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ORIGINAL ARTICLE

Levofloxacin Preventive Treatment in Children Exposed to MDR Tuberculosis

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ABSTRACT

BACKGROUND

Worldwide, approximately 2 million children younger than 15 years of age are infected with multidrug-resistant (MDR) *Mycobacterium tuberculosis*, with MDR tuberculosis developing in approximately 30,000 annually. Evidence from randomized, controlled trials on tuberculosis preventive treatment in persons exposed to MDR tuberculosis is lacking.

METHODS

In this community-based, multisite, double-blind, cluster-randomized, placebo-controlled trial in South Africa, we assessed the efficacy and safety of levofloxacin as preventive treatment in children with household exposure to an adult with bacteriologically confirmed MDR pulmonary tuberculosis. Children younger than 5 years of age were eligible for inclusion regardless of interferon-γ release assay result or human immunodeficiency virus (HIV) status, and children 5 to 17 years of age were eligible if they had a positive interferon-γ release assay or HIV infection. Households were randomly assigned to a trial regimen, and children in the household received levofloxacin or placebo once daily for 24 weeks. The primary efficacy end point was incident tuberculosis, which included death from tuberculosis, by week 48 after randomization. The primary safety end point was any adverse event of grade 3 or higher during the treatment period that was at least possibly related to the trial regimen.

RESULTS

Of 922 participants from 497 households, 453 were assigned to receive levofloxacin and 469 to placebo; 91.0% of the participants were younger than 5 years of age. At least 80% of the assigned doses of levofloxacin or placebo were received by 86% of the participants in each trial group. By week 48, tuberculosis had developed in 5 participants (1.1%) in the levofloxacin group and in 12 participants (2.6%) in the placebo group (hazard ratio, 0.44; 95% confidence interval [CI], 0.15 to 1.25). The results of sensitivity analyses were consistent with those of the primary analysis. Grade 3 or higher adverse events during the treatment period that were considered to be at least possibly related to the trial regimen occurred in 4 participants in the levofloxacin group and in 8 participants in the placebo group (hazard ratio, 0.52; 95% CI, 0.16 to 1.71). Grade 2 tendonitis occurred in 1 child in the levofloxacin group.

CONCLUSIONS

Although preventive treatment with levofloxacin led to a lower incidence of tuberculosis than placebo among children with household exposure to MDR tuberculosis, the difference was not significant. (Supported by Unitaid and others; TB-CHAMP ISRCTN Registry number, ISRCTN92634082.)

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Each year, multidrug-resistant (MDR) tuberculosis develops in approximately half a million people worldwide.[1] MDR tuberculosis is caused by *Mycobacterium tuberculosis* strains that are resistant to isoniazid and rifampin. Treatment of MDR tuberculosis is more challenging than treatment of drug-susceptible tuberculosis and is expensive and complex for health services and families.[2] An estimated 2 million children worldwide are currently infected with MDR *M. tuberculosis*, with MDR tuberculosis developing in approximately 30,000 annually.[3]

Current approaches to controlling the MDR tuberculosis epidemic largely focus on diagnosing the disease in symptomatic persons and initiating effective treatment. However, modeling studies suggest that contact management (investigation of close contacts of persons exposed to a patient with infectious tuberculosis) and delivery of tuberculosis preventive treatment to healthy persons at high risk for disease progression[4] are needed to reach the ambitious targets of the End TB Strategy.[5]

Good evidence is available on the efficacy and safety of tuberculosis preventive treatment for persons exposed to drug-susceptible *M. tuberculosis*, but data from randomized, controlled trials for MDR tuberculosis are lacking.[6] Observational data suggest that regimens containing fluoroquinolones are associated with a low risk of tuberculosis.[7] The World Health Organization currently conditionally recommends the consideration of tuberculosis preventive treatment for selected high-risk household contacts of patients with MDR tuberculosis on the basis of an individualized risk assessment[8] and calls for data from clinical trials owing to the low quality of evidence for this recommendation.

Young children, particularly those under 5 years of age, are an important population for tuberculosis preventive treatment owing to the higher risks of faster disease progression after exposure and severe forms of tuberculosis than among older children and adults.[9] Older children and adolescents with evidence of *M. tuberculosis* infection and those with human immunodeficiency virus (HIV) infection are also at increased risk.[10,11] Among children younger than 5 years of age with exposure to *M. tuberculosis* followed by the onset of disease, tuberculosis developed within 1 year after exposure in 80%.[10]

One of the most efficient strategies for identifying children who have recently been exposed to tuberculosis involves tracing household contacts of patients with newly diagnosed tuberculosis and offering preventive treatment to the contacts after tuberculosis has been ruled out. The TB-CHAMP (Tuberculosis Child Multidrug-Resistant Preventive Therapy) trial was designed to assess the efficacy and safety of levofloxacin as compared with placebo as tuberculosis preventive treatment in children and adolescents with household exposure to an adult with infectious MDR tuberculosis.

