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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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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 https://bit.ly/3Vzw4f0

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Abstract

Background Suboptimal exposure to antituberculosis (anti-TB) drugs has been associated with unfavourable treatment outcomes. We aimed to investigate estimates and determinants of first-line anti-TB 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 anti-TB 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 from 0 to 24 h post-dose ($AUC_{0–24}$) and peak plasma concentration (C_{max}) were assessed with random-effects models, normalised with current World Health Organization-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 of steady-state $AUC_{0–24}$ were summarised for isoniazid (18.7 (95% CI 15.5–22.6) $h \cdot mg \cdot L^{-1}$), rifampicin (34.4 (95% CI 29.4–40.3) $h \cdot mg \cdot L^{-1}$), pyrazinamide (375.0 (95% CI 339.9–413.7) $h \cdot mg \cdot L^{-1}$) and ethambutol (8.0 (95% CI 6.4–10.0) $h \cdot mg \cdot L^{-1}$). Our multivariate models indicated that younger age (especially <2 years) and HIV-positive status were associated with lower $AUC_{0–24}$ for all first-line anti-TB 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 $AUC_{0–24}$.

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

Introduction

Tuberculosis (TB) remains a major global health challenge. Until the coronavirus disease 2019 (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 summarise 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

This study is registered at PROSPERO with identifier number CRD42018110807. The main outcomes registered in the PROSPERO protocol were analysed in this study. We followed the PRISMA-IPD (Preferred Reporting Items for Systematic Review and Meta-Analyses of Individual Participant Data) 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 1 January 1990 and 2 February 2021 were searched in MEDLINE (*via* PubMed), Embase and Web of Science; the search was updated on 31 December 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 (Medical Subject Headings) terms and key words 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) (supplementary appendix 1).

All articles retrieved by the search strategy were uploaded to Rayyan, a web application for systematic reviews (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 (F.G. and R.E.W.). 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 (F.G. and R.E.W.).

In the absence of a validated tool to assess the quality of pharmacokinetic studies, we developed a checklist (supplementary appendix 2) by including relevant criteria according to the ROBINS-I tool for non-randomised studies of interventions [11], supplemented by essential components required for a critical appraisal of clinical pharmacokinetic studies [12]. An expert panel (D.J.T., M.G.G.S., J.S. and J-W.C.A.) 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 (F.G. and R.E.W.).

All discrepancies between the first and second reviewers (F.G. and R.E.W.) 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 anonymised patient-level information on demographics (age, sex, weight and height), clinical and 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) (supplementary appendix 3).

Ethics approval was provided by the Independent Ethics Committee, University Medical Center Groningen, Groningen, The Netherlands (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 $\geqslant -3$ (moderate) or < -3 (severe) in patients aged <5 years and a height-for-age and/or body mass index-for-age z-score < -2 but $\geqslant -3$ (moderate) or < -3 (severe) in patients aged $\geqslant$5 years [13]. Participants were genotypically and phenotypically categorised into rapid, intermediate and slow acetylators based on *NAT2* genetic polymorphisms (where available) and isoniazid elimination half-life, respectively (supplementary appendix 4).

Data analysis

Our primary pharmacokinetic measures were total/extrapolated area under the plasma concentration–time curve from 0 to 24 h 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 (supplementary appendix 5) in patients with intensive sampling were performed non-compartmentally 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 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-squared statistic (I^2); any level of heterogeneity was allowed to emphasise the importance of between-study variability. To allow a comparison between different doses, $AUC_{0–24}$ and C_{max} were dose-normalised by dividing the individual $AUC_{0–24}$ and C_{max} values by $mg \cdot kg^{-1}$ dose, then multiplying by the current WHO-recommended paediatric dose for isoniazid ($10\ mg \cdot kg^{-1}$), rifampicin ($15\ mg \cdot kg^{-1}$), pyrazinamide ($35\ mg \cdot kg^{-1}$) and ethambutol ($20\ mg \cdot kg^{-1}$) [15]; data on high-dose rifampicin $>35\ mg \cdot kg^{-1}$ were excluded from this particular analysis as this drug 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.* $\geqslant$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-normalised 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 (β) 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 $\geqslant$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 2 February 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 31 December 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

