Online data supplement

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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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%)		

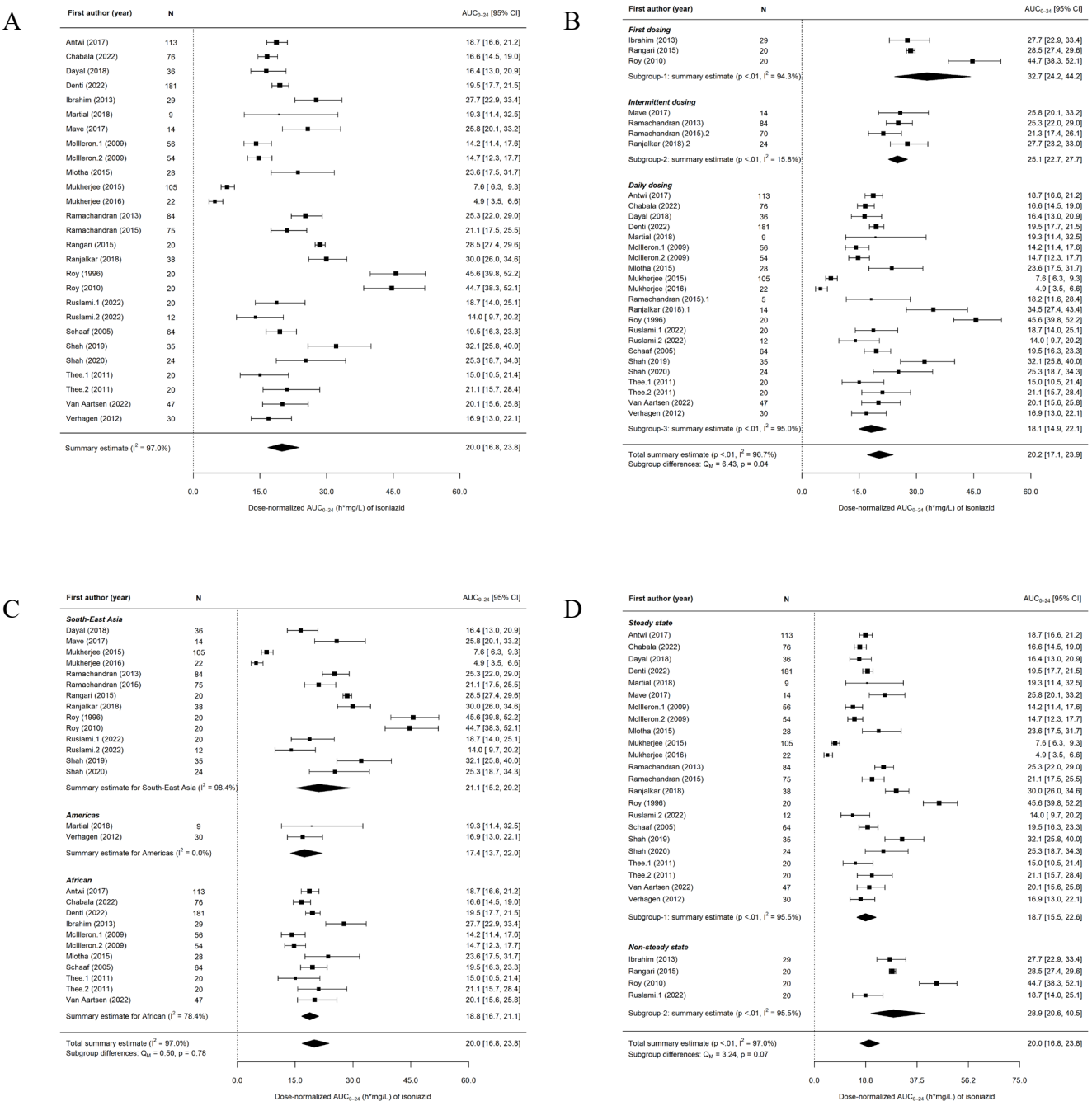

Figure E1. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized AUC_{0-24} for isoniazid in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