Methods

Trial Oversight

The funders had no role in the design or conduct of the trial or the dissemination of the data. Levofloxacin and placebo were purchased from the manufacturer (Macleods Pharmaceuticals), which did not provide funding for the trial.

The trial was approved by institutional review boards in each center and by national ethics committees in each country. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which is available with the full text of this article at NEJM.org. Additional details about trial oversight are provided in the Supplementary Appendix (available at NEJM.org).

Trial Design and Participants

The TB-CHAMP trial was a double-blind, cluster-randomized, placebo-controlled trial conducted at 5 sites in South Africa between September 26, 2017, and January 21, 2023.[12] Adult index patients with a routine diagnosis of bacteriologically confirmed pulmonary tuberculosis and multidrug resistance that was detected on the basis of genotypic or phenotypic approaches were identified and assessed for eligibility. Index patients were eligible if they provided written informed consent and had lived in the same household with at least one child younger than 5 years of age during the previous 6 months. Children younger than 5 years of age were eligible regardless of interferon-γ release assay result or HIV status if their parents or caregivers provided written informed consent and they had been exposed to an index patient during the preceding 6 months.

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Under version 3.0 of the protocol (September 2021), children 5 to 17 years of age were eligible if they had a positive interferon-γ release assay (QuantiFERON-Gold Plus, Qiagen) or HIV infection and their parents or caregivers provided written informed consent; children 7 years of age or older also needed to provide assent.

Before enrollment, children were evaluated for prevalent tuberculosis with the use of history taking, physical examination, and plain-film chest radiography. Respiratory samples for microbiologic testing for *M. tuberculosis* were obtained from children with symptoms or signs consistent with tuberculosis, abnormal findings on chest radiography, or both. Children were given broad-spectrum antibiotic agents on the basis of the clinical judgment of the treating physician and reevaluated. Only children with no evidence of tuberculosis were recruited.

Households were randomly assigned in a 1:1 ratio to the levofloxacin group or the placebo group, with stratification according to trial site. Randomization was conducted according to a computer-generated randomization list that was prepared by the trial statistician with the use of block randomization with varying block sizes and stored in a centralized Web-based database. Additional details about the trial design and participants are provided in the Supplementary Appendix.

TRIAL PROCEDURES

Children were seen at baseline; at weeks 4, 8, 12, 16, 24, 48, and 72 after randomization; and at interim visits as clinically indicated. Disease assessments were conducted during the trial visits if the child had symptoms that were potentially consistent with tuberculosis, including cough or fever for more than 2 weeks and poor weight gain or weight loss, as well as any symptoms without an alternative explanation. Children were also evaluated for adverse events related to levofloxacin or placebo with the use of National Institutes of Health Division of AIDS toxicity tables. Additional information about the trial procedures is provided in the Supplementary Appendix.

TRIAL REGIMENS

Scored 250-mg tablets of levofloxacin (given at a dose of 15 to 20 mg per kilogram of body weight; maximum dose, 750 mg) and matched placebo (primarily microcrystalline cellulose) were administered once daily for 24 weeks. Children were weighed during the trial visits, and doses were adjusted as appropriate. Levofloxacin and placebo were given by parents or caregivers, and adherence was assessed with the use of questionnaires administered during the trial visits, treatment cards, and pill counts. Treatment interruptions of up to 4 weeks overall were allowed.

END POINTS

The primary end point was incident tuberculosis (microbiologically confirmed or clinically diagnosed), which included death from tuberculosis, by week 48 after randomization. An independent end-point review committee whose members were unaware of the trial group assignments adjudicated the primary end-point events with the use of international consensus case definitions.[13] Discordant assessments were resolved by discussion.

The prespecified primary safety end point was any grade 3 or higher adverse event during the treatment period that was at least possibly related to the trial regimen. Secondary end points included incident tuberculosis by week 72, death from any cause, any adverse event of grade 3 or higher between the start of the trial regimen and up to 30 days after the last dose, serious adverse events up to 30 days after the last dose, discontinuation of the trial regimen because of adverse events, selected predefined adverse events (see the Supplementary Appendix for details), and adherence to treatment.

STATISTICAL ANALYSIS

We calculated that 1009 participants would provide the trial with 80% power to detect a 60% reduction in the incidence of tuberculosis in the levofloxacin group as compared with the placebo group by week 48, at a two-sided significance level of 5%. We based this calculation on the assumption of a cumulative tuberculosis incidence of 7% in the placebo group by week 48, the enrollment of a mean of two participants per household, a household intraclass correlation coefficient of 0.10, and a loss to follow-up of 10%.