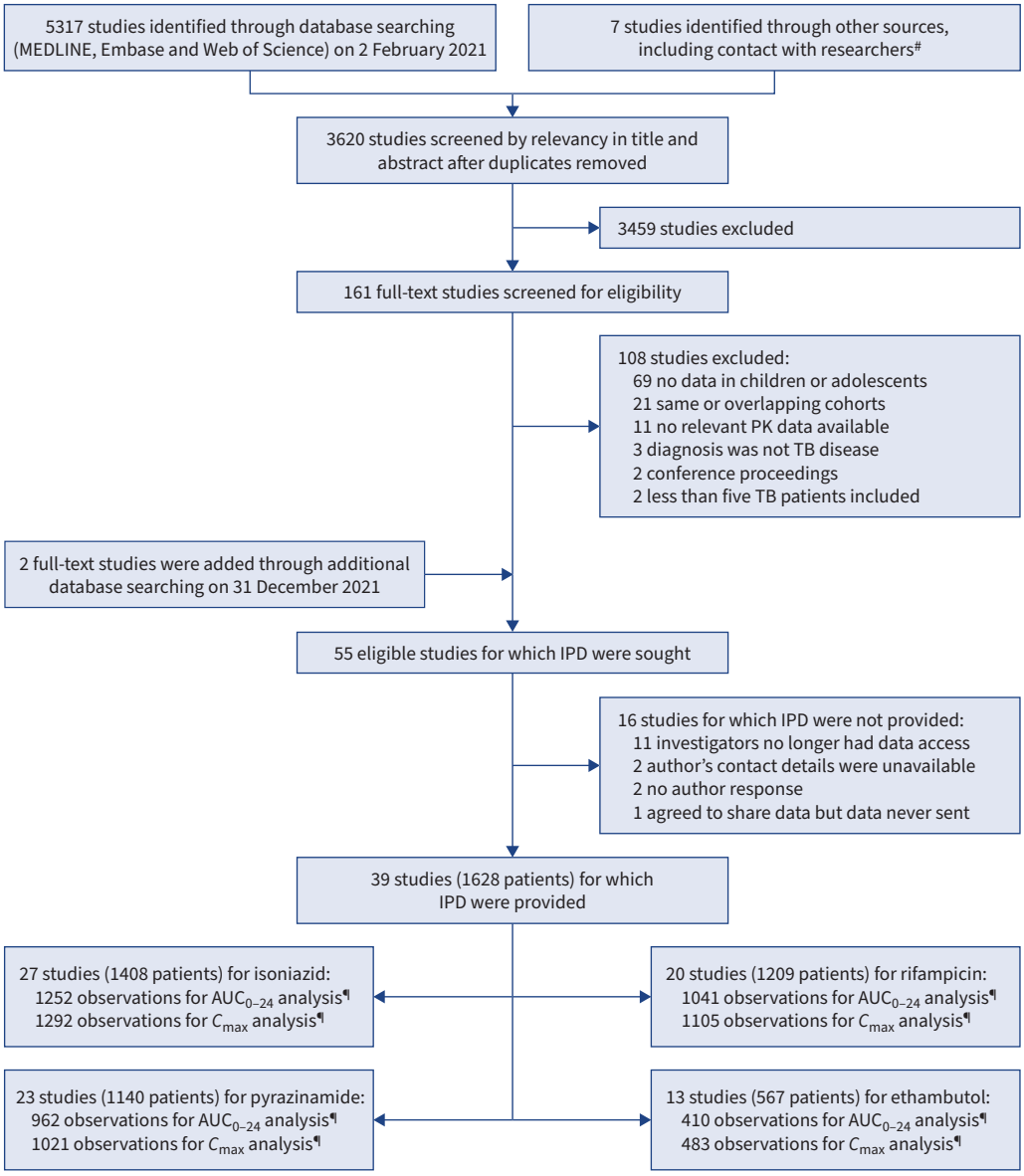


FIGURE 1 Study selection. #: these included unpublished studies or submitted manuscripts identified through contact with investigators (further details are provided in supplementary table E2); ¶: repeated pharmacokinetic measurements in a patient on different days (different sampling occasions). $AUC_{0–24}$: area under the plasma concentration–time curve from 0 to 24 h post-dose; C_{max}: peak plasma concentration; IPD: individual patient data; PK: pharmacokinetic; TB: tuberculosis.

(supplementary table E1). Individual patient data were provided for 39 (71%) out of 55 eligible studies (supplementary table E2) [16–53], including unpublished data from one study by Mlotha-Mitole *et al.* (Blantyre, Malawi). Of these 39 included studies, 26 (67%) were of high quality and 13 (33%) were of moderate quality (supplementary 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 (supplementary 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). $AUC_{0–24}$ values were assessed from 1252 (78.6%) out of 1593 observations (*i.e.* daily occasions) in 1408 patients for isoniazid, 1041 (70.8%) out of 1470 observations in 1209 patients for rifampicin, 962 (73.8%) out of 1304 observations in 1140 patients for pyrazinamide and 410 (72.3%) out of 567 observations in 567 patients for ethambutol (figure 1). A subset of rifampicin data in the study by Denti

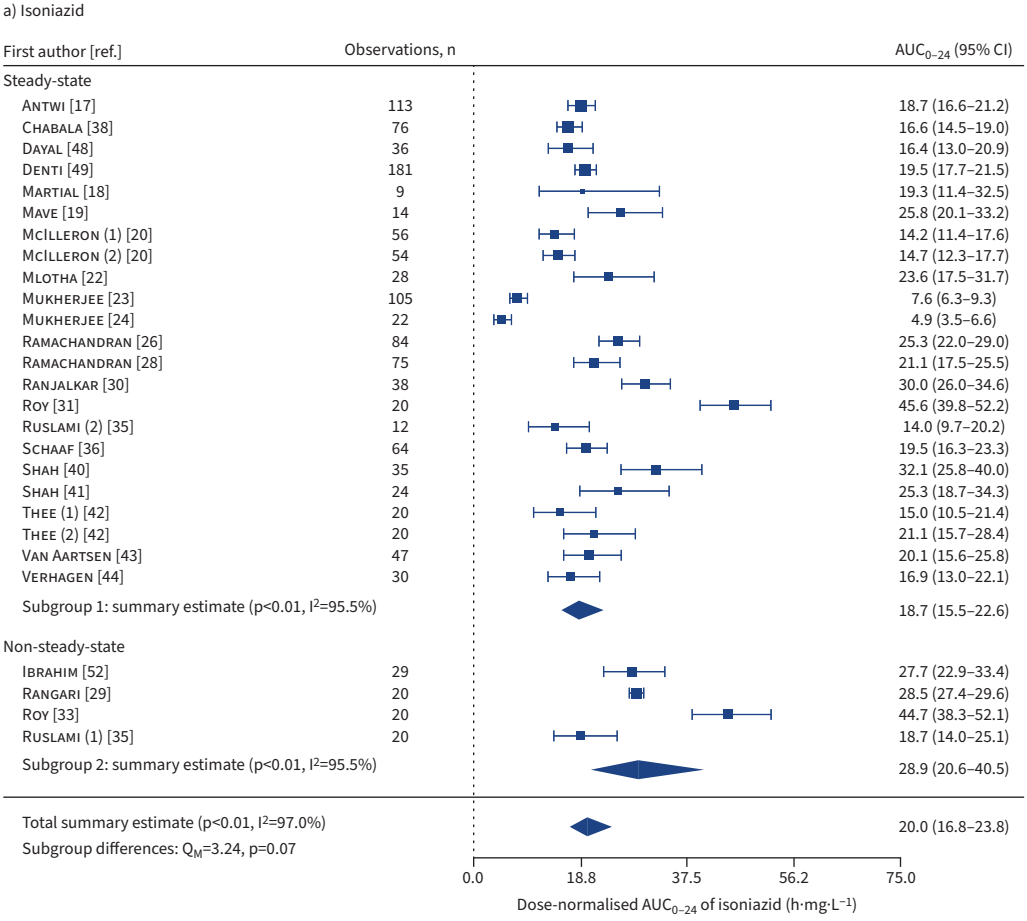
TABLE 1 Demographic and clinical characteristics of children and adolescents with tuberculosis (TB) included in this systematic review and individual patient data meta-analysis

