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Early View

Review

Global estimates and determinants of antituberculosis drug pharmacokinetics in children and adolescents: a systematic review and individual patient data meta-analysis

Fajri Gafar, Roeland E. Wasmann, Helen M. McIlleron, Rob E. Aarnoutse, H. Simon Schaaf, Ben J. Marais, Dipti Agarwal, Sampson Antwi, Nguyen D. Bang, Adrie Bekker, David J. Bell, Chishala Chabala, Louise Choo, Geraint R. Davies, Jeremy N. Day, Rajeshwar Dayal, Paolo Denti, Peter R. Donald, Ephrem Engidawork, Anthony J. Garcia-Prats, Diana Gibb, Stephen M. Graham, Anneke C. Hesseling, Scott K. Heysell, Misgana I. Idris, Sushil K. Kabra, Aarti Kinikar, Agibothu K. Hemanth Kumar, Awewura Kwara, Rakesh Lodha, Cecile Magis-Escurra, Nilza Martinez, Binu S. Mathew, Vidya Mave, Estomih Mduma, Rachel Mlotha-Mitole, Stellah G. Mpagama, Aparna Mukherjee, Heda M. Nataprawira, Charles A. Peloquin, Thomas Pouplin, Geetha Ramachandran, Jaya Ranjalkar, Vandana Roy, Rovina Ruslami, Ira Shah, Yatish Singh, Marieke G. G. Sturkenboom, Elin M. Svensson, Soumya Swaminathan, Urmila Thatte, Stephanie Thee, Tania A. Thomas, Tjokosela Tikiso, Daan J. Touw, Anna Turkova, Thirumurthy Velpandian, Lilly M. Verhagen, Jana L. Winckler, Hongmei Yang, Vycke Yunivita, Katja Taxis, Jasper Stevens, Jan-Willem C. Alffenaar, for the Global Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in Pharmacokinetics of Anti-TB Drugs

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Global estimates and determinants of antituberculosis drug pharmacokinetics in children and adolescents: a systematic review and individual patient data meta-analysis

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Running title:

Pharmacokinetics of anti-TB drugs in children and adolescents

Take home message (256 out of 256 characters)**:**

Summary estimates and key determinants of anti-TB drug pharmacokinetics in children and adolescents were assessed from globally available data, advocating for dose adjustment or therapeutic drug monitoring in certain groups at risk of suboptimal exposures.

Word counts:

Abstract : 250

Main text : 4137

ABSTRACT

Background

Suboptimal exposure to antituberculosis drugs has been associated with unfavourable treatment outcomes. We aimed to investigate estimates and determinants of first-line antituberculosis drug pharmacokinetics in children and adolescents at a global level.

Methods

We systematically searched MEDLINE, Embase, and Web of Science (1990-2021) for pharmacokinetic studies of first-line antituberculosis drugs in children and adolescents. Individual patient data were obtained from authors of eligible studies. Summary estimates of total/extrapolated area under the plasma concentration-time curve (AUC_{0-24}) and peak plasma concentration (C_{max}) were assessed with random-effects models, normalized with current WHO-recommended paediatric doses. Determinants of AUC_{0-24} and C_{max} were assessed with linear mixed-effects models.

Results

Of 55 eligible studies, individual patient data were available for 39 (71%), including 1628 participants from 12 countries. Geometric means (95% CIs) of steady-state AUC_{0-24} were summarized for isoniazid (18.7 [15.5−22.6] h·mg/L), rifampicin (34.4 [29.4−40.3] h·mg/L), pyrazinamide (375.0 [339.9−413.7] h·mg/L), and ethambutol (8.0 [6.4−10.0] h·mg/L). Our multivariate models indicated that younger age (especially <2 years) and HIV-positive status were associated with lower AUC_{0-24} for all antituberculosis drugs, while severe malnutrition was associated with lower AUC_{0-24} for isoniazid and pyrazinamide. N-acetyltransferase *2* rapid acetylators had lower isoniazid AUC_{0-24} and slow acetylators had higher isoniazid

AUC_{0-24} than intermediate acetylators. Determinants of C_{max} were generally similar to those for AUC_{0-24}.

Conclusion

This study provides the most comprehensive estimates of plasma exposures to first-line antituberculosis drugs in children and adolescents. Key determinants of drug exposures were identified. These may be relevant for population-specific dose adjustment or individualized therapeutic drug monitoring.

Keywords

Pharmacokinetics, tuberculosis, antituberculosis drugs, children, adolescents, HIV, malnutrition.

INTRODUCTION

Tuberculosis (TB) remains a major global health challenge. Until the COVID-19 pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS [1]. In children <15 years of age, the World Health Organization (WHO) estimated that there were 1.1 million new TB cases and 226,000 TB-related deaths globally in 2020 [1]. Adolescents also suffer a significant burden of the disease, with an estimated 727,000 TB cases among those aged 10-19 years in 2012 [2]. Adequate access to treatment and optimal dosing strategies are essential components of the global strategy to end childhood and adolescent TB [3].

Suboptimal exposures to anti-TB drugs are associated with poor treatment outcomes, including treatment failure, acquired drug resistance, and death [4, 5]. Target anti-TB drug exposures in children and adolescents are largely based on pharmacokinetic profiles that approximate adult exposures [6], although pharmacokinetics and pharmacodynamics in young children and adults are potentially different due to maturation factors [7]. Moreover, the sources of pharmacokinetic variability of anti-TB drugs in children and adolescents have not been reviewed systematically. This is likely due to differences between studies in the included study population, study design and methods, drug and dosing characteristics, covariates included in the analysis, and pharmacokinetic assessments and parameters used to interpret the results.

To overcome these challenges, we aimed to summarize pharmacokinetic estimates of first-line anti-TB drugs (i.e., isoniazid, rifampicin, pyrazinamide, and ethambutol) in children and adolescents, stratified by study-level characteristics. Furthermore, we aimed to assess patient-level characteristics and key subpopulations in whom pharmacokinetic profiles may differ

from the average observed in children with TB. This would identify the potential need for dose adjustment in particular groups or individuals who are at risk of suboptimal drug exposure using currently WHO-recommended dosing strategies.

METHODS

Search strategy and selection criteria

The study protocol is registered with PROSPERO (CRD42018110807). The main outcomes registered in the PROSPERO protocol were analysed in this study. We followed the Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data (PRISMA-IPD) guidelines to report the findings [8].

All pharmacokinetic studies of first-line anti-TB drugs in children and adolescents aged 0−18 years treated for drug-susceptible pulmonary and/or extrapulmonary TB were eligible for inclusion in this systematic review and individual patient data meta-analysis. Studies in healthy volunteers and in those receiving first-line drugs for indications other than TB disease (e.g., TB infection and staphylococcal bacteraemia) were excluded, because pathology-mediated pharmacokinetic variations may occur in different disease states [9]. Additionally, review articles, commentaries, editorials, and case series with fewer than five patients were excluded.

Relevant studies published between January 1, 1990, and February 2, 2021, were searched in MEDLINE (via PubMed), Embase, and Web of Science; the search was updated on December 31, 2021. This timeframe was chosen because of the expected availability of the original datasets. No restrictions with respect to language were applied. A combination of the following MeSH terms and keywords was used: (tuberculosis or TB) and (first-line anti-TB

drugs or isoniazid or rifampicin or pyrazinamide or ethambutol) and (pharmacokinetics or drug concentrations) and (children or adolescents) (Appendix 1).

All articles retrieved by the search strategy were uploaded to Rayyan, a web application for systematic reviews (https://www.rayyan.ai/) [10]. After removing duplicates, all titles and abstracts were screened for eligibility and relevant full-text studies were reviewed by two independent reviewers (FG and REW). Reasons for excluding studies were noted. To find additional studies not retrieved by the search strategy, manual searching was performed from the reference lists of included studies and relevant review articles by two independent reviewers (FG and REW).

In the absence of a validated tool to assess the quality of pharmacokinetic studies, we developed a checklist (Appendix 2) by including relevant criteria according to the ROBINS-I tool for non-randomized studies of interventions [11], supplemented by essential components required for a critical appraisal of clinical pharmacokinetic studies [12]. An expert panel (DJT, MGGS, JS, and JWCA) evaluated and approved the components to be included in the checklist. Each study was graded as low, moderate or high quality by two independent reviewers (FG and REW).

All discrepancies between the first and second reviewers (FG and REW) during study selection and quality assessment of included studies were resolved by consensus; a third reviewer was not required as there were no persistent disagreements between the two reviewers.

Data management

Authors of eligible studies were asked to provide anonymized patient-level information on demographics (age, sex, weight, and height), clinical/laboratory characteristics (type of TB, HIV status, serum creatinine and albumin, arylamine N-acetyltransferase 2 [*NAT2*] genotypes, and solute carrier organic anion transporter family member 1B1 [*SLCO1B1*] genotypes), medication characteristics (drug dose, drug formulation and administration, dosing time, and dosing interval), and pharmacokinetic characteristics (sampling time and observed plasma concentrations) (Appendix 3).

Ethics approval was provided by the Independent Ethics Committee, University Medical Center Groningen, Groningen, the Netherlands (No. M21.278329). Data collections were approved by local ethics committees involved in the original studies. Written informed consent from parents or legal guardians and written/verbal assent from older participants was obtained at the time of inclusion.

Study definitions

Children and adolescents with drug-susceptible TB included culture-confirmed cases who were susceptible to at least isoniazid and rifampicin, and clinically diagnosed TB cases, who were treated with first-line anti-TB drugs. Anthropometric measurements were transformed into Z-score values based on WHO standard reference populations with the *zscorer* package in R (version 0.3.1). Malnutrition was defined as a weight-for-age and/or height-for-age Z-score <-2 but ≥-3 (moderate) or <-3 (severe) in patients aged <5 years, and a height-for-age and/or BMI-for-age Z-score <-2 but ≥-3 (moderate) or <-3 (severe) in patients aged ≥5 years [13]. Participants were genotypically and phenotypically categorized into rapid, intermediate, and slow acetylators, based on *NAT2* genetic polymorphisms (where available) and isoniazid elimination half-life, respectively (Appendix 4).

Data analysis

Our primary pharmacokinetic measures were total/extrapolated area under the plasma concentration-time curve from 0-24 hours post-dose (AUC_{0-24}) and peak plasma concentration (C_{max}) [14]. AUC_{0-24} was estimated based on the linear-up/log-down trapezoidal rule, and C_{max} was derived directly from the concentration-time curves. Pharmacokinetic assessments (Appendix 5) in patients with intensive sampling were performed noncompartmentally with the *PKNCA* package in R (version 0.9.4); sparse sampling data were excluded.

Study-level summary statistics on geometric means of AUC_{0-24} and C_{max}, and 95% confidence intervals (CIs) of the geometric mean, were estimated with random-effects meta-analyses using the *metafor* package in R (version 2.4.0). Heterogeneity was assessed using the I^2 statistics; any level of heterogeneity was allowed to emphasize the importance of between-study variability. To allow a comparison between different doses, AUC_{0-24} and C_{max} were dose-normalized by dividing the individual AUC_{0-24} and C_{max} values by mg/kg dose, then multiplying by the current WHO-recommended paediatric dose for isoniazid (10 mg/kg), rifampicin (15 mg/kg), pyrazinamide (35 mg/kg), and ethambutol (20 mg/kg) [15]; data on high-dose rifampicin >35 mg/kg were excluded from this particular analysis as it exhibited non-linear kinetics with plasma exposures due to saturation of hepatic clearance [16]. For reporting, AUC_{0-24} and C_{max} estimates were stratified by several groups, including dosing intervals (daily and intermittent [e.g., thrice weekly]), sampling schedules (steady-state [i.e., ≥14 days after the first dose] and non-steady-state), and WHO regions.

The effects of patient-level characteristics on log-transformed AUC_{0-24} and C_{max} were assessed with linear mixed-effects analyses using the *lme4* package in R (version 1.1.28), with

study-level random effects estimated via restricted maximum likelihood. For these mixed-effects analyses, AUC_{0-24} and C_{max} were not dose-normalized to allow adjustment of the models for drug dose, among other variables. To identify the most relevant variables, base models (adjusted for drug dose only) were developed for each patient characteristic; in each model, observations missing a certain variable were excluded. Next, we adjusted our multivariate models for drug dose, age, sex, severity of malnutrition, and HIV status, and completed with variables showing a trend toward association ($p<0.1$) in the base models. Variance components of a mixed-effects model were estimated, including residual variance, random intercept variance, random slope variance for drug dose, random slope-intercept correlation, and intraclass correlation coefficient. The final multivariate models were selected based on the highest total explained variance, the lowest Akaike or Bayesian information criterion value, and the largest number of observations included in the models. Fixed-effects regression coefficients (βs) were used to assess the degree of change in log-transformed AUC_{0-24} and C_{max} for every 1-unit change in the predictor variable. Statistical significance was accepted at $p<0.05$.

Subgroup analyses were performed in children aged <5 and <2 years, those weighing ≥25 kg, with steady-state concentrations, with steady-state and daily dosing, and considering the WHO region as a third-level clustering variable.

RESULTS

From the 3620 individual articles identified in our search on February 2, 2021, we read titles and abstracts and subsequently screened the full text of 163 studies, including two full-text studies added through an updated search on December 31, 2021 (Figure 1). This led to the inclusion of 55 eligible studies, and the exclusion of 108 studies of which 21 had identical or

overlapping cohorts with eligible studies (Table E1). Individual patient data were provided for 39 (71%) of 55 eligible studies (Table E2) [16–54], of which 26 (67%) were of high quality and 13 (33%) of moderate quality (Table E3). Of the 16 studies for which individual patient data were not provided, 13 (81%) were conducted in/before the 1990s, when most of the investigators no longer had access to the data (Table E4).

Among 1628 patients included from 12 countries and three WHO regions, 738 (45.4%) were <5 years of age, 875 (53.7%) were boys, 931 (57.2%) had pulmonary TB, 847 (52.0%) were malnourished, and 324 (19.9%) were HIV-positive (Table 1). $AUC_{0\text{-}24}$ values were assessed, respectively, from 1252 (78.6%) of 1593 observations (i.e., daily occasions) in 1408 patients for isoniazid, 1041 (70.8%) of 1470 observations in 1209 patients for rifampicin, 962 (73.8%) of 1304 observations in 1140 patients for pyrazinamide, and 410 (72.3%) of 567 observations in 567 patients for ethambutol (Figure 1). A subset of rifampicin data in the study by Denti et al [50] (n=60/184 observations) was excluded from all $AUC_{0\text{-}24}$ and C_{max} analyses based on the use of a poor-quality drug product that has been reported to cause a 61% decrease in rifampicin bioavailability [50], as also confirmed in an earlier study by McIlleron et al [55]. Details of the observations for which $AUC_{0\text{-}24}$ and C_{max} values could not be reliably assessed are presented in Table E5.

For isoniazid, dose-normalized estimates were summarized for $AUC_{0\text{-}24}$ (geometric mean: 18.7 [95% CI: 15.5−22.6] h·mg/L; Figure 2A) and C_{max} (geometric mean: 4.9 [95% CI: 4.1−5.8] mg/L; Figure 3A) in patients with steady-state concentrations, and in other study-level groups (Table 2; Figures E1-E2). In multivariate mixed-effects analysis (table 3), lower log-$AUC_{0\text{-}24}$ values were associated with younger age <2 years (fixed-effects coefficient (β): -0.28 [95% CI -0.40 to -0.16]), moderate malnutrition (β: -0.10 [95% CI: -0.19 to -0.01]),

severe malnutrition (*β*: -0.15 [95% CI: -0.24 to -0.06]), HIV-positive status (*β*: -0.15 [95% CI: -0.25 to -0.04]), and half-life rapid acetylator phenotype (*β*: -0.39 [95% CI: -0.50 to -0.28]); while higher log-$AUC_{0\text{-}24}$ values were associated with higher mg/kg doses (*β*: 0.42 [95% CI: 0.34−0.51]), and half-life slow acetylator phenotype (*β*: 0.70 [95% CI: 0.62−0.77]). Based on *NAT2* genotyping, rapid acetylators had lower log-$AUC_{0\text{-}24}$ values (*β*: -0.30 [95% CI: -0.46 to -0.15]), whereas slow acetylators had higher log-$AUC_{0\text{-}24}$ values (*β*: 0.71 [95% CI: 0.58−0.83]) compared with intermediate acetylators (Table E6). Determinants of isoniazid C_{max} were similar to those for $AUC_{0\text{-}24}$, except for moderate malnutrition which had no significant effect on C_{max} (Table 4).

For rifampicin, dose-normalized estimates were summarized for $AUC_{0\text{-}24}$ (geometric mean: 34.4 [95% CI: 29.4−40.3] h·mg/L; Figure 2B) and C_{max} (geometric mean: 7.4 [95% CI: 6.6−8.4] mg/L; Figure 3B) in patients with steady-state concentrations, and in other study-level groups (Table 2; Figures E3-E4). In multivariate mixed-effects analysis (Table 3), lower log-$AUC_{0\text{-}24}$ values were associated with younger age, including ages <2 years (*β*: -0.48 [95% CI: -0.64 to -0.33]) and 2−4 years (*β*: -0.35 [95% CI: -0.50 to -0.21]). Furthermore, lower log-$AUC_{0\text{-}24}$ values were associated with HIV-positive status (*β*: -0.25 [95% CI: -0.39 to -0.11]), whereas higher log-$AUC_{0\text{-}24}$ values were associated with higher mg/kg doses (*β*: 0.65 [95% CI: 0.44−0.85]). Determinants of rifampicin C_{max} were similar to those for $AUC_{0\text{-}24}$, with addition of severe malnutrition which was associated with lower log-C_{max} values (*β*: -0.12 [95% CI: -0.24 to -0.01]) (Table 4).

For pyrazinamide, dose-normalized estimates were summarized for $AUC_{0\text{-}24}$ (geometric mean: 375.0 [95% CI: 339.9−413.7] h·mg/L; Figure 2C) and C_{max} (geometric mean: 41.5 [95% CI: 38.1−45.2] mg/L; Figure 3C) in patients with steady-state concentrations, and in

other study-level groups (Table 2; Figures E5-E6). In multivariate mixed-effects analysis (Table 3), lower log-$AUC_{0\text{-}24}$ values were associated with younger age, including ages <2 years (β: -0.28 [95% CI: -0.38 to -0.17]), 2−4 years (β: -0.24 [95% CI: -0.34 to -0.14]), and 5−9 years (β: -0.12 [95% CI: -0.21 to -0.03]). Furthermore, lower log-$AUC_{0\text{-}24}$ values were associated with male sex (β: -0.08 [95% CI: -0.14 to -0.02]), severe malnutrition (β: -0.08 [95% CI: -0.16 to -0.005]), and HIV-positive status (β: -0.19 [95% CI: -0.29 to -0.10]); whereas higher log-$AUC_{0\text{-}24}$ values were associated with higher mg/kg doses (β: 0.17 [95% CI: 0.10−0.23]). Determinants of pyrazinamide C_{max} were similar to those for $AUC_{0\text{-}24}$, except for male sex which had no significant effect on C_{max} (Table 4).

For ethambutol, dose-normalized estimates were summarized for $AUC_{0\text{-}24}$ (geometric mean: 8.0 [95% CI: 6.4−10.0] h·mg/L; Figure 2D) and C_{max} (geometric mean: 1.4 [95% CI: 1.1−1.6] mg/L; Figure 3D) in patients with steady-state concentrations, and in other study-level groups (Table 2; Figures E7-E8). In multivariate mixed-effects analysis (Table 3), lower log-$AUC_{0\text{-}24}$ values were associated with younger age, including ages <2 years (β: -0.55 [95% CI: -0.76 to -0.33]), 2−4 years (β: -0.35 [95% CI: -0.55 to -0.14]), and 5−9 years (β: -0.19 [95% CI: -0.37 to -0.001]). Furthermore, lower log-$AUC_{0\text{-}24}$ values were associated with HIV-positive status (β: -0.39 [95% CI: -0.56 to -0.21]), whereas higher log-$AUC_{0\text{-}24}$ values were associated with higher mg/kg doses (β: 0.15 [95% CI: 0.05−0.24]). Determinants of ethambutol C_{max} were similar to those for $AUC_{0\text{-}24}$, except for ages 5−9 years which had no significant effect on C_{max} (Table 4).

In dose-adjusted mixed-effects analyses, we identified additional determinants of lower log-$AUC_{0\text{-}24}$ values, including severe stunting (i.e., height-for-age Z-score <-3) for isoniazid (β: -0.13 [95% CI: -0.24 to -0.02]), rifampicin (β: -0.13 [95% CI: -0.25 to -0.01]), pyrazinamide

(*β*: -0.16 [95% CI: -0.24 to -0.07]), and ethambutol (*β*: -0.19 [95% CI: -0.37 to -0.02]); moderate stunting (i.e., height-for-age Z-score ≥-3 but <-2) for pyrazinamide (*β*: -0.09 [95% CI: -0.17 to -0.02]); severe underweight (i.e., weight-for-age Z-score <-3) for pyrazinamide (*β*: -0.10 [95% CI: -0.19 to -0.01]); and *SLCO1B1* (rs4149032) TT genotype for rifampicin (*β*: -0.34 [95% CI: -0.61 to -0.08]). Detailed results of the dose-adjusted analyses for AUC_{0-24} and C_{max} are presented in Tables E7-E14.

The determinants of AUC_{0-24} and C_{max} remained consistent and largely unchanged in several subgroup analyses among children aged <5 years (Tables E15-E16), patients with steady-state concentrations (Tables E19-E20), with steady-state concentrations and daily dosing (Tables E21-E22), and considering WHO region as a third-level clustering variable (Tables E23-E24). Additionally, the adult doses recommended for children weighing ≥25 kg were associated with lower log-AUC_{0-24} values for isoniazid (4−6 mg/kg; *β*: -1.01 [95% CI: -1.27 to -0.76]) and rifampicin (8−10 mg/kg; *β*: -0.35 [95% CI: -0.63 to -0.07]), compared with paediatric doses (Tables E25-E26). Additional pharmacokinetic estimates for time to C_{max}, half-life, and elimination rate constant are presented in Table E27.

DISCUSSION

In this individual patient data meta-analysis, we summarized plasma AUC_{0-24} and C_{max} estimates for first-line anti-TB drugs in several study-level groups of children and adolescents with TB from globally representative studies. We also identified patient-level determinants of plasma exposures to first-line anti-TB drugs in these children and adolescents.

Compared with adult data, our summary estimates for steady-state AUC_{0-24} were comparable for isoniazid (geometric mean: 18.7 [95% CI: 15.5−22.6] *vs* median range: 11.6−26.3 h·mg/L)

[56], pyrazinamide (geometric mean: 375.0 [95% CI: 339.9−413.7] *vs* median range: 233−429 h·mg/L) [56], and rifampicin (geometric mean: 34.4 [95% CI: 29.4−40.3] *vs* mean: 38.7 [95% CI: 34.4−43.0] h·mg/L) [57], but were lower for ethambutol (geometric mean: 8.0 [95% CI: 6.4−10.0] *vs* median range 16−28 h·mg/L) [56], regardless of significant methodological heterogeneities among studies included in two systematic reviews assessing these estimates for adult patients [56, 57]. Ideally, target $AUC_{0\text{-}24}$ and C_{max} values are established based on pharmacokinetic/pharmacodynamic knowledge, taking drug efficacy, safety and tolerability into account [14]. However, unlike pharmacokinetic studies in adults, most paediatric studies lack data on clinical and bacteriological responses to TB treatment, probably due to the paucibacillary disease and the difficulty in obtaining microbiological specimens. This has resulted in a significant challenge in establishing target $AUC_{0\text{-}24}$ and C_{max} values based on pharmacokinetic/pharmacodynamic analyses. Until these pharmacokinetic/pharmacodynamic targets are available, our summary $AUC_{0\text{-}24}$ and C_{max} estimates can serve as real-life reference values for clinicians and researchers working on dosing of first-line anti-TB drugs in children and adolescents.

In general, children under 15 years of age have high TB treatment success rates (88-96%) [1, 58, 59], although among those with severe disease like TB meningitis, mortality rates are high (10-30%) [60–62]. In the present study, the relationship between pharmacokinetics and treatment outcomes was not the primary focus, and the outcome data were unavailable from the majority of included studies (n=34/39, 87%). It should be noted that pharmacokinetic studies of anti-TB drugs in paediatric patients typically have a smaller sample size and are therefore not powered to analyse the impact of drug exposure on treatment outcome. It is therefore important to include pharmacokinetics in large outcome studies [14, 63].

Young children are most vulnerable to severe forms of disease, including miliary TB and TB meningitis. Lower drug exposures in young children, especially those <2 years of age, are likely attributed to the non-linear effect of weight on clearance due to allometric scaling, which result in reduced exposures in smaller children when dosed at the same mg/kg as bigger children and adolescents [64]. Additionally, these could be due to lower bioavailability of isoniazid and rifampicin in children <2-3 years of age [50]. For TB meningitis, these low plasma exposures could lead to extremely low exposures at the site of infection in the meninges, especially for rifampicin and ethambutol which have poor cerebrospinal fluid penetration [26, 36]. Higher rifampicin doses can be considered for paediatric TB meningitis [65], and for paediatric TB in general [16], with good safety profiles [16]. However, higher ethambutol doses may increase the risk of ocular toxicity [66], highlighting the importance of exploring substitutes for ethambutol such as ethionamide or fluoroquinolones (e.g., levofloxacin).

Importantly, children and adolescents weighing ≥25 kg who received WHO-recommended adult doses had lower isoniazid and rifampicin exposures than those on WHO-recommended paediatric doses. The use of adult fixed-dose combination doses has also resulted in suboptimal exposures in South African and Zambian children weighing ≥25 kg [39]. Further investigation on paediatric formulation and revision of weight bands are needed to optimize dosing of first-line anti-TB drugs [50], including those for children weighing ≥25 kg.

Different levels of low exposures to first-line anti-TB drugs in children and adults living with HIV have been reported in two systematic reviews, but the estimates were not adjusted for confounders, and consistent results could not be obtained due to methodological and statistical heterogeneities among the included studies [56, 67]. The impact of HIV on reducing

exposures to first-line anti-TB drugs has been hypothesized to be due to malabsorption of the drugs in patients with advanced HIV coinfection [68]. However, as antiretroviral data were unavailable in our dataset, further research is needed to assess the potential impact of antiretroviral therapy on anti-TB drug pharmacokinetics in children and adolescents living with HIV.

Severe malnutrition was found to have small but significant negative effects on isoniazid and pyrazinamide exposures. For highly protein-bound rifampicin [69], the protein-unbound fraction may be higher in patients with severe protein-energy malnutrition, which may have resulted in similar plasma exposures to protein-unbound rifampicin between patients with and without malnutrition, as supported by an adult study [70]. In our dose-adjusted models, lower exposures to all first-line drugs were observed in severely stunted patients, but our results varied among underweight and wasted patients. Importantly, the same enteropathogens that cause stunting have recently been demonstrated to negatively impact first-line anti-TB drug pharmacokinetics in malnourished children [44]. Taken together, we suspect various degrees and predispositions to malnutrition may have different impacts on physiological alterations that affect anti-TB drug pharmacokinetics [71].

The potential benefits of *NAT2* genotype-guided isoniazid dosing in reducing toxicity and treatment failure have been reported in adult patients [72]. In resource-limited settings where genotyping is rarely available, an automated assay on the GeneXpert platform can be used as an alternative option to detect *NAT2* polymorphisms and guide isoniazid dosing [73]. Next, our results showed that *SLCO1B1* polymorphisms had moderate negative effects on rifampicin exposures, although these results were only obtained from two studies among African children [17, 50]. *SLCO1B1* polymorphisms associated with lower rifampicin

exposures have been reported to be more common in African adult patients [74], and these might partly explain the lower rifampicin exposures in our patients from African versus non-African regions.

There has been growing interest in the use of shorter TB treatment regimens. Recent clinical trials have shown that four months of anti-TB treatment with a rifapentine-based regimen containing moxifloxacin in adults with pulmonary TB [75], and with a standard first-line anti-TB drug regimen in children with non-severe TB [59], were non-inferior to the standard six-month regimen and showed excellent treatment outcomes. High-yield opportunities for stratified and personalized medicine approaches, including differential dosing for key subpopulations, should be explored as potential alternatives to the traditional one-size-fits-all strategy [76]. Although programmatic TB treatment may be suitable for most patients, stratification of treatment and a more person-centred approach in certain groups is necessary to ensure high-quality care, such as in patients at risk of suboptimal exposure to anti-TB drugs, patients at risk of developing drug-related toxicity, and patients who could benefit from therapeutic drug monitoring [63]. In addition, less invasive therapeutic drug monitoring methods using saliva, hair, and dried blood spot samples should be explored in further studies to reduce the burden of venous blood sampling in this population [14, 63, 77].

This study has limitations that should be acknowledged. First, summary pharmacokinetic estimates in study-level groups showed high heterogeneities, although we were able to correct these estimates by individual-level covariates and variance components in mixed-effects models. Second, although dose-normalized exposures for high-dose rifampicin >35 mg/kg were not estimated due to saturation of hepatic clearance (4% of all observations) [16], the effect on standard doses cannot be ruled out [50], and therefore the rifampicin estimates

should be interpreted carefully. Third, we were unable to reliably assess AUC_{0-24} and C_{max} on sparse sampling data [23, 26, 40, 54]. Further studies using pharmacokinetic/pharmacodynamic modelling and Monte Carlo simulations are needed to better characterize the relationships of physiologically sensible covariates with pharmacokinetic parameters (e.g., drug clearance and volume of distribution) and to design more optimal dosing strategies [14], by including both intensive and sparse sampling data. In addition, given that only protein-unbound concentrations are generally considered to exhibit pharmacological effects, the inclusion of a protein binding parameter in future pharmacokinetic/pharmacodynamic models may be important, especially for rifampicin, as only about 10-20% of the total drug concentration can freely penetrate to the site of infection [69, 78]. Fourth, none of the included studies were from European countries, and there was a lack of data in children aged <3 months and adolescents aged 15−18 years. The latter is likely due to the historically fragmented approach of only classifying persons aged <15 years as children, excluding those aged 15−18 years from both paediatric and adult studies [79]. Despite these limitations, our findings provide the most comprehensive study-level estimates of plasma exposures to first-line anti-TB drugs by including ~30 years of available data worldwide, and therefore the results can be generalized to the global population of children aged >3 months to 14 years. Additionally, our mixed-effects models include a wide range of variables, and our results are consistent in various subgroup analyses.

In conclusion, our systematic review and individual patient data meta-analysis summarized pharmacokinetic estimates of first-line anti-TB drugs in children and adolescents using a large amount of globally available data. Although children and adolescents with TB generally have good treatment outcomes with standardized treatment approaches in previous reports, certain subgroups at risk of suboptimal drug exposures, especially children under two years of age

and those with severe malnutrition or HIV, may require population-specific dose adjustment or individualized therapeutic drug monitoring. Designing more optimal dosing strategies using pharmacokinetic/pharmacodynamic modeling and simulations is warranted in these vulnerable groups. This is important for policymakers and TB programs to ensure the best treatment outcome in children and adolescents with TB.

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Author contributions:

F. Gafar, B. Wilffert,[†] and J.W.C. Alffenaar designed the study and protocol. F. Gafar, R.E. Wasmann, H.M. McIlleron, R.E. Aarnoutse, H.S. Schaaf, D. Agarwal, S. Antwi, N.D. Bang, A. Bekker, D.J. Bell, C. Chabala, L. Choo, G.R. Davies, J.N. Day, R. Dayal, P. Denti, P.R. Donald, E. Engidawork, A.J. Garcia-Prats, D. Gibb, S.M. Graham, A.C. Hesseling, S.K. Heysell, M.I. Idris, S.K. Kabra, A. Kinikar, A.K.H. Kumar, A. Kwara, R. Lodha, C. Magis-Escurra, N. Martinez, B.S. Mathew, V. Mave, E. Mduma, R. Mlotha-Mitole, S.G. Mpagama, A. Mukherjee, H.M. Nataprawira, C.A. Peloquin, T. Pouplin, G Ramachandran, J. Ranjalkar, V. Roy, R. Ruslami, I. Shah, Y. Singh, E.M. Svensson, S. Swaminathan, U. Thatte, S. Thee,

T.A. Thomas, T. Tikiso, A. Turkova, T. Velpandian, L.M. Verhagen, J.L. Winckler, H. Yang, and V. Yunivita contributed individual patient data. F. Gafar analysed the data and created tables and figures under the supervision of J. Stevens and J.W.C. Alffenaar. F. Gafar wrote the initial draft of the manuscript under the supervision of K. Taxis, J. Stevens and J.W.C. Alffenaar. R.E. Wasmann, H.M. McIlleron, R.E. Aarnoutse, H.S. Schaaf, and B.J. Marais were members of the writing committee, and helped revise the drafted manuscript before and after circulation to all co-authors. All authors provided critical input and revisions to manuscript drafts and approved the final version of the manuscript before submission for publication.

