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ORIGINAL ARTICLE

A Meta-Analysis of Levofloxacin for Contacts of Multidrug-Resistant Tuberculosis

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Abstract

BACKGROUND Data from randomized trials evaluating the effectiveness of tuberculosis (TB) preventive treatment for contacts of multidrug-resistant (MDR)-TB are lacking. Two recently published randomized trials that did not achieve statistical significance provide the opportunity for a meta-analysis.

METHODS We conducted combined analyses of two phase 3 trials of levofloxacin MDR-TB preventive treatment — Levofloxacin for the Prevention of Multidrug-Resistant Tuberculosis (VQUIN) trial and the Levofloxacin preventive treatment in children exposed to MDR-TB (TB-CHAMP) trial. Following MDR-TB household exposure, VQUIN enrolled mainly adults in Vietnam; TB-CHAMP enrolled mainly young children in South Africa. Random assignment in both trials was 1:1 at the household level to daily levofloxacin or placebo for 6 months. The primary outcome was incident TB by 54 weeks. We estimated the treatment effect overall using individual participant data meta-analysis.

RESULTS The VQUIN trial (n=2041) randomly assigned 1023 participants to levofloxacin and 1018 participants to placebo; TB-CHAMP (n=922) assigned 453 participants to levofloxacin and 469 participants to placebo. Median age was 40 years (interquartile range 28 to 52 years) in VQUIN and 2.8 years (interquartile range 1.3 to 4.2 years) in TB-CHAMP. Overall, 8 levofloxacin-group participants developed TB by 54 weeks versus 21 placebo-group participants; the relative difference in cumulative incidence was 0.41 (95% confidence interval [CI] 0.18 to 0.92; P=0.03). No association was observed between levofloxacin and grade 3 or above adverse events (risk ratio 1.07, 95% CI 0.70 to 1.65). Musculoskeletal events of any grade occurred more frequently in the levofloxacin group (risk ratio 6.36, 95% CI 4.30 to 9.42), but not among children under 10 years of age. Overall, four levofloxacin-group participants and three placebo-group participants had grade 3 events.

CONCLUSIONS In this meta-analysis of two randomized trials, levofloxacin was associated with a 60% relative reduction in TB incidence among adult and child household MDR-TB contacts, but with an increased risk of musculoskeletal adverse events. (Funded by the Australian National Health and Medical Research Council, UNITAID, and others.)

A complete list of investigators in the TB-CHAMP and VQUIN MDR-TB trial teams is provided in the Supplementary Appendix, available at evidence.nejm.org.

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Introduction

Nearly 500,000 people each year are estimated to develop rifampin-resistant or multidrug-resistant (MDR) tuberculosis (TB), defined as a disease caused by *Mycobacterium tuberculosis* (*Mtb*) that is resistant to isoniazid and rifampin.[1] TB preventive treatment protects people with latent *Mtb* infection from progression to TB disease, reducing onward transmission.[2,3] While the effectiveness of TB preventive treatment for drug-susceptible TB is well-established,[4,5] there is limited evidence from randomized trials for TB preventive treatment in individuals exposed to people with rifampin-resistant or MDR-TB.

The Vietnam Quinolones for MDR-TB Trial (VQUIN; registered as ACTRN12616000215426) and Tuberculosis Child Multidrug-Resistant Preventive Therapy Trial (TB-CHAMP; registered as ISRCTN92634082) were separate randomized placebo-controlled trials evaluating levofloxacin as an MDR-TB preventive treatment in adults and children, respectively.[6,7] Both trials observed fewer participants developing TB disease in the levofloxacin group; however, in both trials, the observed difference did not reach statistical significance, potentially due to lower-than-expected underlying TB event rates.[8,9]

In this article, we report a prospectively planned individual participant data (IPD) meta-analysis of the two trials evaluating the efficacy and safety of levofloxacin MDR-TB preventive treatment. We used standard methods to estimate overall treatment effects, and a Bayesian method to estimate the efficacy in each trial with more precision.[10] This Bayesian approach accommodates differences in treatment efficacy between study populations.

Method

STUDY DESIGN

The VQUIN trial was conducted in Vietnam between March 2016 and February 2022, and TB-CHAMP was carried out in South Africa between September 2017 and February 2023. The designs for each trial have been described previously,[6,7] and the individual trial results reported elsewhere.[8,9]

Both trials enrolled participants with household exposure to an individual with microbiologically confirmed pulmonary rifampin-resistant/MDR-TB. VQUIN mainly enrolled household contacts who were 15 years of age and over, and a smaller number of children under 15 years of age. Participants were required either to show evidence of latent *Mtb* infection (i.e., *Mtb* immune sensitization), be living with human immunodeficiency virus (HIV), or have severe malnutrition. TB-CHAMP initially enrolled only children under 5 years of age, with older children and adolescents aged 5 to 17 who either showed evidence of latent *Mtb* infection or were living with HIV later included. Latent *Mtb* infection status was defined as a positive tuberculin skin test (TST) in VQUIN,[6] and positive interferon gamma release assay (IGRA, QuantiFERON-TB Gold Plus, Qiagen) in TB-CHAMP.

Participants in both trials were randomly assigned to daily oral levofloxacin or placebo in a 1:1 assignment ratio, stratified by province (n=10) in VQUIN, and by trial site (n=5) in TB-CHAMP. In TB-CHAMP, all participants within a household were allocated to the same treatment group. In the VQUIN trial, where two or more contacts within a household were randomly assigned within a 90-day period, these household contacts were assigned to the same treatment group; if additional contacts were enrolled 91 days or more after the first contact was enrolled, they were randomly assigned separately. Treatment was administered once daily for 180 days (26 weeks) in VQUIN and 168 days (24 weeks) in TB-CHAMP. The daily dosing was based on 10–15 mg/kg for adults in VQUIN, and 15–20 mg/kg for children in both trials, with a maximum dose of 750 mg. We used the same formulations for levofloxacin and placebo (250-mg tablet; Macleods Pharmaceuticals, India). Follow-up in VQUIN was up to 134 weeks post–random assignment. In TB-CHAMP, follow-up was originally to 96 weeks, reduced to 72 weeks in May 2019, with final analyses undertaken when all participants were followed for a minimum of 24 weeks. The design and methods for the combined analyses of the trials were prespecified before the results for either trial were known.

