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**ORIGINAL ARTICLE**

# COMPARISON OF THE EFFECTIVENESS, SAFETY, COMPLIANCE, AND COST OF THE 6-MONTH ISONIAZID VS 3-MONTH ISONIAZID-RIFAMPICIN REGIMEN FOR LATENT TUBERCULOSIS IN CHILDREN

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## ABSTRACT

**Background:** Tuberculosis remains to be a major cause of morbidity in children and treatment of latent tuberculosis is important to prevent children from developing active tuberculosis. This study aimed to compare the effectiveness, safety, compliance, and cost of the currently available Latent Tuberculosis Infection treatment regimens, 6 months isoniazid (6H) and 3 months isoniazid plus rifampicin (3HR), based on the 2020 Department of Health National Tuberculosis Control Program Tuberculosis Preventive Treatment guidelines for children.

**Methodology:** In this open label randomized controlled trial pilot study, 30 participants were assigned to receive either 6H or 3HR. Medications were administered daily by either participants (with direct supervision of treatment supporters) or treatment supporters (for younger participants). Data on outcome measures in terms of effectiveness, safety, and compliance were obtained. Direct cost of treatment was computed per patient's weight category. Independent Z-test for proportion (for effectiveness, safety, and compliance) and mean (for cost) at 5% level of significance was used to compare the outcomes for each treatment group.

**Results:** Twelve subjects (67%) in the 6H group completed per-protocol therapy, compared to 10 subjects (87%) in the 3HR group. The proportion of adverse events was higher in the 6H group (22%) compared to the 3HR group (8%), but statistical tests showed no significant difference for both compliance and frequency of adverse events. No participant developed active TB disease in both groups. The cost of the 6H treatment regimen was 2,180.18 Php while the cost of the 3HR treatment regimen was 1,526.41 Php, with a p-value of 0.0470 which was statistically significant.

**Conclusions:** Both 6H and 3HR are effective treatments for latent TB infection in patients 0-18 years old. Both treatments were comparable in terms of safety and ease of compliance, but overall cost was higher in the 6H treatment regimen.

**KEYWORDS:** *latent tuberculosis, 6H, 3HR*

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## INTRODUCTION

Tuberculosis (TB) is the leading cause of death from infectious diseases for children of all ages globally, with the Philippines as one of the 30 countries in the WHO high TB burden list[1]. It affected approximately 10.6 million people worldwide in 2021[1]. Around a fourth of the global population have Latent Tuberculosis Infection (LTBI), a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of active TB. [1]

TB is both curable and preventable. The National Tuberculosis Control Program (NTCP) of the Philippine Department of Health (DOH) includes Tuberculosis Preventive Treatment (TPT) as one of its core program indicators[2]. Currently available regimens for children include daily isoniazid for 6 months (6H) and daily isoniazid and rifampicin for 3 months (3HR)[2].

Studies comparing the effectiveness, safety, compliance, and cost between the two regimens have been conducted internationally but to our knowledge, there are no studies yet comparing the 6H and 3HR regimen in Filipino children, hence, this study looked into the effectiveness, safety, compliance, and cost of the currently available LTBI treatment regimens under the DOH NTCP TPT for children.

This study aims to compare the currently available LTBI treatment regimens, 6H and 3HR, under the DOH NTCP TPT for children in terms of effectiveness, safety, compliance, and cost. The results of this study can guide pediatricians and policy makers as to which of the two currently available regimens, 6H or 3HR, under DOH NTCP TPT will yield better outcomes.

## MATERIALS AND METHODS

### Study Design

The study was an open label randomized controlled trial pilot study conducted in a 250-bed pediatric tertiary government institution in Quezon City, Philippines.

### Population and Sample Size

Children 0-18 years old who were eligible for TPT according to the NTCP guidelines were enrolled in the hospital's TB Directly-Observed Therapy, Short-Course (DOTS) Center. A sample size of 30 was enrolled following the recommendations by Hertzog[3] on group comparisons to demonstrate intervention efficacy. Randomization was done using a research randomizer software at www.randomizer.org (Version 4.0, 2013) and yielded the following independent groups: 18 subjects for group 1 and 12 subjects for group 2.

