ORIGINAL ARTICLE

# Safety and Side Effects of Rifampin versus Isoniazid in Children

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## ABSTRACT

### BACKGROUND

The treatment of latent infection with *Mycobacterium tuberculosis* is important in children because of their vulnerability to life-threatening forms of tuberculosis disease. The current standard treatment — 9 months of isoniazid — has been associated with poor adherence and toxic effects, which have hampered the effectiveness of the drug. In adults, treatment with 4 months of rifampin has been shown to be safer and to have higher completion rates than 9 months of isoniazid.

### METHODS

In this multicenter, open-label trial, we randomly assigned 844 children (<18 years of age) with latent *M. tuberculosis* infection to receive either 4 months of rifampin or 9 months of isoniazid. The primary outcome was adverse events of grade 1 to 5 that resulted in the permanent discontinuation of a trial drug. Secondary outcomes were treatment adherence, side-effect profile, and efficacy. Independent review panels whose members were unaware of trial-group assignments adjudicated all adverse events and progression to active tuberculosis.

### RESULTS

Of the children who underwent randomization, 829 were eligible for inclusion in the modified intention-to-treat analysis. A total of 360 of 422 children (85.3%) in the rifampin group completed per-protocol therapy, as compared with 311 of 407 (76.4%) in the isoniazid group (adjusted difference in the rates of treatment completion, 13.4 percentage points; 95% confidence interval [CI], 7.5 to 19.3). There were no significant between-group differences in the rates of adverse events, with fewer than 5% of the children in the combined groups with grade 1 or 2 adverse events that were deemed to be possibly related to a trial drug. Active tuberculosis, including 1 case with resistance to isoniazid, was diagnosed in 2 children in the isoniazid group during 542 person-years of follow-up, as compared with no cases in the rifampin group during 562 person-years (rate difference, −0.37 cases per 100 person-years; 95% CI, −0.88 to 0.14).

### CONCLUSIONS

Among children under the age of 18 years, treatment with 4 months of rifampin had similar rates of safety and efficacy but a better rate of adherence than 9 months of treatment with isoniazid. (Funded by the Canadian Institutes of Health Research and Conselho Nacional de Pesquisa; ClinicalTrials.gov number, NCT00170209.)

Tuberculosis is a major global health problem, with an estimated 10.4 million new cases worldwide in 2016; of these cases, 1.0 million occurred in children.[1] It is estimated that 25% of persons worldwide have latent infection with *Mycobacterium tuberculosis*.[2] From this enormous reservoir, it is estimated that active tuberculosis will develop in approximately 10% of those who are infected.[3]

As a result of growing recognition of the importance of treatment of latent infection as part of the End TB Strategy,[4,5] the World Health Organization (WHO) is now recommending treatment for children under the age of 5 years who are household contacts of a person with tuberculosis in all settings.[6] This strategy benefits the children by reducing their risk of life-threatening forms of the disease[7] and prevents future *M. tuberculosis* transmission.[8] The currently recommended standard treatment for latent tuberculosis infection is isoniazid (a regimen that is considered to be safe in children[9]) for 6 or 9 months,[6] with the longer duration showing greater protective efficacy.[10]

However, both regimens of isoniazid have been limited by poor adherence rates.[11] In adults, 4 months of treatment with rifampin has been shown to be safer (lower frequency of grade 3 or 4 hepatotoxicity)[12,13] and to have better adherence rates[12-15] than 9 months of treatment with isoniazid. In adequately powered tuberculosis prevention trials involving adults, 3 months of rifampin was found to be noninferior to 6 months of isoniazid[16] and 3 months of isoniazid plus rifapentine was found to be noninferior to 9 months of isoniazid.[17] In a recent pediatric trial,[18] investigators found better rates of safety and adherence with 3 months of isoniazid plus rifapentine than with 9 months of isoniazid. We wanted to compare the safety, side-effect profile, and adherence of 4 months of rifampin with 9 months of isoniazid in children in a randomized trial.

## METHODS

### TRIAL DESIGN AND OUTCOMES

This trial was part of a larger one that involved both adults and children. In this issue of the *Journal*, the overall trial design, definitions, randomization procedures, enrollment, and outcomes are described in the article by Menzies et al.,[19] which details the findings in the adult participants. (See the Supplementary Appendix that is provided with the full text of the article by Menzies et al. at NEJM.org, along with the protocol for the trial in children, also available at NEJM.org.)