END POINTS

The primary efficacy end point for the combined analysis was microbiologically confirmed or clinically defined TB, including TB-related death, by 54 weeks following random assignment. This time frame was chosen based on previous studies showing that most contacts who develop TB disease after exposure to *Mtb* do so within 12 months,[11,12] and concerns that subsequent reexposure and exogenous reinfection with longer follow-up could dilute the treatment effect. It also allowed alignment in follow-up duration across the two trials.

Secondary efficacy end points were (1) microbiologically confirmed or clinically defined TB by the end of follow-up; (2) microbiologically confirmed TB by 54 weeks; and (3) all-cause mortality by 134 weeks. In each trial, an independent End Point Review Committee, blinded to treatment assignment, adjudicated TB outcomes and cause of death.

Safety end points were (1) grade 3 or above adverse events (AEs) from starting treatment to 21 days after last drug dose; (2) grade 3 or above AEs associated with the drug; (3) serious adverse events (SAEs) occurring up to 21 days after last drug dose; (4) discontinuation of treatment due to AE(s) of any grade; and (5) five prespecified domains of AEs of special interest (Supplementary Appendix, S2.7), including musculoskeletal effects (arthritis, arthralgia, or tendonitis) occurring any time from the start of treatment. In TB-CHAMP, the site clinician treating the participant determined the causal relationship between the trial drug and AEs (including death). In VQUIN, causality was determined by the End Point Review Committee for grade 3 to 5 AEs, and by the treating clinician for grade 1 and 2 AEs.

STATISTICAL METHODS

IPD Meta-Analysis

The primary efficacy analysis of time-to-TB by 54 weeks included all randomly assigned participants, apart from any late screening failures with TB at baseline (modified intention-to-treat population). Participants without an end point observed had follow-up censored at the earliest time of 54 weeks from random assignment, date of the last trial follow-up, or date of non-TB death. Kaplan–Meier cumulative incidence plots were generated.

We estimated an overall treatment effect across the trials using a one-stage common-effect IPD meta-analysis approach. We planned to use Cox regression to estimate the hazard ratio for levofloxacin versus placebo, allowing for separate baseline hazard functions for each trial. Cluster-robust variance accounted for intrahousehold correlation. We adjusted for province in VQUIN and site in TB-CHAMP (random assignment stratification factors) using inverse probability treatment weighting, owing to the small number of TB events.[13] Analysis assumed noninformative censoring, but otherwise there were no missing data in the model.

We tested the assumption of proportional hazards using scaled Schoenfeld residuals. If there was evidence of nonproportional hazards, the relative difference in cumulative incidence between treatment groups was estimated using a flexible parametric model with time-dependent treatment effect (Supplementary Appendix, S5.4).[14] Hypothesis testing of the relative difference in cumulative incidence was based on the Wald test. The hazard ratio was also estimated separately for the first 6 months and thereafter.

Per-protocol analyses were restricted to participants who were adherent to the allocated treatment (defined in Supplementary Appendix, S5.2), excluding any late screening failures. Prespecified subgroup analyses assessed the heterogeneity of treatment effects. The number-needed-to-treat (NNT) to prevent one TB case was estimated for each trial population, assuming a common relative treatment effect, while allowing for different underlying TB incidence across the two trials (Supplementary Appendix, S5.7).

Safety analyses included all randomly assigned participants who commenced treatment. The risk ratio comparing the proportion of participants experiencing the relevant end point between treatment groups was estimated using modified Poisson regression.[15] Analyses of secondary outcomes did not adjust for multiple comparisons; results are reported as point estimates with 95% confidence intervals and should not be used in place of hypothesis testing.

Bayesian Analysis

We used a Bayesian method to estimate levofloxacin efficacy (based on the primary end point) in the VQUIN population while "borrowing" information from TB-CHAMP, and vice versa.[10] This approach increases power compared with standalone analyses of each trial and addresses a different research question to the IPD primary meta-analysis; here, we assessed separately levofloxacin efficacy within the VQUIN and TB-CHAMP populations. We assumed any difference in treatment efficacy between the trials was due to differences in age distribution and prevalence of *Mtb* infection.

To define the weights given to the borrowed information, we elicited opinions from 15 experts with experience in TB prevention on how levofloxacin efficacy may differ by age group and *Mtb* infection status (Supplementary Appendix, S5.5). Experts were selected to provide a breadth of opinions and a global perspective. To inform the elicitations, participants were provided with summary data on the estimated effect of TB preventive treatment by age and *Mtb* infection status, based on observational TB contact cohorts.[11] Opinions ascertained were pooled to determine weights for the borrowed information, which was incorporated as prior distributions.[16] For each trial, separate Bayesian analyses were performed within predefined subgroups by age group and TB infection status (Supplementary Appendix, S5.5), and combined in an analysis weighted by the number of TB events. We present the overall posterior means for the relative difference in cumulative difference, with 95% credible intervals.

Analyses were performed using Stata version 18.0 (StataCorp). The widths of the intervals have not been adjusted for multiplicity and thus should not be used in place of hypothesis testing.

Results

In total, 2963 participants were randomly assigned across both trials — 1023 from 618 households to levofloxacin, versus 1018 from 581 households to placebo in VQUIN; and 453 from 248 households to levofloxacin, versus 469 from 249 households to placebo, in TB-CHAMP.

At baseline, the median age was 40 years (interquartile range 28 to 52 years) in VQUIN and 2.8 years (interquartile range 1.3 to 4.2 years) in TB-CHAMP (Table 1). The proportion of participants with evidence of latent *Mtb* infection in VQUIN was 99.8%, and in TB-CHAMP, 20% among children below 5 years of age and 95% among those 5 to 17 years of age. The proportion of participants living with HIV was 0.4% in VQUIN, and 2.1% in TB-CHAMP.