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

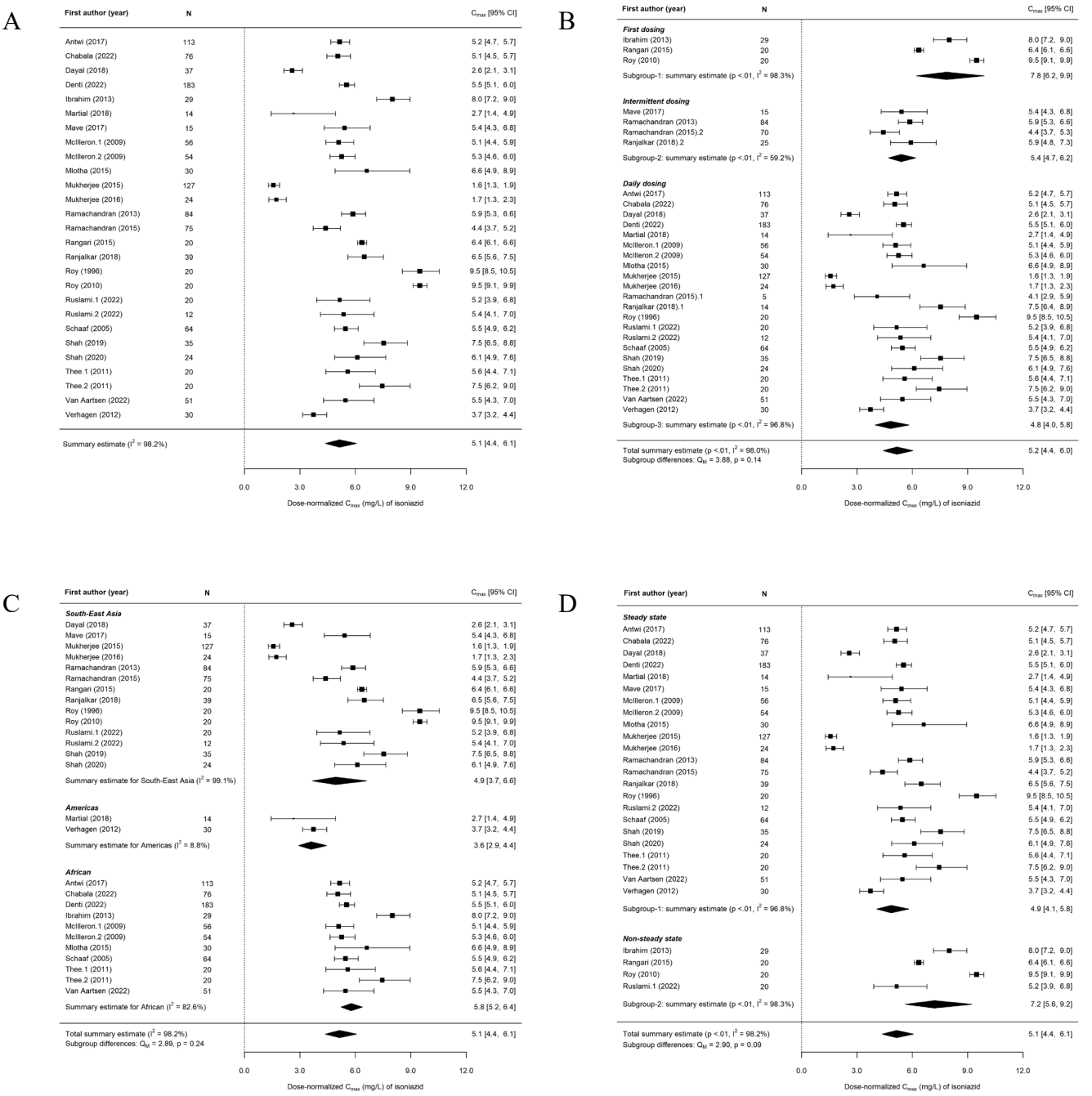

Figure E2. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for isoniazid in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

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.