Briefly, the trial involving children was a noninferiority, open-label, randomized trial to compare 4 months of rifampin with 9 months of isoniazid for the treatment of latent tuberculosis infection in children (0 to 17 years of age) in Australia, Benin, Brazil, Canada, Ghana, Guinea, and Indonesia. Children under the age of 5 years who had a household contact with tuberculosis but had negative results on the tuberculin skin test (<5 mm) could also be enrolled in the trial. The primary outcome was adverse events of grade 1 to 5 that resulted in the permanent discontinuation of a trial drug. Secondary outcomes were treatment adherence, side-effect profile, and microbiologically confirmed active tuberculosis during 16 months of follow-up after randomization.

All the analyses were performed in the modified intention-to-treat population, which included all the children who had undergone randomization with the exception of those under the age of 5 years who had negative results on the tuberculin skin test both at the time of screening and on a second test performed 8 weeks after the end of household exposure to active tuberculosis. (Such exposure was defined as ending when the child's household contact with tuberculosis initiated treatment.) These children with two negative results on testing were excluded from the analysis only if the provider made the decision to stop treatment.

### DRUG TREATMENTS

Children who were assigned to the isoniazid group received 10 to 15 mg of the drug per kilogram of body weight per day, and those assigned to the rifampin group received 10 to 20 mg of the drug per kilogram per day.[6,20,21] The drugs were administered by the participants or their caretakers. At each visit, providers performed pill counts to determine the doses of each drug that had been administered. Details regarding the administration of the two drugs and the preparation of the medications are provided in Table S1 in the Supplementary Appendix. Per-protocol treatment completion was defined as the receipt

of at least 80% of doses during the prespecified period of time.

### TRIAL OVERSIGHT

The overall trial was sponsored by the Canadian Institutes of Health Research, and Conselho Nacional de Pesquisa sponsored the portion of the trial in Brazil. The manufacturers of the trial drugs did not provide the drugs for use in the trial and had no other role in the trial. The trial was approved by the biomedical clinical research ethics board at the McGill University Health Center and by the ethics review committee at each participating site. Parents or legal representatives of the children provided written informed consent, and children who were 7 years of age or older provided assent to participate. All the authors vouch for the accuracy and completeness of the analyses and data reported and for the adherence of the trial to the protocol.

### STATISTICAL ANALYSIS

We determined that the enrollment of 411 children in each group would provide the trial with a power of 80% to detect the noninferiority of rifampin, as compared with isoniazid, with respect to adverse events that resulted in the permanent discontinuation of a trial drug (primary outcome), assuming a 6% rate of adverse events with isoniazid and a maximum between-group difference of 5 percentage points. The expected rate of adverse events was estimated from the frequency of such events among adults receiving 9 months of isoniazid, as we reported previously.[12] This number of participants also provided a power of more than 80% to detect a difference of 10 percentage points favoring rifampin in the rate of completion of treatment, on the assumption that 60% of the children would complete 9 months of treatment with isoniazid. Sample-size estimates were adjusted to account for clustering of children who were assigned to the same trial group in the same household.

The statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute), and were directed by the last author in a blinded manner until the analysis was finalized. The calculation of rates of active tuberculosis was based on the person-time of follow-up; children who were lost to follow-up contributed to person-time until the last contact. Rate differences and their 95% confidence intervals were estimated with the use of generalized estimating equations on the basis of Poisson distribution, with a log link.[22] The completion of treatment was calculated as a proportion, and differences in treatment-completion rates and risk differences for adverse events (with 95% confidence intervals) were calculated with a binomial distribution with an identity link after adjustment for clustering in families with the use of generalized estimating equations. If no adverse events occurred, risk differences were estimated with the use of the method of Newcombe.[23]

## RESULTS

### TRIAL PARTICIPANTS

From October 2011 through January 2014, we assessed 2176 potential participants under the age of 18 years. Of the 890 children who met the inclusion criteria, 46 (5.2%) declined to participate, which left 844 who underwent randomization (Fig. 1). According to the protocol, 15 young children were excluded from the trial after randomization because they had negative results on tuberculin skin testing 8 weeks after the end of household exposure to active tuberculosis and treatment was stopped. Of the 829 children who remained in the trial, 11 (1.3%) did not complete the 16-month follow-up after randomization.