Sampling was done as follows: One subject per index patient referred to the TB DOTS center was included in the study. Once evaluated and considered eligible for TPT, and after ruling out active TB disease, the subjects were randomly assigned to one of the treatment regimens. Other contacts of the index case were also evaluated for TB and those who were eligible for TB treatment but not included in the study were still enrolled at the hospital's TB DOTS center.

Subjects included children 0-18 years old who were eligible for TPT after exclusion of active TB disease following the guidelines in the NTCP Manual of Procedures (MOP)[4]. The following were the inclusion criteria: (1) Children less than 5 years old who are household contacts of bacteriologically confirmed pulmonary TB; (2) Children 5-18 years old who are household contacts of bacteriologically confirmed pulmonary TB with no other risk factors for TB and with a positive TST; (3) Children less than 5 years old who are household contacts of clinically diagnosed pulmonary TB with positive TST; and (4) Children 0-18 years old who are close contacts of bacteriologically confirmed pulmonary TB with positive TST.

The following cases were excluded: (1) People living with HIV and other risk groups such as those with other immune-suppressive medical conditions[4]; (2) Children who have been previously treated for LTBI or active TB disease; (3) Children exposed to drug-resistant TB cases; (4) Children with pre-existing liver disease; and (5) Children with any sign of hepatic abnormalities such as jaundice, ascites, bleeding, etcetera, at the time of initial examination.

The following enrolled study participants were considered dropouts: (1) Those who failed to present at the TB DOTS Center within 3 days from the scheduled follow-up and could not be contacted after at least 3 phone calls within the 3-day allowance for

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follow-up; (2) Those who presented with symptoms suggestive of hepatitis as assessed by the TB DOTS physician; and (3) Those who had treatment interruption for two months or more.

**Data Collection**

The conduct of the study was discussed thoroughly with the parents and/or legally authorized representative as well as with the subjects in a manner that was comprehensible to all. Informed consent was signed by at least 1 parent or guardian who was identified as the subject's treatment supporter. Assent forms were signed by subjects more than 7 years old.

Children enrolled in the study were randomly assigned to either of 2 treatment groups: Group 1 – six (6) months daily isoniazid; Group 2 – three (3) months daily isoniazid + rifampicin. Dosing according to the latest guidelines set by NTCP MOP was followed. Supplemental pyridoxine of 5-10 mg/day was also given to infants who participated in the study. All medications were provided by the TB DOTS clinic free of charge. Allocation concealment was done by a designated resident. The treatment group assignment from the random number generator software was placed in a sealed envelope and given to the investigators.

Participants were registered as regular patients at the TB DOTS Clinic with printed and electronic records. All information were available only to the researchers and de-identified and coded during data analysis. The forms contained the following details: demographic and baseline clinical characteristics such as age, sex, civil status, nationality, educational status, family size, history of BCG vaccination, presence of co-morbidities, and indication for TPT. The following information were noted on each follow up visit: weight, presence of TB signs and symptoms, adverse reactions and issues on compliance. Laboratory (such as complete blood count and liver enzymes) and imaging tests during treatment and until 1 month after completion of treatment were also requested whenever indicated.

Treatment supporters were oriented at the start of TPT regarding possible adverse reactions and given a list of things to monitor during treatment. Adverse drug reactions were graded and managed according to guidelines. Patients and treatment supporters were advised to contact the TB DOTS center or the researcher to report any adverse reactions. Baseline liver function tests (LFTs) were done for subjects 15-18 years old. For other participants, LFTs were only done any time during treatment when symptoms suggestive of hepatitis as assessed by the TB DOTS physician developed.

Subjects with treatment interruptions and those who satisfy the withdrawal criteria were considered dropouts. For treatment interruptions of less than two months, treatment was continued and prolonged to compensate for missed doses. If more than two months of TPT were missed, patients were advised to restart the same regimen from the beginning after ruling out active TB.