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Table 1. Demographic and clinical characteristics of children and adolescents with tuberculosis included in this systematic review and individual patient data meta-analysis.

Characteristic	All patients	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol
Total patients, n	1628	1408	1209	1140	567
Median age, years (IQR)	5.4 (2.2−9.5)	5.5 (2.2−9.6)	5.0 (2.0−9.0)	5.1 (2.0−9.0)	5.9 (2.2−9.8)
Age, n (%)					
<2 years	356 (21.9)	311 (22.1)	301 (24.9)	274 (24.0)	121 (21.3)
<3 months	7 (0.4)	4 (0.3)	4 (0.3)	5 (0.4)	2 (0.3)
3−11 months	162 (9.9)	152 (10.8)	148 (12.2)	137 (12.0)	60 (10.6)
12−23 months	187 (11.5)	155 (11.0)	149 (12.3)	132 (11.6)	59 (10.4)
2−4 years	382 (23.5)	328 (23.3)	291 (24.1)	253 (22.2)	124 (21.9)
5−9 years	507 (31.1)	431 (30.6)	354 (29.3)	360 (31.6)	183 (32.3)
10−14 years	357 (21.9)	316 (22.4)	245 (20.3)	236 (20.7)	130 (22.9)
15−18 years	26 (1.6)	22 (1.6)	18 (1.5)	17 (1.5)	9 (1.6)
Sex, n (%)					
Female	753 (46.3)	641 (45.5)	549 (45.4)	512 (44.9)	270 (47.6)
Male	875 (53.7)	767 (54.5)	660 (54.6)	628 (55.1)	297 (52.4)
WHO region and country, n (%)					
African	827 (50.8)	721 (51.2)	678 (56.1)	570 (50.0)	377 (66.5)
South Africa	390 (24.0)	330 (23.4)	317 (26.2)	232 (20.3)	52 (9.2)
Ghana	113 (6.9)	113 (8.0)	113 (9.3)	113 (9.9)	113 (19.9)
Malawi	150 (9.2)	105 (7.4)	103 (8.5)	128 (11.2)	121 (21.3)
Tanzania	102 (6.3)	102 (7.2)	102 (8.4)	75 (6.6)	69 (12.2)
Ethiopia	29 (1.8)	29 (2.1)	n/a	n/a	n/a
Zambia	43 (2.6)	42 (3.0)	43 (3.5)	22 (1.9)	22 (3.9)
Americas	88 (5.4)	44 (3.1)	41 (3.4)	69 (6.0)	39 (6.9)
Venezuela	30 (1.8)	30 (2.1)	30 (2.5)	30 (2.6)	5 (0.8)
Paraguay	15 (0.9)	14 (1.0)	11 (0.9)	15 (1.3)	15 (2.6)
United States	43 (2.6)	n/a	n/a	24 (2.1)	19 (3.3)
South-East Asian	713 (43.8)	643 (45.7)	490 (40.5)	501 (43.9)	151 (26.6)
India	594 (36.5)	524 (37.2)	371 (30.7)	382 (33.5)	151 (26.6)
Vietnam	99 (6.1)	99 (7.0)	99 (8.2)	99 (8.7)	n/a
Indonesia	20 (1.2)	20 (1.4)	20 (1.6)	20 (1.7)	n/a
Malnourished, n (%)					
No	597 (36.7)	528 (37.5)	517 (42.8)	463 (40.6)	194 (34.2)
Yes, moderate	373 (22.9)	339 (24.1)	328 (27.1)	281 (24.6)	151 (26.6)
Yes, severe	474 (29.1)	404 (28.7)	355 (29.4)	358 (31.4)	196 (34.6)
Unknown	184 (11.3)	137 (9.7)	9 (0.7)	38 (3.3)	26 (4.6)
Type of tuberculosis, n (%)					
Pulmonary	931 (57.2)	809 (57.4)	721 (59.6)	652 (57.2)	413 (72.8)
Extrapulmonary	442 (27.1)	406 (28.8)	316 (26.1)	335 (29.4)	87 (15.3)
Pulmonary + extrapulmonary	123 (7.6)	104 (7.4)	93 (7.7)	64 (5.6)	38 (6.7)
Unspecified	132 (8.1)	89 (6.3)	79 (6.5)	89 (7.8)	29 (5.1)
HIV status, n (%)					
Negative	1052 (64.6)	928 (65.9)	818 (67.6)	758 (66.5)	349 (61.5)
Positive	324 (19.9)	299 (21.2)	279 (23.1)	265 (23.2)	165 (29.1)
Unknown	252 (15.5)	181 (12.8)	112 (9.3)	117 (10.3)	53 (9.3)
Blood test values (median [IQR])					
Albumin, g/dL (total n=826)	4.0 (3.6−4.4)	4.0 (3.6−4.3)	4.1 (3.6−4.4)	4.0 (3.6−4.3)	4.1 (3.7−4.4)
Creatinine, mg/dL (total n=609)	0.5 (0.4−0.7)	0.5 (0.4−0.6)	0.5 (0.4−0.7)	0.5 (0.4−0.6)	0.4 (0.4−0.5)
Drug dose, mg/kg (median [IQR])	n/a	9.1 (5.3−11.0)	11.7 (9.8−15.3)	30.6 (24.9−35.0)	20.0 (16.8−23.0)

Data are presented as n (%), unless otherwise stated. HIV: human immunodeficiency virus; IQR: interquartile range; WHO: World Health Organization.

Table 2. Summary estimates of dose-normalized AUC_{0-24} and C_{max} values for first-line antituberculosis drugs in children and adolescents with tuberculosis, by dosing intervals, sampling schedules and WHO regions.

	Dose-normalized AUC_{0-24}[§,¶]		Dose-normalized C_{max}[§,¶]	
	Summary geometric mean, h·mg/L (95% CI)	Heterogeneity, I^2 statistics	Summary geometric mean, mg/L (95% CI)	Heterogeneity, I^2 statistics
Isoniazid				
All patients	20.0 (16.8−23.8)	97.0%	5.1 (4.4−6.1)	98.2%
Dosing interval				
Daily	18.1 (14.9−22.1)	95.0%	4.8 (4.0−5.8)	96.8%
Intermittent	25.1 (22.7−27.7)	14.8%	5.4 (4.7−6.2)	59.2%
Single-dose	32.7 (24.2−44.2)	94.3%	7.8 (6.2−9.9)	98.3%
Sampling schedule				
Steady sate	18.7 (15.5−22.6)	95.5%	4.9 (4.1−5.8)	96.8%
Non-steady state	28.9 (20.6−40.5)	95.5%	7.2 (5.6−9.2)	98.3%
WHO region				
African	18.8 (16.7−21.1)	78.4%	5.8 (5.2−6.4)	82.6%
South-East Asian	21.1 (15.2−29.2)	98.4%	4.9 (3.7−6.6)	99.1%
Americas	17.4 (13.7−22.0)	0.0%	3.6 (2.9−4.4)	8.8%
Rifampicin				
All patients	36.6 (31.0−43.2)	95.7%	7.7 (6.8−8.6)	92.7%
Dosing interval				
Daily	36.5 (30.8−43.4)	92.8%	7.8 (6.9−8.7)	83.7%
Intermittent	29.4 (17.9−48.4)	95.2%	5.8 (3.9−8.4)	90.2%
Single-dose	51.9 (49.7−54.3)	0.0%	9.6 (9.4−9.8)	0.0%
Sampling schedule				
Steady sate	34.4 (29.4−40.3)	92.4%	7.4 (6.6−8.4)	87.4%
Non-steady state	63.8 (41.9−97.2)	95.2%	9.8 (8.9−10.8)	30.4%
WHO region				
African	29.9 (27.1−33.0)	68.3%	7.3 (6.4−8.2)	79.8%
South-East Asian	47.9 (34.0−67.6)	97.7%	8.5 (6.6−10.9)	95.8%
Americas	37.9 (30.4−47.2)	16.4%	7.1 (5.8−8.7)	28.4%
Pyrazinamide				
All patients	387.0 (350.3−427.5)	91.4%	42.8 (39.2−46.7)	94.1%
Dosing interval				
Daily	384.1 (343.5−429.4)	90.8%	42.0 (38.2−46.2)	92.1%
Intermittent	326.1 (257.5−413.1)	82.4%	38.5 (33.2−44.7)	73.5%
Single-dose	470.4 (323.9−683.2)	92.4%	52.7 (38.6−72.1)	94.7%
Sampling schedule				
Steady sate	375.0 (339.9−413.7)	89.2%	41.5 (38.1−45.2)	91.1%
Non-steady state	431.1 (320.7−579.5)	92.1%	47.8 (37.6−60.6)	94.9%
WHO region				
African	349.9 (318.4−384.5)	78.2%	40.6 (37.4−44.2)	83.0%
South-East Asian	429.9 (360.2−513.1)	93.3%	46.6 (40.2−54.0)	95.4%
Americas	384.3 (328.6−449.4)	33.3%	36.9 (29.4−46.4)	64.7%
Ethambutol				
All patients	7.7 (6.2−9.6)	91.1%	1.3 (1.1−1.6)	87.7%
Dosing interval				
Daily	8.0 (6.4−10.0)	91.6%	1.4 (1.1−1.6)	85.6%
Intermittent	5.2 (3.4−8.0)	0.0%	0.7 (0.5−1.1)	0.0%
Sampling schedule				
Steady sate	8.0 (6.4−10.0)	91.6%	1.4 (1.1−1.6)	85.0%
Non-steady state	5.2 (3.4−8.0)	0.0%	0.7 (0.5−1.1)	0.0%
WHO region				
African	7.5 (7.0−8.0)	0.0%	1.3 (1.0−1.6)	89.4%
South-East Asian	4.8 (1.5−15.6)	95.3%	1.1 (0.4−2.7)	94.5%
Americas	11.5 (9.5−13.8)	0.0%	1.5 (1.2−2.0)	41.8%

Data are presented as geometric mean with 95% confidence intervals of the mean, unless stated otherwise. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; C_{max}: maximum plasma concentration; WHO: World Health Organization. [§]AUC_{0-24} and C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg. [¶]Forest plots for summary estimates of dose-normalized AUC_{0-24} and C_{max} for isoniazid, rifampicin, pyrazinamide, and ethambutol are presented in Figures E1-E2, E3-E4, E5-E6, and E7-E8, respectively.

Table 3. Multivariate linear mixed-effects regression analyses of determinants affecting log-transformed AUC_{0-24} values for first-line antituberculosis drugs in children and adolescents.

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	Fixed-effects coefficient (95% CI)	**Percent change (95% CI)‡**	**Fixed-effects coefficient**	**Percent change (95% CI)‡**	**Fixed-effects coefficient**	**Percent change (95% CI)‡**	**Fixed-effects coefficient**	**Percent change (95% CI)‡**
(Intercept)	2.56 (2.37−2.74)***		3.86 (3.66−4.06)***		6.04 (5.90−6.17)***		2.44 (2.17−2.71)***	
Dose, mg/kg¶	0.42 (0.34−0.51)***	53% (40−66)	0.65 (0.44−0.85)***	91% (55−135)	0.17 (0.10−0.23)***	18% (11−26)	0.15 (0.05−0.24)**	16% (5−27)
Age								
<2 years†	-0.28 (-0.40−-0.16)***	-24% (-33−-15)	-0.48 (-0.64−-0.33)***	-38% (-47−-28)	-0.28 (-0.38−-0.17)***	-24% (-32−-16)	-0.55 (-0.76−-0.33)***	-42% (-53−-28)
2-4 years	-0.07 (-0.18−0.04)	-7% (-17−4)	-0.35 (-0.50−-0.21)***	-30% (-39−-19)	-0.24 (-0.34−-0.14)***	-21% (-29−-13)	-0.35 (-0.55−-0.14)**	-29% (-42−-13)
5-9 years	-0.04 (-0.14−0.06)	-4% (-13−6)	-0.12 (-0.26−0.01)#	-12% (-23−1)	-0.12 (-0.21−-0.03)**	-11% (-19−-3)	-0.19 (-0.37−-0.001)*	-17% (-31−-0.1)
10-14 years††	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
15-18 years	0.05 (-0.24−0.33)	5% (-21−40)	0.22 (-0.16−0.60)	25% (-15−83)	-0.004 (-0.27−0.26)	0.4% (-24−30)	0.32 (-0.25−0.90)	38% (-22−145)
Sex								
Female	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Male	-0.03 (-0.10−0.04)	-3% (-9−4)	-0.05 (-0.13−0.04)	-4% (-12−4)	-0.08 (-0.14−-0.02)**	-8% (-13−-2)	-0.03 (-0.16−0.10)	-3% (-15−11)
Malnourished§§								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.10 (-0.19−-0.01)*	-9% (-17−-1)	0.02 (-0.09−0.12)	2% (-9−13)	-0.03 (-0.10−0.05)	-3% (-10−5)	-0.09 (-0.25−0.08)	-8% (-22−9)
Yes, severe	-0.15 (-0.24−-0.06)**	-14% (-22−-6)	-0.02 (-0.13−0.10)	-2% (-12−10)	-0.08 (-0.16−-0.005)*	-8% (-15−-0.5)	-0.08 (-0.25−0.09)	-7% (-22−10)
Unknown	0.13 (-0.13−0.39)	14% (-12−47)	-0.05 (-0.61−0.51)	-5% (-46−66)	-0.002 (-0.23−0.23)	-0.2% (-21−26)	-0.04 (-0.56−0.47)	-4% (-43−60)
HIV status								
Negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Positive	-0.15 (-0.25−-0.04)**	-14% (-22−-4)	-0.25 (-0.39−-0.11)***	-22% (-32−-11)	-0.19 (-0.29−-0.10)***	-18% (-25−-9)	-0.39 (-0.56−-0.21)***	-32% (-43−-19)
Unknown	-0.06 (-0.30−0.18)	-6% (-26−20)	-0.33 (-0.64−-0.01)*	-28% (-47−-1)	0.01 (-0.18−0.20)	1% (-16−22)	-0.08 (-0.51−0.35)	-8% (-40−42)
Acetylator status, $t_{1/2}$ phenotype¶¶								
Slow	0.70 (0.62−0.77)***	100% (85−117)	n/a	n/a	n/a	n/a	n/a	n/a
Intermediate	Ref.	Ref.	n/a	n/a	n/a	n/a	n/a	n/a
Rapid	-0.39 (-0.50−-0.28)***	-32% (-40−-24)	n/a	n/a	n/a	n/a	n/a	n/a
Unknown	0.44 (0.25−0.63)***	55% (29−88)	n/a	n/a	n/a	n/a	n/a	n/a
Random effects								
σ^2	0.35 (0.59)§		0.47 (0.68)§		0.21 (0.46)§		0.44 (0.66)§	
$\tau_{00\ studies}$	0.12 (0.35)§		0.11 (0.32)§		0.04 (0.21)§		0.08 (0.27)§	
$\tau_{11\ studies*doses}$	0.03 (0.16)§		0.12 (0.34)§		0.01 (0.10)§		n/a	
$\rho_{01\ studies}$	-0.74		-0.25		-0.15		n/a	
ICC	0.27		0.35		0.21		0.15	
$N_{\ studies}$	27		22		23		11	
Observations	1252		1041		962		410	
Conditional R^2	0.59		0.63		0.34		0.28	

Data are presented as fixed-effects estimates (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: interclass correlation estimate, N: number of included studies (studies or study occasions), conditional R^2: the proportion of variance explained by both the fixed and random effects. ‡Percentage change was calculated with the following equation: $(e^{\text{fixed-effects coefficient}} - 1) \times 100\%$. ¶Dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. †Among children <2 years of age, AUC_{0-24} values were significantly higher in patients aged 3−11 months compared with those aged 12−23 months for pyrazinamide (p<0.001), but no significant differences were found for isoniazid, rifampicin, and ethambutol; the results were adjusted for drug dose in mg/kg, sex, nutritional status, and HIV status. ††We used children aged 10−14 years as a reference group, assuming that they were the most adult-like among children under <15 years of age, and also to assess the statistical difference with older adolescents aged 15−18 years. §§Moderate malnutrition was defined as weight-for age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and height-for-age or body mass index-for-age Z-score ≥-3 but <-2in children aged ≥5 years; and severe malnutrition was defined as weight-for age or height-for-age Z-score <-3 in children aged <5 years, and height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Acetylator phenotypes of isoniazid were rapid (elimination half-life [$t_{1/2}$] <1.25 h), intermediate (1.25 h ≤ $t_{1/2}$ ≤2 h), and slow ($t_{1/2}$ >2 h). ***p<0.001, **p<0.01, *p<0.05,

[#]p<0.1.

Table 4. Multivariate linear mixed-effects regression analyses of determinants affecting log-transformed C_{max} values for first-line antituberculosis drugs in children and adolescents.

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	Fixed-effects coefficient (95% CI)	**Percent change (95% CI)[‡]**	**Fixed-effects coefficient**	**Percent change (95% CI)[‡]**	**Fixed-effects coefficient**	**Percent change (95% CI)[‡]**	**Fixed-effects coefficient**	**Percent change (95% CI)[‡]**
(Intercept)	1.46 (1.27−1.65)[***]		2.21 (2.01−2.41)[***]		3.74 (3.62−3.86)[***]		0.75 (0.49−1.00)[***]	
Dose, mg/kg[¶]	0.40 (0.29−0.52)[***]	50% (33−68)	0.52 (0.33−0.72)[***]	69% (38−106)	0.16 (0.11−0.22)[***]	18% (11−25)	0.13 (0.05−0.22)[**]	14% (5−24)
Age								
<2 years[†]	-0.28 (-0.40−-0.16)[***]	-24% (-33−-15)	-0.42 (-0.57−-0.27)[***]	-34% (-43−-24)	-0.18 (-0.28−-0.09)[***]	-17% (-24−-8)	-0.68 (-0.90−-0.46)[***]	-50% (-59−-37)
2-4 years	-0.07 (-0.18−0.04)	-7% (-16−4)	-0.18 (-0.32−-0.04)[**]	-17% (-28−-4)	-0.15 (-0.25−-0.06)[**]	-14% (-22−-6)	-0.32 (-0.53−-0.11)[**]	-27% (-41−-11)
5-9 years	-0.03 (-0.13−0.06)	-3% (-12−6)	-0.09 (-0.22−0.04)	-8% (-19−4)	-0.10 (-0.18−-0.02)[*]	-9% (-16−-2)	-0.12 (-0.31−0.06)	-12% (-26−6)
10-14 years[††]	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
15-18 years	-0.03 (-0.31−0.26)	-3% (-27−29)	0.06 (-0.31−0.42)	6% (-27−52)	-0.02 (-0.26−0.23)	-2% (-23−25)	0.10 (-0.51−0.70)	10% (-40−101)
Sex								
Female	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Male	-0.04 (-0.11−0.03)	-4% (-10−3)	0.02 (-0.07−0.10)	2% (-6−11)	-0.05 (-0.11−0.001)[#]	-5% (-10−-0.1)	-0.03 (-0.17−0.10)	-3% (-15−10)
Malnourished[§§]								
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.06 (-0.14−0.03)	-5% (-13−3)	-0.03 (-0.14−0.07)	-3% (-13−8)	-0.02 (-0.09−0.05)	-2% (-8−5)	-0.10 (-0.27−0.07)	-10% (-24−7)
Yes, severe	-0.09 (-0.18−-0.003)[*]	-9% (-17−-0.3)	-0.12 (-0.24−-0.01)[*]	-12% (-21−-1)	-0.10 (-0.18−-0.03)[**]	-10% (-16−-3)	-0.12 (-0.29−0.06)	-11% (-25−6)
Unknown	0.07 (-0.20−0.34)	7% (-18−40)	-0.14 (-0.67−0.39)	-13% (-49−48)	0.05 (-0.15−0.26)	6% (-14−30)	-0.33 (-0.78−0.12)	-28% (-54−12)
HIV status								
Negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Positive	-0.17 (-0.28−-0.06)[**]	-16% (-24−-6)	-0.25 (-0.39−-0.11)[***]	-22% (-32−-10)	-0.11 (-0.20−-0.03)[*]	-11% (-18−-3)	-0.35 (-0.53−-0.17)[***]	-29% (-41−-15)
Unknown	0.05 (-0.20−0.29)	5% (-18−33)	-0.19 (-0.49−0.11)	-17% (-49−12)	-0.05 (-0.22−0.12)	-5% (-20−13)	0.04 (-0.34−0.43)	4% (-29−53)
Acetylator status, $t_{1/2}$ phenotype[¶¶]								
Slow	0.23 (0.15−0.31)[***]	26% (16−36)	n/a	n/a	n/a	n/a	n/a	n/a
Intermediate	Ref.	Ref.	n/a	n/a	n/a	n/a	n/a	n/a
Rapid	-0.13 (-0.25−-0.02)[*]	-12% (-22−-2)	n/a	n/a	n/a	n/a	n/a	n/a
Unknown	-0.38 (-0.53−-0.23)[***]	-31% (-40−-20)	n/a	n/a	n/a	n/a	n/a	n/a
Random effects								
σ^2	0.35 (0.59)[§]		0.49 (0.73)[§]		0.19 (0.43)[§]		0.53 (0.73)[§]	
$\tau_{00\ studies}$	0.13 (0.35)[§]		0.11 (0.36)[§]		0.03 (0.19)[§]		0.06 (0.24)[§]	
$\tau_{11\ studies*doses}$	0.05 (0.22)[§]		0.10 (0.25)[§]		0.01 (0.09)[§]		n/a	
$\rho_{01\ studies}$	-0.33		0.02		-0.15		n/a	
ICC	0.31		0.32		0.18		0.10	
$N_{\ studies}$	27		22		23		11	
Observations	1292		1105		1021		483	
Conditional R^2	0.51		0.55		0.30		0.23	

Data are presented as fixed-effects estimates (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean and standard deviation. C_{max}: maximum plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: interclass correlation estimate, N: number of included studies (studies or study occasions), conditional R^2: the proportion of variance explained by both the fixed and random effects. [‡]Percent change was calculated with the following equation: $e^{\text{fixed-effects coefficient}} - 1 \times 100\%$. [¶]Dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Among children <2 years of age, C_{max} values were not significantly different in patients aged 3−11 months compared with those aged 12−23 months for isoniazid, rifampicin, pyrazinamide, and ethambutol; the results were adjusted for drug dose in mg/kg, sex, nutritional status, and HIV status. [††]We used children aged 10−14 years as a reference, assuming that they were the most adult-like among children under <15 years of age, and also to assess the statistical difference with older adolescents aged 15−18 years. [§§]Moderate malnutrition was defined as weight-for age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and height-for-age or body mass index-for-age Z-score ≥-3 but <-2in children aged ≥5 years; and severe malnutrition was defined as weight-for age or height-for-age Z-score <-3 in children aged <5 years, and height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. [¶¶]Acetylator phenotypes of isoniazid were rapid (elimination half-life [$t_{1/2}$] <1.25 h), intermediate (1.25 h ≤ $t_{1/2}$ ≤2 h), and slow ($t_{1/2}$ >2 h). [***]p<0.001, [**]p<0.01, [*]p<0.05, [#]p<0.1.

Figure legends

Figure 1. Study selection.

AUC_{0-24}: area under the plasma concentration-time curve from 0-24 h post-dose; C_{max}: peak plasma concentration; IPD: individual patient data; PK: pharmacokinetic; TB: tuberculosis. [*]Repeated pharmacokinetic measurements in a patient in different days (different sampling occasions). [§]These included unpublished studies or submitted manuscripts identified through contact with investigators; further details are shown in Table E2.

Figure 2. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized AUC_{0-24} for isoniazid (A), rifampicin (B), pyrazinamide (C), and ethambutol (D) in children and adolescents with tuberculosis, by sampling schedules (steady state and non-steady state).

AUC_{0-24}: are under the plasma concentration-time curve from 0 to 24 hours after dosing; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. AUC_{0-24} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

Figure 3. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for isoniazid (A), rifampicin (B), pyrazinamide (C), and ethambutol (D) in children and adolescents with tuberculosis, by sampling schedules (steady state and non-steady state).

C_{max}: peak plasma concentration; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

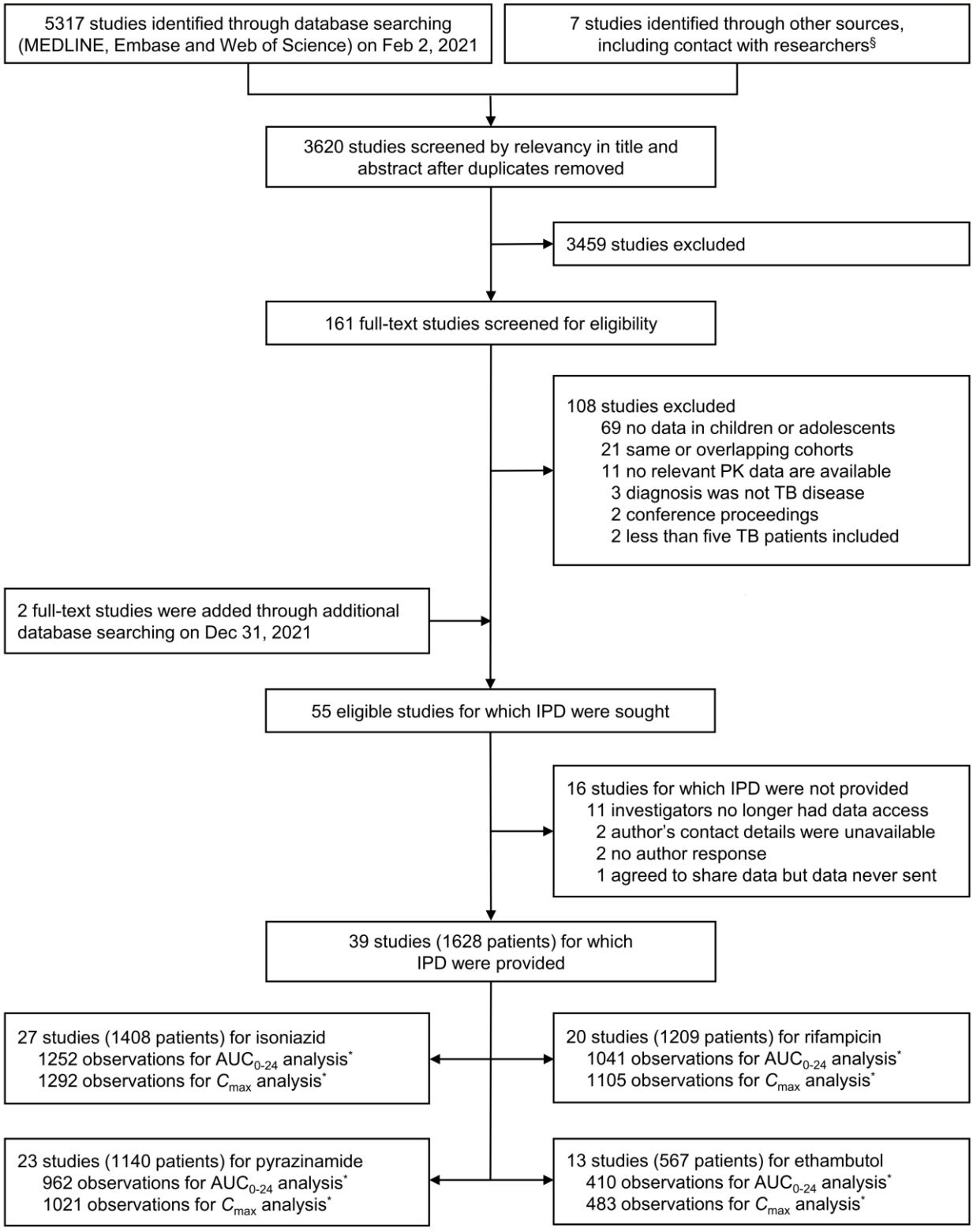
5317 studies identified through database searching (MEDLINE, Embase and Web of Science) on Feb 2, 2021
7 studies identified through other sources, including contact with researchers§
3620 studies screened by relevancy in title and abstract after duplicates removed
3459 studies excluded
161 full-text studies screened for eligibility
108 studies excluded
69 no data in children or adolescents
21 same or overlapping cohorts
11 no relevant PK data are available
3 diagnosis was not TB disease
2 conference proceedings
2 less than five TB patients included
2 full-text studies were added through additional database searching on Dec 31, 2021
55 eligible studies for which IPD were sought
16 studies for which IPD were not provided
11 investigators no longer had data access
2 author's contact details were unavailable
2 no author response
1 agreed to share data but data never sent
39 studies (1628 patients) for which IPD were provided
27 studies (1408 patients) for isoniazid
1252 observations for AUC0-24 analysis*
1292 observations for Cmax analysis*
20 studies (1209 patients) for rifampicin
1041 observations for AUC0-24 analysis*
1105 observations for Cmax analysis*
23 studies (1140 patients) for pyrazinamide
962 observations for AUC0-24 analysis*
1021 observations for Cmax analysis*
13 studies (567 patients) for ethambutol
410 observations for AUC0-24 analysis*
483 observations for Cmax analysis*

Figure 1

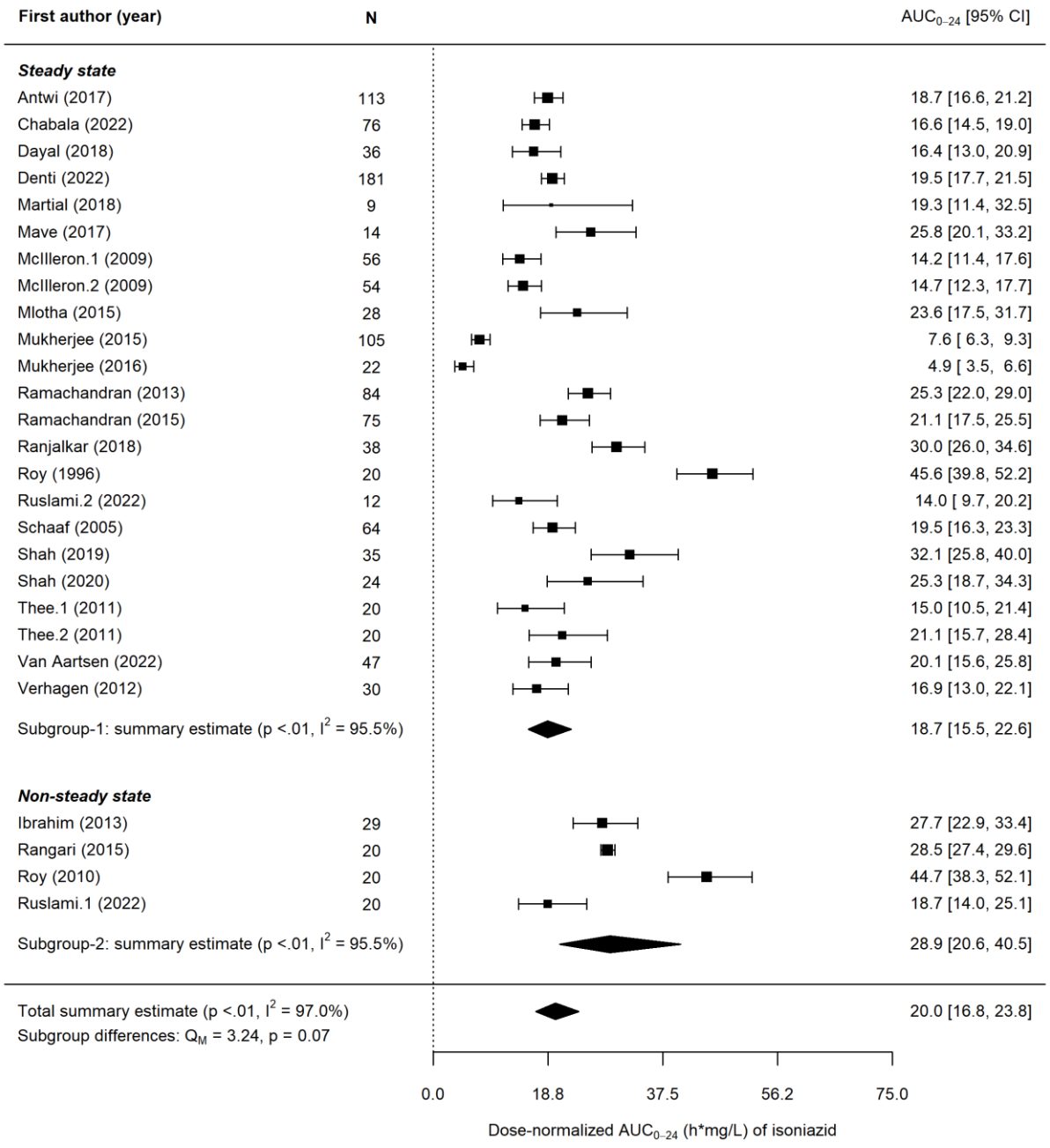
First author (year)
N
AUC0–24 [95% CI]
Steady state
Antwi (2017) 113 18.7 [16.6, 21.2]
Chabala (2022) 76 16.6 [14.5, 19.0]
Dayal (2018) 36 16.4 [13.0, 20.9]
Denti (2022) 181 19.5 [17.7, 21.5]
Martial (2018) 9 19.3 [11.4, 32.5]
Mave (2017) 14 25.8 [20.1, 33.2]
McIlleron.1 (2009) 56 14.2 [11.4, 17.6]
McIlleron.2 (2009) 54 14.7 [12.3, 17.7]
Mlotha (2015) 28 23.6 [17.5, 31.7]
Mukherjee (2015) 105 7.6 [6.3, 9.3]
Mukherjee (2016) 22 4.9 [3.5, 6.6]
Ramachandran (2013) 84 25.3 [22.0, 29.0]
Ramachandran (2015) 75 21.1 [17.5, 25.5]
Ranjalkar (2018) 38 30.0 [26.0, 34.6]
Roy (1996) 20 45.6 [39.8, 52.2]
Ruslami.2 (2022) 12 14.0 [9.7, 20.2]
Schaaf (2005) 64 19.5 [16.3, 23.3]
Shah (2019) 35 32.1 [25.8, 40.0]
Shah (2020) 24 25.3 [18.7, 34.3]
Thee.1 (2011) 20 15.0 [10.5, 21.4]
Thee.2 (2011) 20 21.1 [15.7, 28.4]
Van Aartsen (2022) 47 20.1 [15.6, 25.8]
Verhagen (2012) 30 16.9 [13.0, 22.1]
Subgroup-1: summary estimate (p <.01, I2 = 95.5%) 18.7 [15.5, 22.6]
Non-steady state
Ibrahim (2013) 29 27.7 [22.9, 33.4]
Rangari (2015) 20 28.5 [27.4, 29.6]
Roy (2010) 20 44.7 [38.3, 52.1]
Ruslami.1 (2022) 20 18.7 [14.0, 25.1]
Subgroup-2: summary estimate (p <.01, I2 = 95.5%) 28.9 [20.6, 40.5]
Total summary estimate (p <.01, I2 = 97.0%) 20.0 [16.8, 23.8]
Subgroup differences: QM = 3.24, p = 0.07
0.0
18.8
37.5
56.2
75.0
Dose-normalized AUC0–24 (h*mg/L) of isoniazid