The characteristics of the children were similar in the two groups (Table 1). The mean doses of the two trial drugs were higher in the younger age groups. Of all the participants, 128 were under 5 years of age, and 79 were under 2 years of age. No children who were infected with the human immunodeficiency virus (HIV) were enrolled.

### TREATMENT COMPLETION

The rate of overall treatment completion was significantly higher among children in the rifampin group than among those in the isoniazid group (adjusted difference, 13.4 percentage points; 95% confidence interval [CI], 7.5 to 19.3) (Table 2). The numbers of doses of each drug that were administered were based on pill counts at 90.9% of all visits. The most common reason for not completing the trial therapy was a decision of the children or their parents to stop the trial drug early.

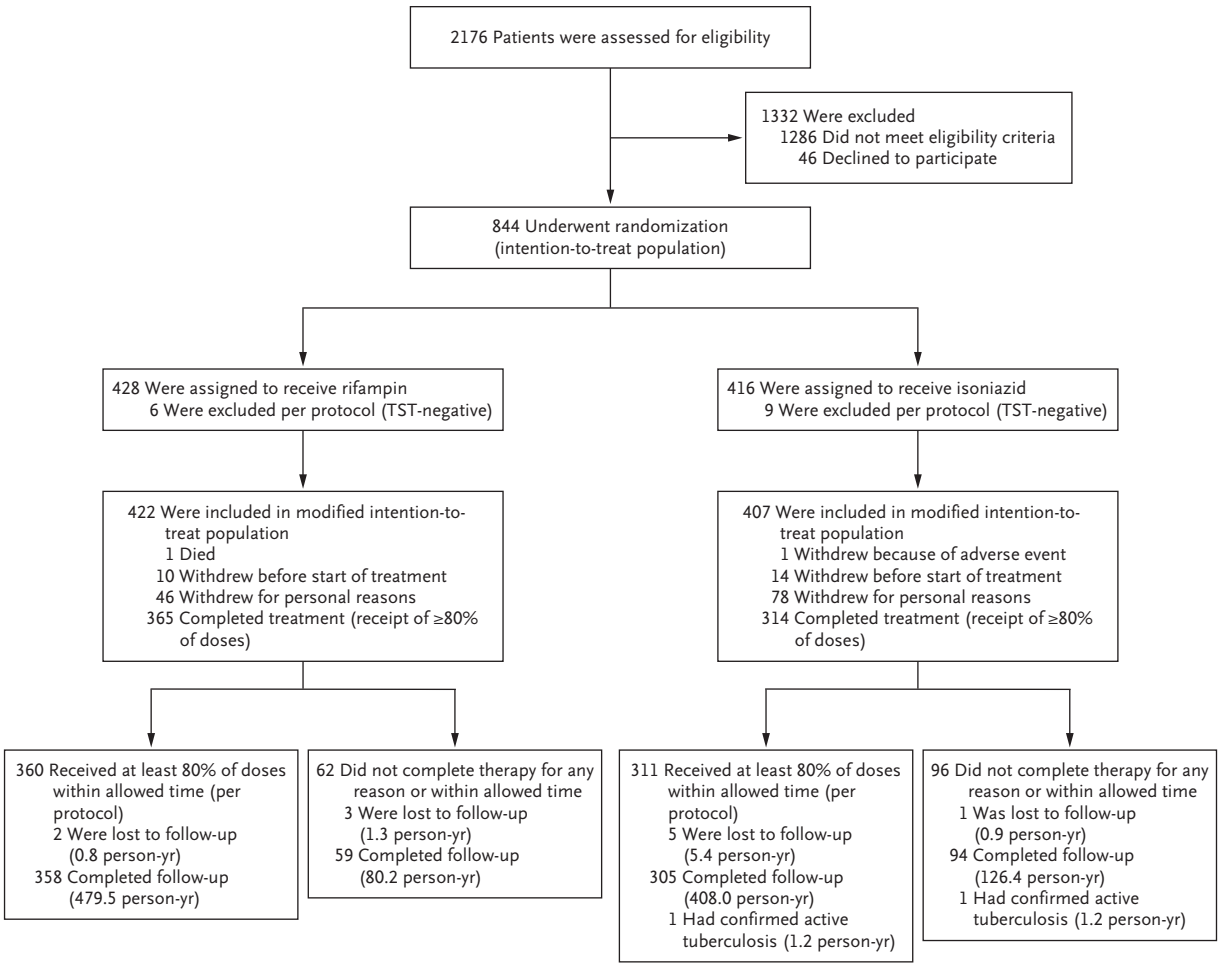


**Figure 1. Enrollment and Outcomes.**
TST denotes tuberculin skin test.

### ADVERSE EVENTS

One death associated with a traffic accident occurred in the rifampin group, and one pregnancy occurred in the isoniazid group (Table 3). No events of grades 1 through 5 were attributed to either trial drug. To account for the longer treatment period and more numerous follow-up visits in the isoniazid group, we estimated the average percentage of visits in which minor symptoms such as stomach upset, poor appetite, or fatigue were reported. Among the children who returned for at least one visit, there was no significant between-group difference in the percentage who reported minor symptoms (Table 3).

### TREATMENT EFFICACY

Among the children in the rifampin group, no cases of active tuberculosis were diagnosed during a total of 562 person-years of follow-up, as compared with 2 cases in 542 person-years of follow-up in the isoniazid group (rate difference; −0.37 cases per 100 person-years; 95% CI, −0.88 to 0.14) (Table S2 in the Supplementary Appendix). The diagnosis was confirmed with culture in one child and with nucleic acid amplification testing in the other (no cultures available). One case occurred in a child who had completed 9 months of isoniazid, which corresponded to a rate of 0.24 (95% CI, 0.03 to 1.71) per 100 person-years, and 1 occurred in a child who had not