The primary efficacy analysis was performed in the modified intention-to-treat population, which comprised all the participants who underwent randomization except those with late screening failure (defined as the identification of a

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participant's ineligibility for the trial after the participant had been assigned to a trial regimen) due to undiagnosed tuberculosis at baseline. Kaplan–Meier methods were used to assess the time from randomization to incident tuberculosis. A prespecified window (±6 weeks) was allowed for the week 48 visit. Follow-up data for participants without incident tuberculosis by the week 48 visit were censored at week 54 after randomization, on the date of last follow-up visit, or on the date of death, whichever occurred first.

We performed Cox regression analysis to estimate the hazard ratio for incident tuberculosis in the levofloxacin group as compared with the placebo group. Intrahousehold correlation was accounted for with the use of a cluster-robust variance estimator. We adjusted for trial site and age group (<5 vs. 5 to 17 years) using the inverse probability of treatment weighting method, owing to the small number of primary end-point events.[14] The analysis was conducted under the assumption of noninformative censoring, but otherwise there were no missing data in the model. We assessed for evidence of nonproportional hazards using the Grambsch–Therneau test based on scaled Schoenfeld residuals.[15]

Safety analyses included all the participants who received at least one dose of levofloxacin or placebo. Follow-up time was censored at 30 days after the last dose of levofloxacin or placebo for the analysis of relevant end points. Treatment adherence was classified according to the percentage of the assigned doses that were received (<80%, 80 to <90%, or ≥90%). Prespecified sensitivity analyses of the primary end point included an analysis with adjustment for prespecified baseline covariates (interferon-γ release assay result, HIV status, and weight-for-age z score), an analysis of incident tuberculosis events that were considered to be adjudicated at the trial site owing to the attending clinician's decision to start treatment, an analysis that included only children younger than 5 years of age, and a per-protocol analysis restricted to participants who adhered to the assigned trial regimen and did not have late screening failure.[16] Confidence intervals for the safety, secondary, and prespecified sensitivity analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

The independent data monitoring committee reviewed unblinded interim data four times during the trial, including findings from formal interim efficacy analysis performed after 500 children had been followed for at least 24 weeks (October 2021). The Haybittle–Peto criterion for efficacy ($P<0.001$) was used to guide recommendations to stop or modify the trial. Analyses were performed with Stata, version 16.0 or later (StataCorp).

RESULTS

PARTICIPANTS

We identified 5063 index patients with MDR tuberculosis, of whom 631 were screened for eligibility (Fig. 1). A total of 1120 children who were household contacts of eligible index patients were screened for eligibility, and 922 children (household contacts of 497 index patients from 497 households) were enrolled between September 27, 2017, and July 29, 2022. Baseline characteristics of the 497 index patients who were household contacts of the participants are provided in Table S5.1 in the Supplementary Appendix.

A total of 453 participants were from households assigned to the levofloxacin group, and 469 participants were from households assigned to the placebo group. Late screening failure occurred in 29 participants, including 6 participants with undiagnosed tuberculosis at baseline (Table S4.4). Thus, 916 participants were included in the modified intention-to-treat population and assessed in the primary efficacy analysis.

Baseline characteristics of the participants from randomized households were reasonably similar in the trial groups (Table 1). The median age of the participants was 2.8 years (interquartile range, 1.3 to 4.2 years), 91.0% were younger than 5 years of age, and 93.8% had received bacille Calmette–Guérin vaccine. Overall, 49.2% of the participants were boys, 2.1% had HIV infection, and 33.9% had been exposed to HIV but were not infected. Of the 815 children younger than 5 years of age with available test results, 163 (20.0%) had a positive interferon-γ release assay.

FOLLOW-UP

Retention was similar in the trial groups, with 81% of the participants followed for at least 48 weeks and 73% followed to week 72 (Table S6.1); 11% of the participants left the trial before their last scheduled visit (Table S6.3). One participant

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did not start the trial regimen because of early withdrawal.

PRIMARY END POINT

Incident tuberculosis as adjudicated by the end-point review committee occurred in 21 of 916 participants (2.3%) during the follow-up period; 10 of the participants had microbiologically confirmed tuberculosis. In 2 participants, incident tuberculosis occurred after the week 72 visit.

Incident tuberculosis by week 48 (primary end point) occurred in 5 of 451 participants (1.1%) in the levofloxacin group and in 12 of 465 participants (2.6%) in the placebo group (Table S8.1), corresponding to 1.2 cases per 100 person-years (95% confidence interval [CI], 0.5 to 2.9) and 2.9 cases per 100 person-years (95% CI, 1.6 to 5.2), respectively (hazard ratio, 0.44; 95% CI, 0.15 to 1.25; P=0.12). Incident tuberculosis occurred during the 24-week treatment period in 1 participant in the levofloxacin group and in 10 participants in the placebo group (P=0.11 by the test for nonproportional hazards) (Fig. 2).

