ORIGINAL ARTICLE

Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis in Vietnam

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ABSTRACT

BACKGROUND

Prevention of drug-resistant tuberculosis is a global health priority. However, trials evaluating the effectiveness of treating *Mycobacterium tuberculosis* infection among contacts of persons with drug-resistant tuberculosis are lacking.

METHODS

We conducted a double-blind, randomized, controlled trial comparing 6 months of daily levofloxacin (weight-based doses) with placebo to treat *M. tuberculosis* infection. The trial population comprised household contacts of persons with bacteriologically confirmed rifampicin-resistant or multidrug-resistant (MDR) tuberculosis in Vietnam. Contacts of any age with a positive tuberculin skin test or immunologic impairment were eligible. The primary end point was bacteriologically confirmed tuberculosis within 30 months. Secondary end points included grade 3 or 4 adverse events, death from any cause, and acquired drug resistance.

RESULTS

Of 3948 persons screened for eligibility, 61 (1.5%) had coprevalent tuberculosis (defined as active tuberculosis disease diagnosed before randomization) and 2041 underwent randomization. Of these 2041 participants, 1995 (97.7%) completed 30 months of follow-up, had a primary end-point event, or died. Confirmed tuberculosis occurred in 6 participants (0.6%) in the levofloxacin group and 11 (1.1%) in the placebo group (incidence rate ratio, 0.55; 95% confidence interval [CI], 0.19 to 1.62); this difference was not significant. There was little difference in grade 3 or 4 adverse events between the two groups (risk difference, 1.0 percentage point; 95% CI, −0.3 to 2.4). Adverse events of any grade were reported in 306 participants (31.9%) taking levofloxacin and 125 (13.0%) taking placebo (risk difference, 18.9 percentage points; 95% CI, 14.2 to 23.6). No acquired fluoroquinolone resistance was observed.

CONCLUSIONS

Although the incidence of tuberculosis was lower in the levofloxacin group than in the placebo group at 30 months, the difference was not significant. (Funded by the National Health and Medical Research Council of Australia; VQUIN MDR Australia New Zealand Clinical Trials Registry number, ACTRN12616000215426.)

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Rifampicin-resistant or multidrug-resistant (MDR) tuberculosis affects 400,000 persons each year worldwide.[1] Treatment outcomes for persons with rifampicin-resistant or MDR tuberculosis are worse than those for persons with drug-susceptible forms of tuberculosis,[2,3] with just 63% of persons treated successfully[1] and a high proportion affected by economic costs[4] and ongoing illness.[5] An estimated 19 million persons are presumed to have MDR *Mycobacterium tuberculosis* infection, a state of persistent immune response to *M. tuberculosis* that confers a higher risk of tuberculosis disease.[6]

The prevention of rifampicin-resistant and MDR tuberculosis is a major clinical, public health priority.[7] Fluoroquinolones are a component of standard therapy for rifampicin-resistant or MDR tuberculosis[8,9] and hold promise for the treatment of *M. tuberculosis* infection among contacts of persons with drug-resistant tuberculosis. Observational studies suggest that the use of levofloxacin may reduce the incidence of tuberculosis among close contacts of persons with rifampicin-resistant or MDR tuberculosis.[10,11] However, the effectiveness and side-effect profile of levofloxacin for preventive treatment of rifampicin-resistant or MDR tuberculosis in adults and children have not been established.[12] The VQUIN MDR trial aimed to determine the effectiveness of a 6-month regimen of levofloxacin for the prevention of active tuberculosis among household contacts of persons with confirmed rifampicin-resistant or MDR tuberculosis.

METHODS

TRIAL DESIGN AND OBJECTIVES

We conducted a double-blind, parallel-group, randomized, controlled trial comparing a 6-month regimen of daily levofloxacin with placebo for the treatment of *M. tuberculosis* infection. The primary objective of this trial was to determine the efficacy of levofloxacin in preventing the development of bacteriologically confirmed tuberculosis. Detailed trial methods have been reported previously[13] and are described in the protocol and the statistical analysis plan, which are available with the full text of this article at NEJM.org.

The trial was approved by the Human Research Ethics Committee of the University of Sydney and by the institutional review board at the Ministry of Health Vietnam. All the authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

INTERVENTION

The intervention comprised 180 days of participant-administered oral levofloxacin or an indistinguishable placebo, composed predominantly of cellulose, once per day. Tablets were dispensed every 4 weeks, and a pill count was performed at each visit. The daily dose range was 10 to 15 mg per kilogram of body weight for adults and 15 to 20 mg per kilogram for children, with a maximum dose of 750 mg (Table S1 in the Supplementary Appendix, available at NEJM.org).