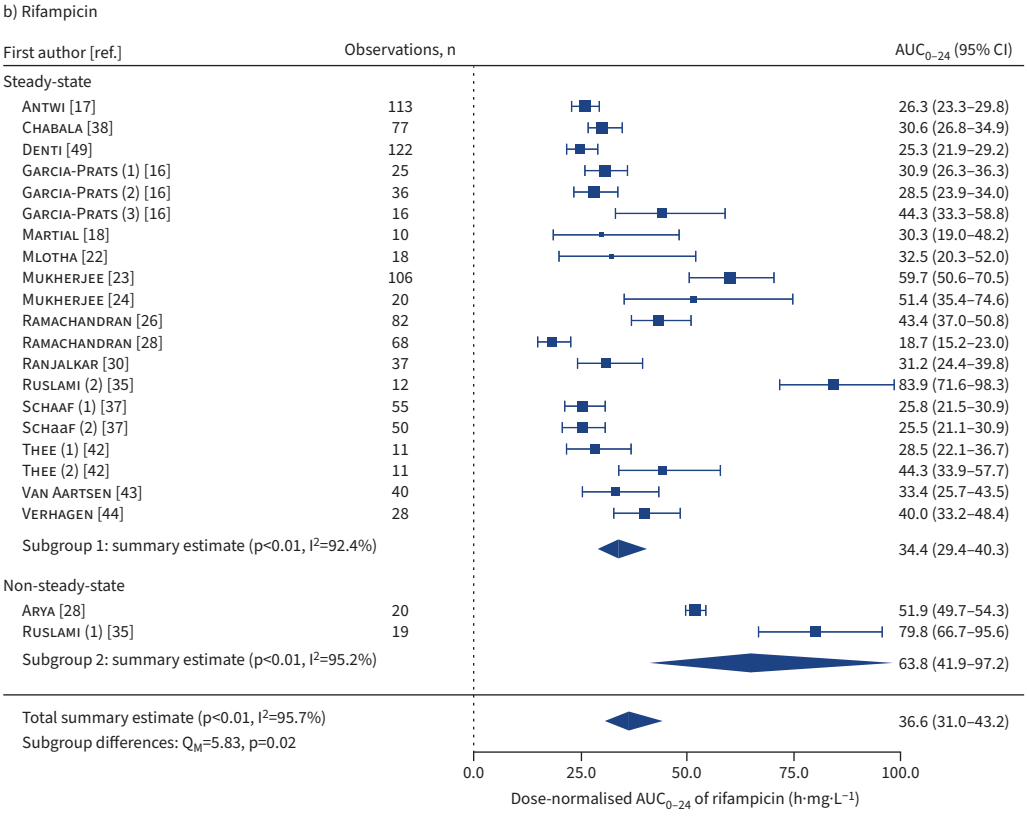
	All patients	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol
Total patients, n	1628	1408	1209	1140	567
Age, years	5.4 (2.2–9.5)	5.5 (2.2–9.6)	5.0 (2.0–9.0)	5.1 (2.0–9.0)	5.9 (2.2–9.8)
Age					
<2 years	356 (21.9)	311 (22.1)	301 (24.9)	274 (24.0)	121 (21.3)
<3 months	7 (0.4)	4 (0.3)	4 (0.3)	5 (0.4)	2 (0.3)
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					
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					
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)			
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)
USA	43 (2.6)			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)	
Indonesia	20 (1.2)	20 (1.4)	20 (1.6)	20 (1.7)	
Malnourished					
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 TB					
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					
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					
Albumin, $g \cdot dL^{-1}$ (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, $mg \cdot dL^{-1}$ (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, $mg \cdot kg^{-1}$		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, median (interquartile range) for continuous variables or n (%) for categorical variables, unless otherwise stated. WHO: World Health Organization.

et al. [49] (n=60/184 observations) was excluded from all AUC_{0-24} 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 [49], as also confirmed in an earlier study by McIlleron *et al.* [54]. Details of the observations for which AUC_{0-24} and C_{max} values could not be reliably assessed are presented in supplementary table E5.

For isoniazid, dose-normalised estimates were summarised for AUC_{0-24} (geometric mean 18.7 (95% CI 15.5–22.6) $h \cdot mg \cdot L^{-1}$) (figure 2a) and C_{max} (geometric mean 4.9 (95% CI 4.1–5.8) $mg \cdot L^{-1}$) (figure 3a) in


a) Isoniazid
First author [ref.]
Observations, n
AUC0–24 (95% CI)
Steady-state
Antwi [17] 113 18.7 (16.6–21.2)
Chabala [38] 76 16.6 (14.5–19.0)
Dayal [48] 36 16.4 (13.0–20.9)
Denti [49] 181 19.5 (17.7–21.5)
Martial [18] 9 19.3 (11.4–32.5)
Mave [19] 14 25.8 (20.1–33.2)
McIlleron (1) [20] 56 14.2 (11.4–17.6)
McIlleron (2) [20] 54 14.7 (12.3–17.7)
Mlotha [22] 28 23.6 (17.5–31.7)
Mukherjee [23] 105 7.6 (6.3–9.3)
Mukherjee [24] 22 4.9 (3.5–6.6)
Ramachandran [26] 84 25.3 (22.0–29.0)
Ramachandran [28] 75 21.1 (17.5–25.5)
Ranjalkar [30] 38 30.0 (26.0–34.6)
Roy [31] 20 45.6 (39.8–52.2)
Ruslami (2) [35] 12 14.0 (9.7–20.2)
Schaaf [36] 64 19.5 (16.3–23.3)
Shah [40] 35 32.1 (25.8–40.0)
Shah [41] 24 25.3 (18.7–34.3)
Thee (1) [42] 20 15.0 (10.5–21.4)
Thee (2) [42] 20 21.1 (15.7–28.4)
Van Aartsen [43] 47 20.1 (15.6–25.8)
Verhagen [44] 30 16.9 (13.0–22.1)
Subgroup 1: summary estimate (p<0.01, I2=95.5%) 18.7 (15.5–22.6)
Non-steady-state
Ibrahim [52] 29 27.7 (22.9–33.4)
Rangari [29] 20 28.5 (27.4–29.6)
Roy [33] 20 44.7 (38.3–52.1)
Ruslami (1) [35] 20 18.7 (14.0–25.1)
Subgroup 2: summary estimate (p<0.01, I2=95.5%) 28.9 (20.6–40.5)
Total summary estimate (p<0.01, 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-normalised AUC0–24 of isoniazid (h·mg·L−1)


