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# Levofloxacin preventive treatment in children exposed to MDR-TB

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Methods
TB-CHAMP was a community-based multi-site household cluster-randomized double-blind placebo-controlled trial investigating levofloxacin as preventive treatment post-MDR-TB exposure, in South Africa. Following household exposure to an adult with bacteriologically-confirmed pulmonary MDR-TB, children 0-4 years were enrolled regardless of Mtb infection or HIV status, with 5-17-year-olds enrolled if Mtb-infected or HIV-positive. Households were randomized to levofloxacin vs. placebo daily for 24 weeks. The primary efficacy endpoint was incident TB, including TB death, by 48 weeks post-randomization. The primary safety outcome was adverse events grade ≥ 3 at least possibly associated with study drug while on treatment.

Results
Of 922 participants from 497 households, 453 were randomly assigned to receive levofloxacin and 469 placebo; 90% were <5 years. Five (1.1%) in the levofloxacin-arm and 12 (2.6%) in the placebo-arm developed TB by 48-weeks (hazard ratio [HR] 0.44; 95% confidence interval 0.15-1.25). All sensitivity analyses were consistent with results from the primary analyses. Four levofloxacin-arm vs. 8 placebo-arm participants developed grade ≥3 adverse events at least possibly related to study drug (HR 0.52; 95% CI 0.16-1.71). One child in the levofloxacin arm developed tendonitis (grade 2).

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**ABSTRACT 236 words**

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**Discussion**

Although fewer developed TB disease in the levofloxacin group this was not statistically significant.

## BACKGROUND

Each year, half a million people are estimated to develop multidrug-resistant (MDR) tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*) resistant to isoniazid and rifampin.[1] MDR-TB is more challenging to treat than drug-susceptible TB and is expensive and complex for health services and families.[2] An estimated 2 million children are currently infected with MDR-*Mtb* globally, with approximately 30,000 developing MDR-TB disease annually.[3]

Current approaches for MDR-TB epidemic control largely focus on diagnosing symptomatic individuals and initiating effective treatment. However, modelling studies suggest that contact management and TB preventive treatment provided to well individuals at high risk of disease progression,[4] are critical to achieve the ambitious End TB Strategy[5] targets.

There is good evidence for the efficacy and safety of TB preventive treatment for individuals exposed to drug-susceptible TB, but data from randomized-controlled trials for MDR-TB are lacking.[6] Observational data suggest that fluoroquinolone-containing regimens are safe and associated with low risk of developing TB.[7] The World Health Organization (WHO) currently conditionally recommends that 'in selected high-risk household contacts of patients with MDR-TB, TB preventive treatment may be considered based on an individualized risk assessment,'[8] and given low quality of evidence, calls for data from clinical trials.

Young children, particularly those <5 years, are an important target population for TB preventive treatment given their high risk of rapid disease progression following TB exposure and risk of severe forms of TB.[9] Older children and adolescents with evidence of *Mtb* infection are also at elevated risk of TB,[10] as are those living with HIV.[11] Of children exposed to TB who progress to disease, >80% progress within the first year.[10] One of the most efficient strategies to identify children recently exposed to TB is through household contact tracing of individuals with newly diagnosed TB, where contacts are offered TB preventive treatment following exclusion of TB. We undertook a clinical trial to compare levofloxacin versus placebo in children/adolescents exposed to a person with infectious MDR-TB in their household.

## METHODS

### Trial design, setting and recruitment

TB-CHAMP (Tuberculosis Child Multidrug-resistant Preventive Therapy ISRCTN92634082) was a multi-site, cluster-randomized, double-blind placebo-controlled trial investigating the efficacy and safety of levofloxacin, conducted at 5 sites in South Africa between 2017 and 2023.[12] Adult index patients were identified following a routine diagnosis of confirmed pulmonary MDR-TB (using genotypic and/or phenotypic approaches; Supplement)[2] and recruited, following written informed consent, if there was at least one child aged <5 years living in the same household in the previous 6 months. Children <5 years were recruited following written informed consent from their parent/caregiver if exposure to the MDR-TB index patient had been substantial in the preceding 6 months. Under protocol version 3.0 (September 2021), children 5-17 years with a positive interferon-gamma release assay (IGRA, QuantiFERON-Gold Plus, Qiagen) or living with HIV were also included (Supplement). For these children, in addition to consent from the parent/caregiver, assent was also obtained from children ≥7 years. Prior to enrolment, children were evaluated for prevalent TB with history, examination, and plain-film chest radiography. Children with any symptoms or signs consistent with TB and/or with abnormal chest radiography underwent respiratory sampling for microbiological examination for *Mtb*. Children were given a course of broad-spectrum antibiotics based on clinical judgment and re-evaluated. Only children in whom TB disease had been confidently excluded were recruited. Randomization was at household-level, stratified by site, with 1:1 allocation to either levofloxacin or placebo. Randomization was by a computer-generated randomization list prepared by the trial statistician using block randomization with varying block size, incorporated in a centralized web-based database. The study was approved by all institutional and national ethics committees (Supplement). All authors vouch for the completeness of the data presented and fidelity to the protocol.

**Trial procedures**

Children were seen at baseline and at 4, 8, 12, 16, 24, 48 and 72-weeks, and at interim visits as clinically indicated. Investigations were completed if the child had any symptoms that could be consistent with TB (including cough or fever >2 weeks, poor weigh gain/weight loss or any unexplained symptoms; Supplement). Children were also evaluated for adverse events (AEs) using DAIDS toxicity tables, to study medications at visits.