This study was conducted according to the ICH-GCP Rules and Regulations and the Data Privacy Act of 2012, and commenced upon IRB approval. Subjects were given the option to withdraw at any point in the study. There was no financial incentive for participants. The authors declare no conflicts of interest regarding the conduct of this study. Partial research funding was granted by the Pediatric Infectious Disease Society of the Philippines.

**Outcome Measures**

The currently available LTBI treatment regimens, 6H and 3HR, under the DOH NTCP TPT were compared in terms of:

1. Effectiveness described as the proportion of compliant patients who did not develop active TB disease (non-development of chest radiograph changes and/or symptoms suggestive of active TB disease) during the course of treatment until 1 month after completion;
2. Safety described to be inversely related to the proportion of adverse events encountered during the course of treatment until 1 month after completion, classified according to severity and by organ system following the NTCP TPT guidelines

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3. Compliance described as the proportion of patients who were able to successfully complete the prescribed duration of treatment; and
4. Cost described as the average total cost inclusive of TB medications and diagnostics for the whole duration of the assigned treatment, and clustered by weight range.

**Statistical Analysis**

The statistical treatment of the study outcomes was as follows:

1. Effectiveness was measured as the proportion of compliant patients who did not develop active TB disease for each treatment regimen, and was compared using the independent Z-test for proportion at 5% level of significance.
2. Safety was measured as inversely related to the proportion of adverse events encountered during treatment for each regimen and was compared using the independent Z-test for proportion at 5% level of significance;
3. Compliance was measured as the proportion of patients considered to have completed treatment for each regimen and compared using the independent Z-test for proportion at 5% level of significance;
4. Cost was measured as the mean total cost for each regimen and was compared using the independent Z-test for mean at 5% level of significance. Parametric statistical tests such as Z-test rely on the normality assumption to make accurate inferences about the population. Hence, to ensure that assumptions for parametric analysis were met, the Normality test was applied to the cost data including weight.

## RESULTS

**Trial Participants**

From September 2021 to July 2022, 30 subjects who met the inclusion criteria and agreed to participate in the pilot study were enrolled and randomly assigned to the treatment regimens. The demographic and clinical characteristics of the trial participants were similar between the two treatment groups except for the indication for TPT (Table 1) where most of the 6H group were exposed to household contacts, while the participants in the 3HR group were exposed to close contacts.

***Table 1. Baseline demographic and clinical characteristics***

| Characteristic | 6H (N=18) | 3HR (N=12) | P-value |
|---|---|---|---|
| **Age** | | | |
| <5 years old | 12 (67%) | 4 (33%) | 0.125 |
| 5 to <15 years old | 5 (28%) | 8 (67%) | |
| 15-18 years old | 1 (5%) | 0 | |
| **Sex** | | | |
| Male | 5 (28%) | 6 (50%) | 0.266 |
| Female | 13 (72%) | 6 (50%) | |
| **Educational status** | | | |
| No formal schooling | 14 (78%) | 6 (50%) | 0.332 |
| Elementary | 3 (17%) | 5 (42%) | |
| High School | 1 (5%) | 1 (8%) | |
| **Family size** | | | |
| Less than 4 members | 2 (11%) | 2 (17%) | 1.000 |
| 4-6 members | 11 (61%) | 7 (58%) | |
| More than 6 | 5 (28%) | 3 (25%) | |
| **Place of residence** | | | |
| Metro Manila | 16 (89%) | 10 (84%) | 1.000 |
| Cavite | 1 (5.5%) | 0 | |
| Rizal | 1 (5.5%) | 1 (8%) | |
| Others | 0 | 1 (8%) | |
| **Indication for treatment** | | | |
| Less than 5 years old household contacts of BC-PTB[1] | 11 (61%) | 3 (25%) | 0.017 |
| 5-18 years old household contacts of BC-PTB[1] with no other risk factors for TB and with (+) TST | 5 (28%) | 3 (25%) | |
| Less than 5 years old household contacts of CD-PTB[2] with (+) TST | 2 (11%) | 1 (8%) | |
| 0-18 years old close contacts of BC-PTB[1] with (+) TST | 0 | 5 (42%) | |
| **Body Mass Index** | | | |
| Obese | 2 (11%) | 1 (8%) | 0.060 |
| Overweight | 0 | 0 | |
| Risk for overweight | 2 (11%) | 0 | |
| Normal | 6 (33%) | 10 (84%) | |
| Wasted | 3 (17%) | 1 (8%) | |
| Severely wasted | 5 (28%) | 0 | |