SECONDARY END POINTS

By the week 72 visit, incident tuberculosis had occurred in 6 participants (1.3%) in the levofloxacin group and in 13 participants (2.8%) in the placebo group (hazard ratio, 0.49; 95% CI, 0.18 to 1.30) (Table S8.6). Safety analyses included 921 participants who started the trial regimen. Four of 452 participants (0.9%) in the levofloxacin group and 8 of 469 participants (1.7%) in the placebo group had a grade 3 or higher adverse event during the treatment period that was assessed by the site investigator to be at least possibly related to the trial regimen (hazard ratio, 0.52; 95% CI, 0.16 to 1.71; P=0.29) (Table 2); 14 participants (3.1%) and 24 participants (5.1%), respectively, had a grade 3 or higher adverse event that occurred up to 30 days after the last dose of levofloxacin or placebo (hazard ratio, 0.64; 95% CI, 0.32 to 1.28; P=0.21).

Two deaths occurred during follow-up. One infant in the levofloxacin group who was 12 months of age died from cardiac arrest caused by a congenital heart defect after week 39, and 1 infant in the placebo group who was 11 months of age died from viral pneumonia after week 11. Neither death was considered by the site investigator to be related to the trial regimen or tuberculosis.

One participant in the levofloxacin group had grade 2 tendonitis, which resolved 21 days after stopping treatment. Seventy-five participants (16.6%) in the levofloxacin group and 80 participants (17.1%) in the placebo group permanently discontinued the trial regimen early for any reason (Table S7.2). Six participants (1.3%) in the levofloxacin group and 1 participant (0.2%) in the placebo group discontinued the trial regimen because of adverse events (hazard ratio, 5.00; 95% CI, 0.61 to 41.32; P=0.14). In each trial group, 86% of the participants received at least 80% of the assigned doses of levofloxacin or placebo (Table S7.3). Poor adherence to the levofloxacin regimen was not associated with an increased incidence of tuberculosis during follow-up.

SENSITIVITY ANALYSES

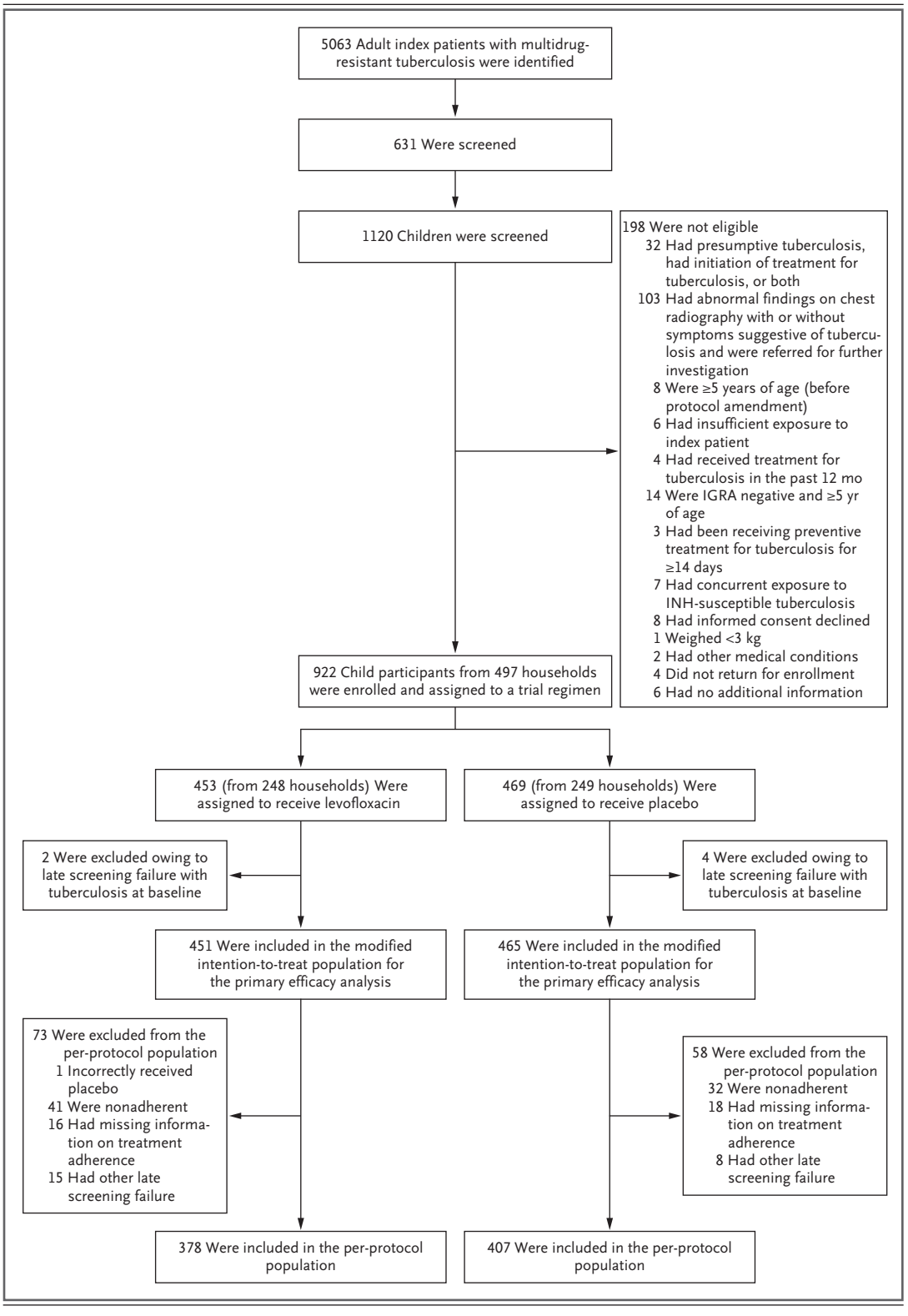
Results of prespecified sensitivity analyses were generally consistent with those of the primary analysis, although the analysis based on the adjudication of incident tuberculosis at the trial site showed a slightly stronger treatment effect than in the primary analysis (Fig. 3). We found no evidence of heterogeneity of treatment effect in prespecified exploratory subgroup analyses, including analyses according to sex, interferon-γ release assay result, and HIV status (Table S8.5), but the numbers of events were small.