**Treatment**

Study medications were manufactured by Macleods Pharmaceuticals, India, as 250mg scored tablets levofloxacin or levofloxacin-placebo (primarily microcrystalline cellulose based), given using weight-bands at 15-20 mg/kg (maximum 750mg) daily for 24-weeks. At visits, children were weighed, and dosages adjusted. Treatment was supervised by parents/caregivers and adherence measured by treatment recall, completion of a treatment card and by pill counts. Pill counts, with

information verified from treatment cards, were used to define adherence. Treatment interruptions of up to 4-weeks overall were allowed, resulting in 28-week maximum treatment duration.

**Primary outcome**

The primary endpoint was incident TB disease (microbiologically-confirmed or clinically-diagnosed) or TB death by 48-weeks following randomization, adjudicated by an independent Endpoint Review Committee (ERC) unaware of treatment allocation, using international consensus case definitions.[13] Discordant reviews were resolved by discussion.

**Secondary outcomes**

The prespecified main safety endpoint was AEs grade ≥3 at least possibly associated with study treatment. Secondary endpoints included TB disease by 72-weeks, all-cause mortality, any AEs grade ≥3 from starting study treatment up to 30 days after last study drug dose, serious AEs (SAEs) up to 30- days after last study drug dose, discontinuation of study treatment due to AEs, selected pre-defined AEs (Supplement) and treatment adherence.

**Statistical Analysis**

We calculated that 1009 participants would provide 80% power to detect a 60% reduction in incident TB by 48-weeks, at a two-sided significance level of 5%. This assumed 7% TB incidence by 48-weeks in the control arm, an average of two participants enrolled per household, household intra-class correlation of 0.10, and 10% loss to follow-up.

In primary efficacy analysis, all randomized participants were included except for late screening failures with TB at baseline [modified intention-to-treat (mITT) population]. Kaplan-Meier methods were used to describe time to incident TB. A pre-specified 6-week window was allowed for the 48-week visit. Participants who did not have a TB endpoint observed by the 48-week visit had follow-up censored at the earliest of: 1) 54-weeks from randomization, 2) date of last study follow-up, or 3) date of death. We used Cox regression to estimate the hazard ratio (HR) comparing levofloxacin versus placebo, with cluster-robust variance accounting for intra-household correlation. We adjusted for site and age group (<5 versus 5-17 years) using the Inverse Probability Treatment Weighting method due to small number of TB events.[14] Analysis assumed non-informative censoring, but otherwise there were no missing data in the model. We assessed for evidence of non-proportional hazards using the Grambsch-Therneau test based on scaled Schoenfeld residuals.[15]

Safety analyses included all participants who received at least one study drug dose. Follow-up time was censored at 30-days after last study drug dose for relevant outcomes. Adherence was classified as





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the proportion of allocated doses taken being <80%, 80-<90% or ≥90%. Multiplicity was not adjusted for in analyses of secondary outcomes.

The Independent Data Monitoring Committee (IDMC) reviewed interim unblinded data 4 times during the trial, including formal interim efficacy analysis when 500 children had been followed for at least 24-weeks (October 2021). The Haybittle-Peto criterion for efficacy (P<0.001) guided a recommendation of stopping or modifying the trial. Analyses used Stata version 16.0 or later (StataCorp).

**Sensitivity analyses**

Pre-specified sensitivity analysis included: 1) adjusting for pre-defined baseline covariates, 2) incident TB based on site-adjudication (decision-to-treat by the attending clinician), 3) including only children <5 years, and 4) per-protocol (PP) analysis restricted to participants adherent to randomized treatment and who were not late screening failures.[16]

## RESULTS

**Participants/trial population**

Of 5,063 MDR-TB index patients identified, 631 were screened for eligibility (Figure 1). From these, 1,120 child contacts were screened, with 922 enrolled, from 497 index patients/households, between 27 September 2017 and 29 July 2022. See Supplementary Appendix S5.1 for index patient characteristics.

Of 922 children enrolled, 453 were assigned to levofloxacin and 469 to placebo. There were 29 late screening failures, including 6 with TB disease at baseline diagnosed following enrolment (Table S4.4). The efficacy mITT analyses therefore included 916 children.

Baseline characteristics of randomized children were reasonably similar between treatment arms (Table 1). Participants had median age 2.8 years (interquartile range (IQR), 1.3 to 4.2 years), with 90% aged <5 years and 94% BCG-vaccinated. Overall, 49% were male, 2% were living with HIV and 34% were HIV-exposed uninfected. Among 839 children aged <5 years with available test results, 163 (20%) were IGRA-positive.

**Follow-up**

Retention was similar between arms, with 81% of participants followed to at least 48-weeks, and 73% reaching 72-weeks (Table S6.1); 11% left the study early before their last scheduled study visit (Table S6.3). One child did not start study treatment due to early withdrawal.

**Primary Outcome**

In total, 21 (2.3%) of 916 children developed TB (as adjudicated by the ERC) during overall study follow-up, 10 with microbiologically-confirmed TB. Two children developed TB after the week-72 visit. Five (1.1%) of 451 children in the levofloxacin-arm and 12 (2.6%) of 465 children in the placebo-arm developed TB by 48-weeks (Supplement). The corresponding rates per 100 person-years were 1.2 (0.5-2.9) and 2.9 (1.6-5.2), respectively (hazard ratio [HR] 0.44; 95% CI 0.15-1.25; P=0.12). One child in the levofloxacin-arm developed TB during the 24-week treatment period, compared to 10 in the placebo-arm (Figure 2; test for non-proportional hazards P=0.11).