FOLLOW-UP AND ADHERENCE

In VQUIN, 97% of participants reached end-of-trial follow-up at 134 weeks. In TB-CHAMP, 91% of participants were followed for at least 24 weeks and 73% for at least 54 weeks (Table S7.1).

A total of 119 (6%) participants in VQUIN and 1 (0.01%) in TB-CHAMP did not start trial treatment. In VQUIN, 70% of participants in the levofloxacin group and 85% in the placebo group took at least 80% of the allocated doses; in TB-CHAMP, this proportion was 86% in both treatment groups.

PRIMARY EFFICACY END POINT

IPD Meta-Analysis

The primary analysis included 2957 participants, excluding 6 individuals who were considered late screening failures in TB-CHAMP with TB at baseline. Overall, 8 levofloxacin-group participants developed TB by 54 weeks versus 21 placebo-group participants, Figure 1. As there was evidence of nonproportional hazards (P=0.009), we present the relative difference in cumulative incidence by 54 weeks (0.41, 95% confidence interval [CI], 0.18 to 0.92; P=0.03).

By trial, the relative difference in 54-week cumulative incidence was 0.34 (95% CI, 0.09 to 1.25) for VQUIN and 0.44 (95% CI, 0.16 to 1.26) for TB-CHAMP. The estimated NNT to prevent one TB case by 54 weeks in VQUIN was 193 (95% CI, 98 to 5158), and in TB-CHAMP was 56 (95% CI, 30 to 466); Table S7.14.

No evidence of heterogeneity in treatment effect was observed in other prespecified subgroup analyses, including by age group (Table S7.15). Results from the per-protocol analysis were consistent with the primary analysis, with a relative difference in cumulative difference of 0.40 (95% CI, 0.16 to 1.02).

Bayesian Analyses

Figure 2 illustrates how the data from each trial (within predefined subgroups) were combined with information from the other trial in the Bayesian analysis. Borrowing information from TB-CHAMP provided a relative difference in cumulative incidence of TB by 54 weeks of 0.41 (95% credible interval [CrI], 0.18 to 0.95) for VQUIN (Figure 3); the posterior probability that levofloxacin is superior to placebo in the VQUIN population was 98%. The relative difference in cumulative incidence for TB-CHAMP, with information borrowed from VQUIN, was 0.38 (95% CrI, 0.16 to 0.95); the corresponding posterior probability for TB-CHAMP was 98%. For both trials, the Bayesian estimate was similar to the overall IPD meta-analysis estimate.

SECONDARY EFFICACY END POINTS

During overall trial follow-up up to 134 weeks, 14 participants developed TB in the levofloxacin group versus 27 in the placebo group. In the prespecified analyses, there was only 1 TB end point in the levofloxacin group versus 14 in the placebo group during the first 6 months post–random assignment (hazard ratio 0.07, 95% CI, 0.01 to 0.56), compared with 13 TB end points in each group thereafter (hazard ratio 1.00, 95% CI, 0.45 to 2.22); Table S7.12. The overall relative difference in cumulative TB incidence by 134 weeks was 0.62 (95% CI, 0.31 to 1.22); Figure 3.

Overall, five deaths occurred in the levofloxacin group and four in the placebo group. None was assessed (per the process described above) as being related to TB or the trial drug.

SAFETY END POINTS

Among 2843 participants who commenced trial treatment, 43 receiving levofloxacin and 42 receiving placebo experienced grade 3 or above AEs (risk ratio 1.07, 95% CI, 0.70 to 1.65; Table 2).

Grade 3 or above AEs considered to be at least possibly related to the trial drug were observed in 14 levofloxacin-group participants and 10 placebo-group participants

Table 1. Baseline Characteristics of Multidrug-Resistant Household Contact Participants Overall and by Trial.*

Characteristic	VQUIN	TB-CHAMP	Overall
Number of overall participants randomly assigned (levofloxacin group, placebo group)	2041 (1023, 1018)	922 (453, 469)	2963 (1476, 1487)
Age (years)			
Median (interquartile range)	40 (28–52)	2.8 (1.3–4.2)	29.0 (4.4–47.0)
Range	(2.0–87.0)	(0.1–17.9)	(0.1–87.0)
<3.0	2 (0.1%)	483 (52.4%)	485 (16.4%)
3.0–4.9	5 (0.2%)	356 (38.6%)	361 (12.2%)
5.0–17.9	149 (7.3%)	83 (9.0%)	232 (7.8%)
18.0–29.9	419 (20.5%)	–	419 (14.1%)
30.0–44.9	614 (30.1%)	–	614 (20.7%)
45.0–59.9	606 (29.7%)	–	606 (20.5%)
≥60.0	246 (12.1%)	–	246 (8.3%)
Sex			
Male	735 (36.0%)	454 (49.2%)	1189 (40.1%)
Female	1306 (64.0%)	468 (50.8%)	1774 (59.9%)
HIV status†			
Positive	8 (0.4%)	19 (2.1%)	27 (0.9%)
Negative	2033 (99.6%)	899 (97.9%)	2932 (99.1%)
Missing	0	4	4
Latent *Mtb* infection status‡			
Positive	2036 (99.8%)	242 (26.9%)§	2278 (77.5%)
Negative	5 (0.2%)	632 (70.4%)	637 (21.7%)
Indeterminate (IGRA)	0 (0%)	24 (2.7%)	24 (0.8%)
Missing	0	24	24
Previously treated for TB disease			
Yes	106 (5.2%)	18 (2.0%)	124 (4.2%)
No	1935 (94.8%)	904 (98.0%)	2839 (95.8%)
BCG vaccination given			
Yes	973 (47.7%)	865 (94.2%)	1838 (62.1%)
No	1068 (52.3%)	53 (5.8%)	1121 (37.9%)
Missing	0	4	4

* Percentages are based on participants without missing information. BCG denotes bacillus Calmette–Guérin; IGRA, interferon gamma release assay; *Mtb*, *Mycobacterium tuberculosis*; TB, tuberculosis; TB-CHAMP, Tuberculosis Child Multidrug-Resistant Preventive Therapy trial; and VQUIN, Vietnam Quinoles for Multidrug-Resistant Tuberculosis trial.
† This was self-reported in VQUIN.
‡ Latent *Mtb* infection was determined by tuberculin skin test in VQUIN and interferon gamma release assay (QuantiFERON-Gold Plus, Qiagen) in TB-CHAMP.
§ In TB-CHAMP, 20% of children were <5 years and 95% of those 5–17 years had evidence of latent *Mtb* infection.