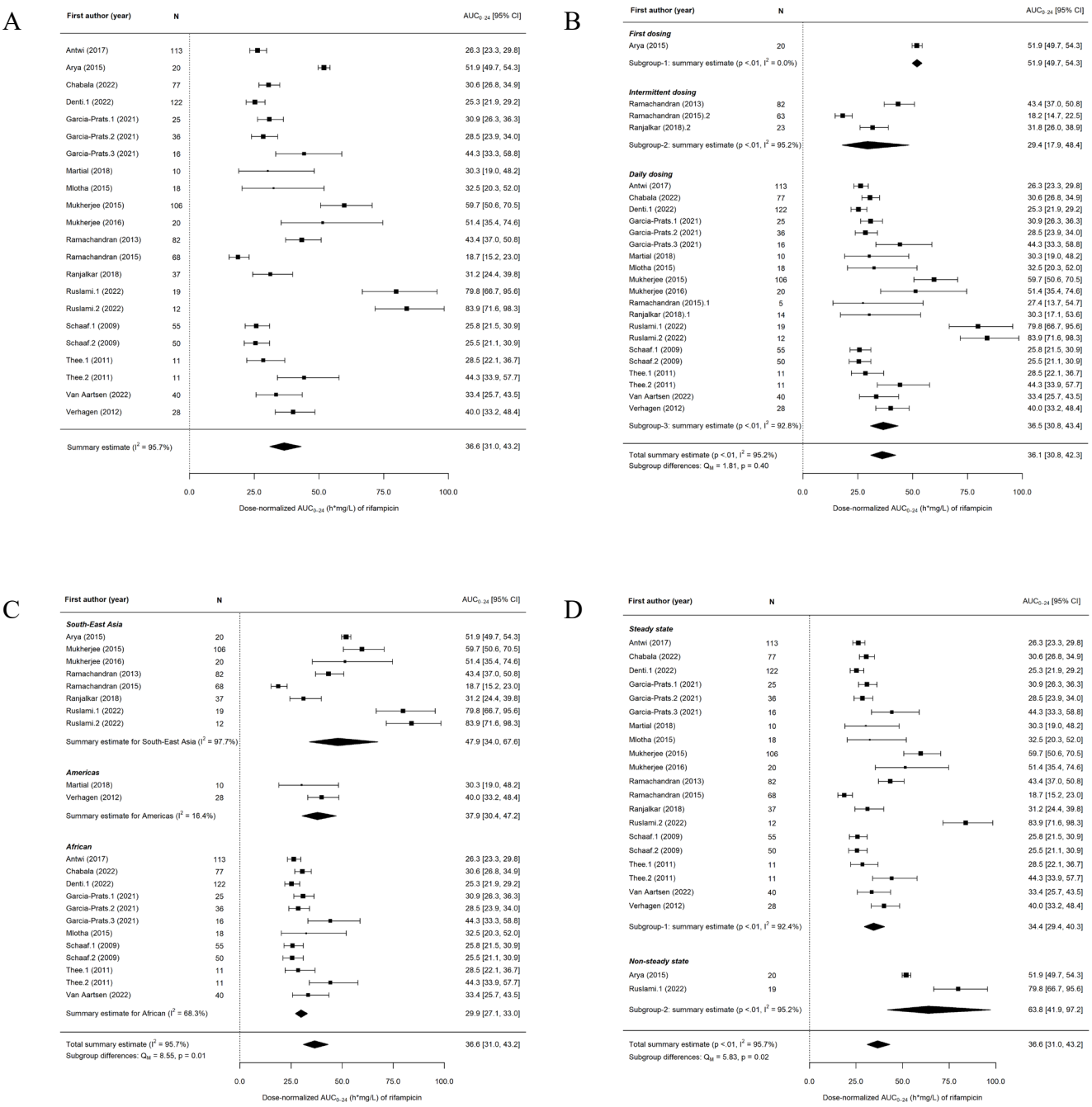

Figure E3. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for rifampicin in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: 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.