A Quick Take is available at NEJM.org

PATIENT ELIGIBILITY AND RANDOMIZATION

The trial was conducted in Vietnam, a high-incidence country for tuberculosis and rifampicin-resistant or MDR tuberculosis.[14] Participants were recruited in 10 provinces, including urban and rural settings. Trial sites delivered standard treatment in accordance with National Tuberculosis Program guidelines.

The trial population comprised household contacts of all ages living with persons who had received a diagnosis of bacteriologically confirmed rifampicin-resistant or MDR tuberculosis and who had commenced treatment within the previous 3 months. Contacts were eligible for enrollment if they had evidence of *M. tuberculosis* infection without the presence of tuberculosis disease. *M. tuberculosis* infection was defined by an induration of 10 mm or more on a tuberculin skin test at the first reading or conversion on a tuberculin skin test. Persons living with human immunodeficiency virus (HIV) or who had a body-mass index (the weight in kilograms divided by the square of the height in meters) of less than 16 were eligible for randomization regardless of the extent of induration on a tuberculin skin test. Pregnant women were eligible to undergo randomization post partum.

During the initial recruitment period, persons 15 years of age or older underwent randomization starting in March 2016; children younger than 15 years of age underwent randomization starting in October 2018, after approval by the institutional review board. Among the exclusion criteria were allergy to fluoroquinolones, use of medications reported to increase the corrected QT interval, previous rifampicin-resistant or MDR tuberculosis, fluoroquinolone use in the preceding

month, liver failure, an estimated glomerular filtration rate of less than 20 ml per minute, or tuberculosis disease.

Before randomization, all the contacts completed a symptom screening, underwent radiography of the chest, and were asked to provide a sputum sample for polymerase-chain-reaction testing with the use of the Xpert MTB/RIF assay. If abnormalities were identified, three additional sputum samples were requested for culture and one for Xpert MTB/RIF testing to rule out coprevalent tuberculosis (defined as active tuberculosis disease diagnosed before randomization). The randomization process is described in the Supplementary Methods section in the Supplementary Appendix.

During the 6-month treatment period, participants attended the clinic monthly to support adherence and assess for toxic effects, according to the Common Terminology Criteria for Adverse Events, version 4.0.[15] Patients were also telephoned between scheduled visits, every 2 weeks. After the treatment period, participants attended follow-up visits to assess for incident tuberculosis with a symptom screening and chest radiography at 6, 12, 18, 24, and 30 months.

OUTCOME ASCERTAINMENT

Outcomes were reported at the level of the individual participant. The primary end point was bacteriologically confirmed tuberculosis, defined as a positive identification of *M. tuberculosis* by culture or a molecular World Health Organization (WHO)–recommended rapid diagnostic test in a close contact with clinical or radiologic evidence of tuberculosis disease. Secondary end points included all forms of tuberculosis (bacteriologically confirmed or clinically probable), completion of the trial regimen, discontinuation of the trial regimen because of an adverse event, grade 3 or 4 adverse events, death, or acquired resistance to fluoroquinolones in comparison to the index isolate with the use of whole-genome sequencing (Supplementary Methods). Completion of the trial regimen was defined as taking at least 80% of doses of levofloxacin or placebo within 270 days, in keeping with trials of the prevention of drug-susceptible tuberculosis.[16]

STATISTICAL ANALYSIS

The risk of incident tuberculosis in the placebo group was expected to be 3% over the follow-up period.[17,18] We expected that levofloxacin would reduce incident tuberculosis by 70%, on the basis of mid-range estimates of isoniazid efficacy for *M. tuberculosis* infection in drug-susceptible tuberculosis.[19] The sample size was increased to allow for 17% fluoroquinolone resistance among persons with rifampicin-resistant or MDR tuberculosis in Vietnam, a 10% dropout rate,[20] and a design effect of 1.04 at the district level and 1.07 at the level of the household.[21] To determine superiority, we calculated that the required sample size was 1003 per group, on the basis of a two-sided alpha level of 0.05 and a power of 80%, allowing for clustering at district and household levels.

Statistical analyses were conducted by the trial statistician in consultation with the investigators, according to a prespecified statistical analysis plan. Trial-group assignments were blinded until analyses were complete. The primary analysis involved the intention-to-treat population, which included all the participants who underwent randomization. Intention-to-treat analyses were also performed on the secondary (composite) end points of bacteriologically confirmed or clinically probable tuberculosis and death from any cause. The per-protocol population included all randomly assigned participants who completed at least 80% of their assigned trial regimen.

