  print(totPercents(.Table))
  .Test <- chisq.test(.Table, correct=FALSE)
  print(.Test)
  cat("\nExpected counts:\n")
  print(.Test$expected)
  print(fisher.test(.Table))})
local({
  .Table <- xtabs(~inicia.IPT+genderKID, data=Dataset)
  cat("\nFrequency table:\n")
  print(.Table)
  cat("\nTotal percentages:\n")
  print(totPercents(.Table))
  .Test <- chisq.test(.Table, correct=FALSE)
  print(.Test)
  cat("\nExpected counts:\n")
  print(.Test$expected)
  print(fisher.test(.Table))})

#RESULTS

Frequency table:
  genderKID
inicia.IPT  F  M
A (SI) 11  7
B (NO) 64 72

Total percentages:
  F    M Total
A (SI)  7.1  4.5  11.7
B (NO) 41.6 46.8  88.3
Total  48.7 51.3 100.0

Pearson's Chi-squared test

data:  .Table
X-squared = 1.2564, df = 1, p-value = 0.2623


Expected counts:
genderKID
inicia.IPT         F         M
A (SI)  8.766234  9.233766
B (NO) 66.233766 69.766234

Fisher's Exact Test for Count Data

data:  .Table
p-value = 0.3198
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
  0.582789 5.700621
sample estimates:
  odds ratio
1.761336

#LOGISTIC REGRESSION (quantitative variables)
#summary
summary(Dataset[,c("inicia.IPT", "idadeKID")])

inicia.IPT     idadeKID
A (SI): 18   Min.   :0.1151
B (NO):136   1st Qu.:1.6390
             Median :3.0836
             Mean   :3.0316
             3rd Qu.:4.3733
             Max.   :5.9918

#run LR analysis
LR <- glm(formula = inicia.IPT ~ idadeKID, family = binomial(), data = Dataset)
```

```
#RESULTS
summary(LR)

Call:
  glm(formula = inicia.IPT ~ idadeKID, family = binomial(), data = Dataset)

Deviance Residuals:
  Min       1Q   Median       3Q      Max
-2.4600   0.2994   0.4128   0.5846   0.7998

Coefficients:
  Estimate Std. Error z value Pr(>|z|)
(Intercept)   0.9277     0.4654   1.993   0.0462 *
  idadeKID      0.4179     0.1736   2.407   0.0161 *
  ---
  Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
(Dispersion parameter for binomial family taken to be 1)

Null deviance: 111.09  on 153  degrees of freedom
Residual deviance: 104.54  on 152  degrees of freedom
AIC: 108.54

Number of Fisher Scoring iterations: 5

exp(LR$coefficients)
(Intercept)    idadeKID
2.528574    1.518820

exp(confint(LR))
2.5 %   97.5 %
  (Intercept) 1.043460 6.577579
idadeKID    1.098738 2.187515

#GRAPHIC(PLOT)
with(Dataset, plot(inicia.IPT, idadeKID))

points(Dataset$inicia.IPT, LR$fitted.values)

#GENERALIZED LINEAR MODEL

Rcmdr>  GLM <- glm(inicia.IPT ~ idadeKID + distancia.al.hospital.kms.,
                   Rcmdr+    family=binomial(logit), data=Dataset)

Rcmdr>  summary(GLM)

Call:
  glm(formula = inicia.IPT ~ idadeKID + distancia.al.hospital.kms.,
      family = binomial(logit), data = Dataset)

Deviance Residuals:
  Min        1Q    Median        3Q       Max
-2.39361   0.03864   0.12708   0.31605   1.59967

Coefficients:
  Estimate Std. Error z value Pr(>|z|)
(Intercept)                -1.3569     0.6589  -2.059 0.039465 *
  idadeKID                    0.5372     0.1888   2.846 0.004431 **
  distancia.al.hospital.kms.   0.2406     0.0658   3.656 0.000256 ***
  ---
  Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 110.836  on 152  degrees of freedom
Residual deviance:  68.568  on 150  degrees of freedom
(1 observation deleted due to missingness)
AIC: 74.568
Number of Fisher Scoring iterations: 7


Rcmdr>  exp(coef(GLM))  # Exponentiated coefficients ("odds ratios")
(Intercept)                   idadeKID
0.2574578                 1.7111704
distancia.al.hospital.kms.
1.2719660

#CONFIDENCE INTERVALS FOR COVERAGE
Rcmdr>  local({
  Rcmdr+    .Table <- xtabs(~ inicia.IPT , data= Dataset )
  Rcmdr+    cat("\nFrequency counts (test is for first level):\n")
  Rcmdr+    print(.Table)
  Rcmdr+    prop.test(rbind(.Table), alternative='two.sided', p=.5, conf.level=.95,
                      Rcmdr+    correct=FALSE)
  Rcmdr+  })

Frequency counts (test is for first level):
  inicia.IPT
A (SI) B (NO)
18    136

1-sample proportions test without continuity correction
data:  rbind(.Table), null probability 0.5
X-squared = 90.416, df = 1, p-value < 2.2e-16
alternative hypothesis: true p is not equal to 0.5
95 percent confidence interval:
  0.07522598 0.17718843
sample estimates:
  p
0.1168831
```

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