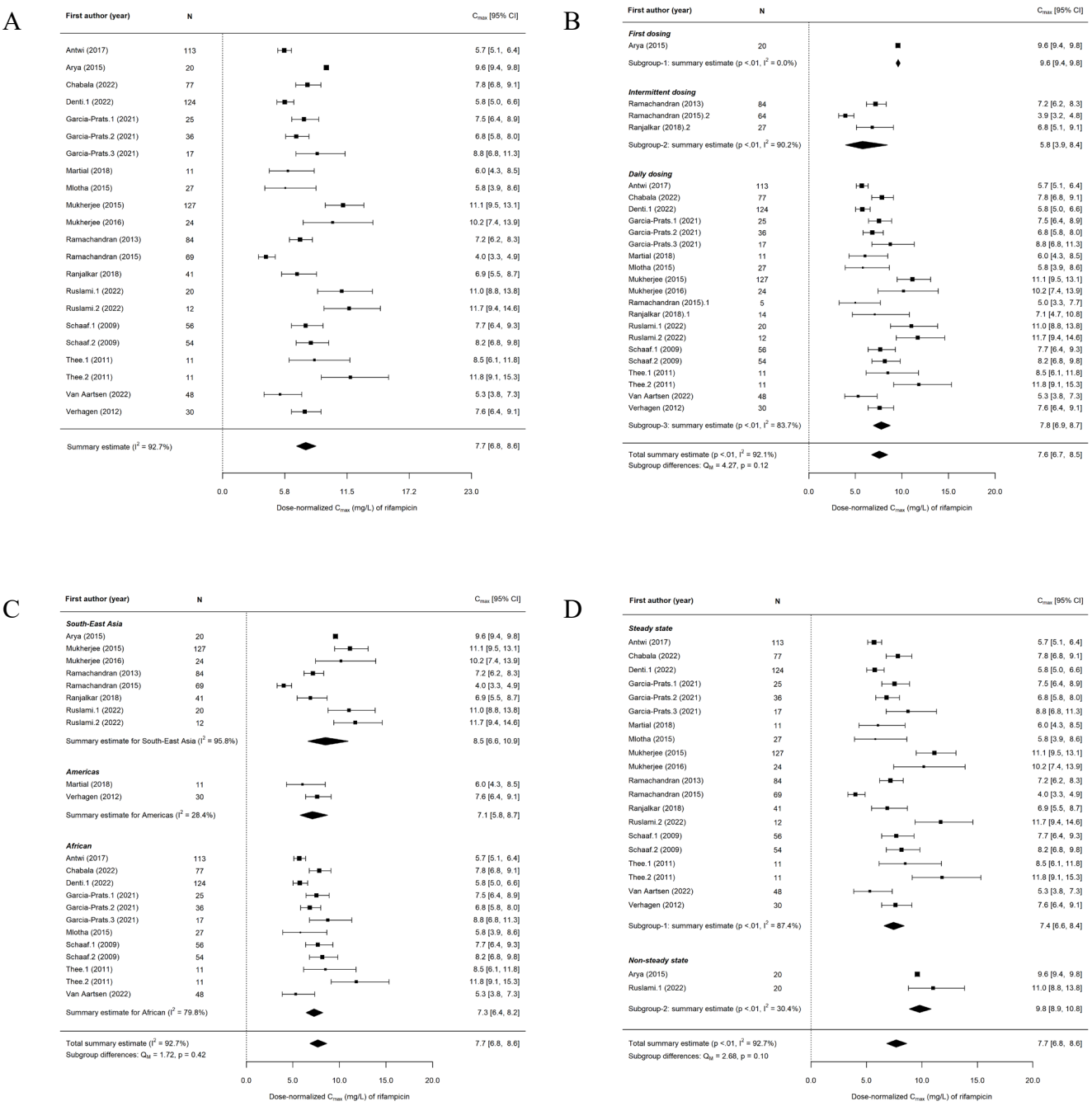

Figure E4. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for rifampicin in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

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.