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***Table 1. Baseline demographic and clinical characteristics (continued)***

| Characteristic | 6H (N=18) | 3HR (N=12) | P-value |
|---|---|---|---|
| **BCG** | | | |
| Given | 18 (100%) | 12 (100%) | -- |
| Not given | 0 | 0 | |
| Unknown | 0 | 0 | |
| **Presence of Comorbidity** | | | |
| Yes | 3 (17%) | 0 | 0.255 |
| No | 15 (83%) | 12 (100%) | |

[1]BC-PTB: Bacteriologically confirmed pulmonary tuberculosis
[2]CD-PTB: Clinically diagnosed pulmonary tuberculosis

## Compliance

The proportion of those who completed treatment was higher in the combination 3HR group (Table 2). However, independent z-test at 5% level of significance showed that the proportion of overall treatment completion was not significantly different between the two groups.

## Safety

The proportion of adverse events reported was higher in the 6H group (Table 2). However, independent z-test at 5% level of significance showed that the proportion of adverse events was not significantly different between the two treatment groups. In those who reported adverse reactions, 80% were from the 6H group. Most reports of adverse events for both treatment groups involved nausea (Grade 1, mild). There was one report of jaundice with elevated liver enzymes (Grade 3, severe) from the 6H group, which resolved after one week. The same regimen was resumed after resolution of symptoms and no further complications were noted.

## Effectiveness

Among the participants in both groups who completed treatment, no case of active tuberculosis was diagnosed during treatment and up to 1 month post-treatment (Table 2). Since both groups had an equal proportion of treatment effectiveness, independent z-test was no longer done. Moreover, since no trial participant developed active TB disease while on TPT and 1 month thereafter, per protocol analysis and intention-to-treat analysis of the effectiveness between the two treatment regimens were also not done.

## Cost

The mean cost for each treatment group, inclusive of cost for medicine and diagnostics, was calculated in those who completed treatment. Computed costs were based on the doses of the treatment regimens and, therefore, were dependent on the weights of the participants in the two treatment groups. Independent t-test at 5% level of significance of the weights of the trial participants who completed treatment under each group showed that there was no significant difference between the weights of both groups. Independent z-test at 5% level of significance showed that the mean cost is significantly higher in the 6H group compared to the 3HR group. However, both p-values computed for the mean weights (P = 0.051) and costs (P = 0.047) were too close to P = 0.05 to be considered not significant and significant, respectively. They can be statistically inconclusive and that additional trial participants can potentially make the results significant and not significant, respectively.

***Table 2. Independent Z-test results for effectiveness, safety, compliance, and cost between 6H and 3HR.***

| Outcome | Group 1 (6H) n= 18 Count (%), Mean (SD) | Group 2 (3HR) n= 12 Count (%), Mean (SD) | P-value | Sig[1] |
|---|---|---|---|---|
| **Non-development of TB Disease** | 12 (100%) (of 12 completed) | 10 (100%) (of 10 completed) | -- | ns[4] |
| **Adverse Events** | 4 (22%) | 1 (8%) | 0.31 | ns[4] |
| **Treatment Completion** | 12 (67%) | 10 (83%) | 0.33 | ns[4] |
| **Weight (in kg)[2]** | 17.125 (1.45) | 24.4 (3.42) | 0.0501 | ns[4] |
| **Cost[3]** | 2180.18 (774.79) | 1526.41 (649.64) | 0.0470 | s[5] |