Incidence rate ratios and 95% confidence intervals were estimated with the use of a marginal Poisson regression model fitted with generalized estimating equations. To account for follow-up time (duration of exposure from randomization to the point of diagnosis with tuberculosis, loss to follow-up or withdrawal from the trial, death, or 30 months, whichever was earliest), log of follow-up time was included as an offset variable in the model. To adjust for correlation of outcomes between persons clustered according to household, robust standard errors with an exchangeable correlation structure were used. Risk differences were calculated with the use of generalized-estimating-equation models with a binomial distribution, identity link, clustering according to household, and an independent correlation structure. Data were assumed to be missing at random. We report point estimates and 95% confidence intervals for trial end points, because we did not prespecify a plan to account for multiplicity. The widths of the intervals have not been adjusted for multiplicity. The interpretation of these confidence

intervals should avoid the language of definitive conclusions used to report significant findings as assessed by formal hypothesis testing.

RESULTS

PARTICIPANTS

We assessed 4104 household contacts between March 2016 and August 2019; 61 of 3948 persons (1.5%) who were screened for eligibility were diagnosed with confirmed tuberculosis before randomization and were deemed to have coprevalent tuberculosis (Fig. 1). Among eligible contacts, 2041 were randomly assigned to receive either levofloxacin or placebo and were included in the intention-to-treat population. Participants were 2 to 87 years of age. The demographic and clinical characteristics of the participants are presented in Table 1 and Tables S2 and S3. Positivity or conversion (as defined) on a tuberculin skin test was documented in 2036 of 2041 participants (99.8%) who underwent randomization. The median number of contacts