DISCUSSION

In this pediatric trial of preventive treatment for MDR tuberculosis, we recruited nearly 1000 children with household exposure to MDR tuberculosis. Incident tuberculosis as adjudicated by the independent end-point review committee occurred in 17 children by week 48. Although tuberculosis occurred in a smaller percentage of children in the levofloxacin group than in the placebo group, the difference was not significant. We have shown that levofloxacin treatment taken once daily for 6 months did not lead to any safety concerns in the children. Adherence to the trial regimen was 86% in the two groups, despite the use of an adult formulation.

We anticipated that the effect size of levofloxacin would be similar to that in the trial, but we had assumed that the risk of incident tuberculosis in the placebo group would be twice that in the trial, owing to results of observational studies of drug-susceptible and drug-resistant

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Figure 1 (facing page). Screening and Trial-Group Assignment.

Reasons for screening ineligibility among the index patients included inability of the trial team to establish contact, death or relocation, age of less than 18 years, presence of rifampicin-monoresistant tuberculosis, receipt of tuberculosis treatment for more than 6 months, presence of nonpulmonary tuberculosis, and no children younger than 5 years of age reported to be living in the household during the past 6 months. In September 2021, the protocol was amended to extend eligibility to children 5 to 17 years of age if they had a positive interferon-γ release assay (IGRA) or human immunodeficiency virus infection and their parents or caregivers provided written informed consent. Cluster randomization was performed at the household level. Late screening failure was defined as the identification of a participant's ineligibility for the trial after the participant had been assigned to a trial regimen. INH denotes isoniazid.

tuberculosis.[16-19] The lower-than-expected incidence of tuberculosis in the placebo group has several potential explanations. First, 20% of the children who were younger than 5 years of age had a positive interferon-γ release assay, a percentage considerably lower than in previous studies in South Africa, in which 40 to 50% of children with household exposure had a positive result.[17] Second, given the wide rollout of the Xpert MTB/RIF assay in South Africa, it is possible that persons with MDR tuberculosis now begin appropriate therapy sooner after disease onset, leading to a decrease in the duration of household exposure and the risk of *M. tuberculosis* transmission. Third, with the widespread rollout of more effective treatments for MDR tuberculosis (particularly bedaquiline and linezolid) since 2018, it is possible that patients with MDR tuberculosis who receive these agents become noninfectious more rapidly. Fourth, to exclude children with prevalent tuberculosis from the trial, we performed rigorous assessments at baseline, including thorough review of medical history, physical examination, and chest radiography, with microbiologic testing performed in those with any symptoms or signs of tuberculosis or abnormal findings on chest radiography. Children with late screening failure owing to the presence of tuberculosis at baseline may not have been detected with less comprehensive screening and would otherwise have been considered to have incident disease when symptoms and signs became more pronounced later during the trial.