completed such therapy, which corresponded to a rate of 0.78 (95% CI, 0.11 to 5.52) per 100 person-years. The latter child had received less than 10% of the assigned doses of isoniazid and was found to have isoniazid-resistant tuberculosis more than 9 months after stopping the drug. This child was a household contact of an index patient in whom tuberculosis had been diagnosed on the basis of smear microscopy in a setting in which cultures and drug-susceptibility testing were not routinely performed, so such results were not available.

## DISCUSSION

In this trial, 829 children were randomly assigned to receive isoniazid for 9 months or rifampin for 4 months, with drugs administered by the par-

**Table 1. Characteristics of the Participants at Baseline.***

| Characteristic | Rifampin (N=422) | Isoniazid (N=407) | All Participants (N=829) |
|---|---|---|---|
| Age | | | |
| Median (IQR) — yr | 10.5 (6.0–13.5) | 10.3 (5.9–14.0) | 10.2 (6.0–13.8) |
| Age group — no. (%) | | | |
| 0–4 yr | 66 (15.6) | 62 (15.2) | 128 (15.4) |
| 5–12 yr | 212 (50.2) | 188 (46.2) | 400 (48.3) |
| 13–17 yr | 144 (34.1) | 157 (38.6) | 301 (36.3) |
| Male sex — no. (%) | 215 (50.9) | 197 (48.4) | 412 (49.7) |
| Trial center — no. (%) | | | |
| Australia | 5 (1.2) | 1 (0.2) | 6 (0.7) |
| Benin | 142 (33.6) | 143 (35.1) | 285 (34.4) |
| Brazil | 64 (15.2) | 54 (13.3) | 118 (14.2) |
| Canada | 15 (3.6) | 11 (2.7) | 26 (3.1) |
| Ghana | 59 (14.0) | 59 (14.5) | 118 (14.2) |
| Guinea | 62 (14.7) | 66 (16.2) | 128 (15.4) |
| Indonesia | 75 (17.8) | 73 (17.9) | 148 (17.9) |
| Median height (IQR) — m | 1.3 (1.1–1.5) | 1.3 (1.1–1.5) | 1.3 (1.1–1.5) |
| Median weight (IQR) — kg† | 27.3 (18.0–42.0) | 29.0 (18.0–42.8) | 28.0 (18.0–42.0) |
| Median body-mass index (IQR)‡ | 16.0 (14.3–18.4) | 16.0 (14.6–18.7) | 16.0 (14.4–18.5) |
| Reaction size on tuberculin skin test — no. (%) | | | |
| <5 mm§ | 25 (5.9) | 20 (4.9) | 45 (5.4) |
| 5–10 mm | 64 (15.2) | 45 (11.1) | 109 (13.1) |
| 11–14 mm | 158 (37.4) | 162 (39.8) | 320 (38.6) |
| ≥15 mm | 175 (41.5) | 180 (44.2) | 355 (42.8) |
| Result on chest radiography | | | |
| Normal | 386 (91.5) | 381 (93.6) | 767 (92.5) |
| Abnormality not related to tuberculosis | 26 (6.2) | 16 (3.9) | 42 (5.1) |
| Hilar lymph node | 7 (1.7) | 7 (1.7) | 14 (1.7) |
| Other possible tuberculosis-related abnormality¶ | 3 (0.7) | 3 (0.7) | 6 (0.7) |
| Reasons for eligibility | | | |
| Household contact of patient with tuberculosis | 416 (98.6) | 401 (98.5) | 817 (98.6) |
| HIV infection‖ | 0 | 0 | 0 |
| Measure of >15 mm on the tuberculin skin test and residence in high-transmission country | 6 (1.4) | 6 (1.5) | 12 (1.4) |