Figure 2A

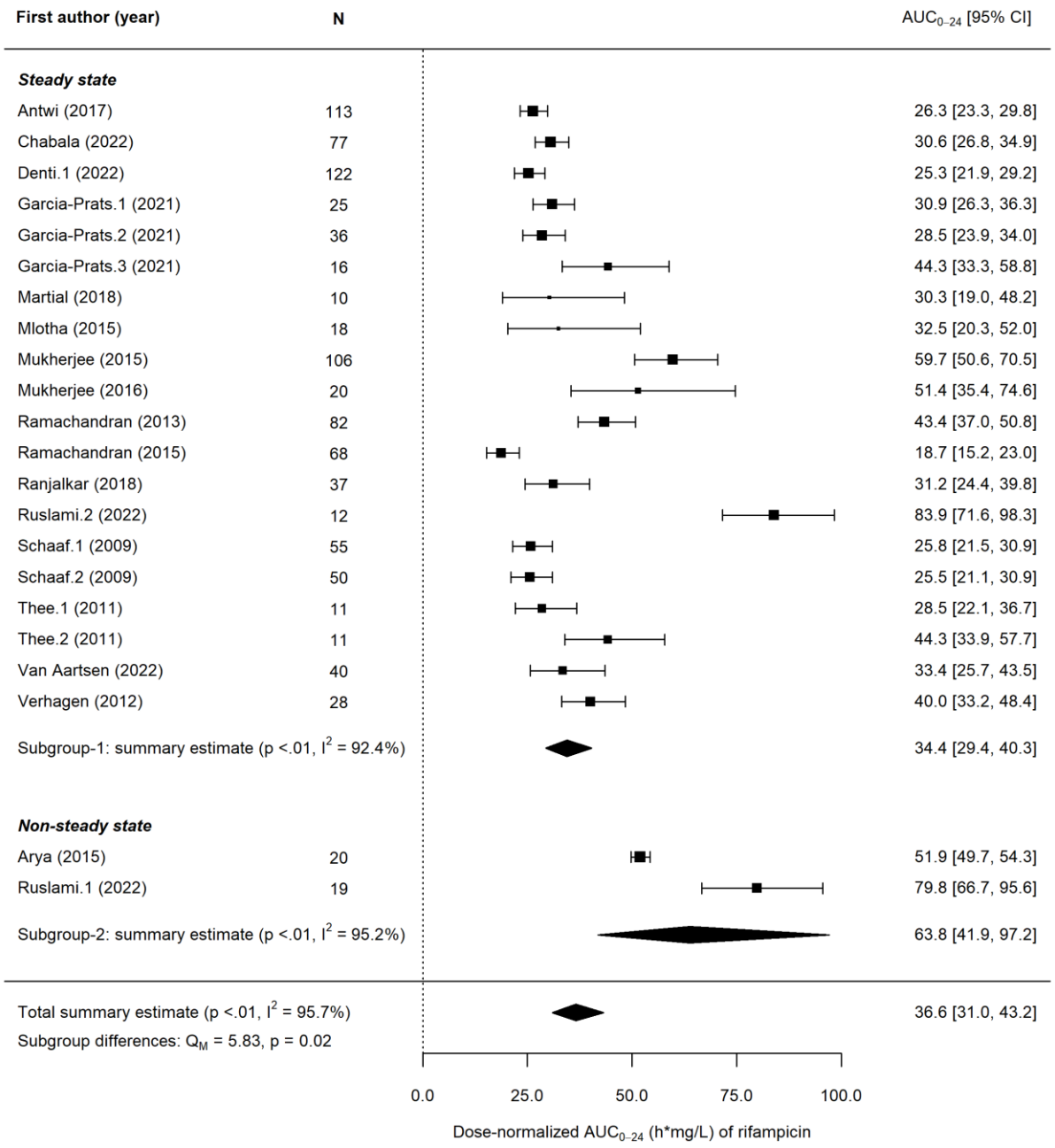
First author (year)
N
AUC0–24 [95% CI]
Steady state
Antwi (2017) 113 26.3 [23.3, 29.8]
Chabala (2022) 77 30.6 [26.8, 34.9]
Denti.1 (2022) 122 25.3 [21.9, 29.2]
Garcia-Prats.1 (2021) 25 30.9 [26.3, 36.3]
Garcia-Prats.2 (2021) 36 28.5 [23.9, 34.0]
Garcia-Prats.3 (2021) 16 44.3 [33.3, 58.8]
Martial (2018) 10 30.3 [19.0, 48.2]
Mlotha (2015) 18 32.5 [20.3, 52.0]
Mukherjee (2015) 106 59.7 [50.6, 70.5]
Mukherjee (2016) 20 51.4 [35.4, 74.6]
Ramachandran (2013) 82 43.4 [37.0, 50.8]
Ramachandran (2015) 68 18.7 [15.2, 23.0]
Ranjalkar (2018) 37 31.2 [24.4, 39.8]
Ruslami.2 (2022) 12 83.9 [71.6, 98.3]
Schaaf.1 (2009) 55 25.8 [21.5, 30.9]
Schaaf.2 (2009) 50 25.5 [21.1, 30.9]
Thee.1 (2011) 11 28.5 [22.1, 36.7]
Thee.2 (2011) 11 44.3 [33.9, 57.7]
Van Aartsen (2022) 40 33.4 [25.7, 43.5]
Verhagen (2012) 28 40.0 [33.2, 48.4]
Subgroup-1: summary estimate (p <.01, I2 = 92.4%) 34.4 [29.4, 40.3]
Non-steady state
Arya (2015) 20 51.9 [49.7, 54.3]
Ruslami.1 (2022) 19 79.8 [66.7, 95.6]
Subgroup-2: summary estimate (p <.01, I2 = 95.2%) 63.8 [41.9, 97.2]
Total summary estimate (p <.01, I2 = 95.7%) 36.6 [31.0, 43.2]
Subgroup differences: QM = 5.83, p = 0.02
0.0
25.0
50.0
75.0
100.0
Dose-normalized AUC0–24 (h*mg/L) of rifampicin

Figure 2B

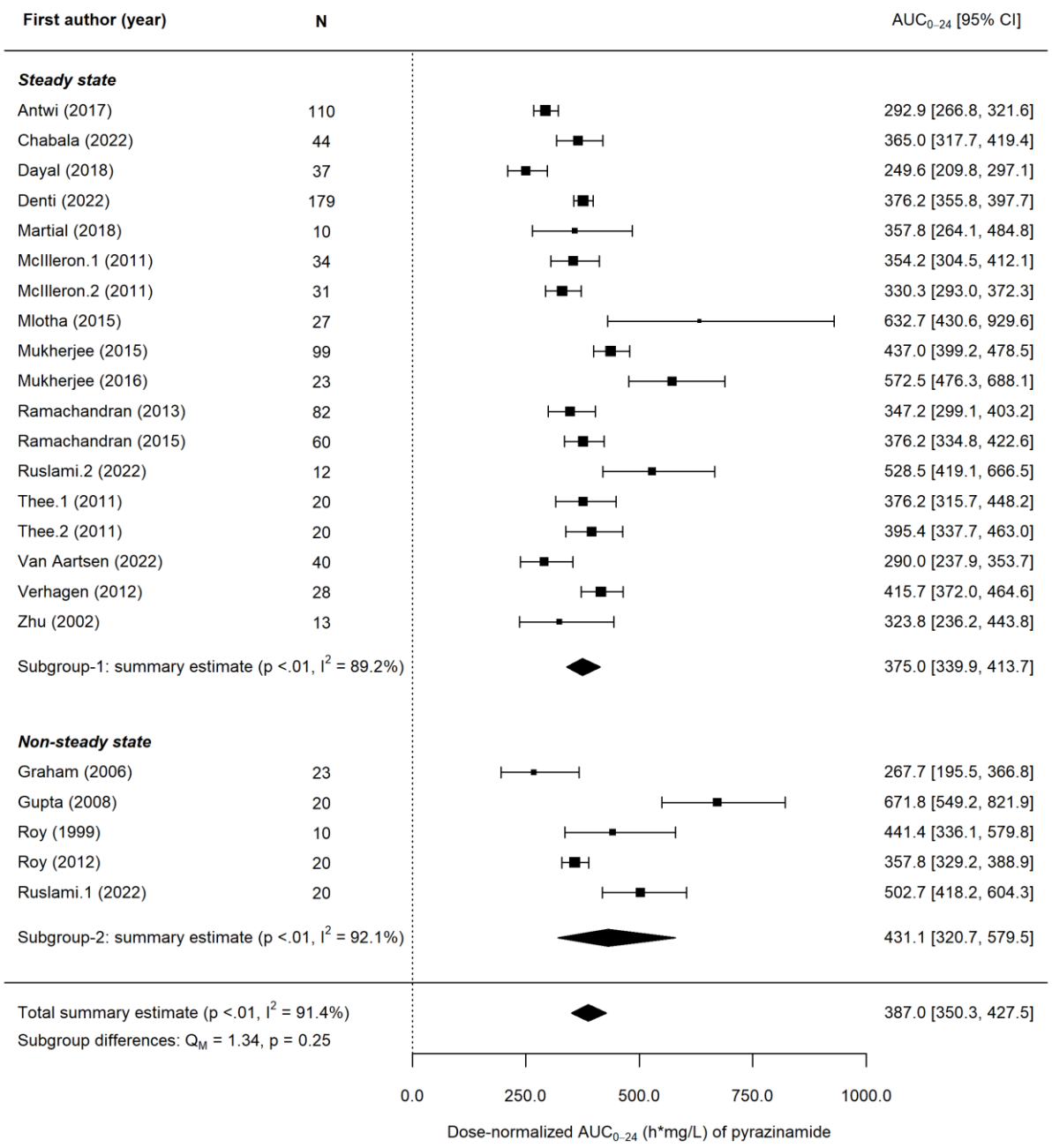
First author (year)
N
AUC0–24 [95% CI]
Steady state
Antwi (2017) 110 292.9 [266.8, 321.6]
Chabala (2022) 44 365.0 [317.7, 419.4]
Dayal (2018) 37 249.6 [209.8, 297.1]
Denti (2022) 179 376.2 [355.8, 397.7]
Martial (2018) 10 357.8 [264.1, 484.8]
McIlleron.1 (2011) 34 354.2 [304.5, 412.1]
McIlleron.2 (2011) 31 330.3 [293.0, 372.3]
Mlotha (2015) 27 632.7 [430.6, 929.6]
Mukherjee (2015) 99 437.0 [399.2, 478.5]
Mukherjee (2016) 23 572.5 [476.3, 688.1]
Ramachandran (2013) 82 347.2 [299.1, 403.2]
Ramachandran (2015) 60 376.2 [334.8, 422.6]
Ruslami.2 (2022) 12 528.5 [419.1, 666.5]
Thee.1 (2011) 20 376.2 [315.7, 448.2]
Thee.2 (2011) 20 395.4 [337.7, 463.0]
Van Aartsen (2022) 40 290.0 [237.9, 353.7]
Verhagen (2012) 28 415.7 [372.0, 464.6]
Zhu (2002) 13 323.8 [236.2, 443.8]
Subgroup-1: summary estimate (p <.01, I2 = 89.2%) 375.0 [339.9, 413.7]
Non-steady state
Graham (2006) 23 267.7 [195.5, 366.8]
Gupta (2008) 20 671.8 [549.2, 821.9]
Roy (1999) 10 441.4 [336.1, 579.8]
Roy (2012) 20 357.8 [329.2, 388.9]
Ruslami.1 (2022) 20 502.7 [418.2, 604.3]
Subgroup-2: summary estimate (p <.01, I2 = 92.1%) 431.1 [320.7, 579.5]
Total summary estimate (p <.01, I2 = 91.4%) 387.0 [350.3, 427.5]
Subgroup differences: QM = 1.34, p = 0.25
0.0
250.0
500.0
750.0
1000.0
Dose-normalized AUC0–24 (h*mg/L) of pyrazinamide

Figure 2C

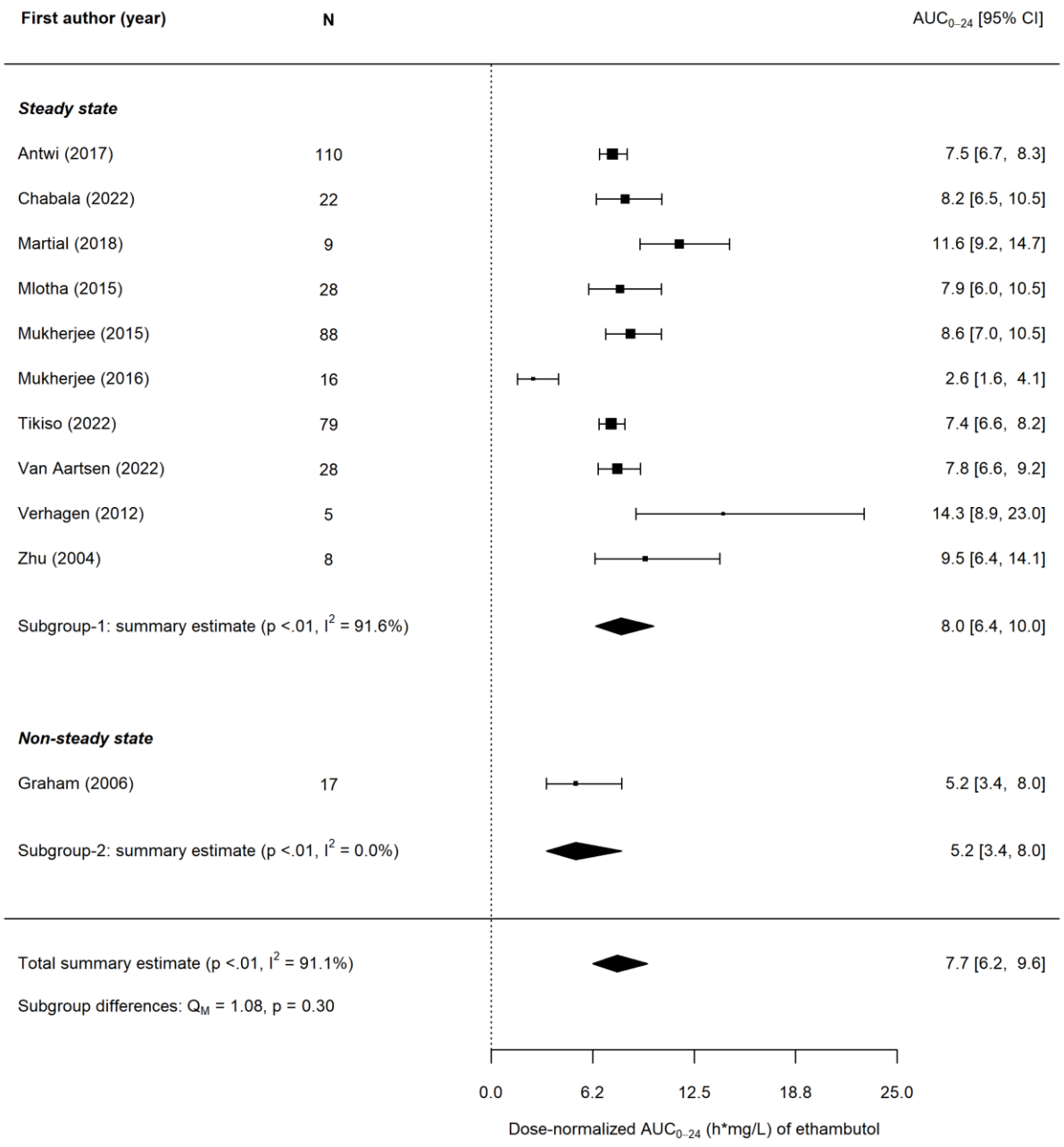
First author (year)
N
AUC0–24 [95% CI]
Steady state
Antwi (2017) 110 7.5 [6.7, 8.3]
Chabala (2022) 22 8.2 [6.5, 10.5]
Martial (2018) 9 11.6 [9.2, 14.7]
Mlotha (2015) 28 7.9 [6.0, 10.5]
Mukherjee (2015) 88 8.6 [7.0, 10.5]
Mukherjee (2016) 16 2.6 [1.6, 4.1]
Tikiso (2022) 79 7.4 [6.6, 8.2]
Van Aartsen (2022) 28 7.8 [6.6, 9.2]
Verhagen (2012) 5 14.3 [8.9, 23.0]
Zhu (2004) 8 9.5 [6.4, 14.1]
Subgroup-1: summary estimate (p <.01, I2 = 91.6%) 8.0 [6.4, 10.0]
Non-steady state
Graham (2006) 17 5.2 [3.4, 8.0]
Subgroup-2: summary estimate (p <.01, I2 = 0.0%) 5.2 [3.4, 8.0]
Total summary estimate (p <.01, I2 = 91.1%) 7.7 [6.2, 9.6]
Subgroup differences: QM = 1.08, p = 0.30
0.0
6.2
12.5
18.8
25.0
Dose-normalized AUC0–24 (h*mg/L) of ethambutol

Figure 2D

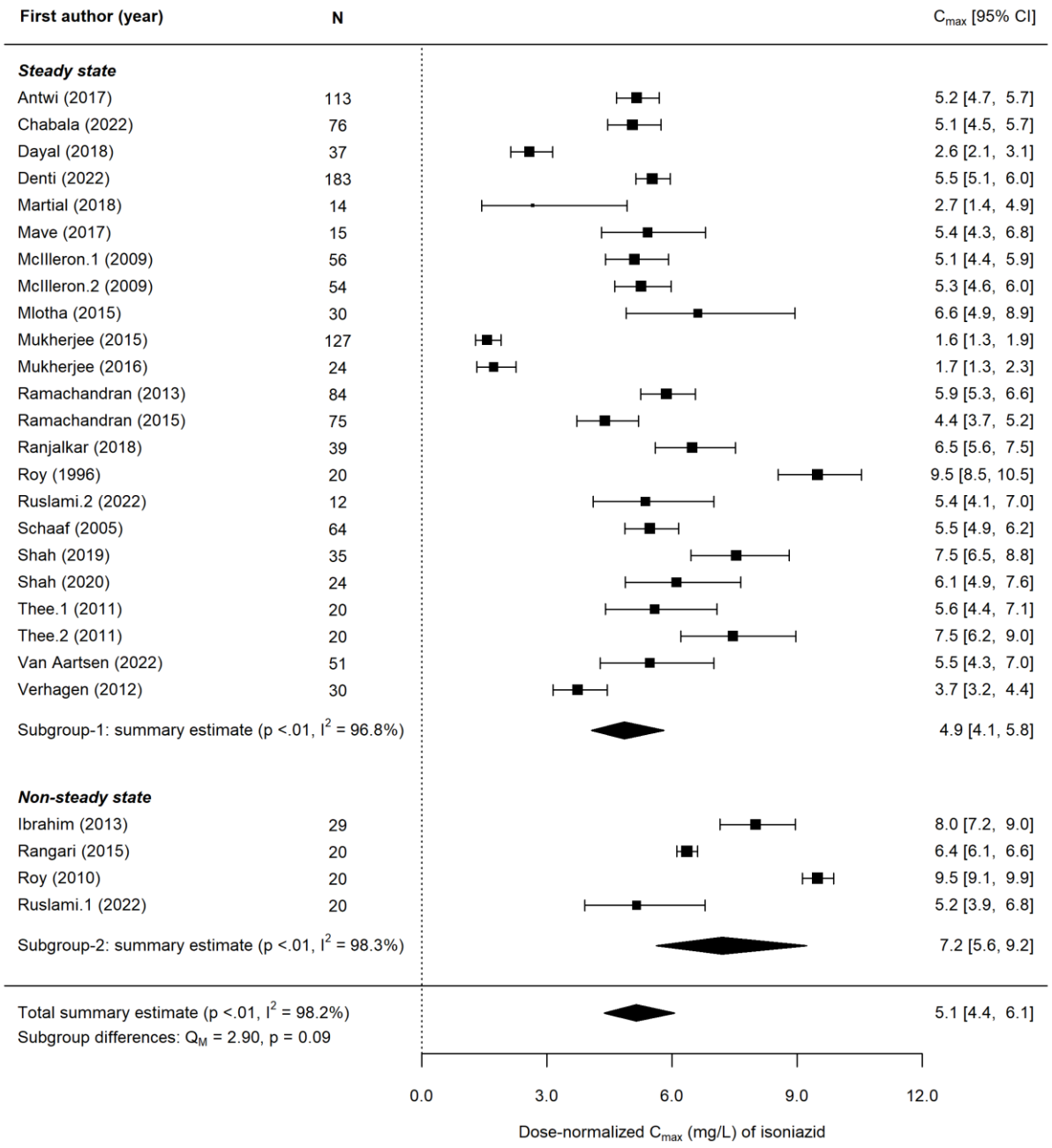
First author (year)
N
C_{max} [95% CI]
Steady state
Antwi (2017) 113 5.2 [4.7, 5.7]
Chabala (2022) 76 5.1 [4.5, 5.7]
Dayal (2018) 37 2.6 [2.1, 3.1]
Denti (2022) 183 5.5 [5.1, 6.0]
Martial (2018) 14 2.7 [1.4, 4.9]
Mave (2017) 15 5.4 [4.3, 6.8]
McIlleron.1 (2009) 56 5.1 [4.4, 5.9]
McIlleron.2 (2009) 54 5.3 [4.6, 6.0]
Mlotha (2015) 30 6.6 [4.9, 8.9]
Mukherjee (2015) 127 1.6 [1.3, 1.9]
Mukherjee (2016) 24 1.7 [1.3, 2.3]
Ramachandran (2013) 84 5.9 [5.3, 6.6]
Ramachandran (2015) 75 4.4 [3.7, 5.2]
Ranjalkar (2018) 39 6.5 [5.6, 7.5]
Roy (1996) 20 9.5 [8.5, 10.5]
Ruslami.2 (2022) 12 5.4 [4.1, 7.0]
Schaaf (2005) 64 5.5 [4.9, 6.2]
Shah (2019) 35 7.5 [6.5, 8.8]
Shah (2020) 24 6.1 [4.9, 7.6]
Thee.1 (2011) 20 5.6 [4.4, 7.1]
Thee.2 (2011) 20 7.5 [6.2, 9.0]
Van Aartsen (2022) 51 5.5 [4.3, 7.0]
Verhagen (2012) 30 3.7 [3.2, 4.4]
Subgroup-1: summary estimate (p <.01, I^2 = 96.8%) 4.9 [4.1, 5.8]
Non-steady state
Ibrahim (2013) 29 8.0 [7.2, 9.0]
Rangari (2015) 20 6.4 [6.1, 6.6]
Roy (2010) 20 9.5 [9.1, 9.9]
Ruslami.1 (2022) 20 5.2 [3.9, 6.8]
Subgroup-2: summary estimate (p <.01, I^2 = 98.3%) 7.2 [5.6, 9.2]
Total summary estimate (p <.01, I^2 = 98.2%) 5.1 [4.4, 6.1]
Subgroup differences: Q_M = 2.90, p = 0.09
0.0
3.0
6.0
9.0
12.0
Dose-normalized C_{max} (mg/L) of isoniazid

Figure 3A

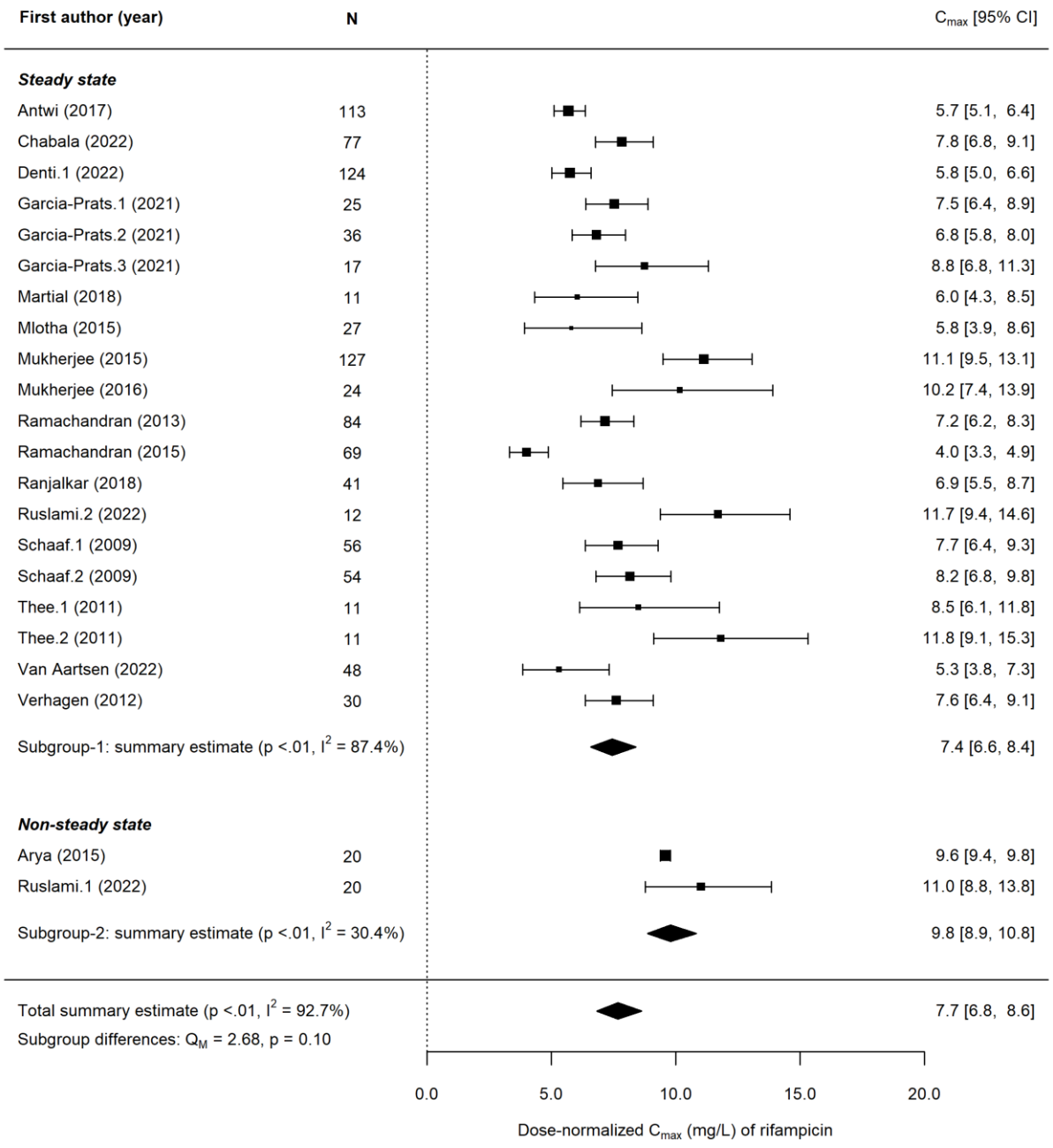
First author (year)
N
C_{max} [95% CI]
Steady state
Antwi (2017) 113 5.7 [5.1, 6.4]
Chabala (2022) 77 7.8 [6.8, 9.1]
Denti.1 (2022) 124 5.8 [5.0, 6.6]
Garcia-Prats.1 (2021) 25 7.5 [6.4, 8.9]
Garcia-Prats.2 (2021) 36 6.8 [5.8, 8.0]
Garcia-Prats.3 (2021) 17 8.8 [6.8, 11.3]
Martial (2018) 11 6.0 [4.3, 8.5]
Mlotha (2015) 27 5.8 [3.9, 8.6]
Mukherjee (2015) 127 11.1 [9.5, 13.1]
Mukherjee (2016) 24 10.2 [7.4, 13.9]
Ramachandran (2013) 84 7.2 [6.2, 8.3]
Ramachandran (2015) 69 4.0 [3.3, 4.9]
Ranjalkar (2018) 41 6.9 [5.5, 8.7]
Ruslami.2 (2022) 12 11.7 [9.4, 14.6]
Schaaf.1 (2009) 56 7.7 [6.4, 9.3]
Schaaf.2 (2009) 54 8.2 [6.8, 9.8]
Thee.1 (2011) 11 8.5 [6.1, 11.8]
Thee.2 (2011) 11 11.8 [9.1, 15.3]
Van Aartsen (2022) 48 5.3 [3.8, 7.3]
Verhagen (2012) 30 7.6 [6.4, 9.1]
Subgroup-1: summary estimate (p <.01, I^2 = 87.4%) 7.4 [6.6, 8.4]
Non-steady state
Arya (2015) 20 9.6 [9.4, 9.8]
Ruslami.1 (2022) 20 11.0 [8.8, 13.8]
Subgroup-2: summary estimate (p <.01, I^2 = 30.4%) 9.8 [8.9, 10.8]
Total summary estimate (p <.01, I^2 = 92.7%) 7.7 [6.8, 8.6]
Subgroup differences: Q_M = 2.68, p = 0.10
0.0
5.0
10.0
15.0
20.0
Dose-normalized C_{max} (mg/L) of rifampicin