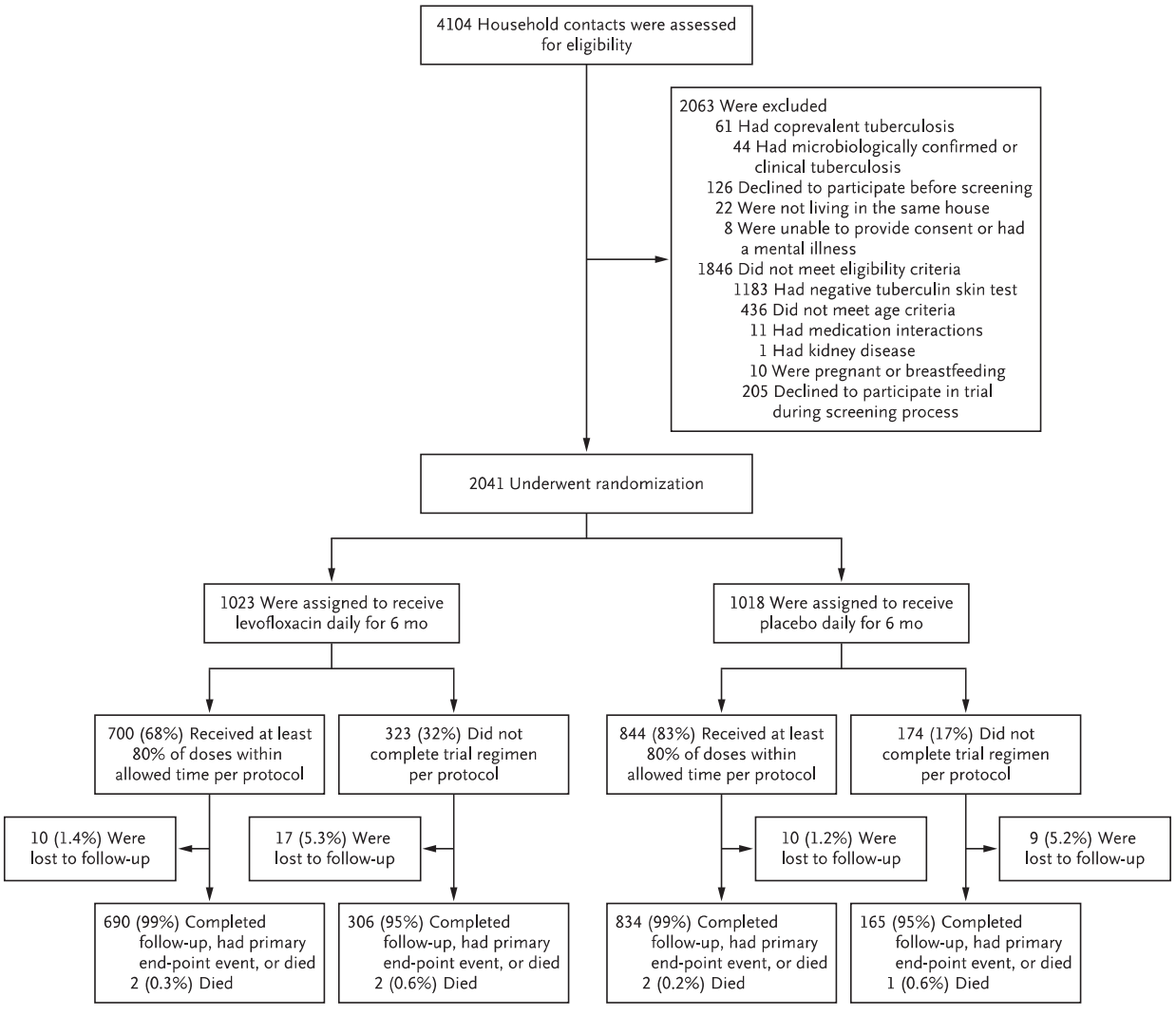

Figure 1. Participant Recruitment and Follow-up.

Shown is the screening and randomization process for household contacts included in the trial. A total of 46 persons (2.3%) did not complete follow-up to 30 months or reach a trial end point. Coprevalent tuberculosis was defined as active tuberculosis disease diagnosed before randomization. Participants younger than 15 years of age were enrolled only in the final 6 months of the trial owing to local institutional review board requirements.

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	Levofloxacin (N=1023)	Placebo (N=1018)	Total (N=2041)
Age			
Median (IQR)	41 (28–52)	39 (28–53)	40 (28–52)
Distribution — no. (%)			
<15 yr	27 (2.6)	33 (3.2)	60 (2.9)
15–29 yr	262 (25.6)	253 (24.9)	515 (25.2)
30–44 yr	290 (28.3)	324 (31.8)	614 (30.1)
45–59 yr	329 (32.2)	277 (27.2)	606 (29.7)
≥60 yr	115 (11.2)	131 (12.9)	246 (12.1)
Male sex — no. (%)	374 (36.6)	361 (35.5)	735 (36.0)
Coexisting conditions — no. (%)			
Diabetes	38 (3.7)	38 (3.7)	76 (3.7)
Treated with insulin	36 (3.5)	35 (3.4)	71 (3.5)
Not treated with insulin	2 (0.2)	3 (0.3)	5 (0.2)
Chronic kidney disease	1 (0.1)	1 (0.1)	2 (0.1)
Hepatitis B virus infection	12 (1.2)	22 (2.2)	34 (1.7)
Hepatitis C virus infection	1 (0.1)	1 (0.1)	2 (0.1)
HIV positivity	2 (0.2)	6 (0.6)	8 (0.4)
Chronic lung disease	12 (1.2)	8 (0.8)	20 (1.0)
History of tuberculosis — no. (%)			
Yes	56 (5.5)	50 (4.9)	106 (5.2)
No	967 (94.5)	968 (95.1)	1935 (94.8)
History of drug-resistant tuberculosis — no. (%)			
Yes	1 (0.1)	1 (0.1)	2 (0.1)
No	1022 (99.9)	1017 (99.9)	2039 (99.9)
Smoking status			
Ever smoked — no. (%)	227 (22.2)	225 (22.1)	452 (22.1)
Current smoker, among participants who had ever smoked — no./total no. (%)	175/227 (77.1)	183/225 (81.3)	358/452 (79.2)
Median pack-yr of smoking, among participants who had ever smoked (IQR)	9.6 (3.5–20.0)	9.5 (3.4–21.0)	9.5 (3.4–20.5)
Median body-mass index (IQR)	21.8 (19.6–24.0)	21.7 (19.8–23.8)	21.8 (19.7–23.9)
TST status†			
TST-positive	920 (89.9)	907 (89.1)	1827 (89.5)
TST conversion	101 (9.9)	108 (10.6)	209 (10.2)
TST-negative and HIV-positive	1 (0.1)	1 (0.1)	2 (0.1)
TST-negative and malnourished‡	1 (0.1)	2 (0.2)	3 (0.1)

* Additional baseline characteristics are reported in Table S2. The intention-to-treat population included all the participants who underwent randomization. Percentages may not total 100 because of rounding. HIV denotes human immunodeficiency virus, and IQR interquartile range.

† Tuberculin skin test (TST) positivity was defined as an induration of 10 mm or more at the first reading. Conversion was defined either as an induration of less than 5 mm at the first reading and an induration of 10 mm or more at the second reading or as an induration of 5 to 9 mm at the first reading and an increase of 6 mm or more at the second reading.