**Table 1. (Continued.)**

| Characteristic | Rifampin (N=422) | Isoniazid (N=407) | All Participants (N=829) |
|---|---|---|---|
| Children with ≥1 sibling in trial — no. (%) | 155 (36.7) | 188 (46.2) | 343 (41.4) |
| Median dose of trial drug (IQR) — mg/kg/day | | | |
| All ages | 16.3 (14.3–19.9) | 10.3 (7.1–11.5) | NA |
| Age 0–4 yr | 18.8 (16.7–20.5) | 12.5 (11.1–13.3) | NA |
| Age 5–12 yr | 16.7 (15.8–18.0) | 10.9 (10.3–11.8) | NA |
| Age 13–17 yr | 13.1 (11.1–15.4) | 6.7 (5.7–7.7) | NA |

* All the analyses were performed in the modified intention-to-treat population, which included all the children who had undergone randomization, except for those under the age of 5 years who had negative results on the tuberculin skin test (<5 mm) both at the time of screening and on a second test performed 8 weeks after the end of household exposure to active tuberculosis if the provider made the decision to stop treatment. There were no significant differences between the groups except for the number of children who had one or more siblings enrolled in the trial (P=0.006). Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, IQR interquartile range, and NA not applicable.
† The dose of the trial drug was increased in 26 children (3.1%) because of an increase in weight.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ All the children who had a tuberculin skin test measuring 0 to 4 mm were under the age of 5 years (median age, 2.4 years; IQR, 1.0 to 3.4).
¶ Children with abnormal results on chest radiography that were considered to be suspicious for tuberculosis underwent sputum examination. If the results were negative, they were enrolled.
‖ Although children with HIV coinfection were eligible to participate in the trial, no such participants were enrolled.

ticipants or their caretakers. Of these children, 79 were under the age of 2 years, an age group with the highest risk of life-threatening tuberculosis disease. No significant safety concerns were identified with either regimen, but the rifampin group had better treatment-completion rates.

No adverse event resulting in the permanent discontinuation of a trial drug occurred in either group. This rate was much lower than expected on the basis of experience with the same regimens in adults.[12-15] However, this result is similar to the finding in a recent trial in which no serious adverse event developed in any of the children who received 3 months of once-weekly isoniazid plus rifapentine,[18] whereas in a large-scale trial involving adults receiving the same regimen, 6% had grade 3 or 4 adverse events, and 5% discontinued treatment.[17] Although the occurrence of adverse events in the isoniazid group was much lower than predicted, we can still conclude that 4 months of rifampin was not inferior to 9 months of isoniazid with respect to safety, given that the upper limit of the 95% confidence interval of the rate difference (0.7 percentage points) was below the prespecified maximal difference of 5 percentage points. In addition, the two regimens were associated with similarly low rates of minor symptoms, a finding that was consistent with the results reported by Lardizabal et al.[15] However, these two findings differed from the results reported by Fresard et al.,[24] who found that patients who received 4 months of rifampin had a significantly greater frequency of gastrointestinal symptoms, asthenia, transient cutaneous reactions, and neurologic symptoms than those who received 6 months of isoniazid, although treatment was not stopped because of these symptoms.