Figure 3B

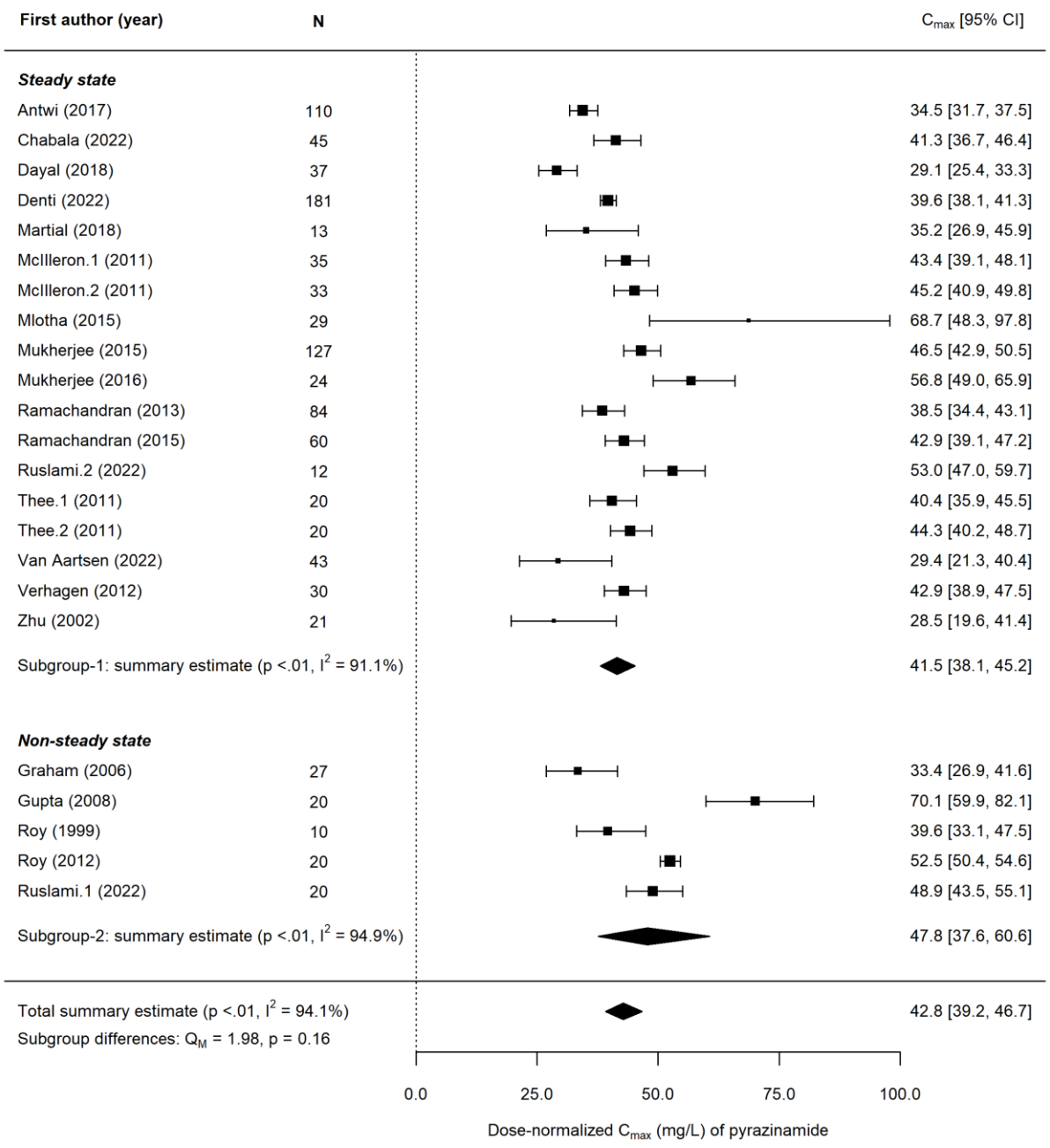
First author (year)
N
C_{max} [95% CI]
Steady state
Antwi (2017) 110 34.5 [31.7, 37.5]
Chabala (2022) 45 41.3 [36.7, 46.4]
Dayal (2018) 37 29.1 [25.4, 33.3]
Denti (2022) 181 39.6 [38.1, 41.3]
Martial (2018) 13 35.2 [26.9, 45.9]
McIlleron.1 (2011) 35 43.4 [39.1, 48.1]
McIlleron.2 (2011) 33 45.2 [40.9, 49.8]
Mlotha (2015) 29 68.7 [48.3, 97.8]
Mukherjee (2015) 127 46.5 [42.9, 50.5]
Mukherjee (2016) 24 56.8 [49.0, 65.9]
Ramachandran (2013) 84 38.5 [34.4, 43.1]
Ramachandran (2015) 60 42.9 [39.1, 47.2]
Ruslami.2 (2022) 12 53.0 [47.0, 59.7]
Thee.1 (2011) 20 40.4 [35.9, 45.5]
Thee.2 (2011) 20 44.3 [40.2, 48.7]
Van Aartsen (2022) 43 29.4 [21.3, 40.4]
Verhagen (2012) 30 42.9 [38.9, 47.5]
Zhu (2002) 21 28.5 [19.6, 41.4]
Subgroup-1: summary estimate (p <.01, I^2 = 91.1%) 41.5 [38.1, 45.2]
Non-steady state
Graham (2006) 27 33.4 [26.9, 41.6]
Gupta (2008) 20 70.1 [59.9, 82.1]
Roy (1999) 10 39.6 [33.1, 47.5]
Roy (2012) 20 52.5 [50.4, 54.6]
Ruslami.1 (2022) 20 48.9 [43.5, 55.1]
Subgroup-2: summary estimate (p <.01, I^2 = 94.9%) 47.8 [37.6, 60.6]
Total summary estimate (p <.01, I^2 = 94.1%) 42.8 [39.2, 46.7]
Subgroup differences: Q_M = 1.98, p = 0.16
0.0
25.0
50.0
75.0
100.0
Dose-normalized C_{max} (mg/L) of pyrazinamide

Figure 3C

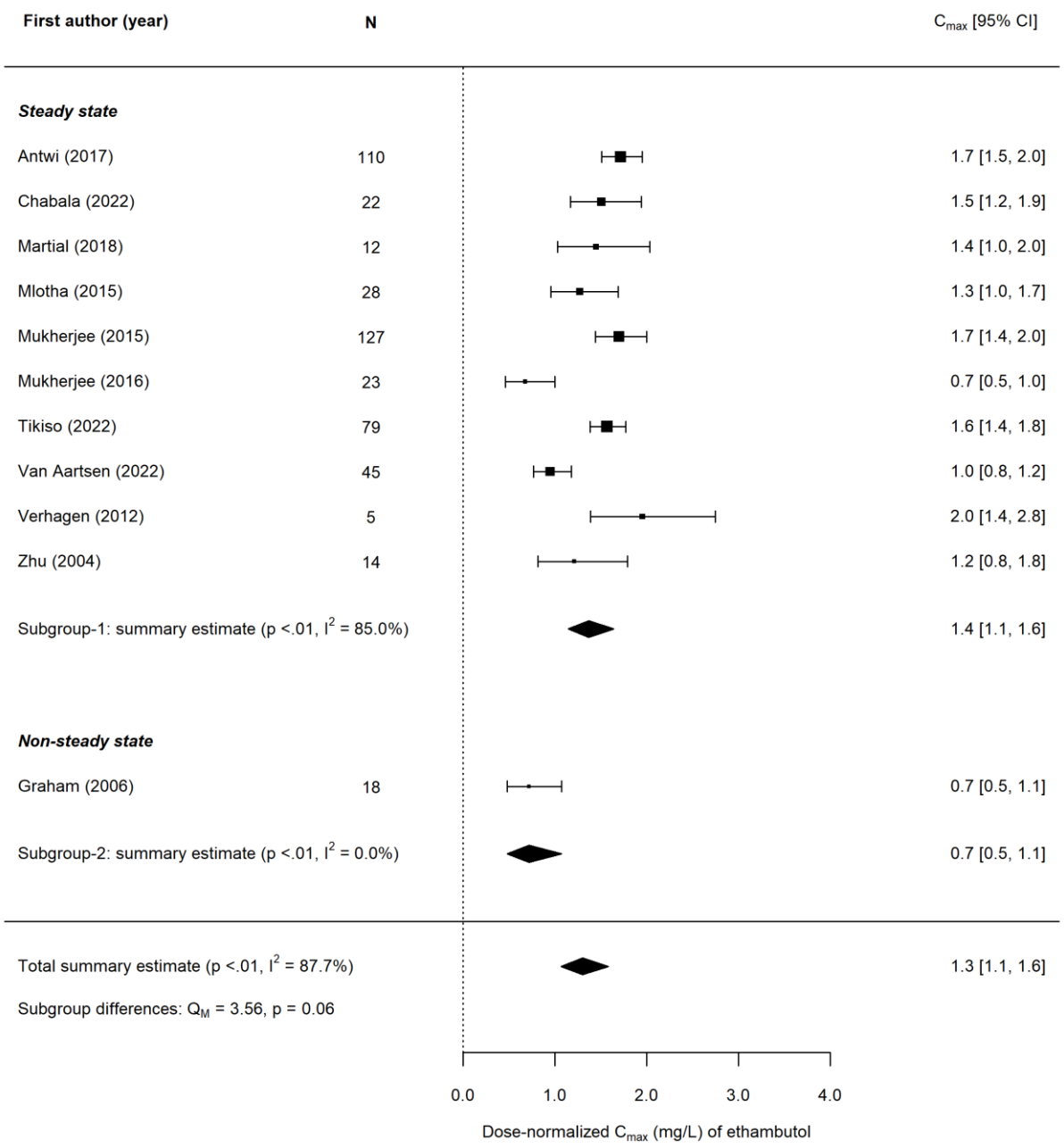
First author (year)
N
C_{max} [95% CI]
Steady state
Antwi (2017) 110 1.7 [1.5, 2.0]
Chabala (2022) 22 1.5 [1.2, 1.9]
Martial (2018) 12 1.4 [1.0, 2.0]
Mlotha (2015) 28 1.3 [1.0, 1.7]
Mukherjee (2015) 127 1.7 [1.4, 2.0]
Mukherjee (2016) 23 0.7 [0.5, 1.0]
Tikiso (2022) 79 1.6 [1.4, 1.8]
Van Aartsen (2022) 45 1.0 [0.8, 1.2]
Verhagen (2012) 5 2.0 [1.4, 2.8]
Zhu (2004) 14 1.2 [0.8, 1.8]
Subgroup-1: summary estimate (p <.01, I^2 = 85.0%) 1.4 [1.1, 1.6]
Non-steady state
Graham (2006) 18 0.7 [0.5, 1.1]
Subgroup-2: summary estimate (p <.01, I^2 = 0.0%) 0.7 [0.5, 1.1]
Total summary estimate (p <.01, I^2 = 87.7%) 1.3 [1.1, 1.6]
Subgroup differences: Q_M = 3.56, p = 0.06
0.0
1.0
2.0
3.0
4.0
Dose-normalized C_{max} (mg/L) of ethambutol

Figure 3D

Online data supplement

Global estimates and determinants of antituberculosis drug pharmacokinetics in children and adolescents: a systematic review and individual patient data meta-analysis

Fajri Gafar,* Roeland E. Wasmann, Helen M. McIlleron, Rob E. Aarnoutse, H. Simon Schaaf, Ben J. Marais, Dipti Agarwal, Sampson Antwi, Nguyen D. Bang, Adrie Bekker, David J. Bell, Chishala Chabala, Louise Choo, Geraint R. Davies, Jeremy N. Day, Rajeshwar Dayal, Paolo Denti, Peter R. Donald, Ephrem Engidawork, Anthony J. Garcia-Prats, Diana Gibb, Stephen M. Graham, Anneke C. Hesseling, Scott K. Heysell, Misgana I. Idris, Sushil K. Kabra, Aarti Kinikar, Agibothu K. Hemanth Kumar, Awewura Kwara, Rakesh Lodha, Cecile Magis-Escurra, Nilza Martinez, Binu S. Mathew, Vidya Mave, Estomih Mduma, Rachel Mlotha-Mitole, Stellah G. Mpagama, Aparna Mukherjee, Heda M. Nataprawira, Charles A. Peloquin, Thomas Pouplin, Geetha Ramachandran, Jaya Ranjalkar, Vandana Roy, Rovina Ruslami, Ira Shah, Yatish Singh, Marieke G. G. Sturkenboom, Elin M. Svensson, Soumya Swaminathan, Urmilla Thatte, Stephanie Thee, Tania A. Thomas, Tjokosela Tikiso, Daan J. Touw, Anna Turkova, Thirumurthy Velpandian, Lilly M. Verhagen, Jana Winckler, Hongmei Yang, Vycke Yunivita, Katja Taxis, Jasper Stevens, Jan-Willem C. Alffenaar.

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Appendix 1. Search strategy

PubMed:

("Tuberculosis"[Mesh] OR tubercul*[tiab] OR TB[tiab] OR TBC[tiab])
AND
("Antitubercular Agents"[Mesh] OR antitubercul*[tiab] OR anti-tubercul*[tiab] OR “anti-TB”[tiab] OR "Isoniazid"[Mesh] OR isoniazid[tiab] OR INH[tiab] OR "Rifampin"[Mesh] OR rifampi*[tiab] OR RMP[tiab] OR RIF[tiab] OR "Pyrazinamide"[Mesh] OR pyrazinamide[tiab] OR PZA[tiab] OR "Ethambutol"[Mesh] OR ethambutol[tiab] OR EMB[tiab])
AND
("Pharmacokinetics"[Mesh] OR "pharmacokinetics"[Subheading] OR pharmacokinetic*[tiab] OR PK OR kinetic*[tiab] OR “clinical pharmacology”[tiab] OR AUC[tiab] OR AUCs[tiab] OR area under the curve*[tiab] OR area under curve*[tiab] OR Cmax[tiab] OR concentration*[tiab] OR level*[tiab] OR (drug*[tiab] AND monitor*[tiab]) OR (therapeutic[tiab] AND monitor*[tiab]) OR TDM[tiab] OR exposure*[tiab])
AND
("Child"[Mesh] OR "Infant"[Mesh] OR “Child, Preschool”[Mesh] OR “Infant, Newborn”[Mesh] OR child*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR infant*[tiab] OR baby[tiab] OR babies[tiab] OR toddler*[tiab] OR kids[tiab] OR minors[tiab] OR newborn*[tiab] OR neonate*[tiab] OR “Adolescent”[Mesh] OR adolescen*[tiab] OR teen*[tiab] OR youth*[tiab] OR young[tiab])

Total articles retrieved from PubMed between January 1st, 1990, and February 2nd, 2021: 2000.
Total articles retrieved from PubMed between February 3rd, 2021, and December 31st, 2021: 113.

Embase:

('tuberculosis'/exp OR (tubercul* OR TB OR TBC):ab,ti)
AND
('isoniazid'/exp OR 'rifampicin'/exp OR 'pyrazinamide'/exp OR 'ethambutol'/exp OR 'tuberculostatic agent'/exp OR (antitubercul* OR ‘anti-tubercul*’ OR ‘anti-TB’ OR isoniazid OR INH OR rifampi* OR RMP OR RIF OR pyrazinamide OR PZA OR ethambutol OR EMB):ab,ti)
AND
('pharmacokinetics'/exp OR (pharmacokinet* OR PK OR kinetic* OR ‘clinical pharmacology’ OR AUC OR AUCs OR ‘area under the curve*’ OR ‘area under curve*’ OR Cmax OR concentration* OR level* OR (drug* AND monitor*) OR (therapeutic AND monitor*) OR TDM OR exposure*):ab,ti)
AND
('child'/exp OR 'adolescent'/exp OR 'infant'/exp OR (child* OR pediatr* OR paediatr* OR infant* OR baby OR babies OR toddler* OR kids OR minors OR newborn* OR neonate* OR adolescen* OR teen* OR youth OR young):ab,ti)

Total articles retrieved from Embase between January 1st, 1990, and February 2nd, 2021: 2416.
Total articles retrieved from Embase between February 3rd, 2021, and December 31st, 2021: 155

Web of Science:

TS=(tuberculosis OR tubercul* OR TB OR TBC)
AND
TS=(isoniazid OR INH OR rifampicin OR Rifampi* OR RMP OR RIF OR pyrazinamide OR PZA OR ethambutol OR EMB OR antitubercul* OR "anti-tubercul*" OR "anti-TB")
AND
TS=(Pharmacokinet* OR PK OR kinetic* OR "clinical pharmacology" OR AUC OR AUCs OR "area under the curve*" OR "area under curve*" OR Cmax OR concentration* OR level* OR (drug* AND monitor*) OR (therapeutic AND monitor*) OR TDM OR exposure*)
AND
TS=(child* OR pediatr* OR paediatr* OR infant* OR baby OR babies OR toddler* OR kids OR minors OR newborn* OR neonate* OR adolescen* OR youth OR teen* OR young)

Total articles retrieved from Web of Science between January 1st, 1990, and February 2nd, 2021: 901.
Total articles retrieved from Web of Science between February 3rd, 2021, and December 31st, 2021: 79

Appendix 2. Checklist and interpretation for quality assessment of included studies

In the absence of a validated tool for quality assessment of pharmacokinetic studies, we developed a checklist to assess the quality of included studies by including some relevant criteria according to the ROBINS-I tool for non-randomized studies of interventions,[1] supplemented by the proposed essential components required for a critical appraisal of clinical pharmacokinetic studies by Soliman et al.[2] The checklist was slightly modified to suit pharmacokinetic studies of first-line antituberculosis drugs in children and adolescents. An expert panel (DJT, MS, JS, and JWCA) evaluated and approved the components to be included in the checklist.

The maximum points obtained from this checklist is 33, including 12 points from the modified ROBINS-I tool,[1] and 21 points from the critical appraisal tool for clinical pharmacokinetic studies.[2] Every 'Yes' answer was given the corresponding two or one point, and every 'No/NA' answer was given zero point. Studies with a total of 23-33 points, 12-22 points, and ≤11 points, were classified as high, moderate, and low quality, respectively.

Below are the study specification, and items to be included in the checklist:

Design	:	Pharmacokinetic or pharmacokinetic/pharmacodynamic study.
Participants	:	Children and adolescents aged 0-18 years with tuberculosis.
Intervention	:	First-line anti-TB drugs, including isoniazid, rifampicin, pyrazinamide and/or ethambutol.
Comparator	:	None
Outcomes	:	Pharmacokinetic measures or clinical responses to treatment, where applicable.

Items adapted from the modified ROBINS-I tool.[1]		**Answer**	**Point given**
Bias due to confounding			
1.	No confounding is expected;	Yes/No/NA	2/0/0
	or		
	Confounding is expected but all known important confounding domains (e.g. co-administration of drugs or foods, liver/kidney impairment, and disease severity, younger vs older age, etc.) are appropriately measured and controlled for.	Yes/No/NA	1/0/0
Bias due to selection of participants into the study			
2.	All patients who would have been eligible for the study were included (e.g., participants were consecutively included in the study); and for each participant, start of follow-up and start of intervention coincided;	Yes/No/NA	2/0/0
	or		
	Selection into the study may have been related to intervention and outcome, and the authors used appropriate methods to adjust for the selection bias; or start of follow-up and start of intervention do not coincided for all participants, and the proportion of participants for which this was the case was too low to induce important bias or the authors used appropriate methods to adjust for the selection bias.	Yes/No/NA	1/0/0
Bias in classification of interventions			
3.	Intervention status (drug and dosing characteristics) is well-defined; and intervention definition is based solely on information collected at the time of intervention and could have not been affected by knowledge of the outcome;	Yes/No/NA	2/0/0
	or		
	Intervention status (drug and dosing characteristics) is well-defined; and some aspects of the assignments of intervention status were determined retrospectively (e.g., based on treatment guidelines recommended by authorities)	Yes/No/NA	1/0/0
Bias due to missing data			
4.	Data were reasonably complete; or proportions of and reasons for missing participants were similar across intervention groups (if there was only one group of intervention	Yes/No/NA	2/0/0

	available, the proportions of missing participants were similar between pre- and post-intervention); or the analysis addressed missing data and is likely to have removed any risk of bias. or Proportions of and reasons for missing participants differ slightly across intervention groups (if there was only one group of intervention available, the proportions of missing participants differ slightly between pre- and post-intervention).	Yes/No/NA	1/0/0
Bias in measurement of outcomes			
5.	The methods of outcome assessment were comparable across intervention groups (if applicable); and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e., is objective) or the outcome assessors were unaware of the intervention received by study participants; and any error in measuring the outcome is unrelated to intervention status. or The methods of outcome assessment were comparable across intervention groups; and the outcome measure is only minimally influenced by knowledge of the intervention received by study participants (e.g., the intervention received by study participants was according to the guidelines recommended by authorities); and any error in measuring the outcome is minimally related to intervention status.	Yes/No/NA Yes/No/NA	2/0/0 1/0/0
Bias in selection of the reported result			
6.	There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts; or The outcome measurements and analyses are consistent with an a priori plan, or are clearly defined and both internally and externally consistent; and there is no indication of selection of the reported analysis from among multiple analyses; and there is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results.	Yes/No/NA Yes/No/NA	2/0/0 1/0/0
Items adapted from the critical appraisal tool for clinical pharmacokinetic studies.[2]			
Appraising Background			
7.	Was a clear description of the objectives of the study provided? Authors should provide a clear statement of the objectives of the research to clarify the purpose and the scope of the study.	Yes/No/NA	1/0/0
8.	Was a clear and comprehensive rationale provided to support the purpose of the study?	Yes/No/NA	1/0/0
Appraising Study Design and Experimental Methods			
9.	Was the chosen study design appropriately selected and justified?	Yes/No/NA	1/0/0
10.	[Slightly modified from the original version] Was the description of at least the drug dose (in mg or mg/kg of body weight) and dosing interval (single-dose, daily, or intermittent [trice weekly] dose, etc.), with addition of drug administration (taken whole by mouth, crushed/dispersed and taken via syringe/nasogastric tube, etc.) justified for the intended study? Examples: Authors should justify the use of single-dose versus steady-state dosing, daily versus intermittent dosing, flat-dosing versus weight-band dosing, etc.).	Yes/No/NA	1/0/0
11.	Were the outcome measures endpoints of the study appropriate to address the objectives of the study?	Yes/No/NA	1/0/0
12.	Were the exclusion criteria of participants included and appropriate for the intended outcomes of the study?	Yes/No/NA	1/0/0

	Examples: The exclusion criteria should be relevant to assist with decreasing significant confounders (e.g. co-administration of drugs and foods, organ impairment, and special populations) that may impact outcomes		
13.	Were the relevant baseline characteristics of the participants adequately described? Examples: Sex, race, age, weight, height, HIV status, nutritional status, concomitant disease, administered medications, severity of illness, and pharmacogenetics that may affect pharmacokinetic parameters, renal function, and hepatic function.	Yes/No/NA	1/0/0
14.	Were plausible interacting covariates described *a priori* or in post hoc evaluation? Examples: Demographic variables, laboratory values, concomitant medications, and relevant disease states to the drug being studied.	Yes/No/NA	1/0/0
15.	Was the description of the used biological sample analytical methods or citations of prior validation studies provided in the publication or affiliated appendix? Examples: - Chromatography type. - Assay characteristics: mobile phase composition, gradient and flow rate, chromatographic column (packing material, dimensions). - Analytical runtime. - Operating temperature. - Detection type and parameters. - Validation method: specificity, recovery, linearity and sensitivity, the stability of the assay and its reproducibility. Refer also to EMA/FDA guidelines for bioanalytical method validation.	Yes/No/NA	1/0/0
16.	Was the method of data sampling of analytics appropriate for the study? Examples: - First vs. zero order absorption, and lag time. - Evaluating for nonlinearity requires multiple dose levels and a complete profile is recommended. - Researchers obtain these data from previously conducted studies with completed concentration-time profile. - The method of data sampling should reference previously validated quantitative bioanalytical methods and if those are not available then the full description or defence of data sampling should be included.	Yes/No/NA	1/0/0
17.	Was a clear description of the sampling site provided and justified? Examples: - Sampling site should be consistent for all subjects in the study. - Venous sampling is preferable during frequent sampling schedule.	Yes/No/NA	1/0/0
18.	[Slightly modified from the original version] Was the number of samples taken within the sampling period appropriate for the assessment of total plasma exposure (i.e., area under the concentration-time curve from 0-24 h post-dose [AUC_{0-24}]), including assessment of AUC_{0-24} using non-compartmental pharmacokinetic analysis or population pharmacokinetic modelling? Examples: - Blood samples taken at 0, 1, 2, 4, and 8 h post-dose were considered sufficient for AUC_{0-24} calculation of isoniazid, rifampicin, pyrazinamide, or ethambutol. - Other possible combinations of sampling time points (more points are preferable).	Yes/No/NA	1/0/0
19.	Were sample storage conditions appropriate and described in a manner that could be accurately replicated? Examples: Sample storage, temperature, use and description of anticoagulants, stabilizers, centrifugation etc.	Yes/No/NA	1/0/0

20.	If applicable, was there a clear description of the pharmacokinetic model, its development, validation and justification for use? It is recommended to provide the following details about the selected modelling process: - Description of studies from which dataset was driven - Model structure - Validated software for the pharmacokinetic analysis - Criteria for accepting valid model's parameters - Fitting procedure defined prior to the initiation of the analysis. - A reasonable assumption based on which the scheme for weighting is considered to be appropriate and the transformation of data [e.g. logarithmic transformation to achieve the homoscedastic (constant) variance requirements] should be provided.	Yes/No/NA	1/0/0
21.	If applicable, was the described population pharmacokinetic approach validation method appropriate for the analysis? Examples: - Basic internal method (e.g., visual predictive checks [VPCs], goodness-of-fit [GOF] plot) - Advanced internal method - External model evaluation	Yes/No/NA	1/0/0
22.	Were the essential pharmacokinetic parameters required to make the results applicable in clinical settings included? Examples: Primary parameters for non-compartmental PK (AUC and C_{max}) and for population PK (total clearance [CL] and volume of distribution at steady state [Vss]). Other secondary parameters, if applicable: terminal half-life ($t_{1/2}$), fraction of the unbound drug in plasma (fu), absorption rate constant (Ka), C_{min}, t_{max}, etc.	Yes/No/NA	1/0/0
23.	Were the pharmacokinetic equations used to calculate the patient's pharmacokinetic parameters presented or cited within the article? Examples: Equations used to calculate the following pharmacokinetic parameters: creatinine clearance, body weight calculations, elimination rate constant, elimination half-life, area under the concentration-time curve, clearance, volume of distribution, etc.	Yes/No/NA	1/0/0
Appraising Applied Statistics			
24	Were the chosen statistical tests and software to perform the statistical analysis appropriate to achieve the study objectives?	Yes/No/NA	1/0/0
Appraising Results			
25	Were all patients enrolled in the study accounted for? Examples: Description of patient screening, enrolment, run-in or wash out phases, study period and follow-up periods are adequately described. Any loss to follow-up or withdrawals are described.	Yes/No/NA	1/0/0
26	In the event of missing data or outliers, was the process for analysis justified and appropriate?	Yes/No/NA	1/0/0
27	Were appropriate summary statistics to describe centrality and variance used to present the pharmacokinetic results? Examples: Descriptive statistics such as confidence interval, standard deviation, mean, median, range, interquartile range, standard error and trimmed range.	Yes/No/NA	1/0/0

Appendix 3. Requested variables from contacted authors with individual-patient data

Demographic characteristics:
Age (in years)*
Sex (male/female)
Site of study
Weight (in kg)*
Height (in cm)
Clinical characteristics:
Type of tuberculosis (pulmonary, extrapulmonary, and pulmonary + extrapulmonary)
HIV status (positive, negative, and unknown)
NAT2 genotypes and acetylator status (slow, intermediate, or rapid acetylator) for isoniazid
SLCO1B1 genotypes for rifampicin
Serum creatinine (in mg/dL)*
Serum albumin (in g/dL)*
Drug and dosing characteristics:
Drug formulation and administration (taken whole tablet orally, crushed tablet swallowed orally or delivered via syringe or nasogastric tube, liquid formulation delivered orally, etc.)
Dose-date
Dose-time (clock time)
Dose-amount administered (in mg)
Dosing interval (daily or intermittent [e.g. thrice weekly] dosing)
Confirmation of drug administration at steady state
Pharmacokinetic information:
Sampling date
Sampling time (clock time)
Observed plasma concentrations (in mg/L)

*At baseline and at pharmacokinetic sampling, if both are available. HIV: human immunodeficiency virus; NAT2: N-acetyltransferase 2; SLCO1B1: solute carrier organic anion transporter 1B1.

Appendix 4. Methods used in the classification of acetylator status of isoniazid.

Acetylator status was defined genotypically based on arylamine N-acetyltransferase 2 (NAT2) genotypes), and phenotypically based on isoniazid elimination half-life ($t_{1/2}$).

Genotypically, acetylator status was defined based on analysis of arylamine N-acetyltransferase 2 (NAT2) genetic polymorphisms. Data on N-acetyltransferase *2* (NAT*2*) genotypes were available from eight studies for which $AUC_{0\text{-}24}$ and C_{max} values for isoniazid could be assessed. In six studies (Schaaf et al., 2005;[3] McIlleron et al., 2009;[4] Thee et al., 2011;[5] Verhagen et al., 2012;[6] Ibrahim et al., 2013;[7] and Denti et al., 2021 [Desmond Tutu TB Center study site][8]), NAT2 genotypes were evaluated according to several established methods for the NAT2*4, NAT2*5, NAT2*6, NAT2*7, NAT2*12, NAT2*13, NAT2*14 alleles.[9,10] In these studies, allele characterization and designation were performed using NAT2 allele nomenclature consensus.[11,12] Based on this nomenclature, the wild-type rapid alleles (R) were assigned as NAT2*4, NAT2*12, and NAT2*13, while decreased NAT2 enzyme activity is encoded by NAT2*5, NAT2*6, NAT2*7, and NAT2*14 alleles, which define the slow mutant alleles (S). Depending on the allele combinations observed, the study participants were classified as homozygous rapid (RR), heterozygous intermediate (RS), or homozygous slow (SS) acetylators. Single-nucleotide polymorphisms (SNPs) genotyping were used in three studies, including one SNP (rs1495741) in Denti et al study (Red Cross Children Hospital study site),[8] four SNPs (rs1801279 [191G>A], rs1801280 [341T>C], rs1799930 [590G>A], and rs1799931 [857G>A]) in Antwi et al study,[13] and three SNPs (rs1801280 [341T>C], rs1799930 [590G>A] and rs1208 [803A>G]) in van Aartsen et al study.[14] For each of the three- and four-SNP panel assays, samples homozygous common for all SNPs were classified as rapid acetylator phenotype, samples heterozygous for any of one of the SNPs were classified as intermediate acetylator phenotype, and samples homozygous variant for one or more SNPs or heterozygous for two or more SNPs were classified as slow acetylator phenotype.[15]

Phenotypically, acetylator status was defined based on isoniazid elimination half-life ($t_{1/2}$), in which patients were categorized as rapid ($t_{1/2}$ <1.25 h), intermediate (1.25 h ≤ $t_{1/2}$ ≤2 h), and slow ($t_{1/2}$ >2 h) acetylator phenotypes.[16]

Appendix 5. Pharmacokinetic assessments

Drug concentrations below the lower limit of quantification (LLOQ) before the time to maximum concentration (T_{max}) were set to half of the LLOQ assuming the drug concentrations to be at steady state (≥14 days after the first dose) or approaching steady state (7-11 days after the first dose), and were set to zero following first dose. After T_{max}, the first LLOQ values were set to half the LLOQ and subsequent LLOQ values were removed from the analysis. Outliers of concentration-time data points were carefully identified by visual inspection and pharmacokinetic plausibility (e.g., data points deviating more than three times the interquartile range). Two reviewers (FG and JS) first identified the possible outliers of drug concentration data. After consultation and agreement with a third reviewer (JWCA), outliers were then excluded from further pharmacokinetic and statistical analyses.

All pharmacokinetic parameters in patients with intensive sampling (Table E2; n=35 studies)[3–8,13,14,17–43] were calculated non-compartmentally with the *PKNCA* package (version 0.9.4) in R for Windows; sparse sampling data, especially in four studies were excluded from the analysis.[44–47] Assessment of individual parameters included area under the concentration-time curve during the daily dosing interval from 0-24 h post-dose (AUC_{0-24}), peak plasma concentration (C_{max}), time to reach peak plasma concentration (T_{max}), first order elimination rate constant (K_e), and elimination half-life ($t_{1/2}$). Both C_{max} and T_{max} were derived directly from the concentration-time observations. K_e and its individual derived parameters (e.g. $t_{½}$) were excluded from analysis when K_e could not be estimated over at least three data points on the apparent terminal slope. Exclusion was done in the following cases: poor fit (adjusted R-squared <0.5), a non-positive value for K_e, and if less than two of the data points were taken after T_{max}.

If drug concentration at pre-dose (C_0) was not measured, C_0 was assumed to reflect the concentration at 24 h post-dose at steady-state or approaching steady-state ($C_0 = C_{24}$). In studies where patients received first-line antituberculosis drugs at first dose, C_0 was set to zero. If C_{24} was not measured, it was estimated using the equation: $C_{24} = C_{last} \times e^{-K_e \times (24 - T_{last})}$, in which C_{last} is the last measurable concentration at T_{last}. For individuals where K_e could not reliably be estimated over at least three data points on the apparent terminal slope, C_{24} was assumed to reflect the concentration at pre-dose at steady-state ($C_{24} = C_0$). In this case, a virtual C_{24} with the same plasma concentration as C_0 was added. The calculation of AUC_{0-24} was performed using the linear-up/log-down trapezoidal method. For reporting, AUC_{0-24} and C_{max} data from a larger group of studies with stead-steady concentrations, were combined with data from two studies with drug concentrations approaching steady state.[21,35]

Table E1. Excluded studies with identical or overlapping cohorts with original eligible studies for which individual patient data were or were not provided.