‡ Malnourishment was defined as a body-mass index of less than 16.

per household was 1 (interquartile range, 1 to 2; maximum, 13). A total of 1995 participants (97.7% of the intention-to-treat population) completed 30 months of follow-up, had a primary endpoint event, or died. No participants had missing data for any baseline characteristics.

The percentage of participants completing the 6-month trial regimen was lower in the levofloxacin group (68.4%) than in the placebo group (82.9%) (difference, –14.5 percentage points; 95% confidence interval [CI], –19.4 to –9.6) (Table S4). Discontinuation of the trial regimen due to a low-grade adverse event occurred more often in the levofloxacin group. Participants taking levofloxacin were more likely than those taking placebo to decide to discontinue the trial regimen (23.2% vs. 9.1%). Age, sex, education level, and coexisting conditions were similar in participants who completed follow-up and those who did not (Table S5). These characteristics did not differ substantially between participants who completed the trial regimen and those who did not (Table S6).

INCIDENCE OF TUBERCULOSIS DISEASE

During the 30-month follow-up period, bacteriologically confirmed tuberculosis occurred in 6 participants (0.6%) in the levofloxacin group and 11 (1.1%) in the placebo group (Table 2 and Fig. 2). In addition, clinically diagnosed tuberculosis occurred in 1 participant in the levofloxacin group and 2 in the placebo group (Table 2). In the intention-to-treat population, the incidence rate ratio for confirmed tuberculosis was 0.55 (95% CI, 0.19 to 1.62); this difference was not significant. In the per-protocol population, the incidence rate ratio was 0.60 (95% CI, 0.15 to 2.40). The characteristics of the 40 participants lost to follow-up are shown in Table S7. In both trial groups, the incidence of tuberculosis disease was higher among participants not completing the trial regimen than among those completing the trial regimen. The characteristics of the participants in whom incident tuberculosis developed are shown in Table S8. Treatment outcomes for participants in whom incident tuberculosis developed are shown in Table S9. The median duration of follow-up was 30 months (interquartile range, 30 to 30) in both trial groups.

SAFETY AND MORTALITY

One or more adverse events of any grade was reported in 306 participants (31.9%) taking levofloxacin and 125 (13.0%) taking placebo (risk difference, 18.9 percentage points; 95% CI, 14.2 to 23.6; P<0.001) (Table 3).[15,22] There was little difference in the incidence of severe (grade 3 or 4) adverse events between the two groups (risk difference, 1.0 percentage point; 95% CI, –0.3 to 2.4). Adverse events resulted in discontinuation of the trial regimen in 71 participants (7.4%) in the levofloxacin group and 11 (1.1%) in the placebo group. Further details about the frequency of adverse events, according to grade, are shown in Tables S10, S11, and S12. No deaths occurred in either group within 21 days after the last dose of levofloxacin or placebo. Seven deaths that occurred during the 30-month follow-up period (four in the levofloxacin group and three in the placebo group) were assessed as being unrelated to tuberculosis by the expert clinical panel, whose members were unaware of the trial-group assignments (Table S13). The population of index patients with whom the trial participants shared households was nationally representative of persons with rifampicin-resistant or MDR tuberculosis (Table S14).

GENOMIC ANALYSES

Among 17 participants with confirmed incident tuberculosis, genotypic drug-resistance predictions were available for 11; a total of 2 had *gyrA* mutations associated with quinolone resistance and 9 did not. Isolates were available for both the index case and the household contact for two pairs in the levofloxacin group and six in the control group. In the levofloxacin group, both contacts had MDR tuberculosis; in the control group, MDR tuberculosis developed in four contacts, isoniazid-resistant tuberculosis developed in one, and pan-susceptible tuberculosis developed in one. Bacterial isolates from the household contact with incident tuberculosis were classified as genotypically matching with baseline isolates of their index case in one of two pairs from the levofloxacin group and four of six pairs from the placebo group. No acquired fluoroquinolone resistance was detected after randomization. The CONSORT checklist is shown in Table S15.