(risk ratio 1.46, 95% CI, 0.65 to 3.26); Table 2 and Table S7.7. In VQUIN, more participants in the levofloxacin group compared with the placebo group had such AEs, with 10 (1.0%) versus 2 (0.2%), respectively (risk ratio 5.26, 95% CI, 1.16 to 23.95); this difference was not observed in TB-CHAMP, with 4 (0.9%) versus 8 (1.7%), respectively (risk ratio 0.53, 95% CI, 0.16 to 1.70).

Participants in the levofloxacin group, compared with the placebo group, were more likely to experience musculoskeletal AEs of any grade (risk ratio 6.36, 95% CI, 4.30 to 9.42; P<0.001). However, this association was driven by VQUIN (Table 2). Moreover, in a post hoc analysis, the difference between treatment groups was only seen in adolescents and adults (Table S7.8). Nearly all musculoskeletal events were either grade 1 (62%) or grade 2 (35%); Table S7.9. Seven participants (four levofloxacin-group, three placebo-group), all over 45 years of age, had grade 3 musculoskeletal events (Table S7.10). Overall, three participants (all in the levofloxacin group) developed tendonitis; two had a grade 2 event and one had a grade 1 event.

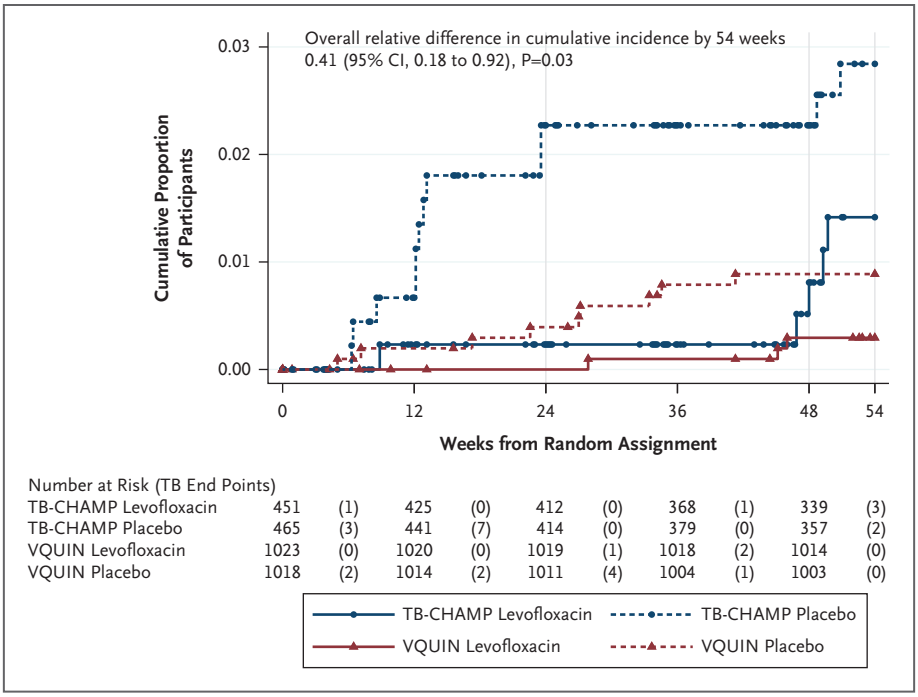

Figure 1. Cumulative Incidence of TB by 54 Weeks, by Treatment Group and Trial.

Excluded six participants in TB-CHAMP who were late screening failure with TB at baseline. The confidence intervals of the Kaplan–Meier cumulative incidence estimates are presented in Supplementary Appendix Table S7.13. CI denotes confidence interval; TB, tuberculosis; TB-CHAMP, Tuberculosis Child Multidrug-Resistant Preventive Therapy trial; and VQUIN, Vietnam Quinoles for Multidrug-Resistant Tuberculosis trial.

Discontinuation of trial treatment early due to any AEs occurred more frequently in the levofloxacin group than in the placebo group, in both VQUIN (7.4% vs. 1.1%, respectively) and TB-CHAMP (1.3% vs. 0.2%, respectively) (overall risk ratio 6.32, 95% CI, 3.43 to 11.63). In a post hoc analysis, the likelihood of stopping treatment early for AEs in the levofloxacin group appeared to increase with age (Table S7.5).

Discussion

In this combined analysis of nearly 3000 children, adolescents, and adults from the TB-CHAMP and VQUIN randomized placebo-controlled trials, we demonstrated that 6-month daily levofloxacin was associated with a 60% relative reduction in TB incidence over 1 year.

While both TB-CHAMP and VQUIN observed fewer participants developing TB in the levofloxacin than in the placebo group, neither trial individually showed a statistically significant difference.[8,9] This could potentially be due to the underlying TB incidence being substantially lower than expected. Pooling data led to a more precise estimate of the treatment effect. Using a Bayesian method, we also provided evidence of treatment efficacy within each trial population separately, and showed the effect was similar among adults and children.

