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# Rifampin versus isoniazid for latent tuberculosis in children

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## 1. Article information

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## 2. Background

Latent tuberculosis (TB) is defined as a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of active TB manifestations. There is no gold standard test for diagnosis of latent TB infection. Upto one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*, and several studies have suggested that 5–10% of them will develop active TB disease within the first 5 years after initial infection if left untreated.

Prevention of progression of latent TB into active TB disease is a critical component of the World Health Organization (WHO) End TB Strategy, and the overall efficacy of the currently available treatments varies from 60% to 90%. Management of latent TB infection involves a comprehensive package of interventions, which include testing, delivering effective and safe treatment, monitoring the adverse effects, and future follow-up. The WHO has given an algorithm for the screening of children, who are household contacts of people with pulmonary TB[1] (Figs. 1 and 2).

The WHO has suggested various regimens for the treatment of latent TB. (Table 1). The current standard treatment with isoniazid for 9 months is associated with poor adherence and toxic effects, rendering the drug less effective. In adults, treatment with rifampin for 4 months has shown higher completion rates with similar safety profiles as compared with isoniazid for 9 months.

## 3. Methods

An open-label, multicentric trial (seven countries with all strata of people) was conducted from October 2011 to January 2014. Eight hundred forty-four children (younger than 18 years) with latent TB were randomly assigned to receive either 4 months of rifampin or 9 months of isoniazid. Children younger than 5 years, who had a contact with household TB and had negative tuberculin test, were also included in the study. The primary outcome was assessed with the adverse effects severe enough to cause termination of the ongoing treatment. The secondary outcome was assessed with treatment adherence, side-effect profile, and efficacy. Children who were assigned to the isoniazid group received 10–15 mg/kg of the drug, and those assigned to the rifampin group received 10–20 mg/kg of the drug. The drugs were administered by the participants themselves or caregivers. The median dose of rifampin was 16.3 mg/kg/day, whereas it was 10.3 mg/kg/day for isoniazid.

## 4. Results

Out of 844 children who underwent randomization, 15 were excluded from the trial after randomization because they had negative tuberculin test 8 weeks after the end of household exposure to active TB cases and treatment was stopped.

### *Treatment completion*

Treatment completion was defined as completion of more than or equal to 80% of the doses.[1] It was much higher in the rifampin group (86.5%) than in the isoniazid group (77.1%). Furthermore, there was a greater percentage of children in the rifampin group (85.3%) who completed the treatment on time than in the isoniazid group (76.4%). The number of children who discontinued the treatment in the midway was greater in the isoniazid group (19.2%), although there were no serious adverse effects reported in both the groups to such an extent to discontinue the treatment. Minor symptoms in the form of stomach upset, poor appetite, fatigue, and headache were reported in both the groups, but the frequencies of these symptoms were much higher in the isoniazid group. Two

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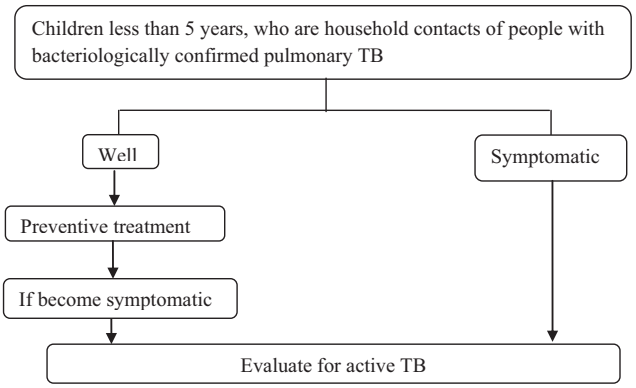


**Fig. 1.** WHO algorithm for screening of children younger than 5 years. TB = tuberculosis; WHO = World Health Organization.

cases of active TB were reported in the isoniazid group. One patient did not receive even 10% of the recommended doses, whereas the other one had completed the full course of treatment for latent TB (Table 2).