DISCUSSION

This randomized trial involving 2041 household contacts of persons with rifampicin-resistant or MDR tuberculosis in Vietnam, with evidence of

Table 2. Incidence of Tuberculosis Disease (Intention-to-Treat Population).*

Variable	Levofloxacin	Incidence per 100 Person-Yr	Placebo	Incidence per 100 Person-Yr	Incidence Rate Ratio (95% CI)†
Intention-to-treat population					
No. of participants	1023	—	1018	—	—
Completed 30 mo of follow-up, had a primary end-point event, or died — no. (%)	996 (97.4)	—	999 (98.1)	—	—
Total person-yr of follow-up	2586.1	—	2564.6	—	—
Bacteriologically confirmed tuberculosis — no.	6	0.232	11	0.429	0.55 (0.19–1.62)
Clinically diagnosed tuberculosis — no.	1	0.039	2	0.078	0.49 (0.04–5.46)
Bacteriologically confirmed or clinically diagnosed tuberculosis — no.‡	7	0.271	13	0.507	0.54 (0.20–1.46)
Per-protocol population§					
No. of participants	700	—	844	—	—
Completed 30 mo of follow-up, had a primary end-point event, or died — no. (%)	690 (98.6)	—	834 (98.8)	—	—
Total person-yr of follow-up	1783.7	—	2145.3	—	—
Bacteriologically confirmed tuberculosis — no.	3	0.168	6	0.280	0.60 (0.15–2.40)
Clinically diagnosed tuberculosis — no.	0	0	1	0.047	Not estimable
Bacteriologically confirmed or clinically diagnosed tuberculosis — no.	3	0.168	7	0.326	0.52 (0.14–1.99)
Modified intention-to-treat population¶					
No. of participants	907	—	897	—	—
Completed 30 mo of follow-up, had a primary end-point event, or died — no. (%)	884 (97.5)	—	881 (98.2)	—	—
Total person-yr of follow-up	2297.9	—	2264.4	—	—
Bacteriologically confirmed tuberculosis — no.	4	0.174	9	0.397	0.44 (0.14–1.41)
Clinically diagnosed tuberculosis — no.	0	0	1	0.044	Not estimable
Bacteriologically confirmed or clinically diagnosed tuberculosis — no.	4	0.174	10	0.442	0.39 (0.12–1.25)

* We report point estimates and 95% confidence intervals for outcomes, because we did not prespecify a plan to account for multiplicity. The widths of the intervals have not been adjusted for multiplicity. The interpretation of these confidence intervals should avoid the language of definitive conclusions used to report significant findings as assessed by formal hypothesis testing.

† Incidence rate ratios account for clustering at the household level. The intraclass correlation for the primary end point (bacteriologically confirmed tuberculosis) was 0.0168.

‡ In the levofloxacin group, among two contacts with drug-susceptibility testing results from whole-genome sequencing, tuberculosis that was resistant to both isoniazid and rifampicin developed in both persons. In the placebo group, among six contacts with drug-susceptibility testing results from whole-genome sequencing, four had tuberculosis that was resistant to both isoniazid and rifampicin, one had resistance only to isoniazid, and one had susceptibility to both isoniazid and rifampicin.

§ The per-protocol population included all randomly assigned participants who completed at least 80% of their assigned trial regimen.

¶ The modified intention-to-treat analyses excluded household contacts of index patients who were incorrectly classified (those in whom the index patient was positive for rifampicin resistance on the Xpert MTB/RIF assay but had a rifampicin-susceptible phenotype) and contacts who did not commence the trial regimen on account of early withdrawal from the trial.

infection but no active disease, showed that the incidence of confirmed tuberculosis was lower among those taking levofloxacin than those taking placebo; however, the difference was not significant. Levofloxacin was associated with a low incidence of serious adverse events and with no evidence for acquired resistance to fluoroquinolones. In the levofloxacin group, a higher proportion of participants discontinued the trial regimen than in the placebo group.

The numerical reduction in incidence with levofloxacin suggests that the drug may have a role in preventing tuberculosis among household contacts of persons with rifampicin-resistant or

MDR tuberculosis. However, the estimate of effect was imprecise. The observed 1.1% incidence in the control group was less than the 3% on which our sample-size estimate was based.[13] The observed value was substantially lower than that reported in a previous cohort study[23] and two meta-analyses.[24,25] A likely explanation for our finding is that a high proportion of contacts in whom tuberculosis developed already had tuberculosis before enrollment. In contrast to the 17 participants with incident confirmed tuberculosis that was diagnosed during follow-up, we identified 44 persons with microbiologically confirmed tuberculosis among persons screened before randomization. The relatively high number of prevalent as compared with incident cases may be attributable to the prolonged period of infectiousness of the index case before treatment was started, resulting from delays in the diagnosis and treatment of drug-resistant tuberculosis, and to the decreasing risk of incident disease over time.[26]