One possible explanation for the low frequency of adverse events and few side effects is that actual drug exposure in this population was too low. In this trial, we followed new WHO age-based dose recommendations, with the highest doses in the drug ranges administered to very young children. Such doses should have been adequate to achieve the target serum concentrations of rifampin.[25] However, recent pharmacokinetic studies[26,27] have shown that even with doses in the recommended range of 10 to 20 mg of rifampin per kilogram, the desired targets for serum concentration may not be achieved in very young children who are being treated for active tuberculosis. In these recent studies, rifampin was administered in fixed-dose combination formats, and it is possible that serum concentrations would be higher when single-drug formulations were used for latent tuberculosis infection. It is clear that further studies of the pharmacokinetic activity of rifampin in this age group are needed.

**Table 2. Completion of Treatment.**

| Variable | Rifampin (N=422) | Isoniazid (N=407) | All Participants (N=829) | Adjusted Difference (95% CI)* |
|---|---|---|---|---|
| | | *number (percent)* | | *percentage points* |
| Treatment completed: ≥80% of doses | 365 (86.5) | 314 (77.1) | 679 (81.9) | 13.6 (7.9 to 19.3) |
| Treatment completed within allowed time: per protocol | 360 (85.3) | 311 (76.4) | 671 (80.9) | 13.4 (7.5 to 19.3) |
| Received 80–89% of doses | 7 (1.7) | 8 (2.0) | 15 (1.8) | |
| Received 90–100% of doses | 353 (83.6) | 303 (74.4) | 656 (79.1) | |
| Treatment completed but not within time allowed per protocol | 5 (1.2) | 3 (0.7) | 8 (1.0) | |
| Treatment not completed | 57 (13.5) | 93 (22.9) | 150 (18.1) | |
| Death | 1 (0.2) | 0 | 1 (0.1) | |
| Pregnancy | 0 | 1 (0.2) | 1 (0.1) | |
| Treatment never started per participant decision | 10 (2.4) | 14 (3.4) | 24 (2.9) | |
| Treatment started but stopped early per participant decision | 46 (10.9) | 78 (19.2) | 124 (15.0) | –11.9 (–17.3 to –6.6) |
| Received 50–79% of doses | 22 (5.2) | 24 (5.9) | 46 (5.5) | |
| Received 1–49% of doses | 24 (5.7) | 54 (13.3) | 78 (9.4) | |

* The difference in treatment-completion rates was calculated as the percentage in the rifampin group minus the percentage in the isoniazid group after adjustment for family clustering with the use of generalized estimating equations. P<0.001 for all the listed comparisons.

In our trial, the completion rate in the rifampin group was significantly higher than the rate in the isoniazid group, a finding that was consistent with the results of two randomized trials involving adults,[12,14] one observational study involving children,[28] and several observational studies involving adults.[13,15,29] Other trials have shown higher completion rates with rifamycin-containing regimens than with 9 months of isoniazid. In one trial, 88% of the children who were assigned to receive 3 months of once-weekly isoniazid plus rifapentine completed therapy, as compared with 81% of those assigned to receive 9 months of isoniazid.[18] In another trial, children who were assigned to receive isoniazid plus rifampin for 3 to 4 months had higher completion rates than those assigned to receive 9 months of isoniazid.[30]

Although the only cases of active tuberculosis were diagnosed in the isoniazid group, we cannot conclude that 4 months of rifampin was either superior or noninferior to 9 months of isoniazid for the prevention of active tuberculosis. However, since there were no cases of active tuberculosis in the rifampin group in our trial or among 434 children who received 3 months of once-weekly isoniazid plus rifapentine in another trial,[18] we suggest that these shorter rifamycin-containing regimens are effective. The likely efficacy of 4 months of rifampin in children is also supported by the results of the companion trial involving adults, especially since the same trial procedures were followed, and adults and children were enrolled at the same trial centers.[19]