b) Rifampicin
First author [ref.]
Observations, n
AUC0–24 (95% CI)
Steady-state
Antwi [17] 113 26.3 (23.3–29.8)
Chabala [38] 77 30.6 (26.8–34.9)
Denti [49] 122 25.3 (21.9–29.2)
Garcia-Prats (1) [16] 25 30.9 (26.3–36.3)
Garcia-Prats (2) [16] 36 28.5 (23.9–34.0)
Garcia-Prats (3) [16] 16 44.3 (33.3–58.8)
Martial [18] 10 30.3 (19.0–48.2)
Mlotha [22] 18 32.5 (20.3–52.0)
Mukherjee [23] 106 59.7 (50.6–70.5)
Mukherjee [24] 20 51.4 (35.4–74.6)
Ramachandran [26] 82 43.4 (37.0–50.8)
Ramachandran [28] 68 18.7 (15.2–23.0)
Ranjalkar [30] 37 31.2 (24.4–39.8)
Ruslami (2) [35] 12 83.9 (71.6–98.3)
Schaaf (1) [37] 55 25.8 (21.5–30.9)
Schaaf (2) [37] 50 25.5 (21.1–30.9)
Thee (1) [42] 11 28.5 (22.1–36.7)
Thee (2) [42] 11 44.3 (33.9–57.7)
Van Aartsen [43] 40 33.4 (25.7–43.5)
Verhagen [44] 28 40.0 (33.2–48.4)
Subgroup 1: summary estimate (p<0.01, I2=92.4%) 34.4 (29.4–40.3)
Non-steady-state
Arya [28] 20 51.9 (49.7–54.3)
Ruslami (1) [35] 19 79.8 (66.7–95.6)
Subgroup 2: summary estimate (p<0.01, I2=95.2%) 63.8 (41.9–97.2)
Total summary estimate (p<0.01, 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-normalised AUC0–24 of rifampicin (h·mg·L−1)

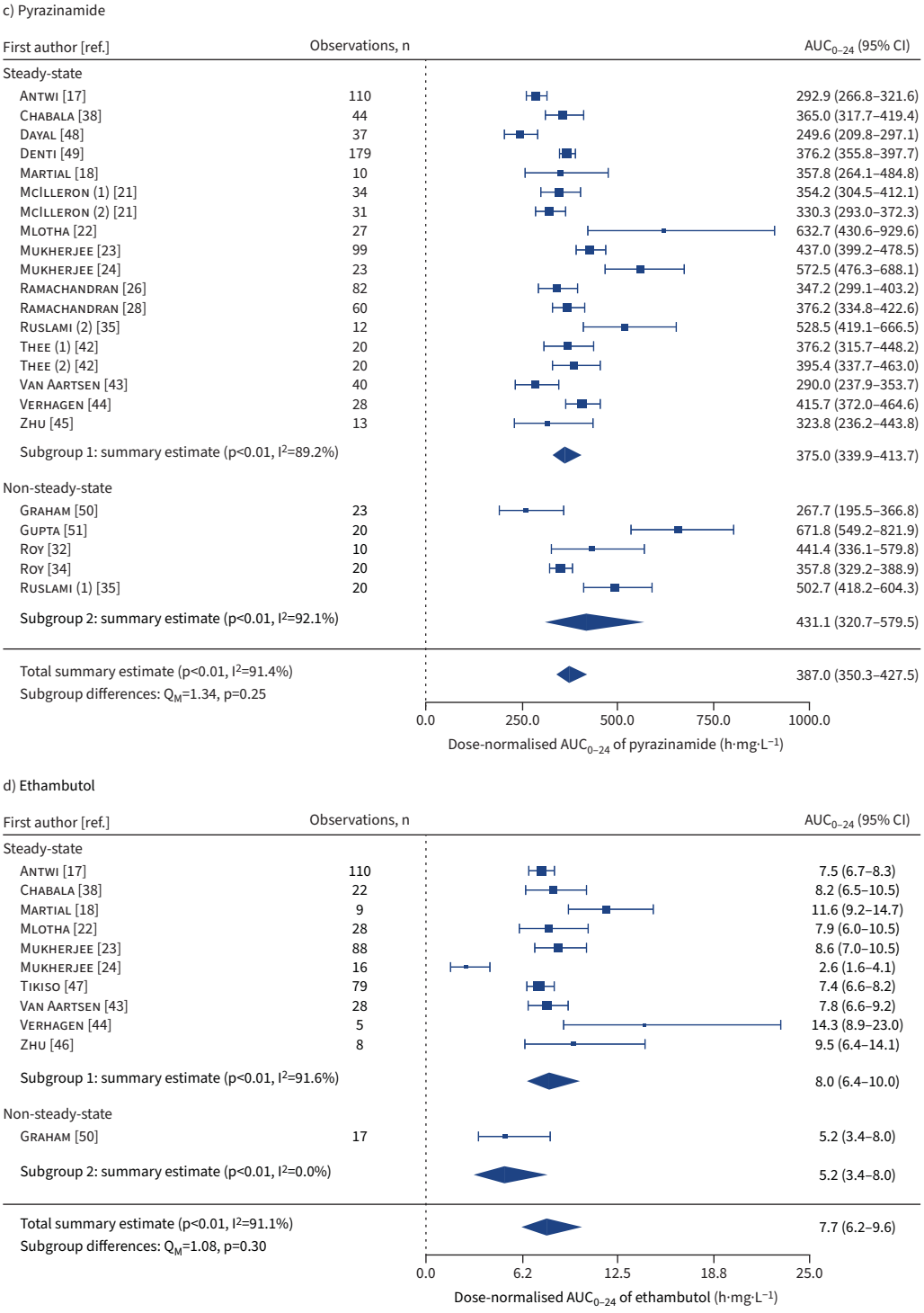
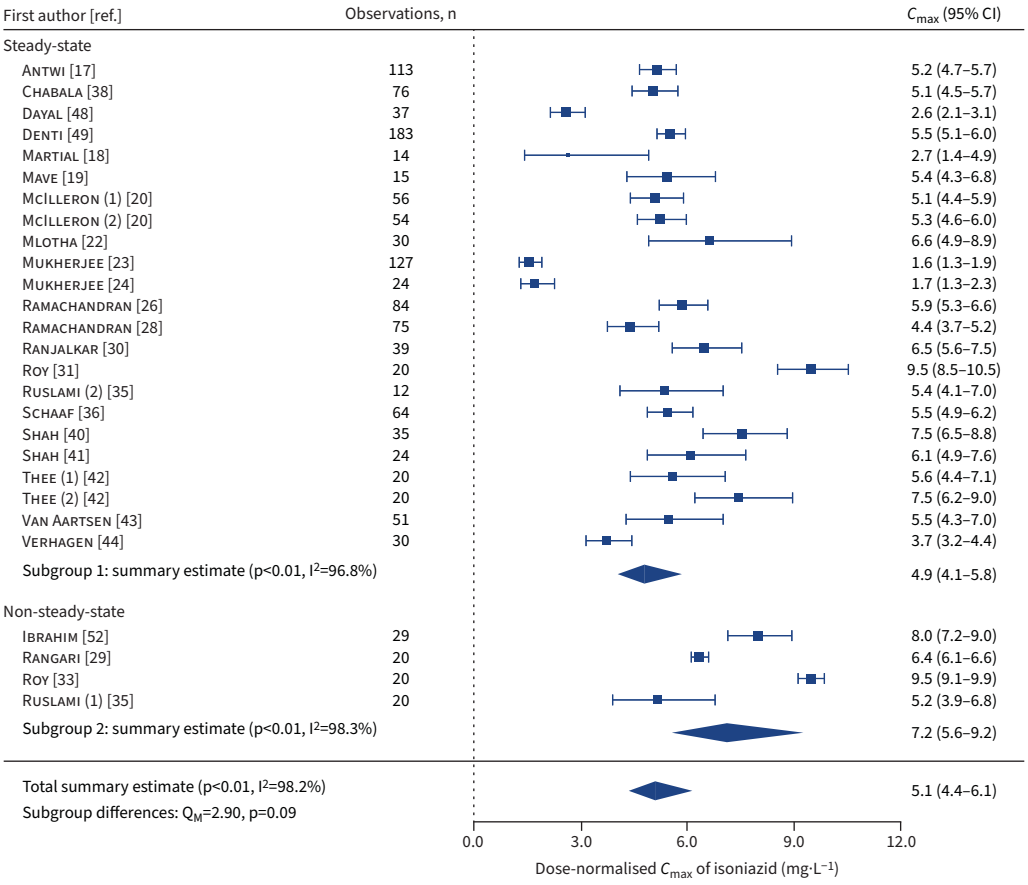
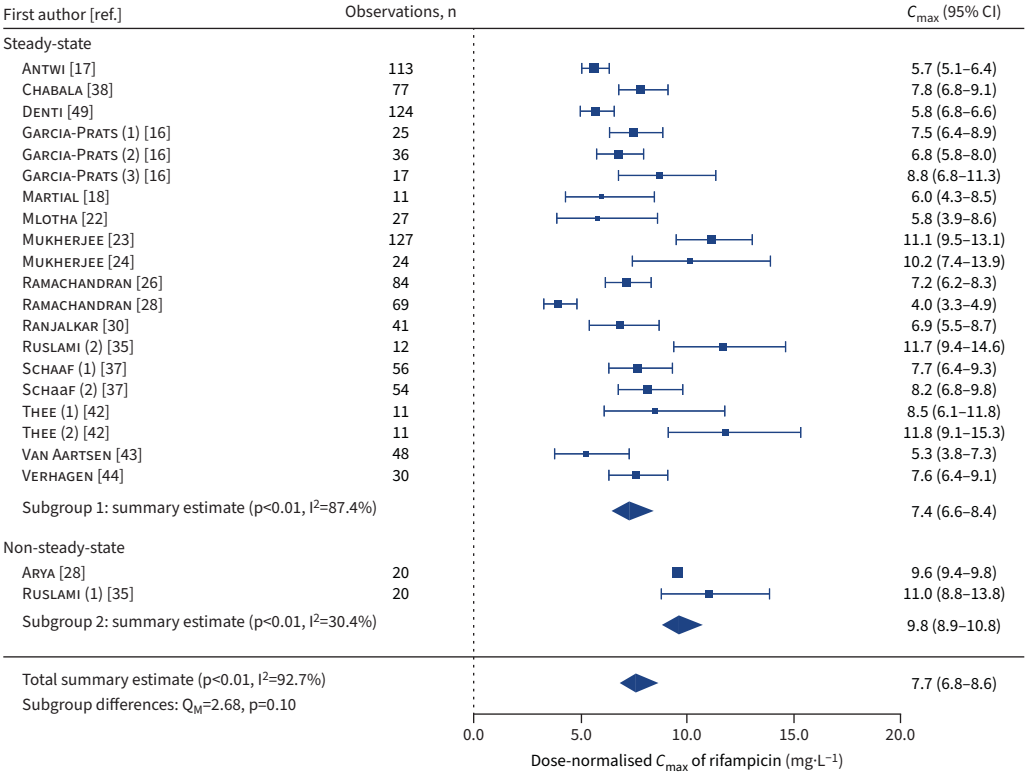