**Secondary Outcomes**

By the 72-week visit, 6 (1.3%) children in the levofloxacin-arm, and 13 (2.8%) in the placebo-arm, developed TB (HR 0.49; 95% CI 0.18-1.30).

Safety analyses included 921 children who started study treatment. Four (0.9%) of 452 children in the levofloxacin-arm had grade ≥3 AEs at least possibly associated with study drug versus 8 (1.7%) of 469 in the placebo-arm (HR 0.52; 95%CI 0.16-1.71; P=0.29l Table 2). The corresponding figures for any grade ≥3 AEs up to 30-days after last study drug dose were 14 (3.1%) versus 24 (5.1%), respectively (HR 0.64; 95% CI 0.32-1.28; P=0.21). Two deaths occurred during follow-up. One infant (levofloxacin-arm) died of cardiac arrest with a congenital heart defect at 12 months of age after 39-weeks on study, and another infant (placebo-arm) died of viral pneumonia at 11 months of age after 11 weeks on study; neither death was considered related to study drug or TB.

One child developed tendonitis (grade 2, levofloxacin-arm), which resolved 21 days after stopping study drug. Seventy-five (17%) children in the levofloxacin-arm and 80 (17%) in the placebo-arm permanently discontinued study drug early for any reason (Table S7.2). Only six (1.3%) children discontinued study drug due to AEs in the levofloxacin-arm versus 1 (0.2 %) the placebo-arm (HR 5.00; 95%CI 0.61-41.32); P=0.14). Adherence was good, with 87% of children in the levofloxacin-arm and 86% in the placebo-arm taking ≥80% of allocated doses. Poor treatment adherence was not associated with developing TB during follow-up in the levofloxacin-arm.

**Sensitivity analyses**

Pre-specified sensitivity analyses were consistent with primary analysis, with analysis based on site-adjudicated TB endpoints showing a slightly stronger treatment effect (Figure 3).

We found no evidence of heterogeneity of treatment effect in prespecified exploratory subgroup analyses, including by gender, IGRA and HIV exposure status (Table S8.5) but numbers are small.

## DISCUSSION

In this pediatric trial of MDR-TB preventive treatment, we recruited nearly a thousand children exposed to MDR-TB. Seventeen children developed TB by 48-weeks as adjudicated by the independent ERC. Although fewer developed TB disease in the levofloxacin group this was not statistically significant. We demonstrate that daily levofloxacin, taken for six months, did not demonstrate any safety concerns in children. Adherence to study drug was good in both arms, despite using an adult formulation.

There are several potential explanations for the lower-than-expected TB event rate. We anticipated a similar effect size of the intervention to that seen in the trial, but had assumed more than double the risk of incident TB in the placebo-arm, based on observational studies of drug-susceptible and drug-resistant TB.[16-19] In children <5 years in our trial, 20% were IGRA-positive, considerably lower than previous studies in South Africa, where 40-50% of children with household exposure had a positive test of *Mtb* infection.[17] Given the wide rollout of Xpert MTB/RIF in South Africa, it is possible that individuals with MDR-TB are now initiated more rapidly onto appropriate MDR-TB therapy, reducing the duration of exposure for household contacts, reducing the risk of *Mtb* transmission. With the widescale rollout of more effective MDR-TB treatment, particularly bedaquiline and linezolid since 2018, MDR-TB patients are now likely to be rendered non-infectious more rapidly. Finally, we rigorously investigated children at baseline to exclude prevalent TB disease, using thorough history, examination, and chest radiography, with microbiological examination in the presence of any symptoms, signs or chest radiographic abnormality. Children screened out with early TB disease may not have been detected with less comprehensive screening and would otherwise have later been considered to have incident disease when symptoms and signs became more pronounced.

An important finding was the timing of incident TB in both arms. In the placebo arm, most events occurred in the first 12 weeks, suggesting that many children, while not having clinically overt disease at baseline, had some form of subclinical disease that rapidly progressed to symptomatic disease. In the levofloxacin-arm, one child developed TB on preventive treatment, with most events occurring around one-year after randomization. Levofloxacin may therefore have treated sub-clinical disease, prevented disease progression, but had minimal post-antibiotic effect. This has important implications for household-contact management and provision of TB preventive treatment early after the diagnosis

of the index patient. The similar rate of TB after week-48 in both arms could be due to subsequent re-infection in this high-burden setting.

A systematic review of MDR-TB preventive treatment[7] demonstrated a risk reduction of 90%. A subsequent observational study in Pakistan[18] evaluated a fluoroquinolone together with either ethambutol or ethionamide as MDR-TB prevention in 172 individuals and compared incident TB to historic controls, finding a risk reduction of 65%. The VQUIN trial in Vietnam enrolled mainly adults (n=2031) comparing levofloxacin vs. placebo with results expected soon. A5300/P2003B (NCT03568383) is ongoing, recruiting adults and children exposed to MDR-TB across multiple sites globally in an open-label trial comparing delamanid to isoniazid[19].