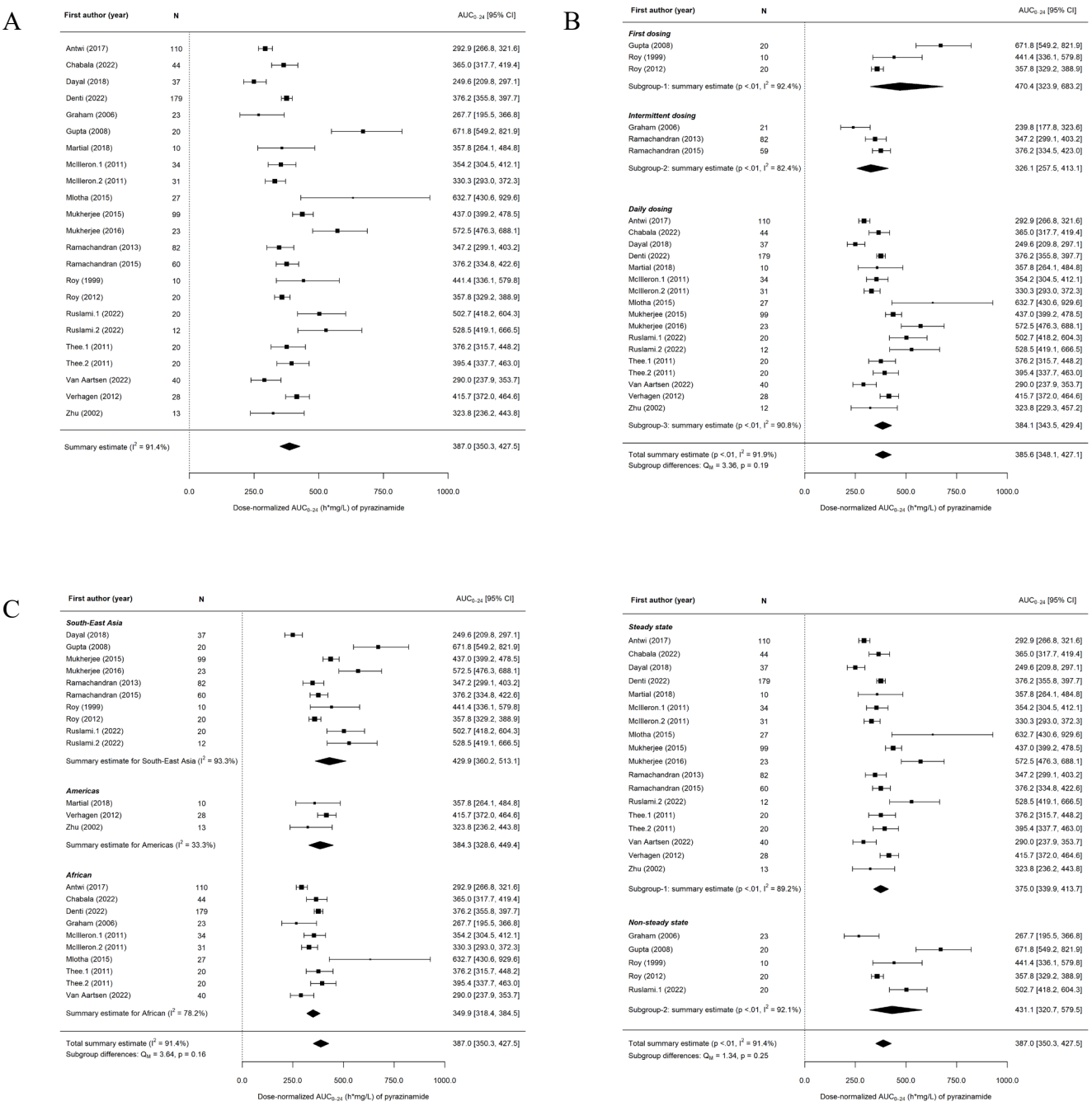

Figure E5. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for pyrazinamide in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: 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.