No	Publication details of studies with identical or overlapping cohorts with original studies	Original studies
1	Aruldhas BW, et al. Optimization of dosing regimens of isoniazid and rifampicin in children with tuberculosis in India. Br Clin Pharmacol. 2019;85(3):644-654.	Ranjalkar et al., 2018.[30]
2	Dompreh A, et al. Effect of genetic variation of NAT2 on isoniazid and SLCO1B1 and CES2 on rifampicin pharmacokinetics in Ghanaian children with tuberculosis. Antimicrob Agents Chemother. 2018;62(3):e02099-17.	Antwi et al., 2017.[13]
3	Gent WL, et al. Factors in hydrazine formation from isoniazid by pediatric and adult patients. Eur J Clin Pharmacol. 1992;43(2):131-6.	Donald et al., 1992.[48]
4	Guiastrennec B, et al. Suboptimal antituberculosis drug concentrations and outcomes in small and HIV-coinfected children in India: Recommendations for dose modifications. Clin Pharmacol Ther. 2018;104(4):733-741.	Ramachandran et al., 2013 & 2015.[27,28]
5.	Horita Y, et al. Evaluation of the adequacy of WHO revised dosages of the first-line antituberculosis drugs in children with tuberculosis using population pharmacokinetic modelling and simulations. Antimicrob Agents Chemother. 2018;62(9):e00008-18.	Antwi et al., 2017.[13]
6	Panjasawatwong N, et al. Population pharmacokinetic properties of antituberculosis drugs in Vietnamese children with tuberculosis meningitis. Antimicrob Agents Chemother. 2020;65(1):e00487.	Pouplin et al., 2016.[46]
7	Pariente-Khayat A, et al. Isoniazid acetylation metabolic ratio during maturation in children. Clin Pharmacol Ther. 1997;62(4):377-83.	Rey et al., 1998.[49]
8	Ramachandran G, et al. Low serum concentrations of rifampicin and pyrazinamide associated with poor treatment outcomes in children with tuberculosis related to HIV status. Pediatr Infect Dis J. 2016;35(5):530-4.	Ramachandran et al., 2013 & 2015.[27,28]
9	Rogers et al. The non-linear child: Ontogeny, isoniazid concentration, and NAT2 genotype modulate enzyme reaction kinetics and metabolism. EBioMedicine. 2016;11:118-126.	Hiruy et al., 2015.[50]
10	Savic RM, et al. Pediatric tuberculous meningitis: Model-based approach to determining optimal doses of the antituberculosis drugs rifampicin and levofloxacin for children. Clin Pharmacol Ther. 2015;98(6):622-9.	McIlleron et al., 2009 & 2011;[4,23] Schaaf et al., 2009;[36] Thee et al., 2011.[5]
11	Seneadza NAH, et al. Effect of malnutrition on the pharmacokinetics of anti-TB drugs in Ghanaian children. Int J Tuberc Lung Dis. 2021;25(1):36-42	Antwi et al., 2017.[13]
12	Swaminathan S, et al. Drug concentration thresholds predictive of therapy failure and death in children with tuberculosis: Bread crumb trails in random forests. Clin Infect Dis. 2016;63:S63-S74	Ramachandran et al., 2013 & 2015.[27,28]
13	Verhagen LM, et al. Full-gene sequencing analysis of NAT2 and its relationship with isoniazid pharmacokinetics in Venezuelan children with tuberculosis. Pharmacogenomics. 2014;15(3):285-96	Verhagen et al., 2012.[6]
14	Yang H, et al. Evaluation of the adequacy of the 2010 revised World Health Organization recommended dosages of the first-line antituberculosis drugs for children: Adequacy of revised dosages of TB drugs for children. Pediatr Infect Dis. 2018;37(1):43-51.	Antwi et al., 2017.[13]
15	Zvada S, et al. Population pharmacokinetics of rifampicin, pyrazinamide and isoniazid in children with tuberculosis: in silico evaluation of currently recommended doses. J Antimicrob Chemother. 2014;69(5):1339-49.	McIlleron et al., 2009 & 2011;[4,23] Schaaf et al., 2009;[36] Thee et al., 2011.[5]
16	Bekker A, et al. Pharmacokinetics of rifampicin, isoniazid, pyrazinamide, and ethambutol in infants dosed according to revised WHO-recommended treatment guidelines. Antimicrob Agents Chemother. 2016;60(4):2171-2179	Denti et al., 2022.[8]
17	Szipszky C, et al. Determination of rifampicin concentrations by urine colorimetry and mobile phone readout for personalized dosing in tuberculosis treatment. J Pediatr Infect Dis Soc. 2021;10(2):104-111.	Van Aartsen et al., 2022.[14]
18	Kwara A, et al. Pharmacokinetics of first-line antituberculosis drugs using WHO revised dosage in children with tuberculosis with and without HIV coinfection. J Pediatr Infect Dis Soc. 2016;5(4):356-65.	Antwi et al., 2017.[13]
19	McIlleron H, et al. Bioavailability of two licensed paediatric rifampicin suspensions: implications for quality control programmes. Int J Tuberc Lung Dis. 2016;20(7):915-919.	Denti et al., 2022.[8]
20	Arya A, et al. Pharmacokinetics of rifampicin in North Indian children with tuberculosis at doses administered under the revised national tuberculosis control program India. Indian J Pharmacol. 2013;45:S102-103.	Arya et al., 2015.[42]
21	Justine M, et al. Therapeutic drug levels of first-line tuberculosis medications among children from rural Tanzania. Am J trop Med Hyg. 2017;97(5):581	Justine et al., 2020.[44]

Table E2. Demographic information of all included studies for which individual patient data were provided.

No	Authors	Year of publication	Country	N patients included	Median age (IQR), years	INH	RIF	PZA	EMB	PK sampling time-points, (h)	Intensive sampling	Steady-state PK
1	Antwi et al.[13]	2017	Ghana	113	5.0 (2.2-8.2)	Yes	Yes	Yes	Yes	0, 2, 4, 8	Yes	Yes
2	Arya et al.[42]	2015	India	20	10.0 (9.0-12.0)	No	Yes	No	No	1, 2, 3, 4, 6, 8, 12	Yes	No
3	Chabala et al.[43]	2022	South Africa, Zambia	77	3.7 (1.4-6.6)	Yes	Yes	Yes	Yes	1, 2, 4, 6, 8, 12	Yes	Yes
4	Dayal et al.[17]	2018	India	37	8.0 (3.0-10.0)	Yes	No	Yes	No	0, 2, 4, 6, 8	Yes	Yes
5	Denti et al.[8,§]	2022	South Africa, Malawi	184	2.0 (0.9-4.9)	Yes	Yes	Yes	No	0, 1, 2, 4, 6, 8	Yes	Yes
6	Garcia-Prats et al.[18]	2021	South Africa	60	2.1 (1.1-4.4)	No	Yes	No	No	0, 1, 2, 4, 6, 8, 24	Yes	Yes
7	Graham et al.[19]	2006	Malawi	27/18	4.1 (2.2-9.6)	No	No	Yes	Yes	0, 2, 3, 4, 7, 24, 48	Yes	No
8	Gupta et al.[20]	2008	India	20	10.0 (6.7-12.0)	No	No	Yes	No	0, 1, 2, 4, 6, 8, 12, 24	Yes	No
9	Ibrahim et al.[7]	2013	Ethiopia	29	9.5 (6.0-9.5)	Yes	No	No	No	2, 3, 4, 5	Yes	No
10	Justine et al.[44]	2020	Tanzania	51	5.3 (2.4-9.5)	Yes	Yes	Yes	Yes	2	No	Yes
11	Martial et al.[21]	2018	Paraguay	15	1.5 (0.9-2.7)	Yes	Yes	Yes	Yes	0, 2, 4, 8	Yes	Yes
12	Mave et al.[22]	2017	India	16	7.7 (5.2-8.9)	Yes	No	No	No	0, 2, 4, 6	Yes	Yes
13	McIlleron et al.[4]	2009	South Africa	56	3.2 (1.5-5.4)	Yes	No	No	No	0.75, 1.5, 3, 4, 6	Yes	Yes
14	McIlleron et al.[23]	2011	South Africa	34	3.1 (1.5-5.2)	No	No	Yes	No	0.75, 1.5, 3, 4, 6	Yes	Yes
15	Mlotha et al.[24]	2014	Malawi	30	7.5 (1.7-10.9)	Yes	Yes	Yes	Yes	0, 0.5, 1, 2, 3, 4, 6, 8, 24	Yes	Yes
16	Mlotha et al.[45]	unpublished	Malawi	47	6.2 (2.5-8.1)	Yes	No	Yes	Yes	(0, 0.5, 1, 2, 3, 4, 6, 8)[*]	No	Yes
17	Mukherjee et al.[25]	2015	India	127	9.4 (6.1-11.6)	Yes	Yes	Yes	Yes	0, 1, 2, (3)[*], 4	Yes	Yes
18	Mukherjee et al.[26]	2016	India	24	9.7 (6.7-11.1)	Yes	Yes	Yes	Yes	0, 1, 2, (3)[*], 4	Yes	Yes
19	Pouplin et al.[46]	2016	Vietnam	99	3.0 (1.0-7.0)	Yes	Yes	Yes	No	(1, 2, 3, 4, 5, 6, 8, 12, 18, 24)[*]	No	Yes
20	Ramachandran et al.[27]	2013	India	84	7.0 (4.0-10.0)	Yes	Yes	Yes	No	0, 2, 4, 6, 8	Yes	Yes
21	Ramachandran et al.[28]	2015	India	77	9.0 (7.0-11.0)	Yes	Yes	Yes	No	0, 2, 4, 6, 8	Yes	Yes
22	Rangari et al.[29]	2015	India	20	10.5 (8.7-11.0)	Yes	No	No	No	0, 1, 2, 4, 6, 10, 24	Yes	No
23	Ranjalkar et al.[30]	2018	India	39	6.8 (3.4-13.5)	Yes	Yes	No	No	0.5, 1, 1.5, 2, 2.5, 4, 6	Yes	Yes
24	Roy et al.[31]	1996	India	20	8.0 (7.0-10.0)	Yes	No	No	No	0, 1, 2, 3, 6, 24	Yes	Yes
25	Roy et al.[32]	1999	India	10	8.0 (7.0-9.7)	No	No	Yes	No	0, 1, 2, 4, 6, 12, 24	Yes	No
26	Roy et al.[33]	2010	India	20	9.0 (8.0-10.0)	Yes	No	No	No	0, 1, 2, 4, 6, 8, 24	Yes	No
27	Roy et al.[34]	2012	India	20	5.5 (5.0-6.0)	No	No	Yes	No	0, 1, 2, 4, 6, 8, 12, 24	Yes	No
28	Ruslami et al.[35,§]	2021	Indonesia	20	11.4 (6.2-14.0)	Yes	Yes	Yes	No	0, 1, 2, 4, 8	Yes	No/Yes
29	Schaaf et al.[3]	2005	South Africa	64	3.7 (1.8-7.7)	Yes	No	No	No	2, 3, 4, 5	Yes	Yes
30	Schaaf et al.[36]	2009	South Africa	54	3.2 (1.5-1.4)	No	Yes	No	No	0.75, 1.5, 3, 4, 6	Yes	Yes
31	Schipani et al.[47]	2016	Malawi	50	6.2 (2.5-8.1)	No	Yes	No	No	(0, 0.5, 1, 2, 3, 4, 6, 8)[*]	No	Yes
32	Shah et al.[37]	2019	India	36	7.0 (3.9-11.0)	Yes	No	No	No	0, 1, 2, 3, 6, 24	Yes	Yes
33	Shah et al.[38]	2020	India	24	6.5 (3.0-10.1)	Yes	No	No	No	0, 2, 4, 6, 8	Yes	Yes
34	Thee et al.[5]	2011	South Africa	20	1.0 (0.8-1.6)	Yes	Yes	Yes	No	0.5, 1.5, 3, 5	Yes	Yes
35	Van Aartsen et al.[14,§]	2022	Tanzania	51	2.2 (1.3-5.2)	Yes	Yes	Yes	Yes	1, 2, 6	Yes	Yes
36	Verhagen et al.[6]	2012	Venezuela	30	3.8 (2.6-8.3)	Yes	Yes	Yes	Yes	0, 2, 4, 8	Yes	Yes
37	Tikiso et al.[41,§]	2022	South Africa, Malawi	79	2.9 (1.0-6.8)	No	No	No	Yes	0, 1, 2, 4, 6, 8	Yes	Yes
38	Zhu et al.[39]	2002	United States	24	3.9 (2.3-5.2)	No	No	Yes	No	0, 0.5, 1, 2, 6, 10	Yes	Yes
39	Zhu et al.[40]	2004	United States	19	4.8 (3.5-8.1)	No	No	No	Yes	0, 0.5, 1, 2, 6, 10	Yes	Yes

[*]Randomly performed in ≤2 sampling-time points for each sampling occasion. INH: isoniazid; RIF: rifampicin, PZA: pyrazinamide; EMB: ethambutol; IQR: interquartile range; PK: pharmacokinetics. [§]Raw data were obtained through contact with investigators before the official publication of the studies.

Table E3. Quality assessment results of the included studies for which individual patient data were provided.

No	Authors	Items included in the developed checklist for quality assessment of included studies (details are shown in Appendix 2)																											Total points	Quality
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27		
1	Antwi et al.[13]	1	1	1	1	1	2	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	1	0	1	23	+++
2	Arya et al.[42]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	1	0	1	21	++
3	Chabala et al.[43]	1	2	1	1	1	2	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	1	25	+++
4	Dayal et al.[17]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	23	+++
5	Denti et al.[8]	2	2	2	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	32	+++
6	Garcia-Prats et al.[18]	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	31	+++
7	Graham et al.[19]	1	2	1	2	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	1	24	+++
8	Gupta et al.[20]	0	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	0	1	0	1	18	++
9	Ibrahim et al.[7]	0	1	1	0	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	0	1	20	++
10	Justine et al.[44]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	1	1	0	1	19	++
11	Martial et al.[21]	0	2	1	2	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	24	+++
12	Mave et al.[22]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	1	0	1	1	0	1	20	++
13	McIlleron et al.[4]	1	2	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	24	+++
14	McIlleron et al.[23]	1	2	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	1	1	23	+++
15	Mlotha et al.[24]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	23	+++
16	Mlotha et al.[45]	0	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	0	0	1	1	1	0	18	++
17	Mukherjee et al.[25]	1	2	1	2	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	25	+++
18	Mukherjee et al.[26]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	0	1	0	0	1	1	1	1	1	1	23	+++
19	Pouplin et al.[46]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	0	1	0	0	1	1	1	1	0	1	21	++
20	Ramachandran et al.[27]	1	1	1	2	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	24	+++
21	Ramachandran et al.[28]	1	1	1	2	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	23	+++
22	Rangari et al.[29]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	0	1	1	0	1	21	++
23	Ranjalkar et al.[30]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	23	+++
24	Roy et al.[31]	0	1	1	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	0	1	0	0	1	16	++
25	Roy et al.[32]	0	1	1	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	0	1	0	0	1	16	++
26	Roy et al.[33]	0	1	1	0	1	0	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	1	0	1	0	0	1	16	++
27	Roy et al.[34]	0	1	1	0	1	0	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	1	0	1	0	0	1	17	++
28	Ruslami et al.[35]	1	2	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	24	+++
29	Schaaf et al.[3]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	1	1	1	1	0	1	22	++
30	Schaaf et al.[36]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	24	+++
31	Schipani et al.[47]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	24	+++
32	Shah et al.[37]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	0	0	1	1	1	1	1	1	23	+++
33	Shah et al.[38]	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	24	+++
34	Thee et al.[5]	1	1	1	2	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	24	+++
35	Van Aartsen et al.[14]	1	2	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	27	+++
36	Verhagen et al.[6]	1	2	1	2	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	0	1	25	+++
37	Tikiso et al.[41]	1	2	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	29	+++
38	Zhu et al.[39]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	24	+++
39	Zhu et al.[40]	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	1	1	1	1	1	24	+++

+++: high quality (total points: 23-33); ++: moderate quality (total points: 12-22); +: low quality (total points: ≤11).

Table E4. Eligible studies for which individual patient data were not provided, and reasons for exclusion.

No	Authors	Year of publication	Year of data collection	Country	N patients included	INH	RIF	PZA	EMB	Reasons for exclusion	Quality
1	Arya et al.[51]	2008	1991-1993	India	40	No	No	Yes	No	Authors no longer had data access.	++
2	Arya et al.[52]	2009	1990s	India	18	No	No	Yes	No	Authors no longer had data access.	++
3	Seth et al.[53]	1993	1990s	India	94	Yes	Yes	No	No	Principal investigator (V. Seth) had passed away; other authors did not have data access.	++
4	Seth et al.[54]	1994	1990s	India	20	Yes	No	No	No	Principal investigator (V. Seth) had passed away; other authors did not have data access.	++
5	Donald et al.[55]	1994	1990s	South Africa	32	Yes	No	No	No	Authors no longer had data access.	++
6	Donald et al.[48]	1992	1990s	South Africa	38	Yes	No	No	No	Authors no longer had data access.	++
7	Hiruy et al.[50]	2015	2012-2013	South Africa	31	Yes	Yes	Yes	Yes	Authors agreed to share the data, but data never sent.	+++
8	Mahajan et al.[56]	1997	1990s	India	20	No	Yes	No	No	Recent contact details of the investigators were unavailable.	+
9	Minchev et al.[57]	2005	unknown	Bulgaria	12	No	Yes	No	No	Recent contact details of the investigators were unavailable.	+
10	Rey et al.[58]	2001	unknown	France	34	Yes	No	No	No	No response from the corresponding author; other co-authors did not have data access.	++
11	Rey et al.[49]	1998	1990-1993	France	61	Yes	No	No	No	No response from the corresponding author; other co-authors did not have data access.	++
12	Seifart et al.[16]	1995	1990s	South Africa	13	Yes	No	No	No	Authors no longer had data access.	++
13	Thee et al.[59]	2010	1960s	Germany	45	Yes	No	No	No	Principal investigator (K. Magdorf) had passed away; other authors did not have data access.	++
14	Thee et al.[60]	2009	1973	Germany	27	No	Yes	No	No	Principal investigator (K. Magdorf) had passed away; other authors did not have data access.	++
15	Thee et al.[61]	2008	1983	Germany	21	No	No	Yes	No	Principal investigator (K. Magdorf) had passed away; other authors did not have data access.	++
16	Thee et al.[62]	2007	1971-1973	Germany	48	No	No	No	Yes	Principal investigator (K. Magdorf) had passed away; other authors did not have data access.	++

INH: isoniazid; RIF: rifampicin, PZA: pyrazinamide; EMB: ethambutol; N: number; +++: high quality (total points: 23-33); ++: moderate quality (total points: 12-22); +: low quality (total points: ≤11).

Table E5. Details of the observations for which AUC_{0-24} and C_{max} could not be assessed due to the limited number of samples available, or due to other reasons (e.g., all/most data were below the lower limit of quantification, and/or drug product of poor quality¶).

AUC_{0-24}		C_{max}	
First author, year	**No. of observations %)**	**First author, year**	**No. of observations (%)**
Total, n (isoniazid)	**341**	**Total, n (isoniazid)**	**301**
Pouplin.1 (2016)[46]	99 (29.0%)	Pouplin.1 (2016)[46]	99 (32.9%)
Pouplin.2 (2016)[46]	99 (29.3%)	Pouplin.2 (2016)[46]	99 (32.9%)
Justine (2020)[44]	51 (15.0%)	Justine (2020)[44]	51 (16.9%)
Mlotha (unpublished)[45]	47 (13.8 %)	Mlotha (unpublished)[45]	47 (15.6%)
Mukherjee (2015)[25]	22 (6.4%)	Ramachandran (2015)[28]	2 (0.7%)
Martial (2018)[21]	5 (1.5%)	Mave (2017)[22]	1 (0.3%)
Van Aartsen (2022)[14]	4 (1.2%)	Shah (2019)[37]	1 (0.3%)
Denti (2022)[8]	3 (0.9%)	Denti (2022)[8]	1 (0.3%)
Mave (2017)[22]	2 (0.6%)		
Mlotha (2015)[24]	2 (0.6%)		
Ramachandran (2015)[28]	2 (0.6%)		
Mukherjee (2016)[26]	2 (0.6%)		
Dayal (2018);[17] Shah (2019);[37] and Ranjalkar (2018),[30] 1 each	3 (0.9%)		
Total, n (rifampicin)	**429**	**Total, n (rifampicin)**	**365**
Pouplin.1 (2016)[46]	99 (23.1%)	Pouplin.1 (2016)[46]	99 (27.1%)
Pouplin.2 (2016)[46]	99 (23.1%)	Pouplin.2 (2016)[46]	99 (27.1%)
Justine (2020)[44]	51 (11.9%)	Justine (2020)[44]	51 (14.0%)
Schipani (2015)[47]	47 (10.9%)	Mlotha (unpublished)[45]	47 (12.9%)
Mukherjee (2015)[25]	21 (4.9%)	Denti.2 (2022)[8]	60 (16.4%)¶
Mlotha (2015)[24]	10 (2.3%)	Ramachandran (2015)[28]	6 (1.6%)
Denti.2 (2022)[8]	60 (14.0%)¶	Van Aartsen (2022)[14]	1 (0.3%)
Van Aartsen (2022)[14]	9 (2.1%)	Mlotha (2015)[24]	1 (0.3%)
Ramachandran (2015)[28]	7 (1.6%)	Garcia-Prats (2021)[18]	1 (0.3%)
Garcia-Prats (2021)[18]	5 (1.1%)	Denti.1 (2022)[8]	1 (0.3%)
Ranjalkar (2018)[30]	4 (0.9%)		
Mukherjee (2016)[26]	4 (0.9%)		
Schaaf.2 (2009)[36]	4 (0.9%)		
Ramachandran (2013)[27]	2 (0.5%)		
Verhagen (2012)[6]	2 (0.5%)		
Martial (2018);[21] Ruslami.1 (2022);[35] and Schaaf.1 (2009),[36] 1 each	3 (0.6%)		
Total, n (pyrazinamide)	**342**	**Total, n (pyrazinamide)**	**283**
Pouplin.1 (2016)[46]	99 (28.9%)	Pouplin.1 (2016)[46]	99 (35.0%)
Pouplin.2 (2016)[46]	99 (28.9%)	Pouplin.2 (2016)[46]	99 (35.0%)
Justine (2020)[44]	28 (8.2%)	Justine (2020)[44]	28 (9.9%)
Mlotha (unpublished)[45]	44 (12.9%)	Mlotha (unpublished)[45]	44 (15.5%)
Mukherjee (2015)[25]	28 (8.2%)	Van Aartsen (2022)[14]	4 (1.4%)
Zhu (2002)[39]	11 (3.2%)	Antwi (2017)[13]	3 (1.1%)
Van Aartsen (2022)[14]	7 (2.0%)	Zhu (2002)[39]	3 (1.1%)
Martial (2018)[21]	5 (1.5%)	Martial (2018)[21]	2 (0.7%)
Graham (2006)[19]	4 (1.2%)	Denti (2022)[8]	1 (0.3%)
Denti (2022)[8]	3 (0.9%)		
Antwi (2017)[13]	3 (0.9%)		
Ramachandran (2013)[27]	2 (0.6%)		
Verhagen (2012)[6]	2 (0.6%)		
McIlleron.2 (2011)[23]	2 (0.6%)		
Mlotha (2015)[24]	2 (0.6%)		
Mukherjee (2016);[26] McIlleron.1 (2011);[23] and Chabala (2022),[43] 1 each	3 (0.9%)		
Total, n (ethambutol)	**157**	**Total, n (ethambutol)**	**84**
Mlotha (unpublished)[45]	47 (29.9%)	Mlotha (unpublished)[45]	47 (55.9%)
Justine (2020)[44]	24 (15.3%)	Justine (2020)[44]	24 (28.6%)
Mukherjee (2015)[25]	39 (24.8%)	Zhu (2004)[40]	5 (5.9%)
Van Aartsen (2022)[14]	17 (10.8%)	Antwi (2017)[13]	3 (3.6%)
Zhu (2004)[40]	11 (7.0%)	Martial (2018)[21]	3 (3.6%)
Mukherjee (2016)[26]	8 (5.1%)	Mukherjee (2016)[26]	1 (1.2%)
Martial (2018)[21]	6 (3.8%)	Tikiso (2022)[41]	1 (1.2%)
Antwi (2017)[13]	3 (1.9%)		
Graham (2016)[19]	1 (0.6%)		
Tikiso (2022)[41]	1 (0.6%)		

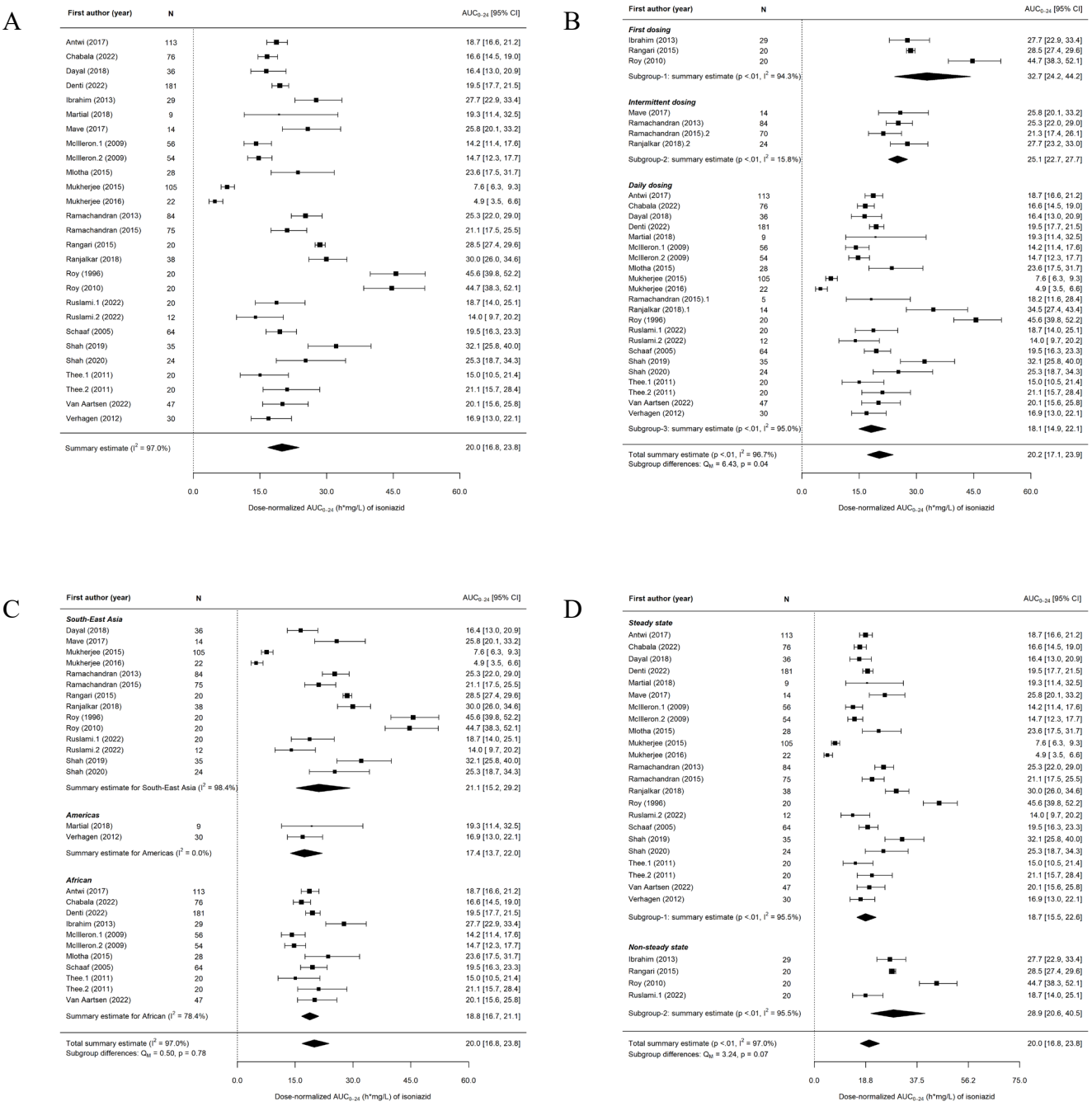

Figure E1. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized AUC_{0-24} for isoniazid in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

AUC_{0-24}: area under the concentration-time curve from 0 to 24 hours post-dose; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. AUC_{0-24} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg

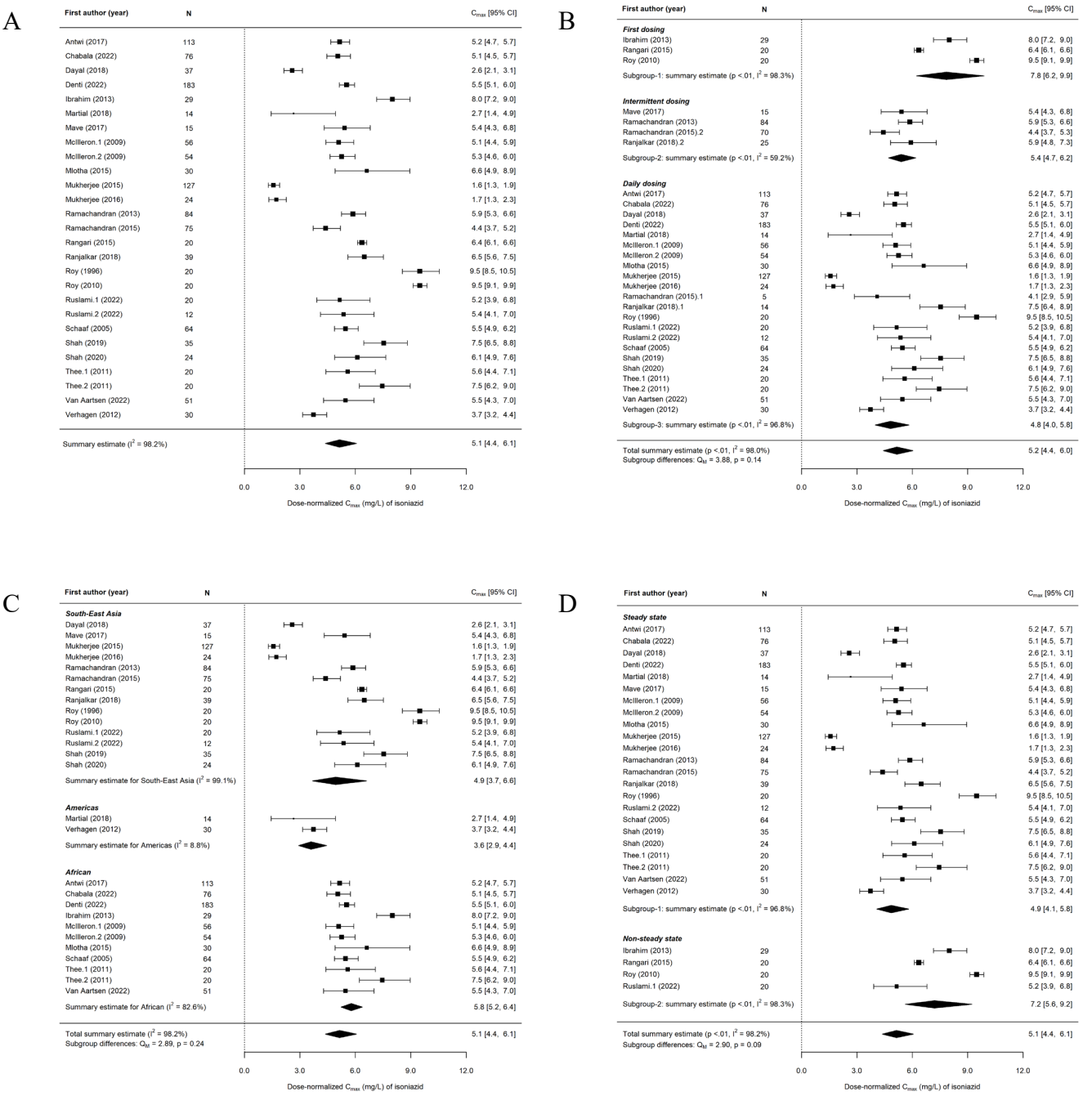

Figure E2. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for isoniazid in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

C_{max}: peak plasma concentration; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

Table E6. Multivariate linear mixed-effects analyses on the effect of NAT2 acetylator genotypes on log-transformed AUC_{0-24} and C_{max} values for isoniazid in children and adolescents with tuberculosis, adjusted for age, sex, nutritional status and HIV status.