These findings confirm previous results from observational studies of preventive treatment among contacts of people with rifampin-resistant or MDR-TB. A recent meta-analysis of 11 cohort studies estimated that MDR-TB preventive treatment reduced TB incidence by 66%.[17] Our results are also consistent with previous trials of isoniazid for preventing drug-susceptible TB. Meta-analysis of 11 placebo-controlled trials showed that 6 to 12 months of isoniazid had 60% efficacy in preventing TB.[4] Similar to isoniazid as TB preventive treatment,[18] the protective effect of levofloxacin appeared to be restricted to the treatment phase in our analysis. During this period, 1 participant in the levofloxacin group developed TB compared with 14 in the placebo group, corresponding to approximately 90% efficacy in a prespecified analysis. Thereafter, TB incidence was similar between treatment groups, which may be due to subsequent *Mtb* reexposure and reinfection, particularly in cases

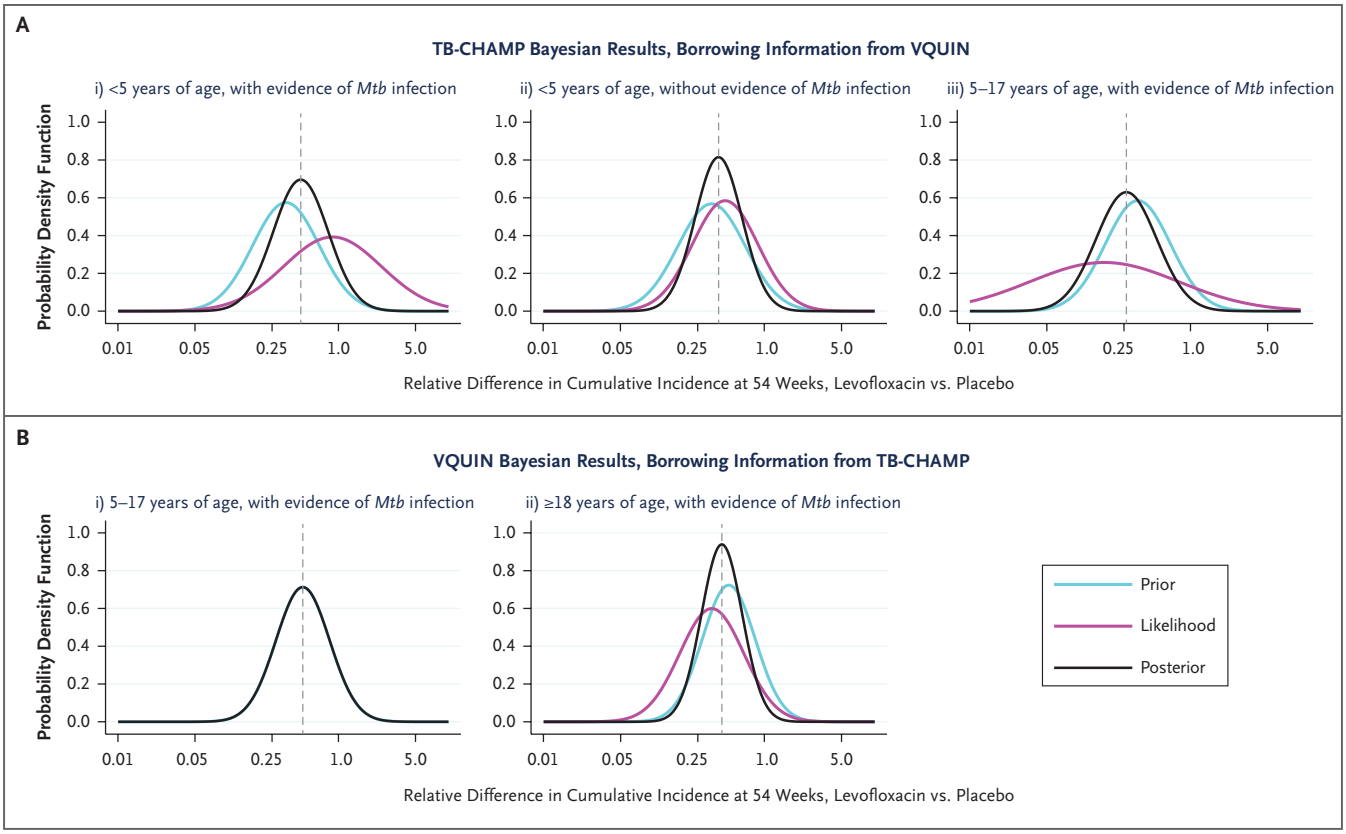

Figure 2. Prior, Likelihood, and Posterior Distributions in the Bayesian Analyses.

Bayesian analyses were performed within predefined subgroups by age group and *Mtb* infection status. Prior distributions represent information borrowed from the other study, likelihoods represent observed information in the source dataset, and posterior distributions are obtained by combining the prior distributions and likelihood in a Bayesian analysis. In Panel B(i), the likelihood is undefined because no TB events were observed, so the posterior and prior distributions correspond; this subgroup does not contribute to the combined Bayesian analysis weighted by number of events. *Mtb* denotes *Mycobacterium tuberculosis*; TB, tuberculosis; TB-CHAMP, Tuberculosis Child Multidrug-Resistant Preventive Therapy trial; and VQUIN, Vietnam Quinoles for Multidrug-Resistant Tuberculosis trial.

identified late in the follow-up period. It is also possible that levofloxacin did not fully clear the latent *Mtb* infection in some participants, resulting in subsequent progression to TB post treatment. While data from randomized trials suggest continuous or extended TB preventive treatment for drug-susceptible TB could be more efficacious than the standard 6-month treatment course,[19,20] such an approach may be offset by greater risk of toxicities, increased cost, and poorer acceptability and treatment adherence.