An important consideration when assessing efficacy is the contribution of TB preventive treatment itself versus the household contact management strategy. In our trial, TB preventive treatment was compared to no treatment, but in both arms, MDR-TB source patients were identified, household contacts were rigorously screened for prevalent disease and child contacts followed regularly. In most high-burden settings, routine programmatic management of close contacts of MDR-TB patients is likely less complete. In a modelling study evaluating the impact of household contact management and TB preventive treatment for children exposed to MDR-TB, 65% of deaths prevented were due to the screening for prevalent disease.[20] Moreover, modelling work indicates that the long-term population impact of TB preventive treatment for MDR-TB, including the reduction in onwards transmission from adult cases prevented, could be greater than suggested by trial outcomes alone.[21] Finally, fluoroquinolones may have substantial negative effects on Gram-positive and Gram-negative bacteria, with potential impact on development of antimicrobial resistance and the microbiome. This was evaluated (analysis ongoing).

Safety results of our trial were reassuring, with 4 children experiencing events of ≥ grade 3 at least possibly associated with study drug in the levofloxacin-arm, compared to 8 in the placebo-arm. There was 1 episode of tendonitis reported (grade 2).

Our trial has limitations. The event rate in the placebo-arm was lower than anticipated. There are also limitations to generalizability. Although we recruited from diverse sites in South Africa, with wide population and mycobacterial strain diversity, we mostly (>90%) included children <5 years of age, expanding later only to selected older children. Care should be taken to extrapolate efficacy to other settings and to older children and adolescents, who may have more non-household TB exposure. Finally, we were not able to collect the *Mtb* strains from all index patients and so were unable to interrogate second-line drug resistance or resistance mechanisms. In South Africa, nationally, 13% of

MDR-*Mtb* isolates were resistant to fluoroquinolones between 2012-2014 and so we might expect levofloxacin preventive treatment to be ineffective in contacts of this proportion of index patients.[22]

In conclusion, fewer children developed TB disease in the levofloxacin group compared to placebo. However, this was not statistically significant. Very few adverse events were seen in children treated with levofloxacin, which is reassuring. These results need to be integrated with results from other trials in other populations and settings to inform global policy and practice.

## ADDITIONAL INFORMATION

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### Conflicts of Interest

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

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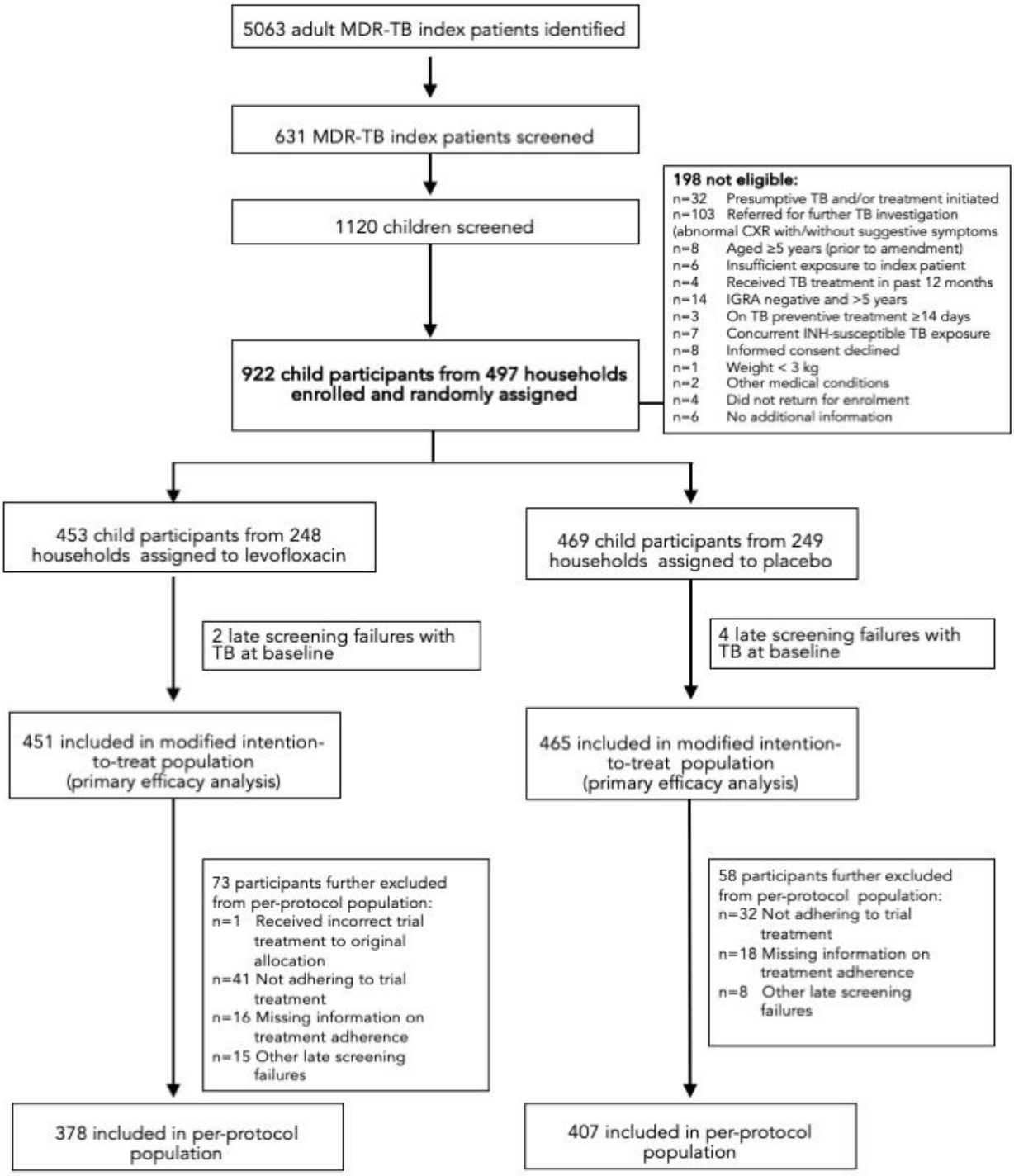
**Table 1. Baseline characteristics of children enrolled in the TB-CHAMP trial**