	Fixed-effects coefficient (95% CI)	
	Isoniazid AUC_{0-24}	**Isoniazid C_{max}**
(Intercept)	2.88 (2.65−3.10)***	1.66 (1.44−1.87)***
Dose, mg/kg¶	0.46 (0.35−0.56)***	0.41 (0.29−0.53)***
Age		
<2 years	-0.32 (-0.45−-0.18)***	-0.30 (-0.42−-0.18)***
2-4 years	-0.12 (-0.24−-0.001)*	-0.10 (-0.20−0.01)#
5-9 years	-0.06 (-0.16−0.05)	-0.05 (-0.14−0.05)
10-14 years	Ref.	Ref.
15-18 years	0.01 (-0.31−0.32)	-0.08 (-0.37−0.20)
Sex		
Female	Ref.	Ref.
Male	-0.08 (-0.15−-0.004)*	-0.05 (-0.12−0.01)
Malnourished§§		
No	Ref.	Ref.
Yes, moderate	-0.04 (-0.14−0.06)	-0.01 (-0.10−0.08)
Yes, severe	-0.07 (-0.17−0.03)	-0.05 (-0.14−0.04)
Unknown	0.26 (-0.04−0.55)	0.21 (-0.06−0.49)
HIV status		
Negative	Ref.	Ref.
Positive	-0.18 (-0.30−-0.06)**	-0.15 (-0.26−-0.04)**
Unknown	0.001 (-0.26−0.27)	0.03 (-0.21−0.28)
Acetylator status, NAT2 genotyping¶¶		
Slow	0.71 (0.58−0.83)***	0.32 (0.21−0.43)***
Intermediate	Ref.	Ref.
Rapid	-0.30 (-0.46−-0.15)***	-0.12 (-0.27−0.02)#
Unknown	-0.07 (-0.25−0.11)	-0.28 (-0.45−-0.10)**
Random effects		
σ^2	0.42 (0.65)§	0.36 (0.60)§
$\tau_{00\ studies}$	0.15 (0.38)§	0.13 (0.36)§
$\tau_{11\ studies*doses}$	0.04 (0.19)§	0.06 (0.24)§
$\rho_{01\ studies}$	-0.63	-0.40
ICC	0.28	0.32
$N_{\ studies}$	27	27
Observations	1252	1292
Conditional R^2	0.494	0.494

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

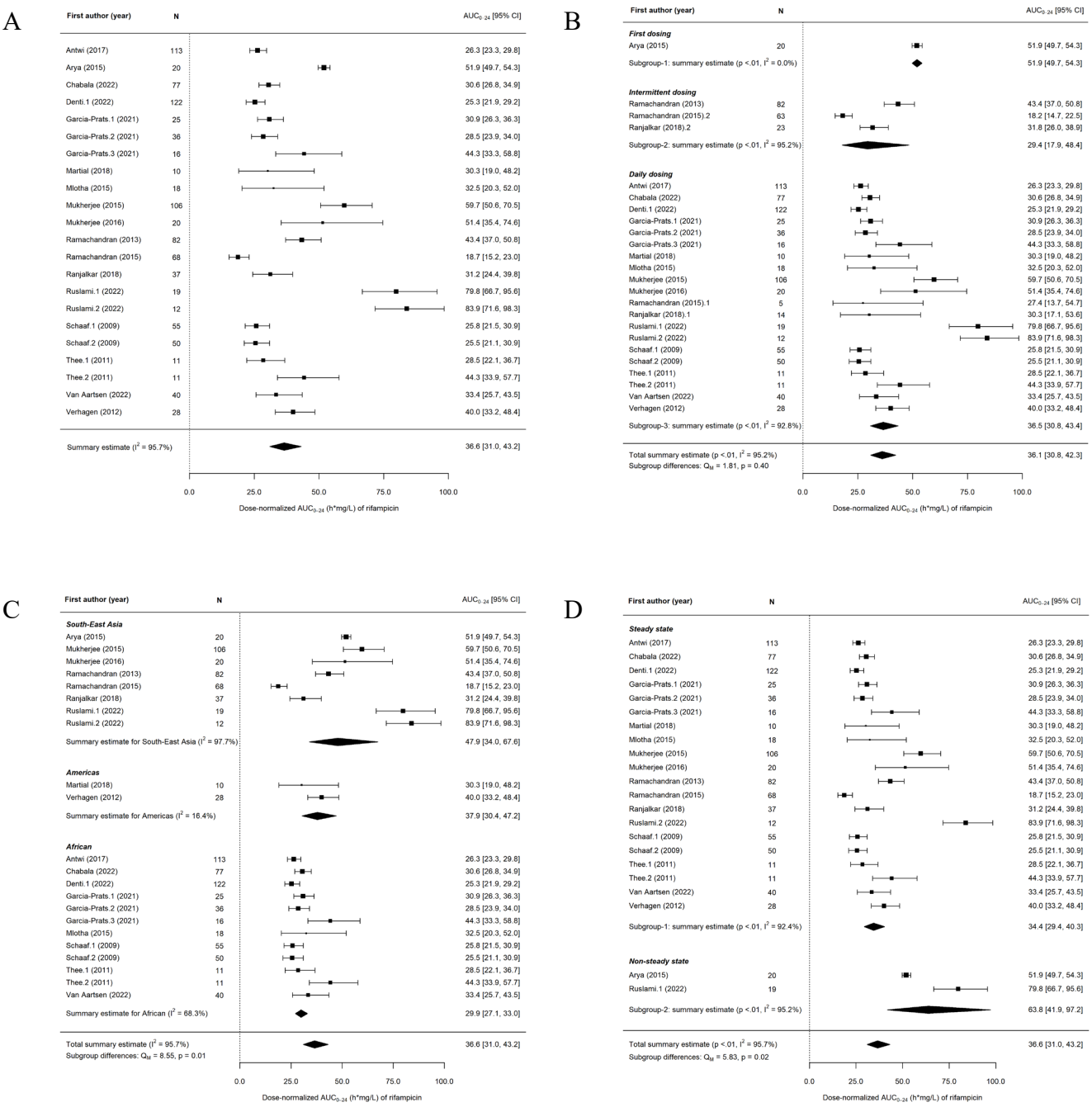

Figure E3. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for rifampicin in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: area under the concentration-time curve from 0 to 24 hours post-dose; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. $AUC_{0\text{-}24}$ values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

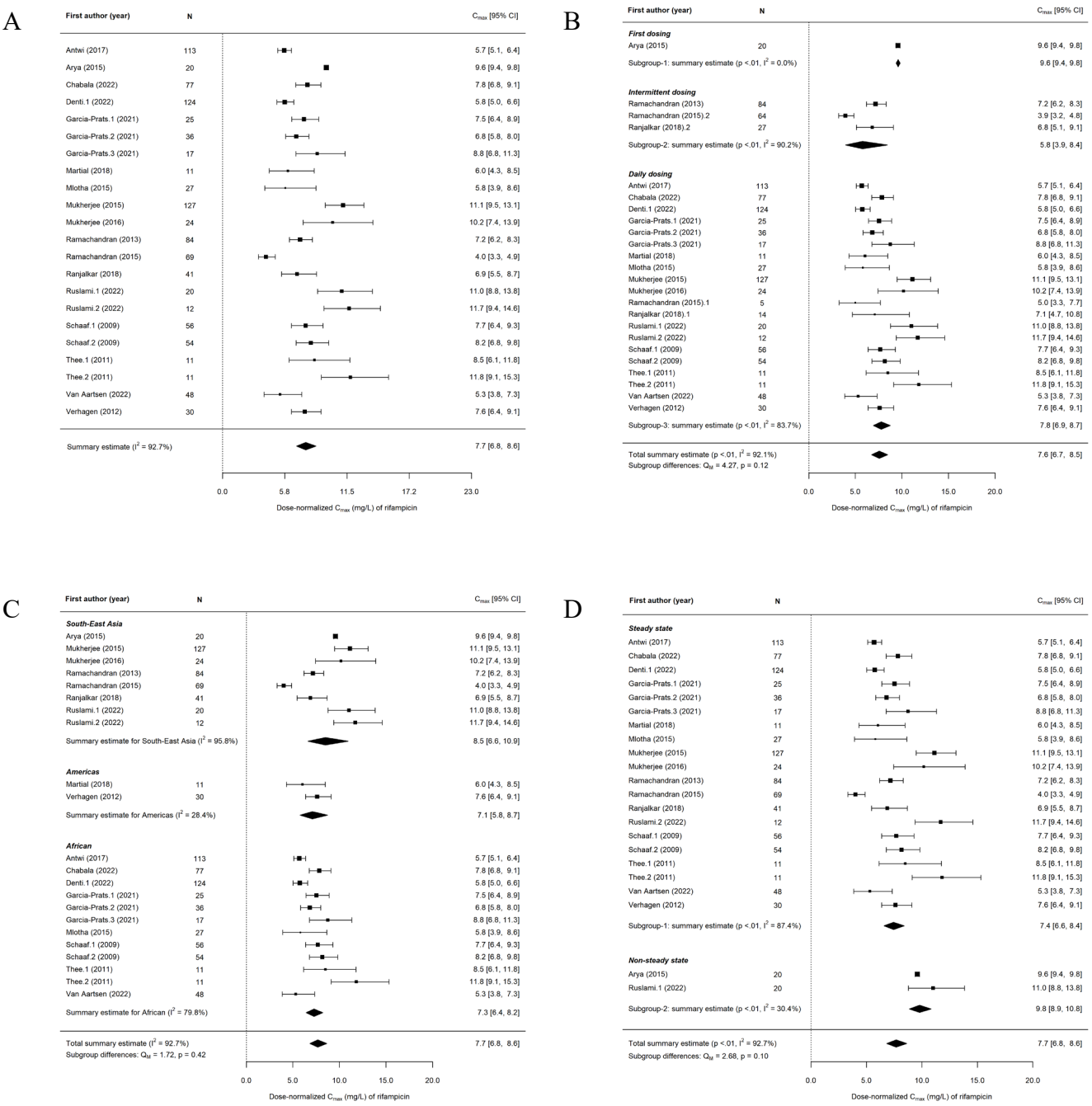

Figure E4. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for rifampicin in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

C_{max}: peak plasma concentration; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

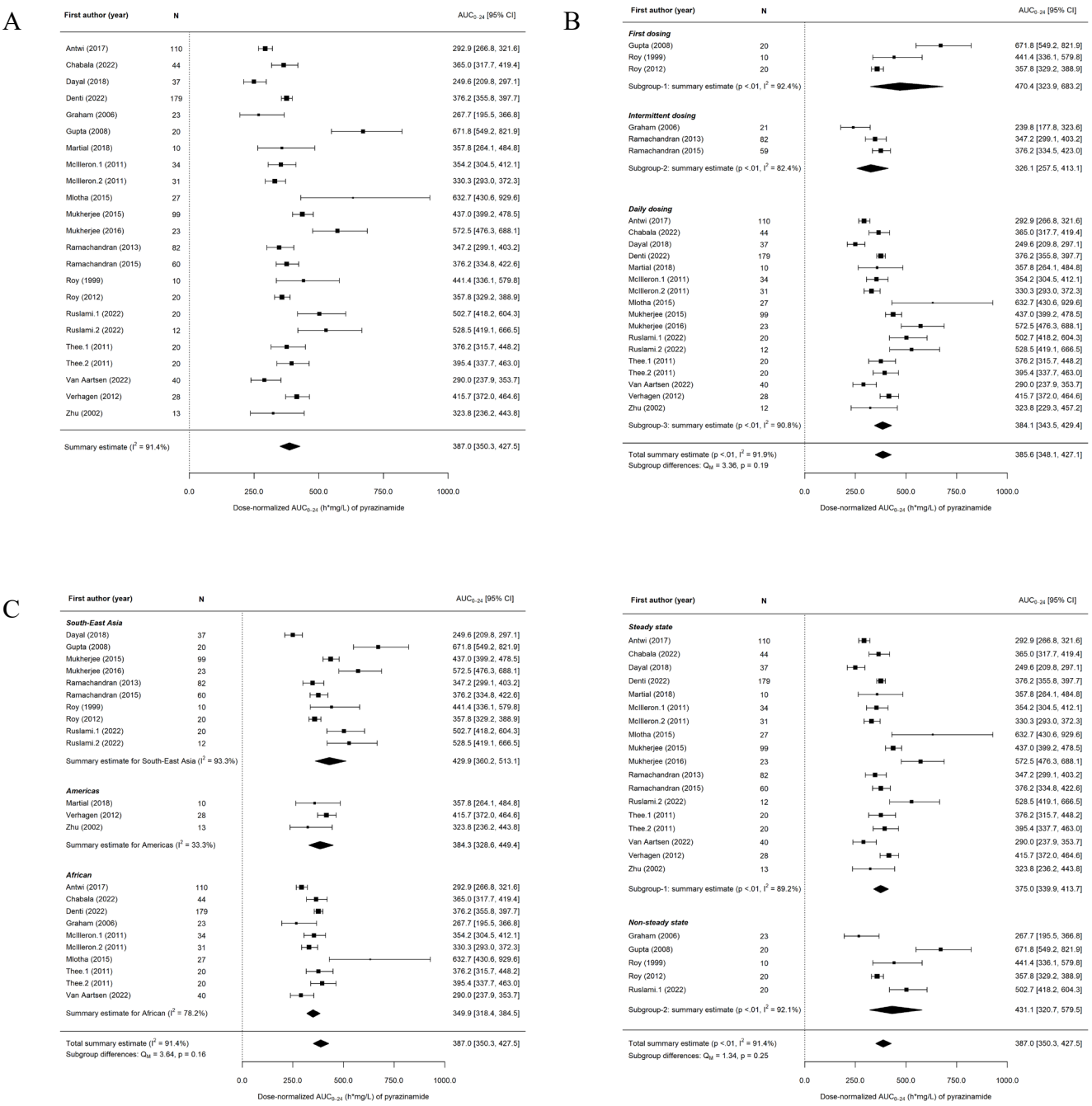

Figure E5. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for pyrazinamide in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: area under the concentration-time curve from 0 to 24 hours post-dose; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. $AUC_{0\text{-}24}$ values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

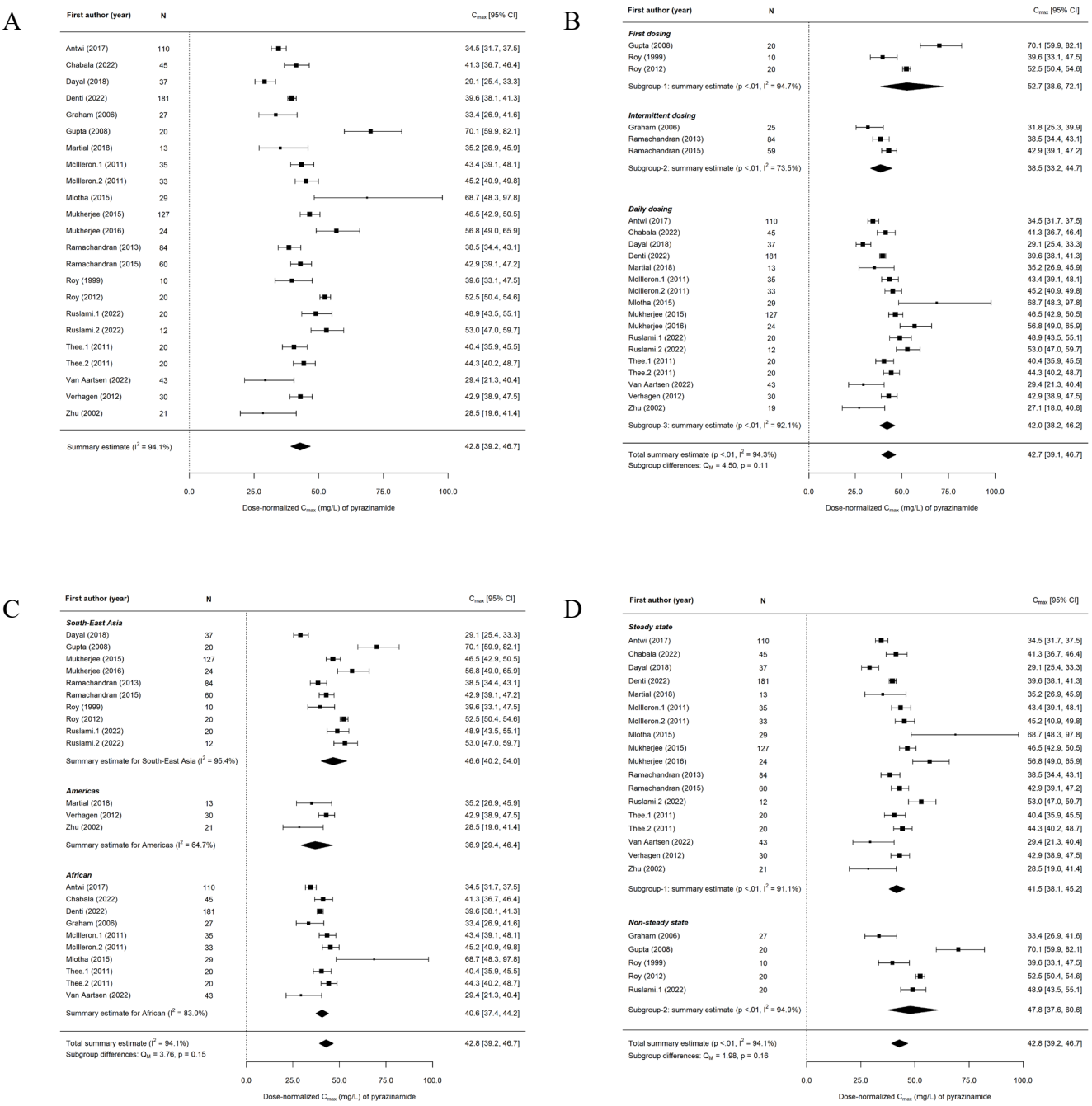

Figure E6. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for pyrazinamide in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

C_{max}: peak plasma concentration; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

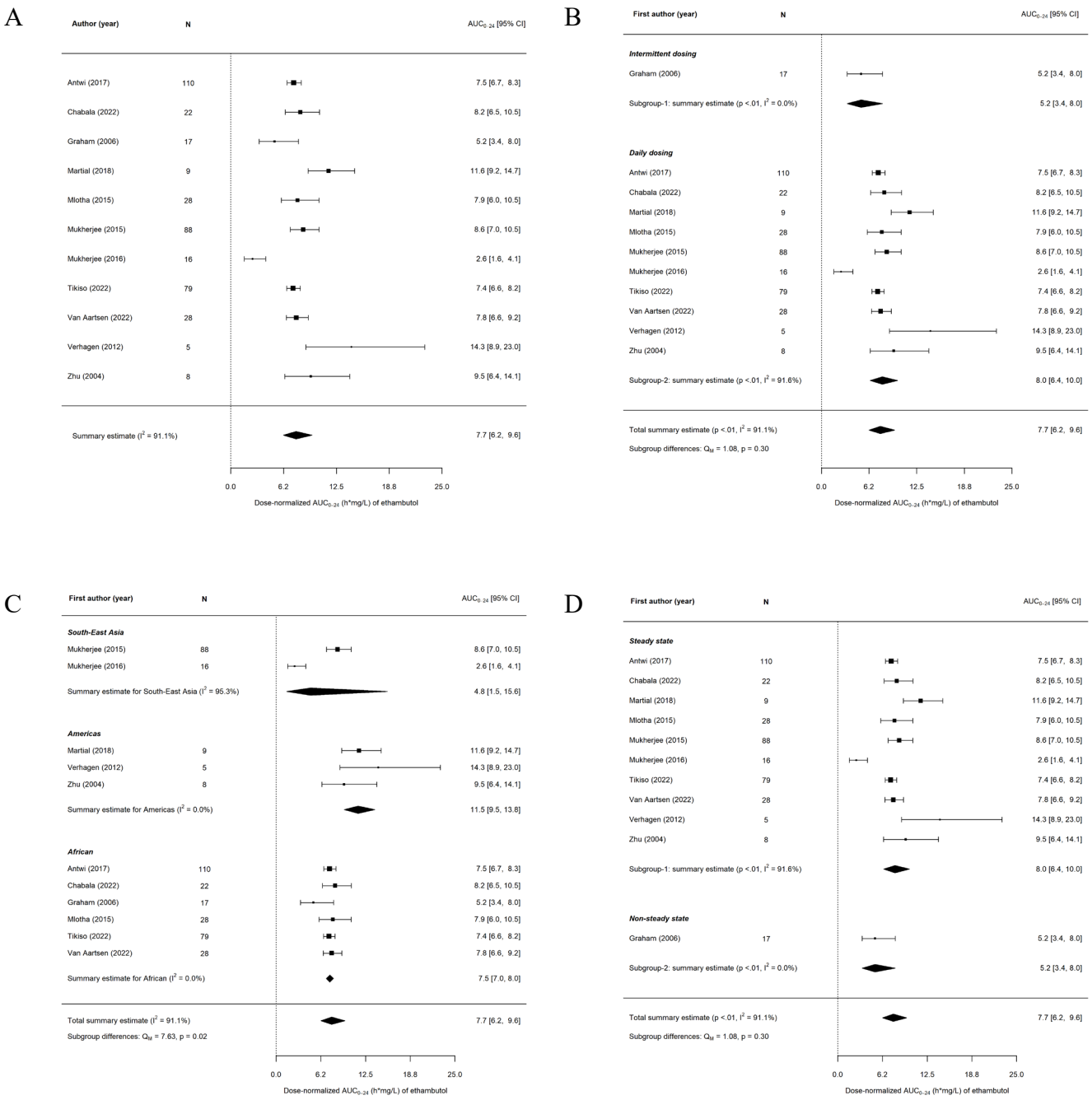

Figure E7. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for ethambutol in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: area under the concentration-time curve from 0 to 24 hours post-dose; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. $AUC_{0\text{-}24}$ values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

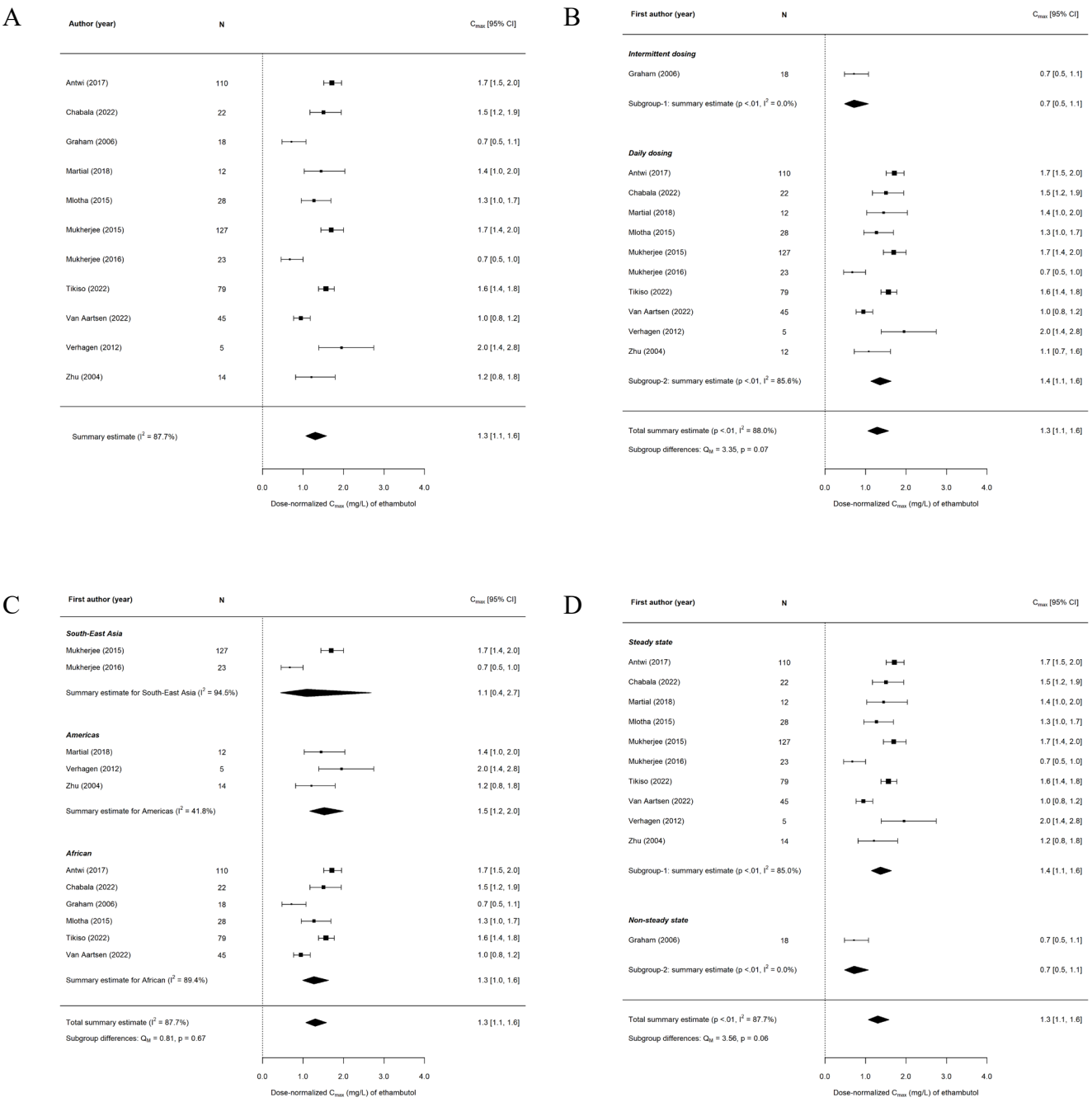

Figure E8. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for ethambutol in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

C_{max}: peak plasma concentration; I^2: the percentage of variation across studies that is due to heterogeneity, Q_M: the omnibus test of all model coefficients. C_{max} values were dose-normalized for isoniazid at 10 mg/kg, rifampicin at 15 mg/kg, pyrazinamide at 35 mg/kg, and ethambutol at 20 mg/kg.

Table E7. Linear mixed-effects models of dose-adjusted AUC_{0-24} in log-transformed values for isoniazid in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model[§]						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§§] studies		
Age, years[¶]	0.09 (0.04−0.14)***	0.50	0.17	0.04	-0.75	0.26	27	1252	0.403
Age									
<2 years	-0.29 (-0.43−-0.15)***	0.50	0.17	0.03	-0.76	0.26	27	1252	0.402
2-4 years	-0.12 (-0.25−0.01)#								
5-9 years	-0.08 (-0.19−0.04)								
10-14 years	Ref.								
15-18 years	0.01 (-0.33−0.35)								
Sex									
Female	Ref.	0.50	0.17	0.04	-0.73	0.26	27	1252	0.397
Male	-0.07 (-0.15−0.01)#								
Weight-for-age Z-score (WFAZ)[¶]	0.08 (0.03−0.12)**	0.48	0.19	0.04	-0.83	0.27	26	979	0.404
Underweight									
No	Ref.	0.48	0.18	0.04	-0.86	0.27	26	979	0.393
Yes, moderate (-3≤WFAZ<-2)	-0.07 (-0.18−0.05)								
Yes, severe (WFAZ<-3)	-0.10 (-0.22−0.02)								
Height-for-age Z-score (HFAZ)[¶]	0.08 (0.03−0.12)**	0.52	0.14	0.04	-0.83	0.22	22	1112	0.378
Stunted									
No	Ref.	0.52	0.14	0.04	-0.85	0.22	22	1112	0.373
Yes, moderate (-3≤HFAZ<-2)	-0.08 (-0.19−0.03)								
Yes, severe (HFAZ<-3)	-0.13 (-0.24−-0.02)*								
Weight-for-height Z-score (WFHZ)[¶]	0.06 (0.01−0.11)*	0.50	0.14	0.05	-0.93	0.21	22	802	0.379
Wasted									
No	Ref.	0.50	0.14	0.05	-0.94	0.22	22	802	0.377
Yes, moderate (-3≤WFHZ<-2)	-0.12 (-0.28−0.04)								
Yes, severe (WFHZ<-3)	-0.06 (-0.24−0.13)								
BMI-for-age Z-score (BFAZ)[¶]	0.04 (-0.01−0.09)	0.53	0.14	0.04	-0.85	0.21	22	1111	0.369
Low BMI									
No	Ref.	0.53	0.14	0.04	-0.85	0.21	22	1111	0.367
Yes, moderate (-3≤BFAZ<-2)	-0.04 (-0.17−0.09)								
Yes, severe (BFAZ <-3)	-0.05 (-0.19−0.10)								
Malnourished[†]									
No	Ref.	0.52	0.14	0.04	-0.85	0.22	24	1118	0.368
Yes, moderate	-0.07 (-0.17−0.04)								
Yes, severe	-0.13 (-0.24−-0.03)*								
Type of tuberculosis									
Pulmonary	Ref.	0.47	0.18	0.05	-0.72	0.28	23	1089	0.410
Extrapulmonary	0.05 (-0.07−0.16)								
Pulmonary + extrapulmonary	-0.09 (-0.26−0.07)								
HIV status									
Negative	Ref.	0.53	0.14	0.04	-0.73	0.22	23	1129	0.377
Positive	-0.17 (-0.30−-0.04)**								
Drug administration									
Taken whole orally	Ref.	0.42	0.03	0.02	0.29	0.15	5	313	0.373
Crushed/dispersed/via NGT	0.08 (-0.08−0.24)								
Creatinine clearance, mL/min[¶,††]	0.03 (-0.05−0.11)	0.43	0.03	-	-	0.07	10	322	0.213
Serum albumin, g/dL[¶]	-0.08 (-0.16−-0.01)*	0.50	0.36	-	-	0.42	11	598	0.486
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.48	0.26	0.11	-0.95	0.28	11	598	0.396
Yes, <3.5 g/dL	0.09 (-0.06−0.24)								
Acetylator status, NAT2 genotype[¥]									
Slow	0.69 (0.59−0.80)***	0.31	0.04	0.03	-0.44	0.17	10	566	0.551
Intermediate	Ref.								
Rapid	-0.29 (-0.42−-0.15)***								
Acetylator status, $t_{1/2}$ phenotype[¥]									
Slow	0.68 (0.60−0.76)***	0.35	0.12	0.03	-0.67	0.27	27	1203	0.570
Intermediate	Ref.								
Rapid	-0.39 (-0.51−-0.28)***								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. [¥]Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E8. Linear mixed-effects models of dose-adjusted C_{max} in log-transformed values for isoniazid in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§] studies		
Age, years[¶]	0.07 (0.03−0.11)***	0.38	0.16	0.06	-0.40	0.34	27	1292	0.466
Age									
<2 years	-0.27 (-0.40−-0.15)***	0.38	0.16	0.06	-0.39	0.34	27	1292	0.470
2-4 years	-0.09 (-0.21−0.02)$^{\#}$								
5-9 years	-0.05 (-0.15−0.05)								
10-14 years	Ref.								
15-18 years	-0.08 (-0.38−0.21)								
Sex									
Female	Ref.	0.39	0.16	0.06	-0.42	0.33	27	1292	0.455
Male	-0.06 (-0.13−0.01)								
Weight-for-age Z-score (WFAZ)[¶]	0.08 (0.04−0.12)**	0.36	0.18	0.07	-0.43	0.38	26	1008	0.497
Underweight									
No	Ref.	0.36	0.18	0.07	-0.46	0.37	26	1008	0.846
Yes, moderate (-3≤WFAZ<-2)	-0.06 (-0.16−0.04)								
Yes, severe (WFAZ<-3)	-0.10 (-0.20−0.00)$^{\#}$								
Height-for-age Z-score (HFAZ)[¶]	0.06 (0.02−0.10)**	0.41	0.15	0.04	-0.67	0.29	22	1151	0.424
Stunted									
No	Ref.	0.41	0.15	0.04	-0.69	0.28	22	1151	0.420
Yes, moderate (-3≤HFAZ<-2)	-0.07 (-0.17−0.02)								
Yes, severe (HFAZ<-3)	-0.10 (-0.20−-0.001)*								
Weight-for-height Z-score (WFHZ)[¶]	0.07 (0.03−0.12)**	0.38	0.18	0.06	-0.95	0.31	22	823	0.459
Wasted									
No	Ref.	0.38	0.18	0.06	-0.95	0.31	22	823	0.455
Yes, moderate (-3≤WFHZ<-2)	-0.16 (-0.30−-0.02)*								
Yes, severe (WFHZ<-3)	-0.11 (-0.28−0.05)								
BMI-for-age Z-score (BFAZ)[¶]	0.05 (0.01−0.09)*	0.42	0.16	0.03	-0.82	0.27	22	1150	0.415
Low BMI									
No	Ref.	0.42	0.16	0.04	-0.78	0.28	22	1150	0.412
Yes, moderate (-3≤BFAZ<-2)	-0.03 (-0.14−0.09)								
Yes, severe (BFAZ <-3)	-0.06 (-0.19−0.07)								
Malnourished[†]									
No	Ref.	0.42	0.16	0.04	-0.75	0.28	24	1158	0.416
Yes, moderate	-0.04 (-0.13−0.06)								
Yes, severe	-0.11 (-0.21−-0.02)*								
Type of tuberculosis									
Pulmonary	Ref.	0.38	0.18	0.08	-0.36	0.37	23	1129	0.467
Extrapulmonary	0.02 (-0.09−0.12)								
Pulmonary + extrapulmonary	-0.04 (-0.18−0.11)								
HIV status									
Negative	Ref.	0.41	0.15	0.06	-0.40	0.31	23	1166	0.454
Positive	-0.17 (-0.28−-0.06)**								
Drug administration									
Taken whole orally	Ref.	0.28	0.00	0.02	0.63	0.13	5	315	0.415
Crushed/dispersed/via NGT	0.10 (-0.03−0.23)								
Creatinine clearance, mL/min[¶,††]	0.10 (0.02−0.18)*	0.35	0.18	-	-	0.34	10	330	0.406
Serum albumin, g/dL[¶]	-0.06 (-0.13−0.00)$^{\#}$	0.38	0.32	-	-	0.45	11	615	0.523
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.36	0.23	0.13	-0.66	0.41	11	615	0.476
Yes, <3.5 g/dL	0.05 (-0.08−0.18)								
Acetylator status, NAT2 genotype[¥]									
Slow	0.31 (0.22−0.39)***	0.22	0.02	0.03	-0.44	0.19	10	570	0.528
Intermediate	Ref.								
Rapid	-0.11 (-0.22−0.01)$^{\#}$								
Acetylator status, $t_{1/2}$ phenotype[¥]									
Slow	0.21 (0.14−0.29)***	0.31	0.12	0.06	-0.31	0.34	27	1203	0.505
Intermediate	Ref.								
Rapid	-0.14 (-0.24−-0.03)*								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. C_{max}: maximum plasma concentration; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. [¥]Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, $^{\#}$p<0.1.