Owing to the low underlying TB rates, the estimated NNT to prevent one TB case for both trial populations was relatively high, particularly in adults. This is an important consideration for MDR-TB preventive treatment implementation across different settings. Modeling work, however, suggests the long-term population-wide impact of household contact investigation and provision of MDR-TB preventive treatment could have a considerably greater effect on MDR-TB prevalence, including reducing onward transmission.[21]

Reassuringly, our two trials showed little evidence of excess risk of AEs at grade 3 or above, or of serious AEs with levofloxacin. Participants in the levofloxacin group were, however, more likely to experience AEs at grade 3 or above at least possibly related to the trial drug in VQUIN, although such events were uncommon. We found trial treatment discontinuation for AEs occurred more frequently in the levofloxacin group and, as previously reported,[22] more so in adults than in children. The AEs leading to treatment discontinuation were mostly low grade.[8,9]

We observed an association between levofloxacin and musculoskeletal events, with most events being

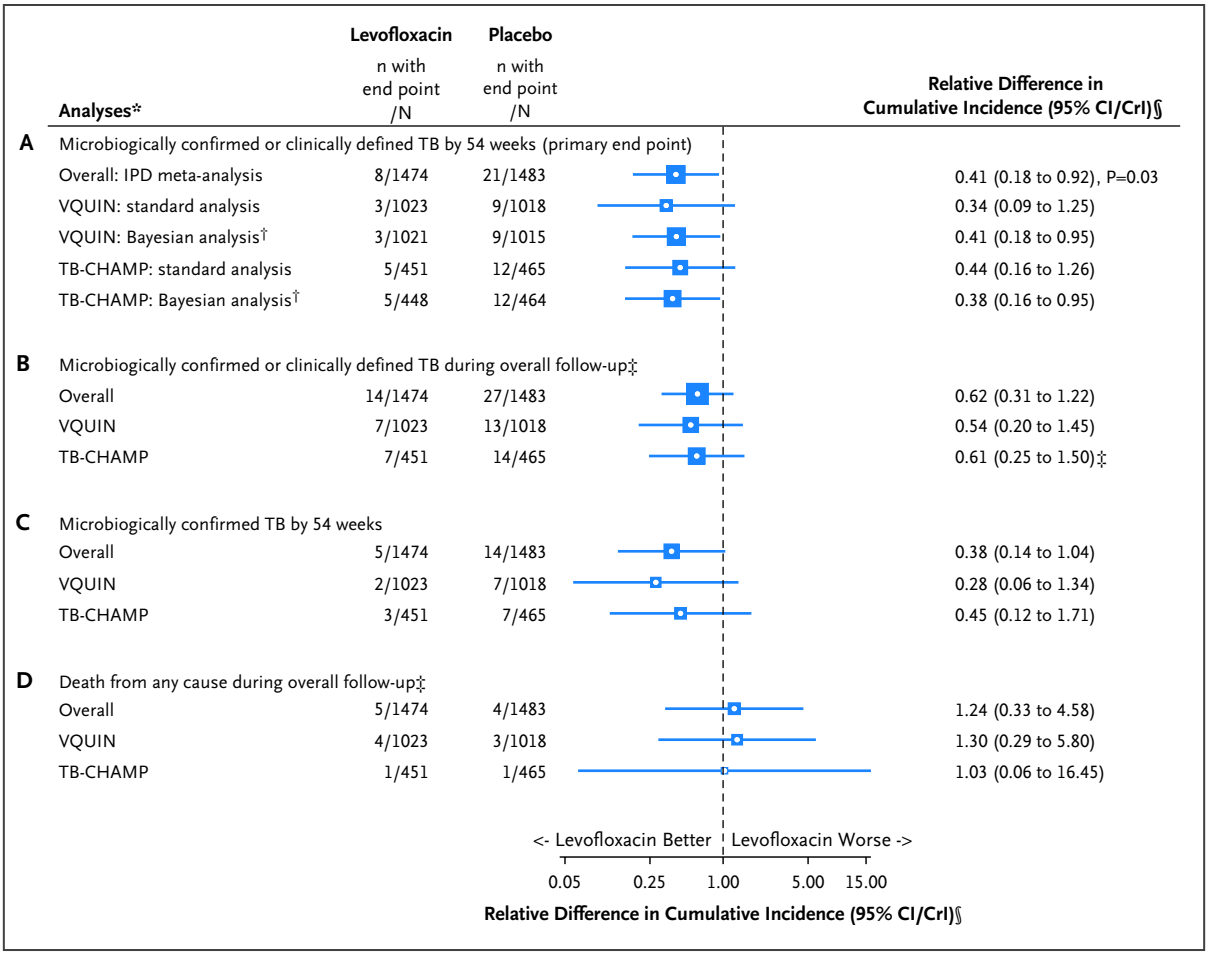

Figure 3. Estimated Treatment Effect of Levofloxacin on TB by 54 Weeks.

*Excluded six participants in TB-CHAMP who were late screening failure with TB at baseline. †The Bayesian analyses excluded five participants from VQUIN and four from TB-CHAMP who were 5 years of age or older and either TST- or IGRA-negative (see Supplementary Appendix S5.5). ‡In the VQUIN trial, follow-up was up to 134 weeks. In TB-CHAMP, scheduled visits were originally at 96 weeks (±6-week window), then reduced to 72 weeks (±6 weeks) in May 2019. However, some participants had unscheduled visits beyond these time frames, with a maximum follow-up of 124 weeks. The relative difference in cumulative incidence by 134 weeks was presented for overall and VQUIN, and by 78 weeks (i.e., 72+6-week window) for TB-CHAMP. §Estimates of the relative difference in cumulative difference were presented since there was evidence of nonproportional hazards in the analyses of microbiologically confirmed or clinically defined TB by 54 weeks (P=0.01); microbiologically confirmed or clinically defined TB during overall follow-up (P=0.003); and microbiologically confirmed TB by 54 weeks (P=0.02). The confidence intervals were not adjusted for multiplicity. CI denotes confidence interval; CrI, credible interval (for Bayesian results); IGRA, interferon gamma release assay; IPD, individual patient data; TB, tuberculosis; TB-CHAMP, Tuberculosis Child Multidrug-Resistant Preventive Therapy trial; TST, tuberculin skin test; and VQUIN, Vietnam Quinoles for Multidrug-Resistant Tuberculosis trial.

mild. This association was not seen in children under 10 years of age. Only three participants on levofloxacin reported symptoms of tendonitis; none was severe. Musculoskeletal toxicities associated with levofloxacin antibiotic therapy have been reported in adults,[23-26] with symptoms that are usually self-limiting.[27] Among 2500 children from open-label randomized trials of levofloxacin for antibiotic treatment of other infections, 12-month incidence of musculoskeletal disorders was higher with levofloxacin compared with non-fluoroquinolone treatment (3.4% vs. 1.8%). This difference was largely due to reports of arthralgia, so potentially subject to reporting bias[28]; moreover, there were no long-term effects observed.[29] Other potential adverse effects of levofloxacin MDR-TB preventive treatment, such as the effect on human microbiome and development of drug-resistant bacteria among other bacterial species, require further evaluation.