The timing of incident tuberculosis differed in the trial groups. Most cases in the placebo group occurred during the first 12 weeks after randomization. This result suggests that although many of the children with incident tuberculosis did not have clinically overt disease at baseline, they had some form of subclinical disease that rapidly progressed to symptomatic disease. In the levofloxacin group, incident tuberculosis occurred in 1 child during preventive treatment, whereas most cases occurred around 1 year after randomization. Levofloxacin may therefore have treated subclinical disease and prevented disease progression, but it appeared to have had minimal effect after the treatment period. This finding has implications for household-contact management and provision of tuberculosis preventive treatment early after the diagnosis of tuberculosis in the index patient. The similar incidence of tuberculosis in both groups after week 48 could have been due to subsequent reinfection in this high-burden setting.

A systematic review from 2017 showed that the incidence of MDR tuberculosis among exposed persons who received preventive treatment was 90% lower than that among those who did not receive preventive treatment.[7] Several studies and trials assessing preventive treatment in household contacts of persons with tuberculosis have since been initiated. An observational study in Pakistan showed that the use of a fluoroquinolone together with either ethambutol or ethionamide as preventive therapy resulted in a decrease of 65% in the risk of drug-resistant tuberculosis among 172 study participants as compared with historical controls.[18] The VQUIN MDR trial in Vietnam compared the efficacy of levofloxacin with that of placebo for the prevention of tuberculosis in 2041 household contacts, mainly adults; results of the trial are reported in this issue of the *Journal*.[20] The Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients trial is an open-label trial comparing delamanid with isoniazid for the prevention of tuberculosis in adults and children with household exposure to MDR tuberculosis, with recruitment ongoing at multiple sites worldwide.[19]

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Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Levofloxacin (N = 453)	Placebo (N = 469)	Total (N = 922)
Male sex — no. (%)	213 (47.0)	241 (51.4)	454 (49.2)
Age			
Median (IQR) — yr	3.0 (1.4 to 4.3)	2.6 (1.3 to 4.1)	2.8 (1.3 to 4.2)
Range — yr	0.1 to 17.9	0.1 to 17.4	0.1 to 17.9
Distribution — no. (%)			
<1 yr	85 (18.8)	83 (17.7)	168 (18.2)
1 to <3 yr	140 (30.9)	175 (37.3)	315 (34.2)
3 to <5 yr	180 (39.7)	176 (37.5)	356 (38.6)
5 to <10 yr	18 (4.0)	17 (3.6)	35 (3.8)
10 to <15 yr	20 (4.4)	13 (2.8)	33 (3.6)
15 to <18 yr	10 (2.2)	5 (1.1)	15 (1.6)
Race or ethnic group — no. (%)†			
Black	362 (79.9)	381 (81.2)	743 (80.6)
South African mixed	81 (17.9)	78 (16.6)	159 (17.2)
Mixed race	8 (1.8)	8 (1.7)	16 (1.7)
Other	2 (0.4)	2 (0.4)	4 (0.4)
IGRA result — no. (%)‡			
Negative	297 (65.6)	335 (71.4)	632 (68.5)
Positive	134 (29.6)	108 (23.0)	242 (26.2)
Indeterminate	12 (2.6)	12 (2.6)	24 (2.6)
Missing data	10 (2.2)	14 (3.0)	24 (2.6)
HIV status — no. (%)			
Positive	10 (2.2)	9 (1.9)	19 (2.1)
HIV-exposed, uninfected	153 (33.8)	160 (34.1)	313 (33.9)
HIV-unexposed	288 (63.6)	298 (63.5)	586 (63.6)
Missing data	2 (0.4)	2 (0.4)	4 (0.4)
Previous BCG vaccination — no. (%)§			
Yes	423 (93.4)	442 (94.2)	865 (93.8)
No	28 (6.2)	25 (5.3)	53 (5.7)
Missing data	2 (0.4)	2 (0.4)	4 (0.4)
Previous tuberculosis treatment — no. (%)			
Yes	10 (2.2)	8 (1.7)	18 (2.0)
No	443 (97.8)	461 (98.3)	904 (98.0)
Current tuberculosis preventive treatment — no. (%)			
Yes	9 (2.0)	6 (1.3)	15 (1.6)
No	444 (98.0)	463 (98.7)	907 (98.4)
Median weight-for-age z score (IQR)¶	−0.4 (−1.2 to 0.3)	−0.4 (−1.2 to 0.4)	−0.4 (−1.2 to 0.3)
Median height-for-age z score (IQR)‖	−0.9 (−1.6 to −0.2)	−0.9 (−1.8 to −0.2)	−0.9 (−1.7 to −0.2)
Trial site — no. (%)			
Desmond Tutu TB Centre	222 (49.0)	230 (49.0)	452 (49.0)

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Table 1. (Continued.)