| | | Levofloxacin (n=453) | Placebo (n=469) | Total (n=922) |
|---|---|---|---|---|
| Sex | Male | 213 (47%) | 241 (51%) | 454 (49%) |
| | Female | 240 (53%) | 228 (49%) | 468 (51%) |
| Age (years) | Median | 3.0 | 2.6 | 2.8 |
| | IQR | 1.4, 4.3 | 1.3, 4.1 | 1.3, 4.2 |
| | Range | 0.1, 17.9 | 0.1, 17.4 | 0.1, 17.9 |
| | <1 | 85 (19%) | 83 (18%) | 168 (18%) |
| | 1 to 2.9 | 140 (31%) | 175 (37%) | 315 (34%) |
| | 3 to 4.9 | 180 (40%) | 176 (38%) | 356 (39%) |
| | 5 to 9.9 | 18 (4%) | 17 (4%) | 35 (4%) |
| | 10 to 14.9 | 20 (4%) | 13 (3%) | 33 (4%) |
| | 15 to 17.9 | 10 (2%) | 5 (1%) | 15 (2%) |
| Ethnicity | Black | 362 (80%) | 381 (81%) | 743 (81%) |
| | South African mixed | 81 (18%) | 78 (17%) | 159 (17%) |
| | Mixed race | 8 (2%) | 8 (2%) | 16 (2%) |
| | Other | 2 (0%) | 2 (0%) | 4 (0%) |
| IGRA status | Negative | 297 (67%) | 335 (74%) | 632 (70%) |
| | Positive | 134 (30%) | 108 (24%) | 242 (27%) |
| | Indeterminate | 12 (3%) | 12 (3%) | 24 (3%) |
| | N missing | 10 | 14 | 24 |
| HIV status | Positive | 10 (2%) | 9 (2%) | 19 (2%) |
| | HIV-exposed uninfected | 153 (34%) | 160 (34%) | 313 (34%) |
| | HIV-unexposed | 288 (64%) | 298 (64%) | 586 (64%) |
| | N missing | 2 | 2 | 4 |
| BCG-vaccinated | Yes | 423 (94%) | 442 (95%) | 865 (94%) |
| | No | 28 (6%) | 25 (5%) | 53 (6%) |
| | N missing | 2 | 2 | 4 |
| Previous TB treatment | Yes | 10 (2%) | 8 (2%) | 18 (2%) |
| | No | 443 (98%) | 461 (98%) | 904 (98%) |
| Current TB preventive treatment | Yes | 9 (2%) | 6 (1%) | 15 (2%) |
| | No | 444 (98%) | 463 (99%) | 907 (98%) |
| Weight-for-age Z score* | Median | -0.4 | -0.4 | -0.4 |
| | IQR | -1.2, 0.3 | -1.2, 0.4 | -1.2, 0.3 |
| Height-for-age Z score* | Median | -0.9 | -0.9 | -0.9 |
| | IQR | -1.6, -0.2 | -1.8, -0.2 | -1.7, -0.2 |
| Site | Desmond Tutu TB Centre | 222 (49%) | 230 (49%) | 452 (49%) |
| | Shandukani | 92 (20%) | 80 (17%) | 172 (19%) |
| | Matlosana | 117 (26%) | 142 (30%) | 259 (28%) |
| | Isanga Lethembo | 3 (1%) | 4 (1%) | 7 (1%) |
| | THINK | 19 (4%) | 13 (3%) | 32 (3%) |

* Standardised to the WHO reference, and for weight-for-age, to UK reference for age >10 years (since WHO weight-for-age growth charts are only available for age ≤10 years). TB=tuberculosis; BCG=bacillus Calmette-Guérin; IGRA=interferon-gamma release assay (QuantiFERON-Gold Plus, Qiagen); IQR=interquartile range THINK: TB and HIV Investigative Network. BCG vaccination status verified through medical records and/or vaccine scar.