FIGURE 2 Forest plots for summary estimates (geometric mean (95% CI)) of dose-normalised area under the plasma concentration–time curve from 0 to 24 h post-dose (AUC_{0-24}) for a) isoniazid, b) rifampicin, c) pyrazinamide and d) ethambutol in children and adolescents with tuberculosis, by sampling schedules (steady-state and non-steady-state). AUC_{0-24} values were dose-normalised for isoniazid at 10 $mg \cdot kg^{-1}$, rifampicin at 15 $mg \cdot kg^{-1}$, pyrazinamide at 35 $mg \cdot kg^{-1}$ and ethambutol at 20 $mg \cdot kg^{-1}$. The number in round brackets after the author's name indicates the different sampling occasions within a study. I^2: percentage of variation across studies that is due to heterogeneity; Q_M: omnibus test of all model coefficients.

a) Isoniazid



b) Rifampicin



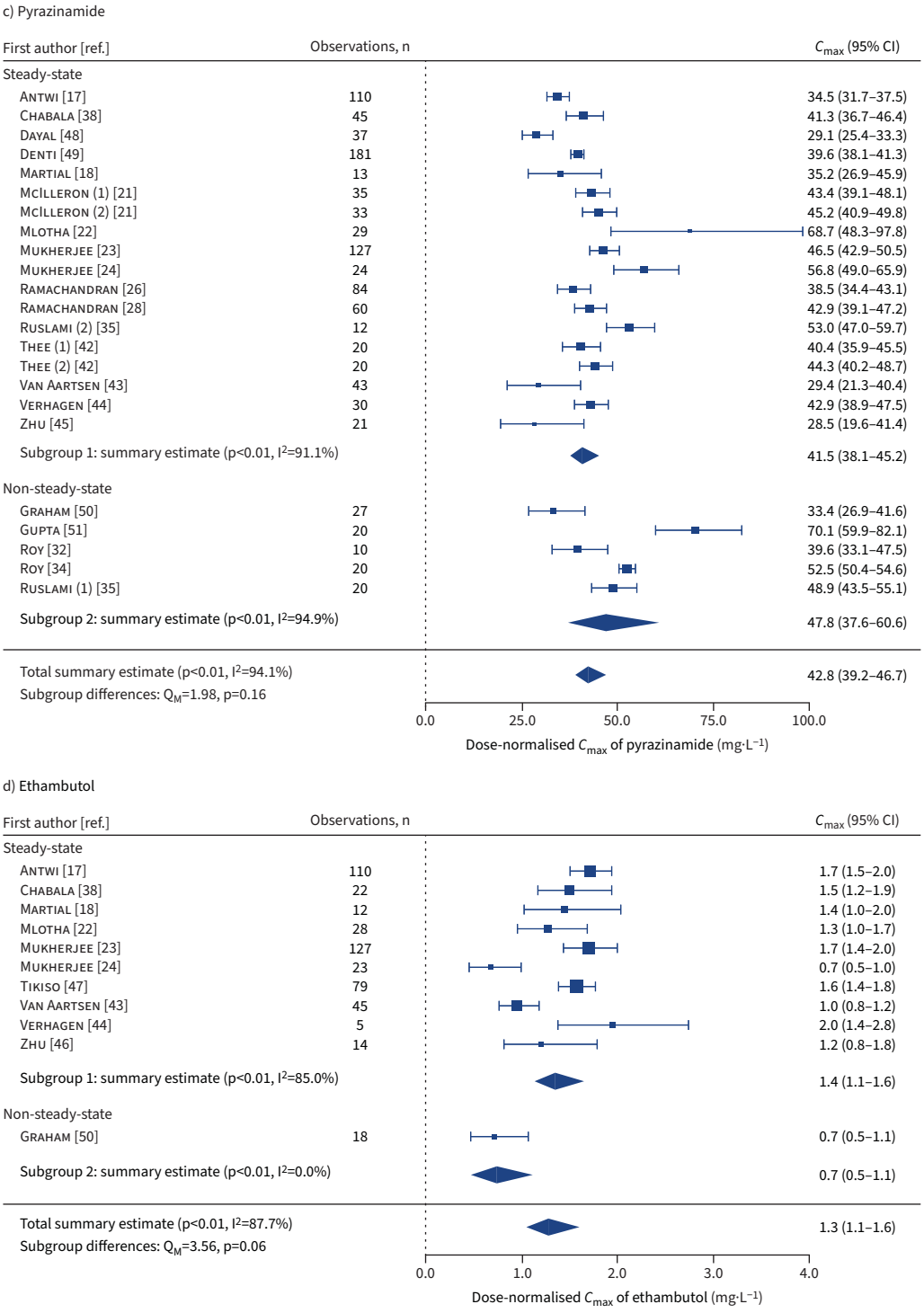


FIGURE 3 Forest plots for summary estimates (geometric mean (95% CI)) of dose-normalised peak plasma concentration (C_{max}) for a) isoniazid, b) rifampicin, c) pyrazinamide and d) ethambutol in children and adolescents with tuberculosis, by sampling schedules (steady-state and non-steady-state). C_{max} values were dose-normalised for isoniazid at 10 mg·kg^{-1}, rifampicin at 15 mg·kg^{-1}, pyrazinamide at 35 mg·kg^{-1} and ethambutol at 20 mg·kg^{-1}. The number in round brackets after the author's name indicates the different sampling occasions within a study. I^2: percentage of variation across studies that is due to heterogeneity; Q_M: omnibus test of all model coefficients.

patients with steady-state concentrations, and in other study-level groups (table 2, and supplementary figures E1 and E2). In multivariate mixed-effects analysis (table 3), lower log $AUC_{0–24}$ values were associated with younger age <2 years (β −0.28 (95% CI −0.40– −0.16)), moderate malnutrition (β −0.10 (95% CI −0.19– −0.01)), severe malnutrition (β −0.15 (95% CI −0.24– −0.06)), HIV-positive status (β −0.15 (95% CI −0.25– −0.04)) and half-life rapid acetylator phenotype (β −0.39 (95% CI −0.50– −0.28)), whereas higher log $AUC_{0–24}$ values were associated with higher $mg \cdot kg^{-1}$ 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 $AUC_{0–24}$ values (β −0.30 (95% CI −0.46– −0.15)), whereas slow acetylators had higher log $AUC_{0–24}$ values (β 0.71 (95% CI 0.58–0.83)) compared with intermediate acetylators (supplementary table E6). Determinants of isoniazid C_{max} were similar to those for $AUC_{0–24}$, except for moderate malnutrition which had no significant effect on C_{max} (table 4).

For rifampicin, dose-normalised estimates were summarised for $AUC_{0–24}$ (geometric mean 34.4 (95% CI 29.4–40.3) $h \cdot mg \cdot L^{-1}$) (figure 2b) and C_{max} (geometric mean 7.4 (95% CI 6.6–8.4) $mg \cdot L^{-1}$) (figure 3b) in patients with steady-state concentrations, and in other study-level groups (table 2, and supplementary figures E3 and E4). In multivariate mixed-effects analysis (table 3), lower log $AUC_{0–24}$ values were associated with younger age, including ages <2 years (β −0.48 (95% CI −0.64– −0.33)) and 2–4 years (β −0.35 (95% CI −0.50– −0.21)). Furthermore, lower log $AUC_{0–24}$ values were associated with HIV-positive status (β −0.25 (95% CI −0.39– −0.11)), whereas higher log $AUC_{0–24}$ values were associated with higher $mg \cdot kg^{-1}$ doses (β 0.65 (95% CI 0.44−0.85)). Determinants of rifampicin C_{max} were similar to those for $AUC_{0–24}$, with addition of severe malnutrition which was associated with lower log C_{max} values (β −0.12 (95% CI −0.24– −0.01)) (table 4).