Levofloxacin satisfies most of the qualities recommended by the WHO for a suitable preventive treatment regimen for tuberculosis, including safety, no evidence of drug-resistance promotion, adequate adherence, and low cost.[27] Although the lower-than-expected number of events in the control group led to a lack of precision in the effect estimate, combining these findings with the results from the TB-CHAMP (Tuberculosis Child Multidrug-Resistant Preventive Therapy) trial reported in this issue of the *Journal*[28] suggests the possible effectiveness of the regimen. Our trial showed that 6 months of fluoroquinolone therapy was associated with a low incidence of serious adverse events. However, approximately a third of contacts taking levofloxacin chose not to complete therapy, and a higher proportion of participants in the levofloxacin group reported grade 1 or 2 adverse events (particularly musculoskeletal symptoms) than in the placebo group (Table S9). For every 100 persons taking levofloxacin, approximately 7 stopped treatment on account of an adverse event (Table 3). This finding indicates that for otherwise healthy contacts, low-grade symptoms can be a substantial barrier to treatment completion. Levofloxacin use was not associated with prolongation of the corrected QT interval or tendinopathy. Potential effects on the human microbiome, including long-term reductions in bacterial diversity and the emergence of resistant organisms in the gastrointestinal and respiratory tracts, are being analyzed.

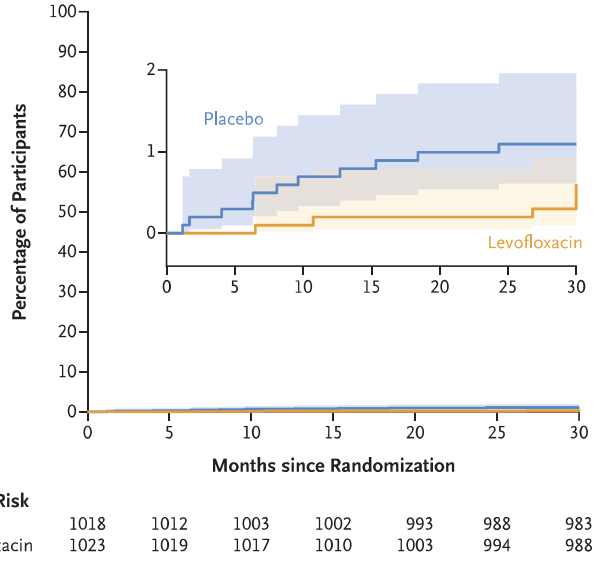

Figure 2. Kaplan–Meier Plot of Incident Bacteriologically Confirmed Tuberculosis over Time.

We report point estimates and 95% confidence intervals (shaded areas) for outcomes, because we did not prespecify a plan to account for multiplicity. The widths of the intervals have not been adjusted for multiplicity. The interpretation of these confidence intervals should avoid the language of definitive conclusions used to report significant findings as assessed by formal hypothesis testing. The inset shows the same data on an expanded y axis.

Nearly half the contacts in whom tuberculosis developed acquired their infection from a different source than the identified index case. This finding reflects the likelihood that a different agent, such as rifampicin or isoniazid, may provide benefit. The trial also reinforces the importance of ongoing efforts to reduce the transmission of *M. tuberculosis* in the community, in addition to among specific high-risk groups.

In contrast to participants in the the placebo group, no participants taking levofloxacin received a diagnosis of incident tuberculosis during the 6 months after randomization. This finding suggests that levofloxacin may have its greatest effect during and shortly after treatment. Beyond 12 months, the parallel lines on the Kaplan–Meier curve imply that the benefit of treatment may not be enduring, probably owing to the high risk of reinfection with tuberculosis in this high-prevalence environment. Underreport-