Table 2. Combined Safety Analyses of the VQUIN and TB-CHAMP Trials (Based on Standard Individual Patient Data Meta-Analysis Methods).*

Safety Analysis by Trial	Levofloxacin	Placebo	Estimated Risk Ratio (95% CI†)	P Value for Overall Treatment Effect
Participants who took at least one trial drug dose‡				
VQUIN	960	962		
TB-CHAMP	452	469		
Overall	1412	1431		
Participants with one or more safety end points				
Grade 3 or above adverse event§				
VQUIN	29 (3.0%)	19 (2.0%)	1.55 (0.87 to 2.76)	
TB-CHAMP	14 (3.1%)	23 (4.9%)	0.67 (0.34 to 1.31)	
Overall	43	42	1.07 (0.70 to 1.65)	0.75
Grade 3 or above adverse event at least possibly related to drug§				
VQUIN	10 (1.0%)	2 (0.2%)	5.26 (1.16 to 23.95)	
TB-CHAMP	4 (0.9%)	8 (1.7%)	0.53 (0.16 to 1.70)	
Overall	14	10	1.46 (0.65 to 3.26)	0.36
Any grade 3 or above serious adverse event§				
VQUIN	20 (2.1%)	12 (1.3%)	1.72 (0.85 to 3.49)	
TB-CHAMP	8 (1.8%)	7 (1.5%)	1.23 (0.45 to 3.35)	
Overall	28	19	1.54 (0.87 to 2.74)	0.14
Discontinuation of treatment due to adverse events of any grade				
VQUIN	71 (7.4%)	11 (1.1%)	6.43 (3.42 to 12.09)	
TB-CHAMP	6 (1.3%)	1 (0.2%)	5.25 (0.64 to 43.13)	
Overall	77	12	6.32 (3.43 to 11.63)	<0.001
Musculoskeletal adverse event of any grade				
VQUIN	220 (22.9%)	32 (3.3%)	7.02 (4.67 to 10.56)	
TB-CHAMP	6 (1.3%)	4 (0.9%)	1.35 (0.36 to 5.06)	
Overall	226	36	6.36 (4.30 to 9.42)	<0.001
Severe rash or cutaneous reaction§				
VQUIN	1 (0.3%)	1 (0.8%)	1.06 (0.07 to 17.00)	
TB-CHAMP	1 (0.2%)	0 (0%)	–	
Overall	2	1	2.06 (0.19 to 22.65)	0.56
Peripheral neuropathy§				
VQUIN	1 (0.1%)	0 (0%)	–	
TB-CHAMP	0 (0%)	0 (0%)	–	
Overall	1 (0.1%)	0 (0%)	–	
Central nervous system effects§				
VQUIN	8 (0.8%)	3 (0.3%)	2.68 (0.71–10.05)	
TB-CHAMP	6 (1.3%)	9 (1.9%)	0.65 (0.23 to 1.88)	
Overall	14 (1.0%)	12 (0.8%)	1.17 (0.53 to 2.58)	0.70

* Note that drug-related fever was also a prespecified adverse event of special interest, but there were no events in either group. CI denotes confidence interval; TB-CHAMP, Tuberculosis Child Multidrug-Resistant Preventive Therapy trial; and VQUIN, Vietnam Quinoles for Multidrug-Resistant Tuberculosis trial.
† The estimated confidence intervals were not adjusted for multiplicity.
‡ Excluded 119 participants in VQUIN and 1 in TB-CHAMP who had not started treatment.
§ Up to 21 days after stopping treatment.

Our analysis has several important strengths. During protocol development of the original trials, the VQUIN and TB-CHAMP investigators collaborated to ensure alignment of end point definitions and data collection. The same drug formulations and doses were used in both trials. The design and methodology for the combined analyses were developed before the results were available for either trial, reducing the potential for bias. Finally, combining data across these

complementary trials allowed a comparison of the efficacy and safety of levofloxacin MDR-TB preventive treatment between adults and children, and between settings.

These analyses have several limitations. First, our results may not be generalizable to all high-risk groups for TB, including people living with HIV, in whom treatment acceptability, tolerability, and/or adherence may differ. Second, further genotypic comparisons between mycobacterial isolates produced by incident cases and their index cases are required to establish whether TB progression was due to the initial exposure or subsequent reexposure to *Mtb*. Third, the number of TB end points was low in subgroup analyses. The Bayesian analyses required data stratification by age and *Mtb* infection status; thus, estimates of treatment efficacy may be sensitive to sparse data. Fourth, our analyses did not consider other potential factors that could have influenced treatment efficacy (such as geographical setting and HIV status of the index case), since the Bayesian elicitations and models would otherwise become challenging to implement. In addition, we observed nonproportional hazards in the efficacy IPD meta-analysis, with this not accounted for a priori in the elicitations, which were based on overall hazard ratios (Supplementary Appendix S8). This required the utilization and reporting of an alternate treatment effect measure from the one that was prespecified for the Bayesian analyses. We assumed the results from the elicitations could be applied to the estimation of the relative difference in cumulative incidence, because this is expected to be numerically similar to the hazard ratio. Finally, the follow-up data beyond 72 weeks mostly came from the VQUIN trial, which had a median duration of follow-up nearly twice that of TB-CHAMP.

These results suggest that MDR-TB preventive treatment with levofloxacin was associated with a 60% relative reduction in TB incidence among adults and children but was associated with increased low-grade adverse events (particularly musculoskeletal). Further evaluation of the risk–benefit balance, tolerability, and cost-effectiveness of MDR-TB preventive treatment in different populations is needed.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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References

1. World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization, October 27, 2022. Licence: CC BY-NC-SA 3.0 IGO (https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022).