For pyrazinamide, dose-normalised estimates were summarised for $AUC_{0–24}$ (geometric mean 375.0 (95% CI 339.9–413.7) $h \cdot mg \cdot L^{-1}$) (figure 2c) and C_{max} (geometric mean 41.5 (95% CI 38.1–45.2) $mg \cdot L^{-1}$) (figure 3c) in patients with steady-state concentrations, and in other study-level groups (table 2, and supplementary figures E5 and E6). In multivariate mixed-effects analysis (table 3), lower log $AUC_{0–24}$ values were associated with younger age, including ages <2 years (β −0.28 (95% CI −0.38– −0.17)), 2–4 years (β −0.24 (95% CI −0.34– −0.14)) and 5–9 years (β −0.12 (95% CI −0.21– −0.03)). Furthermore, lower log $AUC_{0–24}$ values were associated with male sex (β −0.08 (95% CI −0.14– −0.02)), severe malnutrition (β −0.08 (95% CI −0.16– −0.005)) and HIV-positive status (β −0.19 (95% CI −0.29– −0.10)), whereas higher log $AUC_{0–24}$ values were associated with higher $mg \cdot kg^{-1}$ doses (β 0.17 (95% CI 0.10–0.23)). Determinants of pyrazinamide C_{max} were similar to those for $AUC_{0–24}$, except for male sex which had no significant effect on C_{max} (table 4).

For ethambutol, dose-normalised estimates were summarised for $AUC_{0–24}$ (geometric mean 8.0 (95% CI 6.4–10.0) $h \cdot mg \cdot L^{-1}$) (figure 2d) and C_{max} (geometric mean 1.4 (95% CI 1.1–1.6) $mg \cdot L^{-1}$) (figure 3d) in patients with steady-state concentrations, and in other study-level groups (table 2, and supplementary figures E7 and E8). In multivariate mixed-effects analysis (table 3), lower log $AUC_{0–24}$ values were associated with younger age, including ages <2 years (β −0.55 (95% CI −0.76– −0.33)), 2–4 years (β −0.35 (95% CI −0.55– −0.14)) and 5–9 years (β −0.19 (95% CI −0.37– −0.001)). Furthermore, lower log $AUC_{0–24}$ values were associated with HIV-positive status (β −0.39 (95% CI −0.56– −0.21)), whereas higher log $AUC_{0–24}$ values were associated with higher $mg \cdot kg^{-1}$ doses (β 0.15 (95% CI 0.05–0.24)). Determinants of ethambutol C_{max} were similar to those for $AUC_{0–24}$, 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 $AUC_{0–24}$ values, including severe stunting (*i.e.* height-for-age z-score < −3) for isoniazid (β −0.13 (95% CI −0.24– −0.02)), rifampicin (β −0.13 (95% CI −0.25– −0.01)), pyrazinamide (β −0.16 (95% CI −0.24– −0.07)) and ethambutol (β −0.19 (95% CI −0.37– −0.02)); moderate stunting (*i.e.* height-for-age z-score ⩾ −3 but < −2) for pyrazinamide (β −0.09 (95% CI −0.17– −0.02)); severe underweight (*i.e.* weight-for-age z-score < −3) for pyrazinamide (β −0.10 (95% CI −0.19– −0.01)); and *SLCO1B1* (rs4149032) TT genotype for rifampicin (β −0.34 (95% CI −0.61– −0.08)). Detailed results of the dose-adjusted analyses for $AUC_{0–24}$ and C_{max} are presented in supplementary 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 (supplementary tables E15 and E16), patients with steady-state concentrations (supplementary tables E19 and E20), patients with steady-state concentrations and daily dosing (supplementary tables E21 and E22), and considering WHO region as a third-level clustering variable (supplementary tables E23 and E24). Additionally, the adult doses recommended for children weighing ⩾25 kg were associated with lower log $AUC_{0–24}$ values for isoniazid (4–6 $mg \cdot kg^{-1}$; β −1.01

TABLE 2 Summary estimates of dose-normalised area under the plasma concentration–time curve from 0 to 24 h post-dose (AUC_{0-24}) and peak plasma concentration (C_{max}) values for first-line antituberculosis drugs in children and adolescents with tuberculosis, by dosing intervals, sampling schedules and World Health Organization regions

	Dose-normalised AUC_{0-24} [#,¶]		Dose-normalised C_{max} [#,¶]	
	Summary geometric mean, $h \cdot mg \cdot L^{-1}$ (95% CI)	Heterogeneity I^2, %	Summary geometric mean, $mg \cdot L^{-1}$ (95% CI)	Heterogeneity I^2, %
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-state	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-state	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-state	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-state	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

[#]: AUC_{0-24} and C_{max} values were dose-normalised for isoniazid at 10 $mg \cdot kg^{-1}$, rifampicin at 15 $mg \cdot kg^{-1}$, pyrazinamide at 35 $mg \cdot kg^{-1}$ and ethambutol at 20 $mg \cdot kg^{-1}$; [¶]: forest plots for summary estimates of dose-normalised AUC_{0-24} and C_{max} for isoniazid, rifampicin, pyrazinamide and ethambutol are presented in supplementary figures E1–E8.

TABLE 3 Multivariate linear mixed-effects regression analyses of determinants affecting log-transformed area under the plasma concentration–time curve from 0 to 24 h post-dose (AUC_{0-24}) values for first-line antituberculosis drugs in children and adolescents

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage 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^{-1}[¶]	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[§]	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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[f]								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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)						
Intermediate	Reference	Reference						
Rapid	−0.39 (−0.50– −0.28)***	−32 (−40– −24)						
Unknown	0.44 (0.25–0.63)***	55 (29–88)						

Continued

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TABLE 3 Continued

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]
Random effects								
σ^2 (mean±SD)	0.35±0.59		0.47±0.68		0.21±0.46		0.44±0.66	
$\tau_{00\ studies}$ (mean±SD)	0.12±0.35		0.11±0.32		0.04±0.21		0.08±0.27	
$\tau_{11\ studies\times doses}$ (mean±SD)	0.03±0.16		0.12±0.34		0.01±0.10			
$\rho_{01\ studies}$	−0.74		−0.25		−0.15			
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	

β: fixed-effects regression coefficient; $t_{1/2}$: elimination half-life; σ^2: residual variance; τ_{00}: random intercept variance; τ_{11}: random slope variance; ρ_{01}: random slope–intercept correlation, ICC: interclass correlation estimate; $N_{studies}$: number of included studies (studies or study occasions); conditional R^2: proportion of variance explained by both the fixed and random effects. [#]: percentage change was calculated as: $(e^{\beta}-1)\times100\%$; [¶]: dose was mean-centred by subtracting the mean from each data point, then standardised 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 $mg\cdot kg^{-1}$, 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; [f]: 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 < −2 in 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 ($t_{1/2}$ <1.25 h), intermediate ($t_{1/2}$ 1.25–2 h) and slow ($t_{1/2}$ >2 h). ***: p<0.001; **: p<0.01; *: p<0.05; [‡]: p<0.1.