Table 3. Adverse Events.*

Variable	Levofloxacin	Placebo	Risk Difference (95% CI)	P Value
			percentage points	
Participants taking at least one dose of levofloxacin or placebo — no./total no. (%)†	960/1023 (93.8)	962/1018 (94.5)	−0.7 (−3.5 to 2.2)	0.65
Participants with one or more adverse events — no./total no. (%)‡				
Any grade	306/960 (31.9)	125/962 (13.0)	18.9 (14.2 to 23.6)	<0.001
Grade 1 or 2	290/960 (30.2)	111/962 (11.5)	18.7 (14.0 to 23.3)	<0.001
Grade 3 or 4	29/960 (3.0)	19/962 (2.0)	1.0 (−0.3 to 2.4)	0.14
Permanent discontinuation of levofloxacin or placebo because of adverse event — no./total no. (%)				
Total	71/960 (7.4)	11/962 (1.1)	6.3 (4.3 to 8.2)	<0.001
Grade 1 or 2 adverse event§	59/960 (6.2)	7/962 (0.7)	5.4 (3.6 to 7.3)	<0.001
Grade 3, pregnancy only	4/960 (0.4)	3/962 (0.3)	0.1 (−0.4 to 0.6)	0.70
Grade 3, non-pregnancy related	8/960 (0.8)	1/962 (0.1)	0.7 (0.1 to 1.3)	0.02
Grade 3 or 4 hepatotoxic event	1/960 (0.1)	0/962	0.1 (−0.1 to 0.3)¶	0.5¶
Grade 3 or 4 musculoskeletal event	1/960 (0.1)	0/962	0.1 (−0.1 to 0.3)¶	0.5¶
Grade 3 or 4 prolongation of corrected QT interval	0/960	0/962	—	—
Death	0/960	0/962	—	—
Adverse events in participants taking at least one dose of levofloxicin or placebo‖			—	—
Total no. of adverse events	422	162		
Adverse events classified grade 3 or 4 — no. (%)**	31 (7.4)	20 (12.4)	−5.0 (−11.3 to 1.3)	0.12
Grade 3–5 adverse events that were probably related to levofloxacin or placebo — no. of events/total no. (%)				
Grade 3–5 adverse event of any type	10/422 (2.4)	2/162 (1.2)	1.1 (−1.0 to 3.3)	0.31
Grade 3 or 4 hepatotoxic event	1/422 (0.2)	0/162	0.2 (−0.2 to 0.7)¶	1.00¶
Grade 3 or 4 musculoskeletal event	4/422 (0.9)	1/162 (0.6)	0.3 (−1.2 to 1.9)	0.67
Grade 3 or 4 prolongation of corrected QT interval	0/422	0/162	0	—

* Shown are adverse events that were reported up to 21 days after the the last dose of levofloxacin or placebo, among participants taking at least one dose. We report point estimates and 95% confidence intervals for outcomes, because we did not prespecify a plan to account for multiplicity. The widths of the intervals have not been adjusted for multiplicity. The interpretation of these confidence intervals should avoid the language of definitive conclusions used to report significant findings as assessed by formal hypothesis testing.

† Of the 1922 participants who received at least one dose of levofloxacin or placebo, 1491 (77.6%) had no adverse events, 330 (17.2%) had one adverse event, and 101 (5.3%) had more than one adverse event.

‡ Adverse events of grade 3 to 5 were reviewed by a four-member expert clinical panel whose members were unaware of the trial-group assignments. At least three members were required to report each adverse event. Severity was classified according to the Common Terminology Criteria for Adverse Events, version 4.0,[15] and for hepatotoxicity according to American Thoracic Society criteria.[22]

§ Grade 1 or 2 adverse events were classified by the local medical officer. Grade 3 to 5 events were classified by an expert clinical panel.

¶ Confidence interval and P value were calculated with the use of the exact method owing to zero cell count.

‖ If a participant had more than one adverse event, then each adverse event is counted separately.

** The proportion represents the ratio of adverse events per 100 participants.

ing of tuberculosis is an unlikely explanation for the low number of participants in whom incident tuberculosis developed, given the high percentage of participants who completed follow-up and cross-checking of the small number of participants who were lost to follow-up against tuberculosis treatment records.

This trial had a number of strengths. It used a placebo-controlled double-blind design, providing confidence that outcomes were not affected

by behavior relating to the knowledge by participants or health care providers about their trial-group assignments. Almost all the participants had a diagnosis of *M. tuberculosis* infection, and the primary end point was microbiologically confirmed incident tuberculosis. The percentage of participants who completed follow-up was high — more than 97% in both groups. The trial involved contacts of all ages in rural and urban provinces of Vietnam. Hence, the trial findings may be generalizable to household contacts of persons with rifampicin-resistant or MDR tuberculosis in a range of settings where HIV prevalence is low. The findings of our trial complement those of the TB-CHAMP trial, which involved children and adolescents.[28] Combining the data from these two trials, which were designed in collaboration and share common end-point definitions, allows additional insight into the possible effectiveness of levofloxacin for contacts of persons with MDR tuberculosis.[29] Finally, coprevalent disease was carefully ruled out at baseline, including attempted collection of sputum for molecular testing for all the participants, which avoided misclassification of coprevalent disease as incident disease.

In this trial, the point estimate for incidence of tuberculosis was lower among participants taking levofloxacin for the treatment of *M. tuberculosis* infection than among those taking placebo, although this difference was not significant. Levofloxacin use was not associated with a substantially higher incidence of grade 3 or 4 adverse events than placebo, although lower-grade adverse events were more common with levofloxacin. The findings of this trial should be combined with those from other settings to allow additional insights.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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