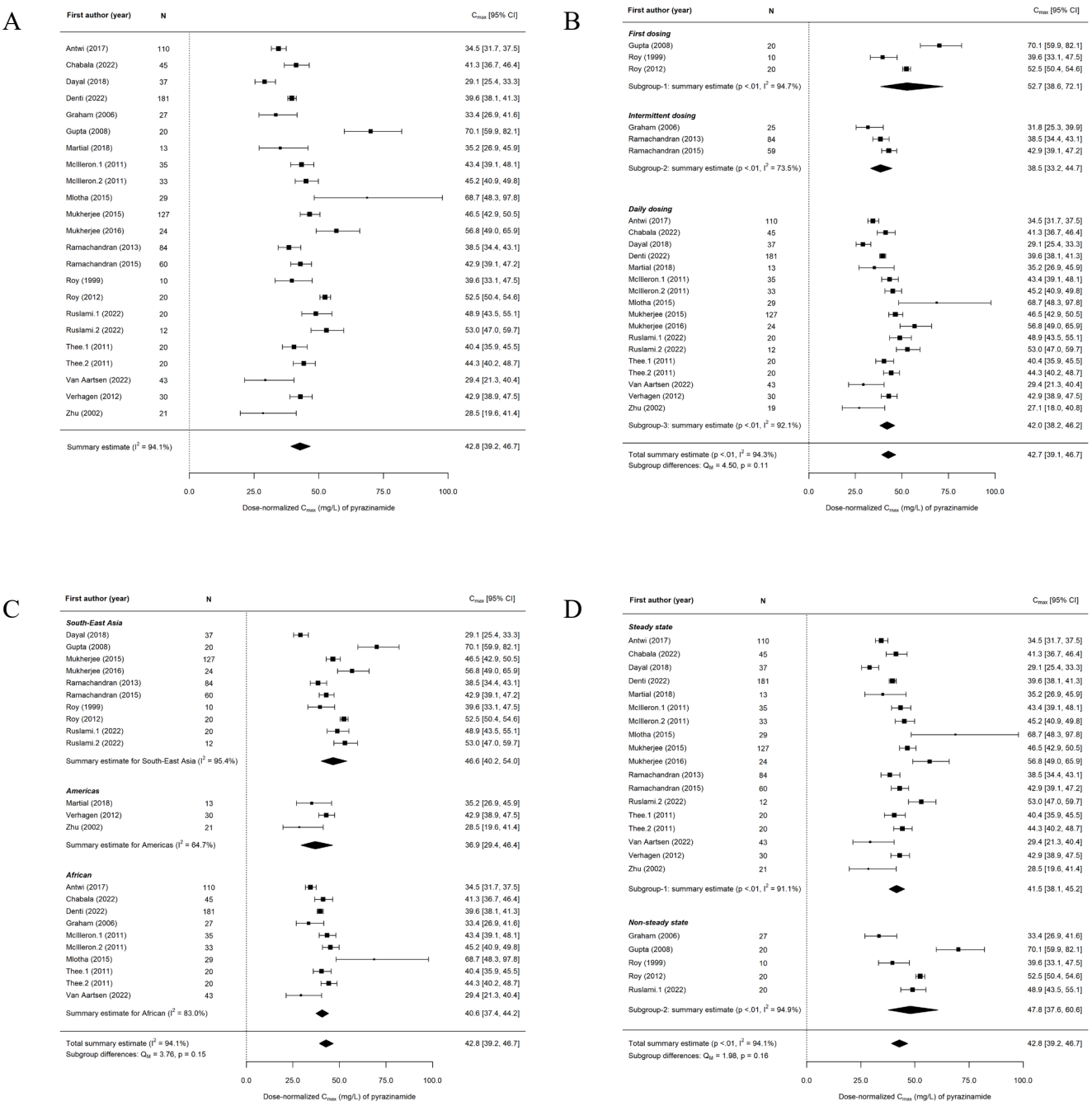

Figure E6. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for pyrazinamide in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

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.