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TABLE 4 Multivariate linear mixed-effects regression analyses of determinants affecting log-transformed peak plasma concentration (C_{max}) values for first-line antituberculosis drugs in children and adolescents

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage 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^{-1}[¶]	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[§]	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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[ƒ]								
No	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
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)						
Intermediate	Reference	Reference						
Rapid	−0.13 (−0.25– −0.02)*	−12 (−22– −2)						
Unknown	−0.38 (−0.53– −0.23)***	−31 (−40– −20)						

Continued

TABLE 4 Continued

	Isoniazid		Rifampicin		Pyrazinamide		Ethambutol	
	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]	β (95% CI)	Percentage change, % (95% CI)[#]
Random effects								
σ^2 (mean±SD)	0.35±0.59		0.49±0.73		0.19±0.43		0.53±0.73	
$\tau_{00\ studies}$ (mean±SD)	0.13±0.35		0.11±0.36		0.03±0.19		0.06±0.24	
$\tau_{11\ studies\times doses}$ (mean±SD)	0.05±0.22		0.10±0.25		0.01±0.09			
$\rho_{01\ studies}$	−0.33		0.02		−0.15			
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	

β: fixed-effects regression coefficient; $t_{1/2}$: elimination half-life; σ^2: residual variance; τ_{00}: random intercept variance; τ_{11}: random slope variance; ρ_{01}: random slope–intercept correlation, ICC: interclass correlation estimate; $N_{studies}$: number of included studies (studies or study occasions); conditional R^2: proportion of variance explained by both the fixed and random effects. [#]: percentage change was calculated as: $(e^{\beta}-1)\times 100\%$; [¶]: dose was mean-centred by subtracting the mean from each data point, then standardised 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 $mg\cdot kg^{-1}$, 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; [ƒ]: 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 < −2 in 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 ($t_{1/2}$ <1.25 h), intermediate ($t_{1/2}$ 1.25–2 h) and slow ($t_{1/2}$ >2 h). ***: p<0.001; **: p<0.01; *: p<0.05; [‡]: p<0.1.

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(95% CI −1.27– −0.76)) and rifampicin (8–10 mg·kg^{-1}; β −0.35 (95% CI −0.63– −0.07)) compared with paediatric doses (supplementary tables E25 and E26). Additional pharmacokinetic estimates for time to C_{max}, elimination half-life and elimination rate constant are presented in supplementary table E27.

Discussion

In this individual patient data meta-analysis, we summarised 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) *versus* median range 11.6–26.3 h·mg·L^{-1}) [55], pyrazinamide (geometric mean 375.0 (95% CI 339.9–413.7) *versus* median range 233–429 h·mg·L^{-1}) [55] and rifampicin (geometric mean 34.4 (95% CI 29.4–40.3) *versus* mean 38.7 (95% CI 34.4–43.0) h·mg·L^{-1}) [56], but were lower for ethambutol (geometric mean 8.0 (95% CI 6.4–10.0) *versus* median range 16–28 h·mg·L^{-1}) [55], regardless of significant methodological heterogeneities among studies included in two systematic reviews assessing these estimates for adult TB patients [55, 56]. Ideally, target $AUC_{0–24}$ 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 $AUC_{0–24}$ and C_{max} values based on pharmacokinetic/pharmacodynamic analyses. Until these pharmacokinetic/pharmacodynamic targets are available, our summary $AUC_{0–24}$ 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 <15 years of age have high TB treatment success rates (88–96%) [1, 57, 58], although among those with severe disease like TB meningitis, mortality rates are high (10–30%) [59–61]. 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 pharmacokinetic data in large outcome studies [14, 62].

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 results in reduced exposures in smaller children when dosed at the same mg·kg^{-1} as bigger children and adolescents [63]. Additionally, these could be due to lower bioavailability of isoniazid and rifampicin in children <2–3 years of age [49]. 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 [25, 35]. Higher rifampicin doses can be considered for paediatric TB meningitis [64], and for paediatric TB in general [16], with good safety profiles [16]. However, higher ethambutol doses may increase the risk of ocular toxicity [65], 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 [38]. Further investigation on paediatric formulation and revision of weight bands are needed to optimise dosing of first-line anti-TB drugs [49], 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 recently 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 [55, 66]. The impact of HIV on reducing exposures to first-line anti-TB drugs has been hypothesised to be due to malabsorption of the drugs in patients with advanced HIV co-infection [67]. 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 [68], 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 [69]. 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 [43]. Taken together, we suspect various degrees and predispositions to malnutrition may have different impacts on physiological alterations that affect anti-TB drug pharmacokinetics [70].

The potential benefits of *NAT2* genotype-guided isoniazid dosing in reducing toxicity and treatment failure have been reported in adult patients [71]. 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 [72]. 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, 49]. *SLCO1B1* polymorphisms associated with lower rifampicin exposures have been reported to be more common in African adult patients [73] 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 4 months of anti-TB treatment with a rifapentine-based regimen containing moxifloxacin in adults with pulmonary TB [74], and with a standard first-line anti-TB drug regimen in children with non-severe TB [58], were non-inferior to the standard 6-month regimen and showed excellent treatment outcomes. High-yield opportunities for stratified and personalised medicine approaches, including differential dosing for key subpopulations, should be explored as potential alternatives to the traditional one-size-fits-all strategy [75]. 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 [62]. 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, 62, 76].

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-normalised exposures for high-dose rifampicin >35 $mg \cdot kg^{-1}$ were not estimated due to saturation of hepatic clearance (4% of all observations) [16], the effect on standard doses cannot be ruled out [49] 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 from three published studies [25, 39, 53] and one unpublished study (Mlotha-Mitole *et al.*, Blantyre, Malawi). Further studies using pharmacokinetic/pharmacodynamic modelling and Monte Carlo simulations are needed to better characterise 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 ~10–20% of the total drug concentration can freely penetrate to the site of infection [68, 77]. 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 [78]. 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 generalised 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 summarised 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 standardised treatment approaches in previous reports, certain subgroups at risk of suboptimal drug exposures, especially children <2 years of age and those with severe malnutrition or HIV, may require population-specific dose adjustment or individualised therapeutic drug monitoring. Designing more optimal dosing strategies using pharmacokinetic/pharmacodynamic modelling and simulations is warranted in these vulnerable groups. This is important for policymakers and TB programmes to ensure the best treatment outcome in children and adolescents with TB.

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