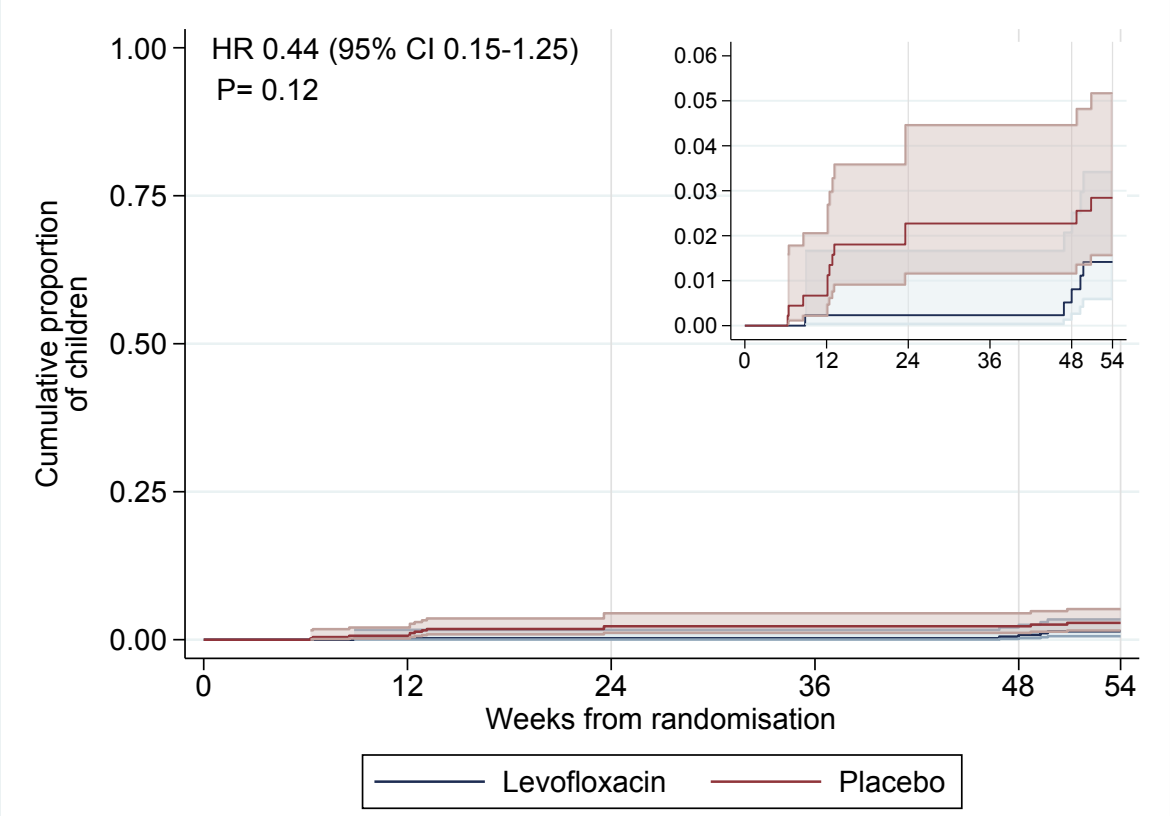
**Figure 1. Overview of enrolment, randomization, and analysis of child multi-drug resistant tuberculosis child household contacts**




MDR=multidrug-resistant; TB=tuberculosis; CXR=chest x-ray; IGRA=interferon-gamma release assay; INH=isoniazid

Of the 5,063 adult index patients identified, 631 were screened. Reasons why for index patient were ineligible for screening included the following: the study team was unable to establish contact with the index patient, the index patient had died or moved away, the index patient was <18 years of age, the index patient had rifampicin-mono-resistant TB, they had been on treatment for more than 6 months already, they had non-pulmonary TB, or there were no children <5 years reported to be living in the household over the past 6 months.

**Figure 2. Tuberculosis disease by 48-weeks visit in child and adolescent household contacts of multidrug-resistant tuberculosis, by treatment arm**