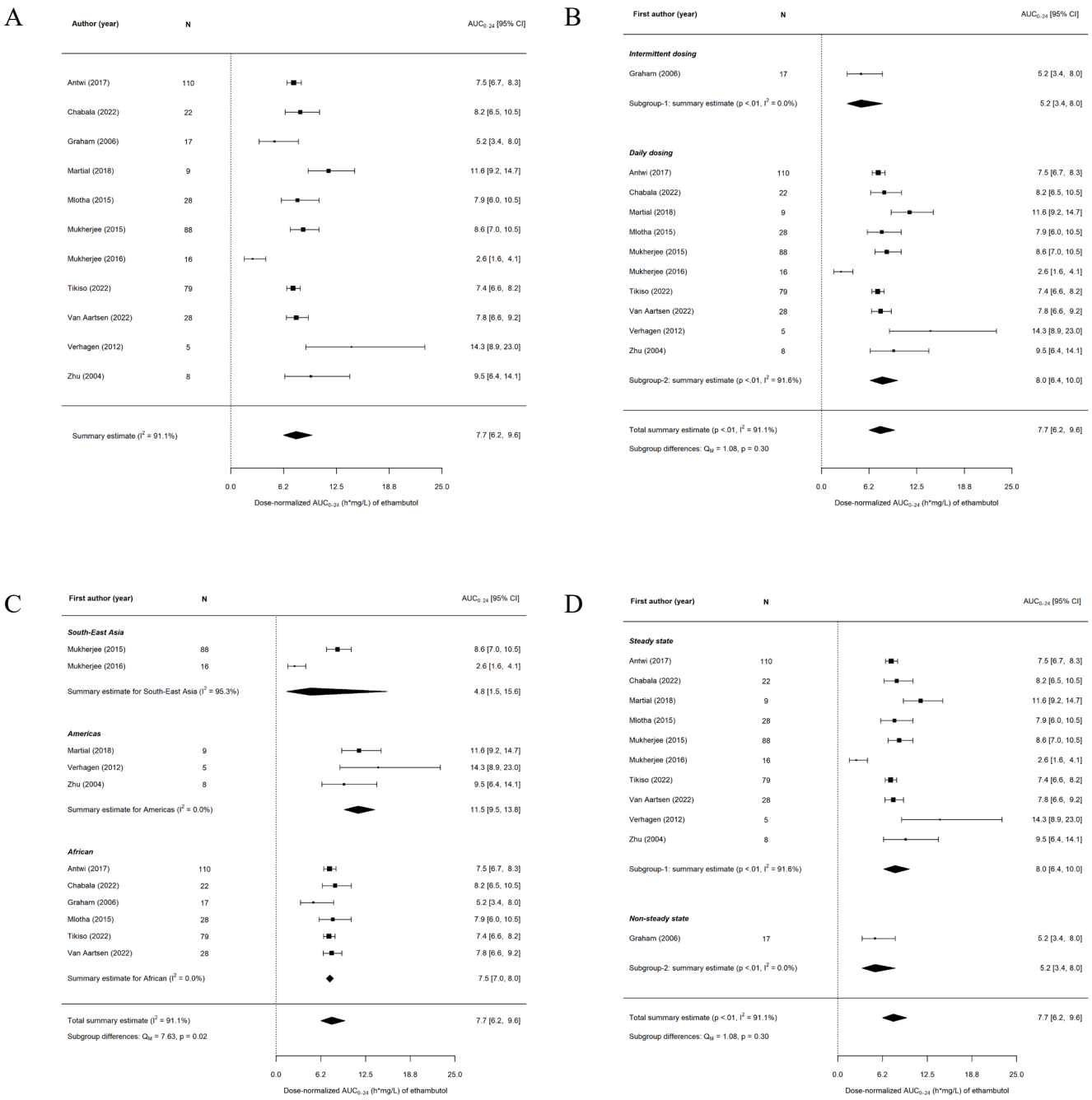

Figure E7. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized $AUC_{0\text{-}24}$ for ethambutol in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

$AUC_{0\text{-}24}$: 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.