Table E9. Linear mixed-effects models of dose-adjusted AUC_{0-24} in log-transformed values for rifampicin in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model[§]						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§§] studies		
Age, years[¶]	0.18 (0.13−0.24)***	0.47	0.13	0.13	-0.12	0.37	22	1041	0.631
Age									
<2 years	-0.48 (-0.63−-0.33)***	0.47	0.14	0.12	-0.18	0.37	22	1041	0.624
2-4 years	-0.35 (-0.49−-0.21)***								
5-9 years	-0.13 (-0.26−0.00)								
10-14 years	Ref.								
15-18 years	0.22 (-0.16−0.60)								
Sex									
Female	Ref.	0.49	0.16	0.11	-0.17	0.37	22	1041	0.582
Male	-0.05 (-0.14−0.04)								
Weight-for-age Z-score (WFAZ)[¶]	0.04 (-0.02−0.09)	0.52	0.15	n/a	n/a	0.23	22	843	0.402
Underweight									
No	Ref.	0.52	0.15	n/a	n/a	0.23	22	843	0.397
Yes, moderate (-3≤WFAZ<-2)	-0.02 (-0.15−0.11)								
Yes, severe (WFAZ<-3)	0.01 (-0.14−0.16)								
Height-for-age Z-score (HFAZ)[¶]	0.08 (0.04−0.13)**	0.49	0.15	0.13	-0.18	0.38	22	1035	0.599
Stunted									
No	Ref.	0.49	0.15	0.12	-0.16	0.37	22	1035	0.594
Yes, moderate (-3≤HFAZ<-2)	-0.11 (-0.22−0.00)#								
Yes, severe (HFAZ<-3)	-0.13 (-0.25−-0.01)*								
Weight-for-height Z-score (WFHZ)[¶]	0.01 (-0.07−0.05)	0.48	0.15	0.21	0.26	0.49	22	753	0.721
Wasted									
No	Ref.	0.48	0.16	0.21	0.27	0.49	22	753	0.717
Yes, moderate (-3≤WFHZ<-2)	0.10 (-0.06−0.27)								
Yes, severe (WFHZ<-3)	0.15 (-0.06−0.37)								
BMI-for-age Z-score (BFAZ)[¶]	-0.05 (-0.10−-0.001)*	0.49	0.15	0.12	-0.16	0.37	22	1034	0.583
Low BMI									
No	Ref.	0.49	0.15	0.13	-0.07	0.39	22	1034	0.591
Yes, moderate (-3≤BFAZ<-2)	0.27 (0.14−0.41)***								
Yes, severe (BFAZ <-3)	0.14 (-0.02−0.30)#								
Malnourished[†]									
No	Ref.	0.49	0.15	0.12	-0.19	0.37	22	1035	0.585
Yes, moderate	-0.003 (-0.11−0.11)								
Yes, severe	-0.07 (-0.18−0.05)								
Type of tuberculosis									
Pulmonary	Ref.	0.48	0.16	0.11	-0.13	0.39	18	903	0.590
Extrapulmonary	0.11 (-0.03−0.25)								
Pulmonary + extrapulmonary	-0.04 (-0.21−0.14)								
HIV status									
Negative	Ref.	0.50	0.13	0.14	-0.26	0.37	21	990	0.604
Positive	-0.23 (-0.37−-0.09)**								
Drug administration									
Taken whole orally	Ref.	0.45	0.18	n/a	n/a	0.29	7	370	0.520
Crushed/dispersed/via NGT	-0.02 (-0.18−0.13)								
Creatinine clearance, mL/min[¶,††]	0.05 (-0.04−0.13)	0.32	0.17	n/a	n/a	0.35	12	415	0.555
Serum albumin, g/dL[¶]	-0.05 (-0.13−0.02)	0.50	0.21	n/a	n/a	0.29	12	611	0.457
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.50	0.20	n/a	n/a	0.29	12	611	0.458
Yes, <3.5 g/dL	0.17 (-0.001−0.33)#								
SLCO1B1 rs4149032									
CC	Ref.	0.37	0.03	n/a	n/a	0.08	2	190	0.163
CT	-0.11 (-0.33−0.11)								
TT	-0.34 (-0.61−-0.08)*								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E10. Linear mixed-effects models of dose-adjusted C_{max} in log-transformed values for rifampicin in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model[§]						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§§] studies		
Age, years[¶]	0.13 (0.08−0.18)***	0.50	0.13	0.12	0.16	0.35	22	1105	0.550
Age									
<2 years	-0.40 (-0.55−-0.25)***	0.49	0.13	0.10	0.03	0.33	22	1105	0.532
2-4 years	-0.16 (-0.30−-0.02)*								
5-9 years	-0.07 (-0.19−0.06)								
10-14 years	Ref.								
15-18 years	0.10 (-0.27−0.46)								
Sex									
Female	Ref.	0.51	0.12	0.11	0.19	0.34	22	1105	0.518
Male	-0.00 (-0.08−0.09)								
Weight-for-age Z-score (WFAZ)[¶]	0.08 (0.03−0.14)**	0.54	0.11	0.12	0.26	0.34	22	893	0.551
Underweight									
No	Ref.	0.55	0.11	0.12	0.25	0.33	22	893	0.549
Yes, moderate (-3≤WFAZ<-2)	0.03 (-0.10−0.16)								
Yes, severe (WFAZ<-3)	-0.17 (-0.32−-0.02)*								
Height-for-age Z-score (HFAZ)[¶]	0.09 (0.05−0.14)***	0.50	0.11	0.12	0.18	0.34	22	1098	0.538
Stunted									
No	Ref.	0.51	0.12	0.12	0.21	0.34	22	1098	0.537
Yes, moderate (-3≤HFAZ<-2)	-0.15 (-0.26−-0.04)**								
Yes, severe (HFAZ<-3)	-0.16 (-0.27−-0.04)**								
Weight-for-height Z-score (WFHZ)[¶]	0.02 (-0.03−0.08)	0.56	0.12	0.16	0.27	0.39	22	793	0.602
Wasted									
No	Ref.	0.56	0.12	0.16	0.27	0.39	22	793	0.600
Yes, moderate (-3≤WFHZ<-2)	-0.06 (-0.23−0.11)								
Yes, severe (WFHZ<-3)	0.05 (-0.18−0.28)								
BMI-for-age Z-score (BFAZ)[¶]	0.00 (-0.05−0.05)	0.51	0.12	0.11	0.18	0.34	22	1097	0.517
Low BMI									
No	Ref.	0.51	0.12	0.12	0.24	0.34	22	1097	0.524
Yes, moderate (-3≤BFAZ<-2)	0.14 (0.01−0.27)*								
Yes, severe (BFAZ <-3)	-0.07 (-0.22−0.09)								
Malnourished[†]									
No	Ref.	0.51	0.11	0.12	0.17	0.34	22	1098	0.531
Yes, moderate	-0.06 (-0.16−0.05)								
Yes, severe	-0.17 (-0.28−-0.06)**								
Type of tuberculosis									
Pulmonary	Ref.	0.48	0.14	0.10	0.19	0.37	18	961	0.526
Extrapulmonary	0.06 (-0.08−0.20)								
Pulmonary + extrapulmonary	-0.03 (-0.20−0.14)								
HIV status									
Negative	Ref.	0.51	0.10	0.13	0.19	0.35	21	1049	0.543
Positive	-0.26 (-0.40−-0.12)***								
Drug administration									
Taken whole orally	Ref.	0.44	0.04	n/a	n/a	0.08	7	377	0.380
Crushed/dispersed/via NGT	-0.04 (-0.12−0.19)								
Creatinine clearance, mL/min[¶,††]	0.09 (0.01−0.17)*	0.32	0.16	n/a	n/a	0.34	12	432	0.493
Serum albumin, g/dL[¶]	0.02 (-0.05−0.09)	0.44	0.14	n/a	n/a	0.25	12	634	0.417
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.44	0.15	n/a	n/a	0.25	12	634	0.414
Yes, <3.5 g/dL	0.03 (-0.12−0.19)								
SLCO1B1 rs4149032									
CC	Ref.	0.31	0.06	n/a	n/a	0.16	2	190	0.228
CT	-0.10 (-0.30−0.11)								
TT	-0.30 (-0.54−-0.05)*								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. C_{max}: maximum plasma concentration; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E11. Linear mixed-effects models of dose-adjusted AUC_{0-24} in log-transformed values for pyrazinamide in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model[§]						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§§] studies		
Age, years[¶]	0.11 (0.07−0.14)***	0.22	0.04	0.01	-0.23	0.19	23	962	0.290
Age									
<2 years	-0.28 (-0.38−-0.17)***	0.22	0.04	0.01	-0.26	0.19	23	962	0.289
2-4 years	-0.24 (-0.34−-0.14)***								
5-9 years	-0.13 (-0.22−-0.04)**								
10-14 years	Ref.								
15-18 years	-0.003 (-0.28−0.27)								
Sex									
Female	Ref.	0.22	0.06	0.02	-0.63	0.24	23	962	0.304
Male	-0.10 (-0.16−-0.04)**								
Weight-for-age Z-score (WFAZ)[¶]	0.05 (0.02−0.09)**	0.23	0.06	0.01	-0.61	0.24	23	781	0.306
Underweight									
No	Ref.	0.23	0.05	0.01	-0.54	0.22	23	781	0.293
Yes, moderate (-3≤WFAZ<-2)	0.03 (-0.06−0.12)								
Yes, severe (WFAZ<-3)	-0.10 (-0.19−-0.01)*								
Height-for-age Z-score (HFAZ)[¶]	0.06 (0.02−0.10)**	0.21	0.06	0.02	-0.60	0.25	21	921	0.315
Stunted									
No	Ref.	0.21	0.06	0.02	-0.63	0.26	21	921	0.323
Yes, moderate (-3≤HFAZ<-2)	-0.09 (-0.17−-0.02)*								
Yes, severe (HFAZ<-3)	-0.16 (-0.24−-0.07)***								
Weight-for-height Z-score (WFHZ)[¶]	0.02 (-0.03−0.07)	0.22	0.05	0.01	-0.18	0.20	21	665	0.274
Wasted									
No	Ref.	0.22	0.05	0.01	-0.29	0.19	21	665	0.270
Yes, moderate (-3≤WFHZ<-2)	-0.11 (-0.22−0.01)#								
Yes, severe (WFHZ<-3)	-0.05 (-0.18−0.08)								
BMI-for-age Z-score (BFAZ)[¶]	-0.04 (-0.10−0.03)	0.22	0.06	0.02	-0.60	0.25	21	921	0.302
Low BMI									
No	Ref.	0.22	0.06	0.02	-0.66	0.25	21	921	0.304
Yes, moderate (-3≤BFAZ<-2)	-0.02 (-0.11−0.08)								
Yes, severe (BFAZ <-3)	0.00 (-0.10−0.10)								
Malnourished[†]									
No	Ref.	0.22	0.06	0.02	-0.65	0.25	22	929	0.304
Yes, moderate	-0.04 (-0.12−0.04)								
Yes, severe	-0.13 (-0.21−-0.05)**								
Type of tuberculosis									
Pulmonary	Ref.	0.22	0.07	0.01	-0.79	0.25	18	834	0.272
Extrapulmonary	0.06 (-0.03−0.15)								
Pulmonary + extrapulmonary	0.05 (-0.10−0.19)								
HIV status									
Negative	Ref.	0.23	0.07	0.02	-0.60	0.28	20	882	0.346
Positive	-0.21 (-0.30−-0.11)***								
Drug administration									
Taken whole orally	Ref.	0.16	0.03	0.01	0.95	0.22	4	255	0.325
Crushed/dispersed/via NGT	-0.02 (-0.13−0.09)								
Creatinine clearance, mL/min[¶,††]	0.01 (-0.05−0.07)	0.22	0.03	-	-	0.13	12	323	0.204
Serum albumin, g/dL[¶]	-0.02 (-0.07−0.03)	0.23	0.07	-	-	0.23	11	577	0.277
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.22	0.10	0.04	-0.80	0.34	11	577	0.360
Yes, <3.5 g/dL	-0.03 (-0.13−0.08)								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E12. Linear mixed-effects models of dose-adjusted C_{max} in log-transformed values for pyrazinamide in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model						Obs.[§§]	Cond. R^2
		σ^2	τ_{00} studies	τ_{11} studies*doses	ρ_{01} studies	ICC	N[§] studies		
Age, years[¶]	0.07 (0.03−0.10)***	0.20	0.03	0.01	-0.21	0.17	23	1021	0.269
Age									
<2 years	-0.19 (-0.28−-0.09)***	0.20	0.03	0.01	-0.18	0.17	23	1021	0.270
2-4 years	-0.16 (-0.25−-0.06)***								
5-9 years	-0.10 (-0.18−-0.02)*								
10-14 years	Ref.								
15-18 years	-0.01 (-0.26−0.23)								
Sex									
Female	Ref.	0.20	0.04	0.01	-0.43	0.20	23	1021	0.279
Male	-0.07 (-0.12−-0.01)*								
Weight-for-age Z-score (WFAZ)[¶]	0.05 (0.02−0.09)**	0.21	0.04	0.01	-0.25	0.19	23	827	0.282
Underweight									
No	Ref.	0.21	0.04	0.01	-0.21	0.18	23	827	0.274
Yes, moderate (-3≤WFAZ<-2)	0.03 (-0.06−0.11)								
Yes, severe (WFAZ<-3)	-0.14 (-0.22−-0.05)**								
Height-for-age Z-score (HFAZ)[¶]	0.05 (0.01−0.09)**	0.19	0.04	0.01	-0.26	0.19	21	974	0.274
Stunted									
No	Ref.	0.19	0.04	0.01	-0.34	0.20	21	974	0.285
Yes, moderate (-3≤HFAZ<-2)	-0.07 (-0.14−0.001)#								
Yes, severe (HFAZ<-3)	-0.14 (-0.21−-0.06)***								
Weight-for-height Z-score (WFHZ)[¶]	-0.04 (-0.08−0.003)#	0.20	0.04	0.01	0.34	0.21	21	694	0.329
Wasted									
No	Ref.	0.20	0.05	0.01	0.08	0.23	21	694	0.328
Yes, moderate (-3≤WFHZ<-2)	-0.13 (-0.23−-0.02)*								
Yes, severe (WFHZ<-3)	-0.05 (-0.17−0.08)								
BMI-for-age Z-score (BFAZ)[¶]	0.00 (-0.05−0.05)	0.19	0.04	0.01	-0.39	0.21	21	974	0.279
Low BMI									
No	Ref.	0.19	0.04	0.01	-0.40	0.21	21	974	0.276
Yes, moderate (-3≤BFAZ<-2)	0.002 (-0.08−0.09)								
Yes, severe (BFAZ <-3)	-0.07 (-0.16−0.03)								
Malnourished[†]									
No	Ref.	0.20	0.04	0.01	-0.45	0.20	22	987	0.286
Yes, moderate	-0.02 (-0.09−0.05)								
Yes, severe	-0.13 (-0.20−-0.06)***								
Type of tuberculosis									
Pulmonary	Ref.	0.19	0.04	0.01	-0.58	0.19	18	882	0.231
Extrapulmonary	0.05 (-0.03−0.14)								
Pulmonary + extrapulmonary	0.03 (-0.10−0.17)								
HIV status									
Negative	Ref.	0.17	0.04	0.01	-0.25	0.25	20	939	0.340
Positive	-0.14 (-0.22−-0.06)**								
Drug administration									
Taken whole orally	Ref.	0.09	0.02	0.01	0.14	0.23	4	258	0.363
Crushed/dispersed/via NGT	0.05 (-0.04−0.13)								
Creatinine clearance, mL/min[¶]	0.02 (-0.03−0.08)	0.18	0.04	-	-	0.17	12	337	0.214
Serum albumin, g/dL[¶,††]	-0.02 (-0.06−0.02)	0.13	0.05	-	-	0.25	11	596	0.316
Hypoalbuminemia									
No, ≥3.5 g/dL	Ref.	0.13	0.05	0.01	-0.59	0.29	11	596	0.344
Yes, <3.5 g/dL	-0.003 (-0.08−0.08)								

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. C_{max}: maximum plasma concentration; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E13. Linear mixed-effects models of dose-adjusted AUC_{0-24} in log-transformed values for ethambutol in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model				Obs.[§§]	Cond. R^2
		σ^2	$\tau_{00\ studies}$	ICC	$N^{\S}_{studies}$		
Age, years[¶]	0.20 (0.13−0.27)***	0.45	0.15	0.25	11	410	0.315
Age							
<2 years	-0.52 (-0.74−-0.30)***	0.45	0.14	0.24	11	410	0.305
2-4 years	-0.33 (-0.54−-0.13)**						
5-9 years	-0.18 (-0.37−0.01)#						
10-14 years	Ref.						
15-18 years	0.35 (-0.24−0.94)						
Sex							
Female	Ref.	0.49	0.11	0.18	11	410	0.200
Male	-0.03 (-0.16−0.11)						
Weight-for-age Z-score (WFAZ)[¶]	0.08 (0.003−0.16)*	0.45	0.03	0.07	11	321	0.121
Underweight							
No	Ref.	0.45	0.04	0.08	11	321	0.125
Yes, moderate (-3≤WFAZ<-2)	-0.07 (-0.25−0.12)						
Yes, severe (WFAZ<-3)	-0.13 (-0.33−0.06)						
Height-for-age Z-score (HFAZ)[¶]	0.09 (-0.01−0.19)#	0.47	0.16	0.25	10	390	0.278
Stunted							
No	Ref.	0.47	0.12	0.21	10	390	0.238
Yes, moderate (-3≤HFAZ<-2)	-0.11 (-0.29−0.07)						
Yes, severe (HFAZ<-3)	-0.19 (-0.37−-0.02)*						
Weight-for-height Z-score (WFHZ)[¶]	0.06 (-0.04−0.17)	0.40	0.09	0.18	10	267	0.215
Wasted							
No	Ref.	0.40	0.09	0.18	10	267	0.214
Yes, moderate (-3≤WFHZ<-2)	-0.004 (-0.25−0.24)						
Yes, severe (WFHZ<-3)	-0.10 (-0.39−0.18)						
BMI-for-age Z-score (BFAZ)[¶]	-0.01 (-0.15−0.14)	0.47	0.14	0.23	10	390	0.249
Low BMI							
No	Ref.	0.48	0.13	0.21	10	390	0.229
Yes, moderate (-3≤BFAZ<-2)	-0.03 (-0.22−0.16)						
Yes, severe (BFAZ <-3)	0.04 (-0.22−0.30)						
Malnourished[†]							
No	Ref.	0.48	0.11	0.19	11	392	0.221
Yes, moderate	-0.10 (-0.27−0.08)						
Yes, severe	-0.19 (-0.36−-0.01)*						
Type of tuberculosis							
Pulmonary	Ref.	0.48	0.11	0.19	10	392	0.223
Extrapulmonary	0.24 (0.04−0.44)*						
Pulmonary + extrapulmonary	0.22 (-0.07−0.50)						
HIV status							
Negative	Ref.	0.48	0.03	0.07	11	391	0.143
Positive	-0.39 (-0.56−-0.23)***						
Drug administration							
Taken whole orally	Ref.	0.25	0.00	-	2	101	0.059[¥]
Crushed/dispersed/via NGT	-0.15 (-0.35−0.05)						
Creatinine clearance, mL/min[¶, ††]	0.03 (-0.13−-0.07)	0.31	0.04	0.12	7	166	0.291
Serum albumin, g/dL[¶]	-0.09 (-0.18−0.01)#	0.45	0.28	0.38	4	221	0.409
Hypoalbuminemia							
No, ≥3.5 g/dL	Ref.	0.45	0.26	0.36	4	221	0.386
Yes, <3.5 g/dL	0.11 (-0.12−0.33)						

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. [¥]Marginal R^2. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E14. Linear mixed-effects models of dose-adjusted C_{max} in log-transformed values for ethambutol in children and adolescents with tuberculosis, by patient characteristics.

Patient characteristics	Fixed-effects coefficient (95% CI)	Random effects for each model				Obs.[§§]	Cond. R^2
		σ^2	$\tau_{00\ studies}$	ICC	$N^{\S}_{studies}$		
Age, years[¶]	0.22 (0.15−0.29)***	0.54	0.08	0.13	11	483	0.204
Age							
<2 years	-0.62 (-0.84−-0.40)***	0.53	0.09	0.14	11	467	0.229
2-4 years	-0.29 (-0.50−-0.09)**						
5-9 years	-0.10 (-0.29−0.08)						
10-14 years	Ref.						
15-18 years	0.18 (-0.44−0.79)						
Sex							
Female	Ref.	0.58	0.06	0.09	11	483	0.104
Male	-0.04 (-0.18−0.10)						
Weight-for-age Z-score (WFAZ)[¶]	0.09 (0.01−0.18)*	0.58	0.06	0.09	11	371	0.125
Underweight							
No	Ref.	0.59	0.06	0.10	11	371	0.122
Yes, moderate (-3≤WFAZ<-2)	0.01 (-0.18−0.21)						
Yes, severe (WFAZ<-3)	-0.11 (-0.32−0.10)						
Height-for-age Z-score (HFAZ)[¶]	0.09 (-0.005−0.18)$^{\#}$	0.57	0.07	0.11	10	459	0.129
Stunted							
No	Ref.	0.58	0.06	0.09	10	459	0.112
Yes, moderate (-3≤HFAZ<-2)	-0.07 (-0.26−0.11)						
Yes, severe (HFAZ<-3)	-0.20 (-0.38−-0.03)*						
Weight-for-height Z-score (WFHZ)[¶]	0.08 (-0.03−0.18)	0.54	0.09	0.15	10	304	0.172
Wasted							
No	Ref.	0.54	0.09	0.14	10	304	0.161
Yes, moderate (-3≤WFHZ<-2)	-0.16 (-0.42−0.09)						
Yes, severe (WFHZ<-3)	-0.20 (-0.50−0.10)						
BMI-for-age Z-score (BFAZ)[¶]	-0.03 (-0.14−0.09)	0.58	0.07	0.11	10	459	0.123
Low BMI							
No	Ref.	0.57	0.06	0.09	10	459	0.113
Yes, moderate (-3≤BFAZ<-2)	-0.22 (-0.40−-0.03)*						
Yes, severe (BFAZ <-3)	-0.10 (-0.34−0.15)						
Malnourished[†]							
No	Ref.	0.58	0.05	0.09	11	461	0.109
Yes, moderate	-0.10 (-0.28−0.07)						
Yes, severe	-0.20 (-0.38−-0.03)*						
Type of tuberculosis							
Pulmonary	Ref.	0.57	0.07	0.11	10	459	0.113
Extrapulmonary	0.28 (0.07−0.49)*						
Pulmonary + extrapulmonary	0.29 (-0.02−0.60)$^{\#}$						
HIV status							
Negative	Ref.	0.58	0.04	0.06	11	455	0.101
Positive	-0.33 (-0.51−-0.15)***						
Drug administration							
Taken whole orally	Ref.	0.31	0.00	-	2	101	0.052[¥]
Crushed/dispersed/via NGT	-0.19 (-0.41−0.04)						
Creatinine clearance, mL/min[¶,††]	0.04 (-0.06−0.15)	0.38	0.03	0.06	7	174	0.234
Serum albumin, g/dL[¶]	-0.10 (-0.20−-0.004)*	0.57	0.16	0.22	4	249	0.252
Hypoalbuminemia							
No, ≥3.5 g/dL	Ref.	0.58	0.16	0.21	4	249	0.240
Yes, <3.5 g/dL	0.19 (-0.07−0.44)						

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean or [§§]number. C_{max}: maximum plasma concentration; BMI: body mass index; HIV: human immunodeficiency virus; NGT: nasogastric tube, σ^2: residual variance, τ_{00}: random intercept variance, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. Obs.: observations; Cond.: conditional. [¶]All continuous variables were mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [†]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2 in children aged <5 years, and HFAZ or BFAZ ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as WFAZ or HFAZ <-3 in children aged <5 years, and HFAZ or BFAZ <-3 in children aged ≥5 years. [††] Model for creatinine clearance was adjusted for drug dose and age. [¥]Marginal R^2. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E15. Multivariate linear mixed-effects analyses of factors associated with log-transformed AUC_{0-24} values for first-line antituberculosis drugs in children under 5 years of age with tuberculosis.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	2.50 (2.30−2.70)***	3.40 (3.16−3.63)***	5.77 (5.64−5.90)***	2.26 (1.94−2.59)***
Dose, mg/kg[¶]	0.39 (0.29−0.48)***	0.35 (0.27−0.43)***	0.18 (0.11−0.24)***	0.16 (0.06−0.26)***
Age				
<2 years	-0.22 (-0.33−-0.11)***	-0.16 (-0.29−-0.03)*	-0.05 (-0.14−0.04)	0.23 (-0.04−0.50)$^{\#}$
2-4 years	Ref.	Ref.	Ref.	Ref.
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	0.02 (-0.08−0.13)	-0.004 (-0.13−0.12)	-0.10 (-0.19−-0.02)*	0.01 (-0.17−0.20)
Malnourished[§§]				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.16 (-0.30−-0.03)*	-0.07 (-0.22−0.08)	-0.05 (-0.16−0.06)	-0.10 (-0.34−0.14)
Yes, severe	-0.11 (-0.24−0.01)$^{\#}$	-0.07 (-0.23−0.10)	-0.05 (-0.15−0.06)	-0.06 (-0.28−0.16)
Unknown	0.13 (-0.22−0.48)	-0.08 (-1.11−1.95)	0.13 (-0.24−0.49)	-0.02 (-0.66−0.62)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.18 (-0.32−-0.04)*	-0.22 (-0.40−-0.03)*	-0.26 (-0.38−-0.14)***	-0.44 (-0.66−-0.23)***
Unknown	0.05 (-0.26−0.35)	-0.22 (-0.61−0.17)	0.02 (-0.22−0.26)	-0.11 (-0.47−0.24)
Acetylator status, $t_{1/2}$ phenotype[¶¶]				
Slow	0.67 (0.55−0.78)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.46 (-0.62−-0.30)***	n/a	n/a	n/a
Unknown	0.30 (0.00−0.61)*	n/a	n/a	n/a
Random effects				
σ^2	0.36 (0.60)[§]	0.48 (0.69)[§]	0.19 (0.44)[§]	0.37 (0.61)[§]
$\tau_{00\ studies}$	0.10 (0.31)[§]	0.19 (0.43)[§]	0.03 (0.19)[§]	0.01 (0.05)[§]
$\tau_{11\ studies*doses}$	0.01 (0.12)[§]	n/a	0.01 (0.08)[§]	n/a
$\rho_{01\ studies}$	-0.64	n/a	0.38	n/a
ICC	0.21	0.28	0.19	0.01
$N_{\ studies}$	24	21	20	11
Observations	577	524	450	184
Conditional R^2	0.57	0.46	0.35	0.19

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. [¶]Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [§§]Moderate malnutrition was defined as a weight-for-age or height-for-age Z-score ≥-3 but <-2; and severe malnutrition was defined as a weight-for-age or height-for-age Z-score <-3. [¶¶]Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E16. Multivariate linear mixed-effects analyses of factors associated with log-transformed C_{max} values for first-line antituberculosis drugs in children under 5 years of age with tuberculosis

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	1.38 (1.15−1.61)***	1.95 (1.71−2.19)***	3.53 (3.42−3.63)***	0.32 (0.002−0.63)*
Dose, mg/kg¶	0.38 (0.27−0.50)***	0.30 (0.22−0.38)***	0.20 (0.13−0.27)***	0.14 (0.04−0.24)**
Age				
<2 years	-0.22 (-0.33−-0.11)***	-0.27 (-0.40−-0.14)***	-0.03 (-0.10−0.05)	-0.36 (-0.56−-0.15)**
2-4 years	Ref.	Ref.	Ref.	Ref.
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	0.03 (-0.07−0.13)	0.06 (-0.06−0.19)	-0.04 (-0.11−0.03)	0.07 (-0.14−0.28)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.13 (-0.26−0.01)$^{\#}$	-0.13 (-0.28−0.03)	-0.05 (-0.14−0.04)	0.005 (-0.27−0.28)
Yes, severe	-0.09 (-0.22−0.03)	-0.11 (-0.28−0.06)	-0.07 (-0.16−0.02)	-0.04 (-0.28−0.20)
Unknown	-0.01 (-0.39−0.37)	-0.15 (-1.22−0.92)	-0.05 (-0.35−0.24)	-0.36 (-1.07−0.35)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.20 (-0.34−-0.06)**	-0.25 (-0.44−-0.06)**	-0.18 (-0.27−-0.08)***	-0.43 (-0.69−-0.17)***
Unknown	0.19 (-0.12−0.50)	0.04 (-0.34−0.43)	0.08 (-0.12−0.27)	0.10 (-0.36−0.56)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.23 (0.12−0.35)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.19 (-0.36−-0.03)*	n/a	n/a	n/a
Unknown	-0.36 (-0.62−-0.10)**	n/a	n/a	n/a
Random effects				
σ^2	0.35 (0.59)§	0.52 (0.72)§	0.14 (0.37)§	0.50 (0.71)§
$\tau_{00\ studies}$	0.16 (0.40)§	0.20 (0.45)§	0.02 (0.14)§	0.11 (0.33)§
$\tau_{11\ studies*doses}$	0.03 (0.18)§	n/a	0.01 (0.10)§	n/a
$\rho_{01\ studies}$	-0.47	n/a	0.47	n/a
ICC	0.33	0.28	0.20	0.18
$N_{studies}$	24	21	20	11
Observations	589	549	470	208
Conditional R^2	0.52	0.43	0.41	0.29

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weight-for-age or height-for-age Z-score ≥-3 but <-2; and severe malnutrition was defined as a weight-for-age or height-for-age Z-score <-3. ¶¶Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, $^{\#}$p<0.1.