[1]5% Level of Significance; ns-not significant; s-significant
[2]Independent t-test for mean
[2,3]Only those who completed the treatment
[4]NS: not significant
[5]S: significant

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## DISCUSSION

Our study showed that the overall treatment completion rate was higher in the 3-month combination therapy than the 6-month monotherapy. Although there was no noted statistically significant difference between the two treatment groups, a larger sample size is needed to produce more conclusive results. Similarly, an 11-year RCT by Spyridis *et al*.[5] showed that compliance is better with the short-course combination therapy. Moreover, systematic reviews and RCTs on LTBI treatment in children and adolescents by Assefa *et al*.[6] and Cruz *et al*.[7] showed that overall completion rate was either equivalent or higher in the short-course combination therapy.

It was found that in those who did not complete treatment (8 from each of the treatment groups), 50% or 4 in 8 were not able to visit the TB DOTS Center due to loss of accompanying treatment supporters secondary to either migration *i.e*. moved to provinces away from Metro Manila, or to limitations in public transportation during the COVID-19 surges early in 2022. In the 6H group, 2 subjects had treatment supporters who opted to discontinue treatment because participants persistently complained of nausea after intake of isoniazid. The last 2 subjects were declared lost to follow-up after failure to visit the TB DOTS Center within 3 days from the scheduled regular follow-up and 3 failed phone calls within the 3-day allowance for follow-up. These factors which led to non-compliance and discontinuation of therapy are important aspects of the program that should be investigated and dealt with to ensure success.

The proportion of adverse effects was higher by three times as much in the 6H group compared to the 3HR group. The difference was not statistically significant, but a larger sample size is needed to provide more conclusive results. Our findings are consistent with the systematic review by Assefa *et al*.[6] and the RCT by Spyridis *et al*.[5] where pediatric patients on isoniazid monotherapy were reported to be more likely to have transient elevation of liver enzymes than those under the combination therapy of isoniazid + rifampicin. In contrast, a systematic review by Cruz *et al*.[7] showed that children given isoniazid therapy had similar or lower frequency of adverse events including hepatoxicity compared with those given isoniazid + rifampicin therapy. Also, in this review, Cruz *et al*. cited studies showing that isoniazid is actually well tolerated by pediatric patients.[7]

No participant developed active TB disease among those who completed treatment. This suggests that both treatment regimens are effective, although a larger sample size is needed to derive more conclusive results. It is interesting to note that in the study of Assefa *et al*.[6] and in the RCT by Spyridis *et al*.[5], pediatric patients given isoniazid monotherapy had twice the risk of developing active TB disease than those given isoniazid + rifampicin combination therapy. In both studies, TB disease was reported along with findings on chest radiographs and suggested that combination therapy has a faster effect in decreasing the microbial load, which might have impeded the development of radiologic changes in participants on combination therapy. In contrast, Cruz *et al*.[7] showed in a systematic review that the estimated efficacy of LTBI treatment in children was equivalent in both treatment groups similar to our findings.

This pilot study showed that the cost of treatment with 6H was statistically higher than that of 3HR inclusive only of medications and laboratory procedures during treatment until 1 month after completion of treatment. Cost of treatment is not limited to direct costs as what was included in this study but should also include indirect costs incurred such as transportation cost, and loss of work wages.

## CONCLUSION AND RECOMMENDATIONS

This pilot study showed that both 6H and 3HR can be effective treatments for latent TB infection in children and adolescents 0-18 years of age with no significant difference in terms of compliance and adverse reactions between treatment groups. The cost of the 6H treatment regimen is significantly higher than that of the 3HR treatment regimen. Although medications are given for free at the TB DOTS Center where this study was conducted, policy-makers can

make use of this financial advantage in future amendments of the TB DOTS guidelines.

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**CONFLICT OF INTEREST**

None declared.

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