## 5. Commentary

It was remarkable that such a trial was possible in seven different countries, with the investigators being able to obtain a comparable data on safety, efficacy, and side effects of rifampin and isoniazid for the treatment of latent TB in children. The present trial provides a comprehensive overview of comparison of rifampin and isoniazid for the management of latent TB. Completion rate was significantly higher in the rifampin group, and similar findings were found in the trial conducted in adults for management of latent TB. There was one trial that compared the efficacy of isoniazid and rifapentine (weekly regimen for 3 months) with that of isoniazid alone and found combination therapy for shorter duration to be efficient because of higher completion rates and lesser side effects.[2] Although only cases of active TB were reported in the isoniazid group, it was difficult to conclude on superiority of rifampin (4 month therapy) over isoniazid (9 month therapy).

Remarkably, the trial had more than 98% follow-up rates. The sample size was large enough to fill an important knowledge gap regarding safety, side-effect profile, and adherence to rifampin in children, for whom the study is limited.[3–5] The trial included children from all the strata of the country so that results could be generalized. Being an open-label trial, chances of biasing was higher, particularly for ascertainment of completion or adherence events. In conclusion, a regimen of 4 months of rifampin had better completion rates than isoniazid therapy over 9 months for treatment of latent TB in children. Rifampin has the advantage of being single-drug regimen with existing palatable formulation for children. In India, similar trials are required so as to increase the detection and eradication of latent TB in children.

**Table 1**
WHO guidelines (2018) available for treatment of LTBI: The following options are recommended for the treatment of LTBI.[1]

| Drug regimen | Dose (mg/kg body wt) | Maximum dose (mg/day) |
|---|---|---|
| Isoniazid alone for 6 or 9 months | 7–15 | 300 |
| Rifampin alone for 3–4 months | 10–20 | 600 |
| Isoniazid plus rifampin daily for 3–4 months | 7–15/10–20 | 300/600 |
| Isoniazid plus rifapentine for 3 months (12 doses) | INH (<12 years, 15 mg; ≥12 years, 25 mg)<br>Rifapentin:<br>10.0–14 kg = 300 mg<br>14.1–25 kg = 450 mg<br>25.1–32 kg = 600 mg<br>32.1–50 kg = 750 mg<br>>50 kg = 900 mg | |

LTBI = latent tuberculosis infection; WHO = World Health Organization, IHN = Isoniazid.

**Table 2**
Completion of treatment.

| Variable | Rifampin (%) | Isoniazid (%) |
|---|---|---|
| Treatment completed (≥80% of the doses) | 86.5 | 77.1 |
| Treatment completed within allowed time | 85.3 | 76.4 |
| Treatment started but stopped early as per participant decision | 10.9 | 19.2 |

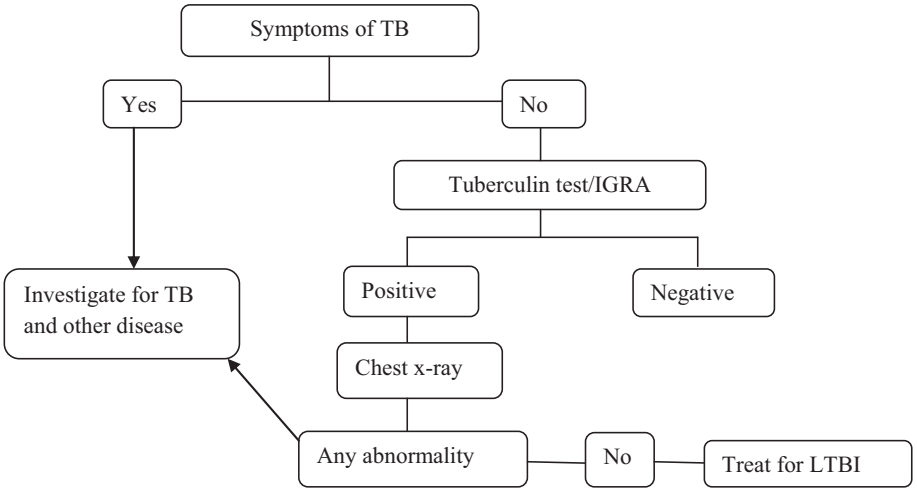


**Fig. 2.** WHO algorithm for the screening of children older than 5 years. IGRA= interferon-gamma release assays; LTBI = latent tuberculosis infection; TB = tuberculosis; WHO = World Health Organization.

## Conflict of interest

Authors have no conflict of Interest.

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