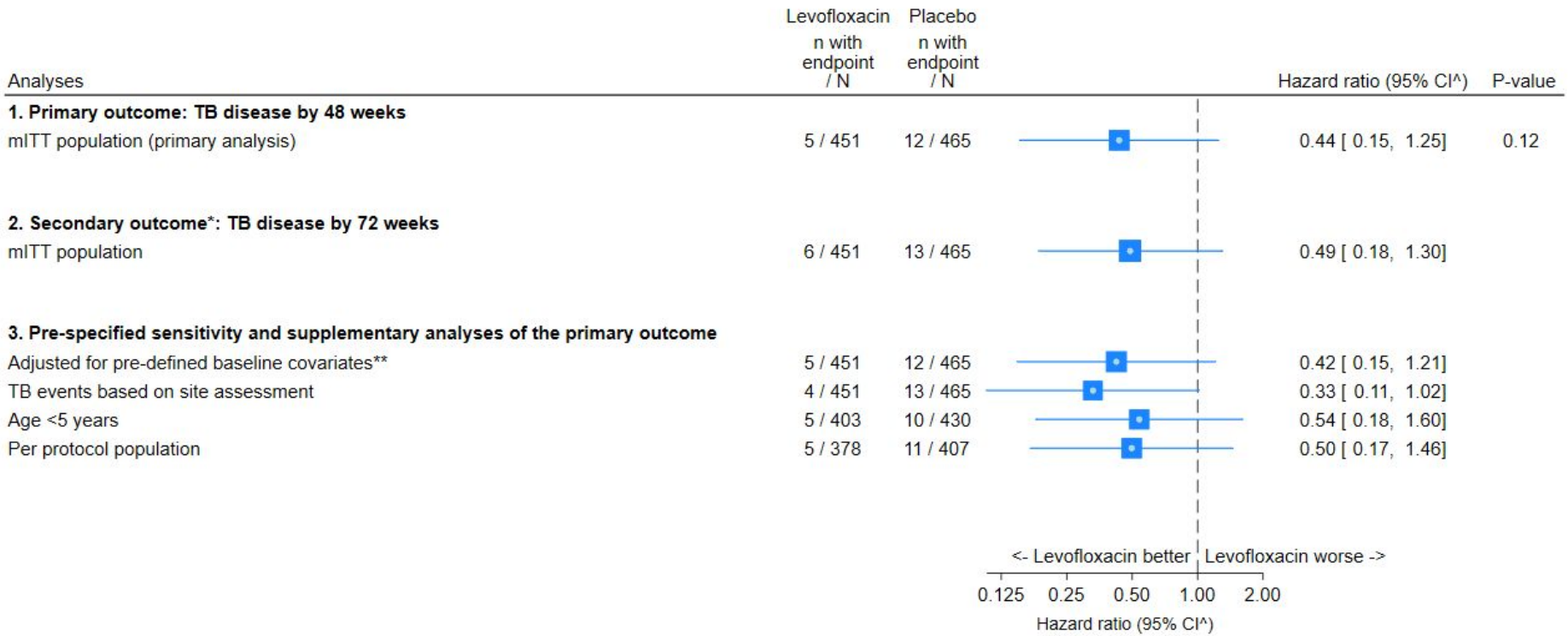

**Number at risk (TB endpoints)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Levofloxacin | 451 | (1) | 425 | (0) | 412 | (0) | 368 | (1) | 339 (3) 323 |
| Placebo | 465 | (3) | 441 | (7) | 414 | (0) | 379 | (0) | 357 (2) 334 |

A pre-defined 6-week window was allowed for scheduled visits, therefore, follow-up time in analysis of primary endpoint was censored at 48+6=54 weeks. Confidence bands are adjusted for household clustering.

HR=hazard ratio; CI=confidence interval

**Figure 3. Primary and pre-defined sensitivity analyses of tuberculosis disease by 48-weeks**




A pre-defined 6 weeks window was allowed for the week-48 visit, therefore, follow-up time in analysis of primary endpoint was censored at 48+6=54 weeks.

^ The confidence intervals were not adjusted for multiplicity.

* All-cause mortality was also a secondary endpoint and there was one death in each treatment group,

**Adjusted for the following baseline covariates: TB infection status, HIV exposure status, and weight-for-age Z-score.

CI=confidence interval; TB=tuberculosis; mITT=modified intention-to-treat

**Table 2. Number (%) of children experiencing safety endpoints**

| Endpoints | Levofloxacin (n=452*) | Placebo (n=469*) | Hazard ratio (95% CI^) | P-value |
|---|---|---|---|---|
| 1. Grade ≥3 AEs at least possibly associated with study drug | 4 (0.9%) | 8 (1.7%) | 0.52 (0.16-1.71) | 0.29 |
| 2. Grade ≥3 AEs[$] | 14 (3.1%) | 24 (5.1%) | 0.64 (0.32-1.28) | 0.21 |
| 3. Serious adverse events[$] | 9 (2.0%) | 8 (1.7%) | 1.22 (0.45-3.34) | 0.69 |
| 4. Permanently discontinued study treatment due to AE(s) | 6 (1.3%) | 1 (0.2%) | 5.00 (0.61-41.32) | 0.14 |
| 5. Pre-specified AE's[+] | | | | |
| 5a. Arthritis/arthralgia/tendinopathy (any grade) | 6 (1.3%) | 4 (0.9%) | 1.32 (0.35-4.98) | 0.69 |
| 5b. Central nervous system effects[$] | 7 (1.5%) | 11 (2.3%) | 0.59 (0.21-1.62) | 0.30 |
| 5c. Severe rash or cutaneous reaction[$] | 1 (0.2%) | 0 (0%) | - | |

* Number of participants receiving ≥1 study drug dose.

$ Up to 30 days after last study drug dose.

+ Note that drug-related fever and peripheral neuropathy were also pre-specified adverse events but there were no events in either treatment group. Central nervous system effects included altered mood or behavior including hyperactivity, insomnia, vivid dreams, changes in vision, and headache. Further details on the reported adverse events for each safety endpoint are included in Tables S9.9-9.11.

^ The confidence intervals were not adjusted for multiplicity.