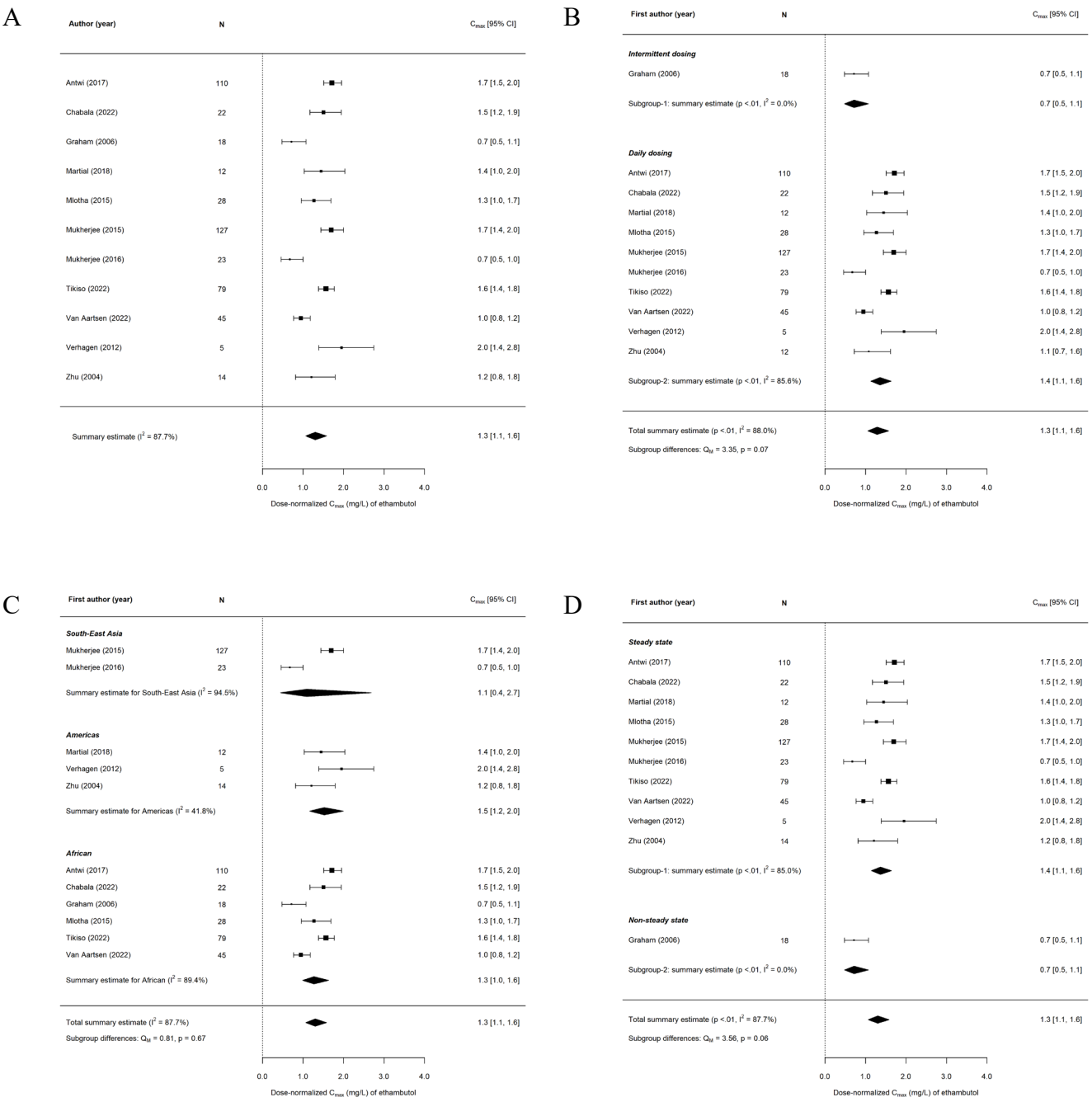

Figure E8. Forest plots for summary estimates (geometric means [95% CIs]) of dose-normalized C_{max} for ethambutol in all children and adolescents with tuberculosis (A), stratified by dosing intervals (B), World Health Organization Regions (C), and pharmacokinetic sampling schedules (D).

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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