2. World Health Organization. Module 1: prevention — tuberculosis preventive treatment. Geneva: World Health Organization, February 25, 2020. Licence: CC BY-NC-SA 3.0 IGO (https://www.who.int/publications/i/item/9789240001503).
3. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. Annu Rev Public Health 2013;34:271-286. DOI: 10.1146/annurev-publhealth-031912-114431.
4. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev 2000;1999:CD001363. DOI: 10.1002/14651858.CD001363.
5. Ayele HT, Mourik MS, Debray TP, Bonten MJ. Isoniazid prophylactic therapy for the prevention of tuberculosis in HIV infected adults: a systematic review and meta-analysis of randomized trials. PLoS One 2015;10:e0142290. DOI: 10.1371/journal.pone.0142290.
6. Fox GJ, Nguyen CB, Nguyen TA, et al. Levofloxacin versus placebo for the treatment of latent tuberculosis among contacts of patients with multidrug-resistant tuberculosis (the VQUIN MDR trial): a protocol for a randomised controlled trial. BMJ Open 2020;10:e033945. DOI: 10.1136/bmjopen-2019-033945.
7. Seddon JA, Garcia-Prats AJ, Purchase SE, et al. Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP). Trials 2018;19:693. DOI: 10.1186/s13063-018-3070-0.
8. Fox GJ, Nguyen VN, Nguyen CB, et al. Levofloxacin for the prevention of multidrug-resistant tuberculosis in Vietnam. N Engl J Med 2024; DOI: 10.1056/NEJMoa2314325.
9. Hesseling AC, Purchase SE, Martinson NA, et al. Levofloxacin preventive treatment in children exposed to MDR-TB. N Engl J Med 2024; DOI: 10.1056/NEJMoa2314318.
10. Turner RM, Turkova A, Moore CL, et al. Borrowing information across patient subgroups in clinical trials, with application to a paediatric trial. BMC Med Res Methodol 2022;22:49. DOI: 10.1186/s12874-022-01539-3.
11. Martinez L, Seddon JA, Horsburgh CR, Lange C, Mandalakas AM, TB Contact Studies Consortium. Effectiveness of preventive treatment among different age groups and *Mycobacterium tuberculosis* infection status: a systematic review and individual-participant data meta-analysis of contact tracing studies. Lancet Respir Med 2024;12:633-641. DOI: 10.1016/S2213-2600(24)00083-3.
12. Reichler MR, Khan A, Sterling TR, et al. Risk and timing of tuberculosis among close contacts of persons with infectious tuberculosis. J Infect Dis 2018;218:1000-1008. DOI: 10.1093/infdis/jiy265.
13. Morris TP, Walker AS, Williamson EJ, White IR. Planning a method for covariate adjustment in individually randomised trials: a practical guide. Trials 2022;23:328. DOI: 10.1186/s13063-022-06097-z.
14. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J 2009;9:265-290. DOI: 10.1177/1536867x0900900206.
15. Zou G. A modified Poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004;159:702-706. DOI: 10.1093/aje/kwh090.
16. Morris DE, Oakley JE, Crowe JA. A web-based tool for eliciting probability distributions from experts. Environ Model Softw 2014;52:1-4. DOI: 10.1016/j.envsoft.2013.10.010.
17. Zhou G, Luo S, He J, et al. Effectiveness and safety of tuberculosis preventive treatment for contacts of patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. Clin Microbiol Infect 2024;30:189-196. DOI: 10.1016/j.cmi.2023.09.015.
18. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. AIDS 2001;15:2137-2147. DOI: 10.1097/00002030-200111090-00009.
19. 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. DOI: 10.1056/NEJMoa1005136.
20. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. Lancet 2011;377:1588-1598. DOI: 10.1016/S0140-6736(11)60204-3.
21. Kasaie P, Pennington J, Gupta A, Dowdy DW, Kendall EA. The impact of preventive treatment for multidrug- and rifampin-resistant tuberculosis exceeds trial-based estimates. Clin Infect Dis 2024;78:133-143. DOI: 10.1093/cid/ciad557.
22. Marks SM, Mase SR, Morris SB. Systematic review, meta-analysis, and cost-effectiveness of treatment of latent tuberculosis to reduce progression to multidrug-resistant tuberculosis. Clin Infect Dis 2017;64:1670-1677. DOI: 10.1093/cid/cix208.
23. Arabyat RM, Raisch DW, McKoy JM, Bennett CL. Fluoroquinolone-associated tendon-rupture: a summary of reports in the Food and Drug Administration's adverse event reporting system. Expert Opin Drug Saf 2015;14:1653-1660. DOI: 10.1517/14740338.2015.1085968.
24. Bidell MR, Lodise TP. Fluoroquinolone-associated tendinopathy: does levofloxacin pose the greatest risk? Pharmacotherapy 2016;36:679-693. DOI: 10.1002/phar.1761.
25. Lapi F, Tuccori M, Motola D, et al. Safety profile of the fluoroquinolones: analysis of adverse drug reactions in relation to prescription data using four regional pharmacovigilance databases in Italy. Drug Saf 2010;33:789-799. DOI: 10.2165/11536810-000000000-00000.
26. Scavone C, Mascolo A, Ruggiero R, et al. Quinolones-induced musculoskeletal, neurological, and psychiatric ADRs: a pharmacovigilance study based on data from the Italian spontaneous reporting system. Front Pharmacol 2020;11:428. DOI: 10.3389/fphar.2020.00428.
27. Pierfitte C, Royer RJ. Tendon disorders with fluoroquinolones. Therapie 1996;51:419-420.
28. Noel GJ, Bradley JS, Kauffman RE, et al. Comparative safety profile of levofloxacin in 2523 children with a focus on four specific musculoskeletal disorders. Pediatr Infect Dis J 2007;26:879-891. DOI: 10.1097/INF.0b013e3180cbd382.
29. Bradley JS, Kauffman RE, Balis DA, et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Pediatrics 2014;134:e146-e153. DOI: 10.1542/peds.2013-3636.