AEs=adverse events; CI=confidence interval

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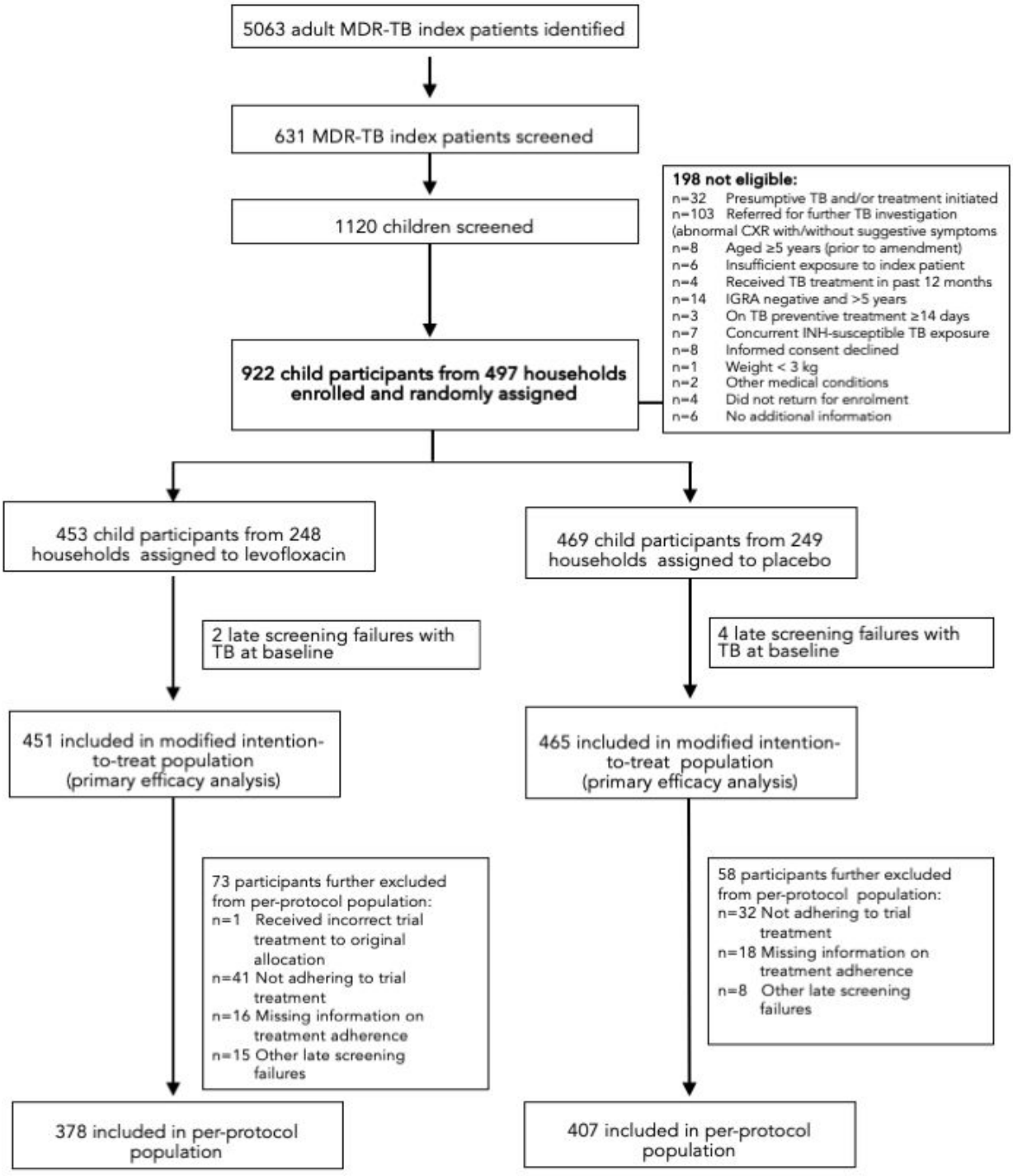


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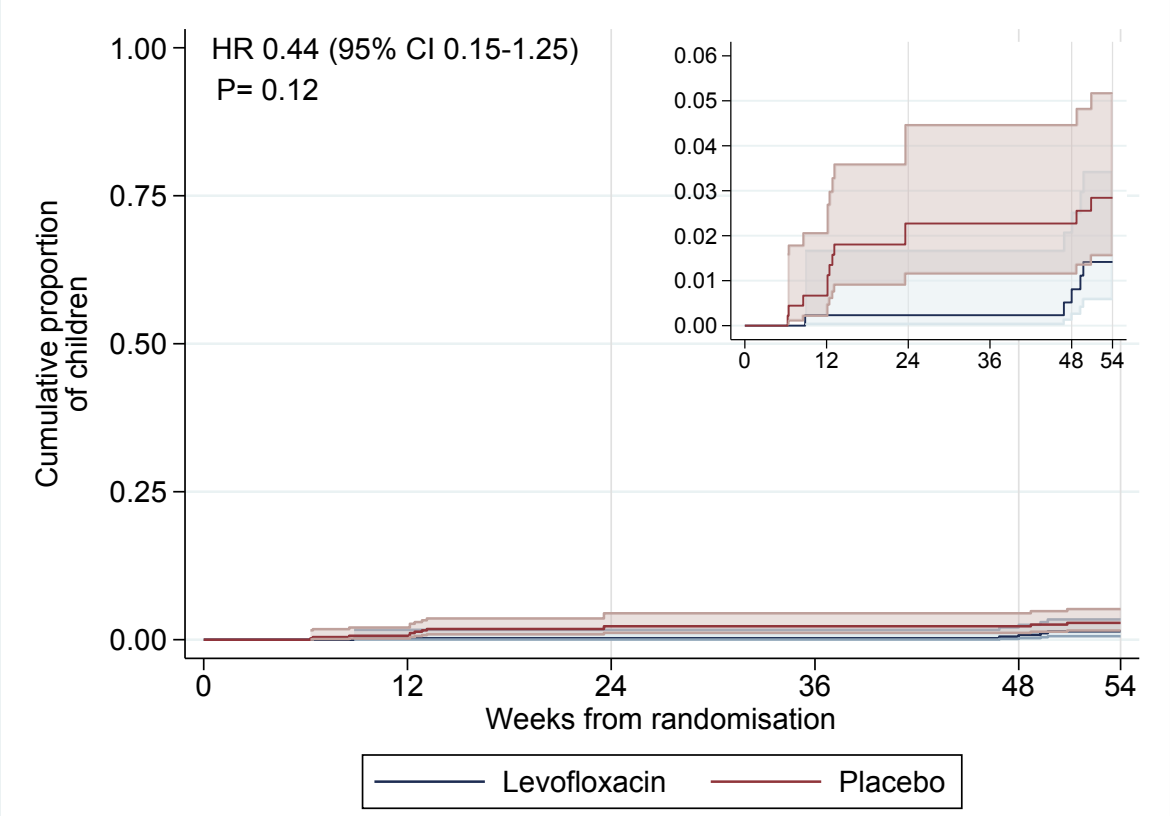


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HR=hazard ratio; CI=confidence interval