Characteristic	Levofloxacin (N=453)	Placebo (N=469)	Total (N=922)
Shandukani	92 (20.3)	80 (17.1)	172 (18.7)
Matlosana	117 (25.8)	142 (30.3)	259 (28.1)
Isanga Lethembo	3 (0.7)	4 (0.9)	7 (0.8)
TB and HIV Investigative Network	19 (4.2)	13 (2.8)	32 (3.5)

* Percentages may not sum to 100 because of rounding. IQR denotes interquartile range.
† Race or ethnic group was reported by the parents or caregivers.
‡ *Mycobacterium tuberculosis* infection status at baseline was assessed with the use of the QuantiFERON-Gold Plus (Qiagen) interferon-γ release assay (IGRA).
§ Previous bacille Calmette–Guérin (BCG) vaccination was verified on the basis of a review of medical records, the presence of a vaccine scar, or both.
¶ Weight-for-age z scores for participants 10 years of age or younger were calculated with the use of the World Health Organization (WHO) reference standard. Scores were calculated with the use of the U.K. reference standard for participants older than 10 years of age, because WHO weight-for-age growth charts are only available for children 10 years of age and younger.
‖ Height-for-age z scores were calculated with the use of the WHO reference standard.

An important consideration when assessing the efficacy of tuberculosis preventive treatment is the contribution of the preventive treatment itself as compared with that of the household-contact management strategy. In our trial, tuberculosis preventive treatment was compared with no treatment, but in both trial groups, the index patients with MDR tuberculosis were identified, the household contacts were rigorously screened for prevalent disease, and the participating child contacts were followed regularly. In most areas with a high burden of tuberculosis, evaluation and treatment of close contacts of patients with MDR tuberculosis in routine care is probably less complete. In a modeling study of the effect of household-contact management and tuberculosis preventive treatment in children exposed to MDR tuberculosis, screening for prevalent disease was responsible for 65% of the total number of deaths prevented.[21] Moreover, modeling work indicates that the long-term population-level effects of preventive treatment for MDR tuberculosis, including the reduction in onward transmission owing to the prevention of cases in adults, could be greater than suggested by trial end points alone.[22] In addition, fluoroquinolones may have substantial negative effects on gram-positive and gram-negative bacteria, potentially leading to the development of antimicrobial resistance and alterations in the gut microbiome[23]; these possible effects are being evaluated. Safety results of our trial were reassuring, with no concerning patterns of grade 3 or higher adverse events identified. One episode of tendonitis (grade 2 in severity) was reported.

Our trial has limitations. First, the incidence of tuberculosis in the placebo group was lower than anticipated. Second, findings of the trial

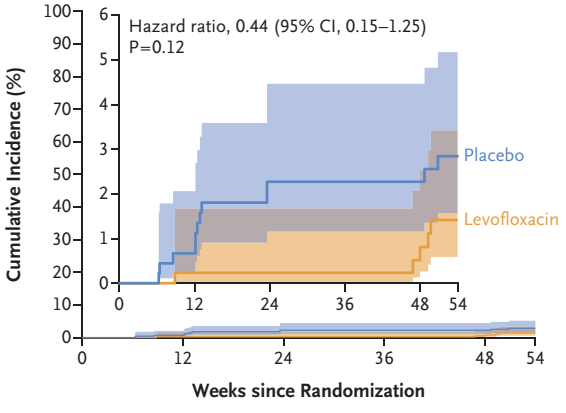


Figure 2. Incident Tuberculosis by Week 48 According to Trial Group.
Shown are Kaplan–Meier estimates of the cumulative incidence of tuberculosis. A prespecified window (±6 weeks) was allowed for scheduled visits. Therefore, follow-up time in the analysis of incident tuberculosis, which included death from tuberculosis, by week 48 after randomization (primary end point) was censored at 54 weeks. Shaded regions indicate confidence bands, which were adjusted for household clustering.

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Table 2. Safety End Points.*

End Point	Levofloxacin (N=452)	Placebo (N=469)	Hazard Ratio (95% CI)	P Value
	no. of participants (%)			
Grade ≥3 adverse event during treatment period at least possibly related to trial regimen	4 (0.9)	8 (1.7)	0.52 (0.16–1.71)	0.29
Any grade ≥3 adverse event†	14 (3.1)	24 (5.1)	0.64 (0.32–1.28)	0.21
Serious adverse event	9 (2.0)	8 (1.7)	1.22 (0.45–3.34)	0.69
Adverse event that led to permanent discontinuation of trial regimen	6 (1.3)	1 (0.2)	5.00 (0.61–41.32)	0.14
Prespecified adverse events‡				
Arthritis, arthralgia, or tendinopathy of any grade, alone or in combination	6 (1.3)	4 (0.9)	1.32 (0.35–4.98)	0.69
Central nervous system disorders	7 (1.5)	11 (2.3)	0.59 (0.21–1.62)	0.30
Severe rash or cutaneous reaction	1 (0.2)	0	—	—