Table E17. Multivariate linear mixed-effects analyses of factors associated with log-transformed AUC_{0-24} values for first-line antituberculosis drugs in children under 2 years of age with tuberculosis.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	2.45 (1.64−3.25)***	2.80 (1.86−3.75)***	4.99 (4.40−5.57)***	1.78 (0.36−3.21)*
Dose, mg/kg¶	0.42 (0.29−0.55)***	0.32 (0.22−0.42)***	0.12 (-0.02−0.27)$^{\#}$	0.33 (0.16−0.50)***
Age	0.19 (-0.49−0.86)	-0.42 (-1.31−0.47)	-0.74 (-1.24−-0.24)**	-0.17 (-1.27−0.93)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	0.19 (0.05−0.34)*	-0.06 (-0.13−0.24)	-0.11 (-0.23−0.00)$^{\#}$	0.11 (-0.16−0.37)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.14 (-0.33−0.05)	-0.02 (-0.21−0.24)	-0.04 (-0.18−0.10)	-0.11 (-0.44−0.22)
Yes, severe	-0.19 (-0.36−-0.02)*	-0.12 (-0.36−0.11)	0.00 (-0.14−0.14)	-0.11 (-0.41−0.20)
Unknown	-0.12 (-0.76−0.51)	n/a	-0.25 (-0.91−0.41)	-0.34 (-0.62−-0.06)**
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.24 (-0.43−-0.05)*	-0.16 (-0.43−0.10)	-0.24 (-0.39−-0.09)**	-0.34 (-0.62−-0.06)*
Unknown	0.10 (-0.30−0.50)	0.03 (-0.47−0.53)	0.11 (-0.20−0.41)	-0.20 (-0.76−0.36)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.66 (0.49−0.82)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.53 (-0.77−-0.30)***	n/a	n/a	n/a
Unknown	-0.14 (-0.62−0.33)	n/a	n/a	n/a
Random effects				
σ^2	0.35 (0.59)§	0.54 (0.73)§	0.17 (0.41)§	0.30 (0.54)§
$\tau_{00\ studies}$	0.11 (0.34)§	0.08 (0.28)§	0.14 (0.38)§	0.04 (0.20)§
$\tau_{11\ studies*doses}$	0.02 (0.14)§	n/a	0.05 (0.22)§	n/a
$\rho_{01\ studies}$	-0.49	n/a	-0.32	n/a
ICC	0.26	0.13	0.54	0.12
$N_{\ studies}$	23	20	20	8
Observations	289	263	244	90
Conditional R^2	0.62	0.33	0.59	0.30

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weight-for-age or height-for-age Z-score ≥-3 but <-2; and severe malnutrition was defined as a weight-for-age or height-for-age Z-score <-3. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E18. Multivariate linear mixed-effects analyses of factors associated with log-transformed C_{max} values for first-line antituberculosis drugs in children under 2 years of age with tuberculosis.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	1.27 (0.45−2.09)**	1.79 (0.78−2.80)**	3.38 (2.87−3.88)***	0.32 (-1.36−2.00)
Dose, mg/kg¶	0.44 (0.30−0.57)***	0.28 (0.16−0.39)***	0.21 (0.11−0.31)***	0.15 (0.02−0.28)*
Age	0.06 (-0.62−0.74)	0.06 (-0.87−1.00)	-0.13 (-0.59−0.32)	0.29 (-1.00−1.58)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	0.15 (0.002−0.29)*	0.11 (-0.09−0.30)	-0.00 (-0.10−0.10)	0.16 (-0.16−0.47)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.08 (-0.27−0.11)	-0.18 (-0.42−0.06)	-0.09 (-0.21−0.04)	-0.07 (-0.45−0.31)
Yes, severe	-0.15 (-0.32−0.02)$^{\#}$	-0.26 (-0.51−-0.01)*	-0.10 (-0.22−0.03)	-0.08 (-0.44−0.27)
Unknown	0.32 (-0.30−0.95)	n/a	-0.30 (-0.75−0.16)	-1.00 (-2.43−0.42)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.21 (-0.41−-0.02)*	-0.21 (-0.49−0.07)	-0.13 (-0.27−-0.001)*	-0.40 (-0.75−-0.05)*
Unknown	0.12 (-0.27−0.51)	0.32 (-0.22−0.86)$^{\#}$	0.19 (-0.07−0.46)	0.39 (-0.22−1.00)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.37 (0.19−0.56)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	0.01 (-0.23−0.24)	n/a	n/a	n/a
Unknown	-0.30 (-0.56−-0.04)*	n/a	n/a	n/a
Random effects				
σ^2	0.36 (0.60)§	0.62 (0.79)§	0.14 (0.38)§	0.45 (0.67)§
$\tau_{00\ studies}$	0.10 (0.31)§	0.27 (0.52)§	0.04 (0.21)§	0.16 (0.41)§
$\tau_{11\ studies*doses}$	0.03 (0.16)§	n/a	0.02 (0.14)§	n/a
$\rho_{01\ studies}$	-0.34	n/a	0.34	n/a
ICC	0.25	0.30	0.35	0.26
$N_{\ studies}$	23	21	20	10
Observations	294	278	254	102
Conditional R^2	0.55	0.41	0.51	0.37

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weight-for-age or height-for-age Z-score ≥-3 but <-2; and severe malnutrition was defined as a weight-for-age or height-for-age Z-score <-3. ¶¶Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, $^{\#}$p<0.1.

Table E19. Multivariate linear mixed-effects analyses of factors associated with log-transformed AUC_{0-24} values for first-line antituberculosis drugs in children and adolescents with tuberculosis who had pharmacokinetic sampling at steady state or approaching steady state.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	2.56 (2.36−2.77)***	3.83 (3.62−4.03)***	6.08 (5.93−6.22)***	2.48 (2.20−2.77)***
Dose, mg/kg¶	0.43 (0.34−0.53)***	0.65 (0.44−0.86)***	0.16 (0.09−0.24)***	0.23 (0.11−0.34)***
Age				
<2 years	-0.31 (-0.43−-0.18)***	-0.49 (-0.65−-0.33)***	-0.34 (-0.45−-0.23)***	-0.53 (-0.75−-0.32)***
2-4 years	-0.10 (-0.21−0.02)	-0.36 (-0.51−-0.21)***	-0.26 (-0.37−-0.16)***	-0.37 (-0.58−-0.17)***
5-9 years	-0.06 (-0.16−0.05)	-0.13 (-0.27−0.01)$^{\#}$	-0.16 (-0.26−-0.07)**	-0.16 (-0.35−0.02)$^{\#}$
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	0.08 (-0.26−0.42)	0.27 (-0.16−0.71)	-0.04 (-0.37−0.29)	0.31 (-0.26−0.87)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.03 (-0.11−0.04)	-0.05 (-0.14−0.04)$^{\#}$	-0.06 (-0.13−-0.002)*	-0.06 (-0.19−0.08)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.12 (-0.21−-0.02)*	-0.01 (-0.10−0.12)	-0.03 (-0.11−0.05)	-0.09 (-0.26−0.07)
Yes, severe	-0.16 (-0.25−-0.06)**	-0.03 (-0.15−0.09)	-0.08 (-0.16−-0.003)*	-0.09 (-0.26−0.08)
Unknown	0.08 (-0.21−0.37)	-0.11 (-0.74−0.51)	-0.10 (-0.45−0.25)	0.13 (-0.63−0.89)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.15 (-0.26−-0.04)**	-0.25 (-0.39−-0.10)**	-0.22 (-0.31−-0.12)***	0.40 (-0.57−-0.22)***
Unknown	-0.11 (-0.38−0.17)	-0.38 (-0.72−0.04)*	0.02 (-0.21−0.25)	-0.08 (-0.51−0.35)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.70 (0.62−0.78)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.38 (-0.50−-0.26)***	n/a	n/a	n/a
Unknown	0.47 (0.27−0.66)***	n/a	n/a	n/a
Random effects				
σ^2	0.36 (0.60)§	0.48 (0.69)§	0.21 (0.45)§	0.43 (0.65)§
$\tau_{00\ studies}$	0.14 (0.38)§	0.09 (0.30)§	0.05 (0.23)§	0.09 (0.30)§
$\tau_{11\ studies*doses}$	0.03 (0.17)§	0.12 (0.35)§	0.01 (0.11)§	n/a
$\rho_{01\ studies}$	-0.75	-0.33	-0.17	n/a
ICC	0.28	0.33	0.24	0.17
$N_{\ studies}$	23	20	18	10
Observations	1163	1002	869	393
Conditional R^2	0.59	0.62	0.37	0.31

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E20. Multivariate linear mixed-effects analyses of factors associated with log-transformed C_{max} values for first-line antituberculosis drugs in children and adolescents with tuberculosis who had pharmacokinetic sampling at steady state or approaching steady state.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	1.46 (1.26−1.67)***	2.21 (2.00−2.42)***	3.75 (3.62−3.88)***	0.76 (0.50−1.02)***
Dose, mg/kg¶	0.42 (0.29−0.54)***	0.52 (0.32−0.73)***	0.16 (0.10−0.22)***	0.17 (0.07−0.27)**
Age				
<2 years	-0.30 (-0.43−-0.17)***	-0.44 (-0.59−-0.28)***	-0.20 (-0.31−-0.10)***	-0.67 (-0.89−-0.44)***
2-4 years	-0.09 (-0.20−0.03)	-0.19 (-0.34−-0.05)**	-0.16 (-0.26−-0.06)**	-0.33 (-0.54−-0.12)**
5-9 years	-0.04 (-0.15−0.06)	-0.10 (-0.23−0.04)	-0.13 (-0.21−-0.04)**	-0.09 (-0.28−0.09)
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	-0.02 (-0.35−0.31)	0.08 (-0.34−0.50)	-0.06 (-0.36−0.25)	0.11 (-0.50−0.71)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.05 (-0.12−0.02)	-0.02 (-0.07−0.10)	-0.06 (-0.12−0.002)$^{\#}$	-0.05 (-0.18−0.09)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.07 (-0.16−0.02)	-0.04 (-0.15−0.07)	-0.02 (-0.09−0.06)	-0.10 (-0.27−0.07)
Yes, severe	-0.09 (-0.18−0.01)$^{\#}$	-0.13 (-0.24−-0.01)*	-0.10 (-0.18−-0.02)*	-0.11 (-0.28−0.06)
Unknown	0.04 (-0.27−0.34)	-0.16 (-0.73−0.42)	-0.07 (-0.39−0.25)	-0.29 (-0.89−0.31)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.17 (-0.28−-0.06)**	-0.24 (-0.38−-0.10)**	-0.11 (-0.20−-0.02)*	-0.39 (-0.57−-0.20)***
Unknown	0.02 (-0.26−0.29)	-0.22 (-0.55−0.11)	-0.13 (-0.35−0.08)	0.04 (-0.34−0.42)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.24 (0.15−0.32)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.12 (-0.24−0.001)$^{\#}$	n/a	n/a	n/a
Unknown	-0.35 (-0.51−-0.20)***	n/a	n/a	n/a
Random effects				
σ^2	0.37 (0.61)§	0.50 (0.71)§	0.20 (0.44)§	0.52 (0.72)§
$\tau_{00\ studies}$	0.15 (0.38)§	0.11 (0.34)§	0.03 (0.18)§	0.06 (0.25)§
$\tau_{11\ studies*doses}$	0.05 (0.23)§	0.11 (0.33)§	0.01 (0.09)§	n/a
$\rho_{01\ studies}$	-0.33	-0.01	-0.10	n/a
ICC	0.33	0.33	0.18	0.11
$N_{\ studies}$	23	20	18	10
Observations	1203	1065	924	465
Conditional R^2	0.52	0.56	0.30	0.26

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E21. Multivariate linear mixed-effects analyses of factors associated with log-transformed AUC_{0-24} values for first-line antituberculosis drugs, in children and adolescents with tuberculosis who had pharmacokinetic sampling at steady state or approaching steady state, and who received daily dosing.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	2.50 (2.28−2.72)***	3.83 (3.61−4.05)***	6.11 (5.95−6.28)***	2.48 (2.20−2.77)***
Dose, mg/kg¶	0.44 (0.33−0.55)***	0.62 (0.40−0.84)***	0.18 (0.08−0.27)***	0.23 (0.11−0.34)***
Age				
<2 years	-0.27 (-0.40−-0.13)***	-0.51 (-0.68−-0.34)***	-0.32 (-0.44−-0.21)***	-0.53 (-0.75−-0.32)***
2-4 years	-0.05 (-0.18−0.08)	-0.34 (-0.51−-0.18)***	-0.25 (-0.36−-0.13)***	-0.37 (-0.58−-0.17)***
5-9 years	-0.05 (-0.17−0.07)	-0.18 (-0.34−-0.02)*	-0.19 (-0.29−-0.08)***	-0.16 (-0.35−0.02)$^{\#}$
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	0.03 (-0.36−0.42)	0.24 (-0.27−0.74)	-0.09 (-0.44−0.25)	0.31 (-0.26−0.87)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.04 (-0.12−0.04)	-0.04 (-0.13−0.06)	-0.07 (-0.14−-0.01)*	-0.06 (-0.19−0.08)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.14 (-0.24−-0.04)**	-0.04 (-0.08−0.15)	-0.06 (-0.14−0.02)	-0.09 (-0.26−0.07)
Yes, severe	-0.17 (-0.27−-0.07)**	-0.01 (-0.14−0.12)	-0.08 (-0.16−0.002)$^{\#}$	-0.09 (-0.26−0.08)
Unknown	0.08 (-0.22−0.38)	-0.09 (-0.70−0.52)	-0.10 (-0.43−0.23)	0.13 (-0.63−0.89)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.16 (-0.27−-0.05)**	-0.24 (-0.38−-0.10)**	-0.22 (-0.31−-0.13)***	-0.40 (-0.57−-0.22)***
Unknown	-0.12 (-0.39−0.16)	-0.37 (-0.71−-0.04)*	0.02 (-0.20−0.23)	-0.08 (-0.51−0.35)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.73 (0.64−0.83)***	n/a	n/a	n/a
Intermediate	Ref.	n/a	n/a	n/a
Rapid	-0.38 (-0.51−-0.24)***	n/a	n/a	n/a
Unknown	0.46 (0.25−0.66)***	n/a	n/a	n/a
Random effects				
σ^2	0.37 (0.60)§	0.46 (0.68)§	0.18 (0.43)§	0.43 (0.65)§
$\tau_{00\ studies}$	0.14 (0.38)§	0.10 (0.31)§	0.06 (0.25)§	0.09 (0.09)§
$\tau_{11\ studies*doses}$	0.03 (0.18)§	0.11 (0.33) §	0.02 (0.15)§	n/a
$\rho_{01\ studies}$	-0.64	-0.16	-0.22	n/a
ICC	0.30	0.36	0.32	0.17
$N_{\ studies}$	21	19	17	10
Observations	971	834	727	393
Conditional R^2	0.61	0.65	0.45	0.31

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E22. Multivariate linear mixed-effects analyses of factors associated with log-transformed C_{max} values for first-line antituberculosis drugs, in children and adolescents with tuberculosis who had pharmacokinetic sampling at steady state or approaching steady state, and who received daily dosing.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	1.43 (1.20−1.66)***	2.23 (2.01−2.44)***	3.77 (3.63−3.92)***	0.74 (0.47−1.01)***
Dose, mg/kg¶	0.43 (0.28−0.58)***	0.51 (0.29−0.73)***	0.17 (0.09−0.25)***	0.16 (0.06−0.26)**
Age				
<2 years	-0.26 (-0.40−-0.12)***	-0.42 (-0.58−-0.25)***	-0.21 (-0.32−-0.09)***	-0.66 (-0.88−-0.44)***
2-4 years	-0.04 (-0.17−0.09)	-0.17 (-0.33−-0.004)*	-0.16 (-0.27−-0.04)**	-0.33 (-0.54−-0.12)**
5-9 years	-0.03 (-0.15−0.09)	-0.12 (-0.28−0.03)	-0.17 (-0.27−-0.07)**	-0.10 (-0.29−0.08)
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	-0.10 (-0.49−0.28)	0.03 (-0.45−0.52)	-0.11 (-0.44−0.21)	0.14 (-0.46−0.75)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.05 (-0.13−0.03)	0.01 (-0.09−0.10)	-0.07 (-0.13−-0.001)*	-0.04 (-0.18−0.09)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.09 (-0.19−0.01)$^{\#}$	0.002 (-0.12−0.12)	-0.03 (-0.11−0.05)	-0.10 (-0.27−0.07)
Yes, severe	-0.09 (-0.19−0.01)$^{\#}$	-0.12 (-0.25−0.01)	-0.10 (-0.19−-0.02)*	-0.11 (-0.28−0.06)
Unknown	0.03 (-0.28−0.34)	-0.13 (-0.71−0.44)	-0.06 (-0.38−0.27)	-0.27 (-0.87−0.33)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.17 (-0.28−-0.06)**	-0.24 (-0.38−-0.10)**	-0.11 (-0.21−-0.02)*	-0.38 (-0.57−-0.19)***
Unknown	0.01 (-0.27−0.28)	-0.23 (-0.55−0.10)	-0.13 (-0.34−0.09)	0.06 (-0.33−0.44)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.26 (0.17−0.35)***	n/a	n/a	n/a
Intermediate	Ref	n/a	n/a	n/a
Rapid	-0.08 (-0.22−0.05)	n/a	n/a	n/a
Unknown	-0.36 (-0.53−-0.20)***	n/a	n/a	n/a
Random effects				
σ^2	0.37 (0.61)§	0.49 (0.70)§	0.20 (0.45)§	0.52 (0.72)§
$\tau_{00\ studies}$	0.15 (0.39)§	0.10 (0.32)§	0.04 (0.20)§	0.07 (0.26)§
$\tau_{11\ studies*doses}$	0.08 (0.28)§	0.10 (0.32)§	0.01 (0.10)§	n/a
$\rho_{01\ studies}$	-0.22	0.17	0.00	n/a
ICC	0.37	0.35	0.21	0.12
$N_{\ studies}$	21	19	17	10
Observations	1009	890	779	463
Conditional R^2	0.55	0.58	0.33	0.26

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E23. Multivariate linear mixed-effects analyses of factors associated with log-transformed AUC_{0-24} values for first-line antituberculosis drugs in children and adolescents with tuberculosis, considering WHO region as a third-level clustering variable.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	2.55 (2.37−2.74)***	3.86 (3.66−4.06)***	6.04 (5.90−6.17)***	2.44 (2.05−2.83)***
Dose, mg/kg¶	0.42 (0.34−0.51)***	0.65 (0.44−0.85)***	0.17 (0.10−0.23)***	0.15 (0.06−0.24)**
Age				
<2 years	-0.28 (-0.40−-0.16)***	-0.48 (-0.64−-0.33)***	-0.28 (-0.38−-0.17)***	-0.56 (-0.78−-0.34)***
2-4 years	-0.07 (-0.18−0.04)	-0.35 (-0.50−-0.21)***	-0.24 (-0.34−-0.14)***	-0.36 (-0.57−-0.16)**
5-9 years	-0.04 (-0.14−0.06)	-0.12 (-0.26−0.01)$^{\#}$	-0.12 (-0.21−-0.03)**	-0.19 (-0.38−-0.01)*
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	0.05 (-0.24−0.33)	0.22 (-0.16−0.60)	-0.004 (-0.27−0.26)	0.24 (-0.34−0.83)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.03 (-0.10−0.04)	-0.05 (-0.13−0.04)	-0.08 (-0.14−-0.02)**	0.03 (-0.16−0.10)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.10 (-0.19−-0.01)*	0.02 (-0.09−0.12)	-0.03 (-0.10−0.05)	-0.09 (-0.25−0.08)
Yes, severe	-0.15 (-0.24−-0.06)**	-0.02 (-0.13−0.10)	-0.08 (-0.16−-0.004)*	-0.09 (-0.26−0.08)
Unknown	0.13 (-0.13−0.39)	-0.05 (-0.61−0.51)	-0.002 (-0.23−0.23)	-0.12 (-0.61−0.37)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.15 (-0.25−-0.04)**	-0.25 (-0.39−-0.11)***	-0.19 (-0.29−-0.10)***	-0.39 (-0.56−-0.22)***
Unknown	-0.06 (-0.30−0.18)	-0.33 (-0.64−-0.01)*	0.01 (-0.18−0.20)	-0.10 (-0.51−0.31)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.70 (0.62−0.77)***	n/a	n/a	n/a
Intermediate	Ref	n/a	n/a	n/a
Rapid	-0.39 (-0.50−-0.28)***	n/a	n/a	n/a
Unknown	0.44 (0.25−0.63)***	n/a	n/a	n/a
Random effects				
σ^2	0.35 (0.59)§	0.47 (0.68)§	0.21 (0.46)§	0.44 (0.66)§
$\tau_{00\ \text{WHO regions:studies}}$	0.12 (0.35)§	0.11 (0.32)§	0.04 (0.21)§	0.04 (0.20)§
$\tau_{00\ \text{WHO regions}}$	0.00 (0.04)§	n/a	n/a	0.07 (0.26)§
$\tau_{11\ \text{WHO regions:studies*doses}}$	0.03 (0.16)§	0.12 (0.35)§	0.01 (0.10)§	n/a
$\rho_{01\ \text{WHO regions:studies}}$	-0.74	-0.25	-0.15	n/a
ICC	0.27	0.35	0.21	0.19
$N_{\text{WHO regions}}$	3	3	3	3
N_{studies}	27	22	23	11
Observations	1252	1041	962	410
Conditional R^2	0.58	0.63	0.34	0.32

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E24. Multivariate linear mixed-effects analyses of factors associated with log-transformed C_{max} values for first-line antituberculosis drugs in children and adolescents with tuberculosis, considering WHO region as a third-level clustering variable.

	Fixed-effects coefficient (95% CI)			
	Isoniazid	**Rifampicin**	**Pyrazinamide**	**Ethambutol**
(Intercept)	1.42 (1.11−1.72)***	2.21 (2.01−2.41)***	3.73 (3.58−3.88)***	0.75 (0.49−1.00)***
Dose, mg/kg¶	0.41 (0.30−0.52)***	0.52 (0.33−0.72)***	0.16 (0.11−0.22)***	0.13 (0.05−0.22)**
Age				
<2 years	-0.28 (-0.40−-0.16)***	-0.42 (-0.57−-0.27)***	-0.18 (-0.28−-0.08)***	-0.68 (-0.90−-0.46)***
2-4 years	-0.08 (-0.18−0.03)	-0.18 (-0.32−-0.04)*	-0.15 (-0.24−-0.06)**	-0.32 (-0.53−-0.11)**
5-9 years	-0.03 (-0.13−0.06)	-0.09 (-0.22−0.04)	-0.10 (-0.18−-0.02)*	-0.12 (-0.31−0.06)
10-14 years	Ref.	Ref.	Ref.	Ref.
15-18 years	-0.01 (-0.30−0.27)	0.06 (-0.31−0.42)	-0.01 (-0.26−0.23)	0.10 (-0.51−0.70)
Sex				
Female	Ref.	Ref.	Ref.	Ref.
Male	-0.04 (-0.11−0.03)	-0.02 (-0.07−0.10)	-0.05 (-0.11−0.001)#	-0.03 (-0.17−0.10)
Malnourished§§				
No	Ref.	Ref.	Ref.	Ref.
Yes, moderate	-0.06 (-0.14−0.03)	-0.03 (-0.14−0.07)	-0.02 (-0.09−0.05)	-0.10 (-0.27−0.07)
Yes, severe	-0.09 (-0.18−-0.003)*	-0.12 (-0.24−-0.01)*	-0.10 (-0.18−-0.03)**	-0.12 (-0.29−0.06)
Unknown	0.12 (-0.14−0.38)	-0.14 (-0.67−0.39)	0.05 (-0.16−0.26)	-0.33 (-0.78−0.12)
HIV status				
Negative	Ref.	Ref.	Ref.	Ref.
Positive	-0.18 (-0.28−-0.07)**	-0.25 (-0.39−-0.11)***	-0.11 (-0.20−-0.02)*	-0.35 (-0.53−-0.17)***
Unknown	0.06 (-0.18−0.29)	-0.19 (-0.49−0.11)	-0.06 (-0.23−0.11)	0.04 (-0.34−0.43)
Acetylator status, $t_{1/2}$ phenotype¶¶				
Slow	0.23 (0.16−0.31)***	n/a	n/a	n/a
Intermediate	Ref	n/a	n/a	n/a
Rapid	-0.13 (-0.25−-0.02)*	n/a	n/a	n/a
Unknown	-0.38 (-0.53−-0.22)***	n/a	n/a	n/a
Random effects				
σ^2	0.35 (0.59)§	0.49 (0.70)§	0.19 (0.44)§	0.53 (0.73)
$\tau_{00\ \text{WHO regions:studies}}$	0.10 (0.31)§	0.11 (0.33)§	0.03 (0.17)§	0.06 (0.24)
$\tau_{00\ \text{WHO regions}}$	0.04 (0.20)§	n/a	0.01 (0.08)§	n/a
$\tau_{11\ \text{WHO regions:studies*doses}}$	0.04 (0.21)§	0.10 (0.32)§	0.01 (0.09)§	n/a
$\rho_{01\ \text{WHO regions:studies}}$	-0.33	0.02	-0.04	n/a
ICC	0.33	0.32	0.19	0.10
$N_{\text{WHO regions}}$	3	3	3	3
N_{studies}	27	22	23	11
Observations	1292	1105	1021	483
Conditional R^2	0.52	0.55	0.31	0.23

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. $AUC_{0\text{-}24}$: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. ¶Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. §§Moderate malnutrition was defined as a weigh-for-age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score ≥-3 but <-2 in children aged ≥5 years; and severe malnutrition was defined as a weigh-for-age or height-for-age Z-score <-3 in children aged <5 years, and a height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Details are described in Appendix 4. ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

Table E25. Multivariate linear mixed-effects analyses on the effect of paediatric/adult dosing category on log-transformed AUC_{0-24} values for isoniazid, rifampicin and pyrazinamide in tuberculosis patients weighing ≥25 kg, adjusted for at least age, sex, nutritional status, and HIV status.[¥]

	Fixed-effects coefficient (95% CI)		
	Isoniazid	**Rifampicin**	**Pyrazinamide**
(Intercept)	2.98 (2.58−3.38)***	3.54 (3.09−3.98)***	5.81 (5.51−6.11)***
Dose category[†]			
Paediatric dosing	Ref.	Ref.	Ref.
Adult dosing	-1.01 (-1.27−-0.76)***	-0.35 (-0.63−-0.07)*	-0.14 (-0.34−0.06)
Age	-0.08 (-0.30−0.13)	0.15 (-0.09−0.39)	0.13 (-0.02−0.28)$^{\#}$
Sex			
Female	Ref.	Ref.	Ref.
Male	-0.12 (-0.32−0.07)	-0.17 (-0.40−0.05)	-0.06 (-0.20−0.08)
Malnourished[§§]			
No	Ref.	Ref.	Ref.
Yes, moderate	-0.14 (-0.39−0.11)	0.14 (-0.13−0.41)	0.05 (-0.11−0.21)
Yes, severe	-0.42 (-0.75−-0.09)*	-0.12 (-0.49−0.24)	0.07 (-0.14−0.29)
Unknown	-0.07 (-0.66−0.51)	n/a	-0.57 (-1.10−-0.05)*
HIV status			
Negative	Ref.	Ref.	Ref.
Positive	-0.27 (-0.65−0.10)	-0.44 (-0.82−-0.06)*	-0.17 (-0.43−0.09)
Unknown	0.34 (-0.46−1.13)	0.12 (-0.81−1.04)	0.02 (-0.41−0.45)
Acetylator status, $t_{1/2}$ phenotype[¶¶]			
Slow	0.82 (0.59−1.05)***	n/a	n/a
Intermediate	Ref.	n/a	n/a
Rapid	-0.45 (-0.85−-0.06)*	n/a	n/a
Unknown	0.52 (0.08−0.97)*	n/a	n/a
Random effects			
σ^2	0.45 (0.67)[§]	0.47 (0.68)[§]	0.16 (0.40)[§]
$\tau_{00\ studies}$	0.12 (0.34)[§]	0.08 (0.29)[§]	0.06 (0.23)[§]
ICC	0.21	0.15	0.25
$N_{\ studies}$	24	17	20
Observations	213	160	160
Conditional R^2	0.57	0.28	0.34

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. [¥]Current paediatric and adult dosing for ethambutol overlap significantly (15-25 mg/kg *vs* 15-20 mg/kg, respectively), and therefore the data for ethambutol were not analysed. [†]Drug doses were categorized as adult dosing (i.e., isoniazid <7 mg/kg, rifampicin <10 mg/kg, and pyrazinamide <30 mg/kg) and paediatric dosing (i.e., isoniazid 7-15 mg/kg, rifampicin 10-20 mg/kg, and pyrazinamide 30-40 mg/kg). [¶]Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [§§]Moderate malnutrition was defined as a height-for-age or body mass index-for-age Z-score ≥-3 but <-2, and severe malnutrition was defined as a height-for-age or body mass index-for-age Z-score <-3. [¶¶]Further details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E26. Multivariate linear mixed-effects analyses on the effect of paediatric/adult dosing category on log-transformed C_{max} values for isoniazid, rifampicin and pyrazinamide in tuberculosis patients weighing ≥25 kg, adjusted for at least age, sex, nutritional status, and HIV status.[¥]

	Fixed-effects coefficient (95% CI)		
	Isoniazid	**Rifampicin**	**Pyrazinamide**
(Intercept)	1.80 (1.41−2.19)***	2.02 (1.66−2.39)***	3.49 (3.16−3.81)***
Dose category[†]			
Paediatric dosing	Ref.	Ref.	Ref.
Adult dosing	-0.97 (-1.22−-0.73)***	-0.30 (-0.53−-0.06)*	-0.21 (-0.42−0.01)$^{\#}$
Age	-0.01 (-0.23−0.20)	0.01 (-0.19−0.21)	0.17 (0.01−0.34)*
Sex			
Female	Ref.	Ref.	Ref.
Male	-0.17 (-0.36−0.02)$^{\#}$	-0.001 (-0.19−0.19)	-0.06 (-0.21−0.09)
Malnourished[§§]			
No	Ref.	Ref.	Ref.
Yes, moderate	-0.11 (-0.35−0.13)	0.09 (-0.15−0.33)	0.03 (-0.15−0.21)
Yes, severe	-0.35 (-0.67−-0.03)*	-0.26 (-0.57−0.04)$^{\#}$	-0.08 (-0.32−0.16)
Unknown	-0.01 (-0.57−0.55)	n/a	-0.24 (-0.81−0.32)
HIV status			
Negative	Ref.	Ref.	Ref.
Positive	-0.28 (-0.64−0.09)	-0.43 (-0.74−-0.13)*	-0.06 (-0.35−0.23)
Unknown	0.66 (-0.04−1.36)	0.14 (-0.64−0.93)	0.08 (-0.39−0.54)
Acetylator status, $t_{1/2}$ phenotype[¶¶]			
Slow	0.22 (-0.001−0.45)$^{\#}$	n/a	n/a
Intermediate	Ref.	n/a	n/a
Rapid	-0.25 (-0.64−0.14)	n/a	n/a
Unknown	-0.70 (-1.06−-0.34)***	n/a	n/a
Random effects			
σ^2	0.44 (0.66)[§]	0.39 (0.62)[§]	0.21 (0.46)[§]
$\tau_{00\ studies}$	0.11 (0.34)[§]	0.03 (0.16)[§]	0.06 (0.24)[§]
ICC	0.21	0.07	0.21
$N_{\ studies}$	24	17	20
Observations	223	173	173
Conditional R^2	0.53	201	0.27

Data are presented as fixed-effects coefficients (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: [§]mean and standard deviation. C_{max}: peak plasma concentration; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: intraclass correlation coefficient, N: number of included studies, conditional R^2: the proportion of variance explained by both the fixed and random effects. [¥]Current paediatric and adult dosing for ethambutol overlap significantly (15-25 mg/kg *vs* 15-20 mg/kg, respectively), and therefore the data for ethambutol were not analysed. [†]Drug doses were categorized as adult dosing (i.e., isoniazid <7 mg/kg, rifampicin <10 mg/kg, and pyrazinamide <30 mg/kg) and paediatric dosing (i.e., isoniazid 7-15 mg/kg, rifampicin 10-20 mg/kg, and pyrazinamide 30-40 mg/kg). [¶]Drug dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. [§§]Moderate malnutrition was defined as WFAZ or HFAZ ≥-3 but <-2, and severe malnutrition was defined as WFAZ or HFAZ <-3. [¶¶]Further details are described in Appendix 4. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$, $^{\#}p<0.1$.

Table E27. Summary estimates of T_{max}, $t_{1/2}$, and K_e for first-line antituberculosis drugs in children and adolescents with tuberculosis.

	No. of studies	No. of observations	Summary estimates (95% CI)	Heterogeneity I^2 statistics
Isoniazid				
$^{§}T_{max}$, h	24	1219	1.6 (1.4−1.8)	99.0%
$t_{1/2}$, h	27	1203	2.2 (2.0−2.5)	97.9%
Ke, h^{-1}	27	1203	0.31 (0.27−0.35)	97.9%
Rifampicin				
$^{§}T_{max}$, h	22	1037	2.3 (2.0−2.5)	93.2%
$t_{1/2}$, h	22	814	2.1 (1.9−2.3)	94.1%
Ke, h^{-1}	22	814	0.33 (0.30−0.37)	94.0%
Pyrazinamide				
$^{§}T_{max}$, h	22	1001	1.9 (1.6−2.2)	98.4%
$t_{1/2}$, h	23	872	6.1 (5.7−6.6)	83.1%
Ke, h^{-1}	23	872	0.11 (0.11−0.12)	83.0%
Ethambutol				
$^{§}T_{max}$, h	11	483	2.6 (2.3−3.0)	90.8%
$t_{1/2}$, h	10	321	3.4 (2.5−4.6)	98.8%
Ke, h^{-1}	10	321	0.20 (0.15−0.27)	98.8%

Data are presented as geometric mean, unless stated otherwise: §mean. T_{max}: time to maximum concentration in plasma; $t_{1/2}$: elimination half-life; K_e: elimination rate constant.

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