Our trial has several strengths. These factors include the randomized design, with complete follow-up of more than 98% of the participants in the modified intention-to-treat population. The sample size was large for a pediatric trial of treatments for latent tuberculosis infection, which fills an important knowledge gap concerning safety, side-effect profile, and adherence to the rifampin regimen in children, for whom study data are limited.[13,15,28] Our trial included children from high-income countries as well as those from low- and middle-income countries, which enhances the generalizability of our results. The two trial drugs were administered daily without direct supervision, in contrast to trials in which isoniazid was administered without direct supervision daily but the isoniazid-plus-rifapentine combination was administered weekly under

**Table 3. Adverse Events.***

| Adverse Event | Rifampin (N=422) | Isoniazid (N=407) | All Participants (N=829) | Adjusted Risk Difference (95% CI)† |
|---|---|---|---|---|
| | | | | *percentage points* |
| **Serious adverse event‡** | | | | |
| Resulted in discontinuation of a trial drug (cause) — no. | 1 (death from traffic accident) | 1 (pregnancy) | 2 | 0.0 (−0.6 to 0.7) |
| Was attributed to a trial drug and resulted in discontinuation — no.§ | 0 | 0 | 0 | 0.0 (−0.1 to 0.1) |
| Occurred during first 22 wk after randomization and resulted in discontinuation — no. | 1 | 0 | 1 | 0.2 (−0.2 to 0.7) |
| **Minor adverse event¶** | | | | |
| As determined at ≥1 follow-up visit — no. (%) | | | | |
| No | 26 (6.2) | 25 (6.1) | 51 (6.2) | |
| Yes | 396 (93.8) | 382 (93.9) | 778 (93.8) | |
| No minor symptom | 376 (89.1) | 330 (81.1) | 706 (85.2) | |
| ≥1 minor symptom | 20 (4.7) | 52 (12.8) | 72 (8.7) | |
| Percentage of visits during follow-up when a minor symptom was reported | | | | |
| Any minor symptom‖** | 8.1±20.3 | 8.5±18.9 | 8.3±19.6 | −0.3 (−3.3 to 2.7) |
| Minor symptom that may have been related to a trial drug**†† | 4.4±14.5 | 4.2±11.1 | 4.3±13.0 | 0.3 (−1.7 to 2.4) |
| Minor skin problem | 1.2±9.6 | 1.3±6.2 | 1.3±8.1 | |
| Minor gastrointestinal symptom | 1.6±9.5 | 1.5±6.1 | 1.6±8.0 | |
| Minor neurologic symptom | 0.1±1.7 | 0.1±1.0 | 0.1±1.4 | |
| Another minor symptom that may have been related to a trial drug‡‡ | 2.2±9.3 | 1.8±7.4 | 2.0±8.4 | |

* Plus–minus values are means ±SD.
† The risk difference was calculated as the value in the rifampin group minus the value in the isoniazid group after adjustment for family clustering with the use of generalized estimating equations.
‡ A serious adverse event was defined as an event of any severity (grade 1 to 5) that was associated with permanent discontinuation of a trial drug. Such events were judged in terms of type, severity, and relationship to a trial drug by an independent three-member adverse-events panel in a blinded fashion.
§ This category was the primary outcome of the trial. The risk difference was estimated with the use of the method of Newcombe.[23]
¶ A minor adverse event was defined as one that did not result in the discontinuation of a trial drug.
‖ Minor symptoms included fever or night sweats, weight loss, sputum, cough, skin problems, gastrointestinal problems, and neurologic problems.
** This was a secondary outcome of the study.
†† This category included minor symptoms with the exclusion of fever or night sweats, weight loss, sputum, and cough.
‡‡ This category included headache (in 16 participants), rhinitis (in 13), oral problem (in 5), fatigue (in 5), and other more infrequent symptoms (in 30).

direct supervision.[17,18,31,32] Therefore, measures of completion rates were not confounded by different modes of administration, and our results should be applicable in settings in which directly observed treatment is not available.

The main limitation of the trial was its open-label design, which may introduce bias, particularly for the ascertainment of completion or adverse events. However, such a design has been used in all other trials of the shorter rifamycin-based regimens,[17,18,31,32] simply because the shorter duration is one of the major advantages of these regimens. To reduce the risk of bias in ascertaining and reporting outcomes, all adverse events and active cases of tuberculosis were adjudicated by independent panels in a blinded manner. We also enrolled only 128 children under the age of 5 years and no HIV-infected children,

which reduces the potential applicability of our findings in these higher-risk populations.