* Data are for participants who received at least one dose of levofloxacin or placebo. The confidence intervals were not adjusted for multiplicity and should not be used to infer definitive treatment effects. Additional details about the reported adverse events for each safety end point are provided in Tables S9.9 through S9.11.
† Data are for events that occurred up to 30 days after receipt of the last dose of levofloxacin or placebo.
‡ Central nervous system disorders included altered mood or behavior including hyperactivity, insomnia, vivid dreams, changes in vision, and headache. Drug-related fever and peripheral neuropathy were also prespecified adverse events, but neither event occurred in the trial groups.

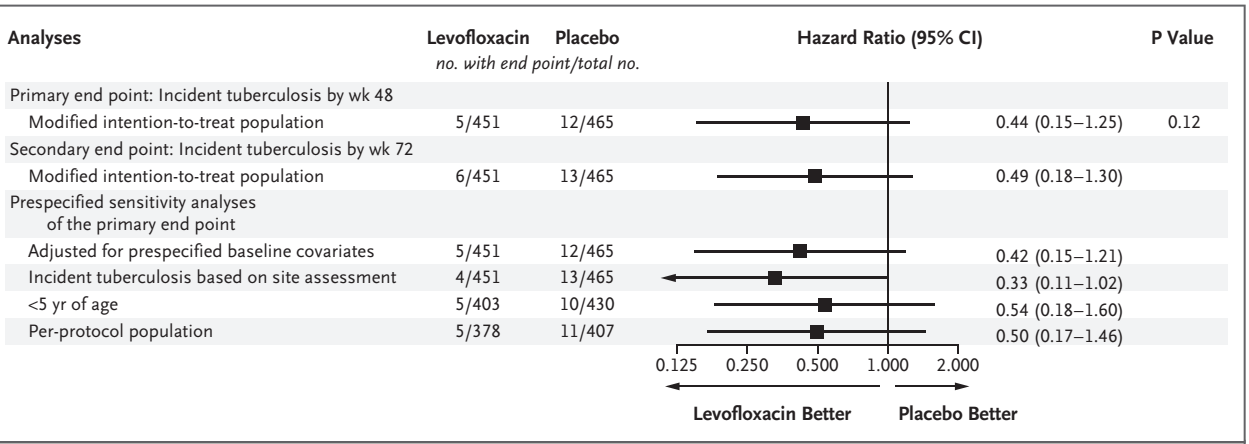


Figure 3. Primary, Secondary, and Prespecified Sensitivity Analyses of Incident Tuberculosis by Week 48.

A prespecified window (±6 weeks) was allowed for the week 48 visit. Therefore, follow-up time was censored at 54 weeks. Death from any cause was also a secondary end point; 1 participant in each trial group died. The sensitivity analyses of the primary end point included an analysis with adjustment for prespecified baseline covariates (interferon-γ release assay result, human immunodeficiency virus status, and weight-for-age z score), an analysis of incident tuberculosis events that were considered to be adjudicated at the trial site owing to the attending clinician's decision to start treatment, an analysis that included only children younger than 5 years of age, and a per-protocol analysis restricted to participants who adhered to the assigned trial regimen and did not have late screening failure. The confidence intervals for the secondary end-point analyses and the prespecified sensitivity analyses were not adjusted for multiplicity and should not be used to infer definitive treatment effects.

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may have limited generalizability. Although we recruited index patients and children from sites in South Africa with diverse populations and mycobacterial strains, more than 90% of the participating children were younger than 5 years of age, with enrollment expanded only later during the trial to selected older children. Care should be taken when extrapolating the findings of our trial to other settings and to older children and adolescents, who may have more nonhousehold exposure to tuberculosis than younger children. Fourth, we could not collect *M. tuberculosis* strains from all the index patients, and we were thus unable to assess second-line drug resistance or resistance mechanisms. In South Africa, 13% of MDR *M. tuberculosis* isolates obtained between 2012 and 2014 were resistant to fluoroquinolones, so we might expect levofloxacin preventive treatment to be ineffective in contacts of a similar percentage of index patients.[24]

In this trial involving children with household exposure to an adult with MDR tuberculosis, tuberculosis occurred in a smaller percentage of children in the levofloxacin group than in the placebo group. However, this difference was not significant. These results need to be integrated with results from other trials in other populations and settings to inform global policy and practice.

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APPENDIX

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