In conclusion, in children with latent tuberculosis, a regimen of 4 months of rifampin had better rates of completion than 9 months of isoniazid, with similar safety profiles in the two trial groups. Rifampin has the advantage of being a single-drug regimen with existing palatable formulations for children.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## APPENDIX

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## REFERENCES

1. World Health Organization. Global Tuberculosis Report 2017 (http://www.who.int/tb/publications/global_report/en/).
2. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016;13(10):e1002152.
3. Rieder HL. Epidemiologic basis of tuberculosis control. Paris: International Union Against Tuberculosis and Lung Disease, 1999.
4. Reid A, Grant AD, White RG, et al. Accelerating progress towards tuberculosis elimination: the need for combination treatment and prevention. Int J Tuberc Lung Dis 2015;19:5-9.
5. Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. Lancet 2015;385:1799-801.
6. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization, 2015.
7. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intrathoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004;8:392-402.
8. Fox GJ, Dobler CC, Marais BJ, Denholm JT. Preventive therapy for latent tuberculosis infection — the promise and the challenges. Int J Infect Dis 2017;56:68-76.
9. Tuberculosis: Red Book online. Chicago: American Academy of Pediatrics, 2009:680-701 (https://redbook.solutions.aap.org/book.aspx?bookid=2205).
10. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int J Tuberc Lung Dis 1999;3:847-50.
11. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. Int J Tuberc Lung Dis 2008;12:1235-54.
12. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008;149:689-97.
13. Page KR, Sifakis F, Montes de Oca R, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med 2006;166:1863-70.
14. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. Am J Respir Crit Care Med 2004;170:445-9.
15. Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest 2006;130:1712-7.
16. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Am Rev Respir Dis 1992;145:36-41.
17. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365:2155-66.
18. Villarino ME, Scott NA, Weis SE, et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr 2015;169:247-55.
19. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. N Engl J Med 2018;379:440-53.
20. Menzies D, Alvarez GG, Khan K. Treatment of latent tuberculosis infection. In: Menzies D, ed. Canadian TB standards. 7th ed. Ottawa: Public Health Agency and Canadian Thoracic Society, 2013:227.
21. Targeted tuberculin testing and treat-

ment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 2000;161:S221-S247.

**22.** SAS Institute. Estimating nonlinear combinations of model parameters (http://support.sas.com/kb/58/775.html).

**23.** Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 1998;17:873-90.

**24.** Fresard I, Bridevaux PO, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicin 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. Swiss Med Wkly 2011;141:w13240.

**25.** Thee S, Seddon JA, Donald PR, et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother 2011;55:5560-7.

**26.** Kwara A, Enimil A, Gillani FS, et al. Pharmacokinetics of first-line antituberculosis drugs using WHO revised dosage in children with tuberculosis with and without HIV coinfection. J Pediatric Infect Dis Soc 2016;5:356-65.

**27.** Hiruy H, Rogers Z, Mbowane C, et al. Subtherapeutic concentrations of first-line anti-TB drugs in South African children treated according to current guidelines: the PHATISA study. J Antimicrob Chemother 2015;70:1115-23.

**28.** Cruz AT, Starke JR. Safety and completion of a 4-month course of rifampicin for latent tuberculous infection in children. Int J Tuberc Lung Dis 2014;18:1057-61.

**29.** Haley CA, Stephan S, Vossel LF, Sherfy EA, Laserson KF, Kainer MA. Successful use of rifampicin for Hispanic foreign-born patients with latent tuberculosis infection. Int J Tuberc Lung Dis 2008;12:160-7.

**30.** Spyridis NP, Spyridis PG, Gelesme A, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis 2007;45:715-22.

**31.** Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. N Engl J Med 2011;365:11-20.

**32.** Schechter M, Zajdenverg R, Falco G, et al. Weekly rifapentine/isoniazid or daily rifampin/pyrazinamide for latent tuberculosis in household contacts. Am J Respir Crit Care Med 2006;173:922-6.



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