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

Fajri Gafar,[1,*] Roeland E. Wasmann,[2] Helen M. McIlleron,[2,3] Rob E. Aarnoutse,[4] H. Simon Schaaf,[5] Ben J. Marais,[6,7] Dipti Agarwal,[8] Sampson Antwi,[9,10] Nguyen D. Bang,[11] Adrie Bekker,[5] David J. Bell,[12] Chishala Chabala,[2,13,14] Louise Choo,[15] Geraint R. Davies,[16,17] Jeremy N. Day,[18,19] Rajeshwar Dayal,[20] Paolo Denti,[2] Peter R. Donald,[5] Ephrem Engidawork,[21] Anthony J. Garcia-Prats,[5,22] Diana Gibb,[15] Stephen M. Graham,[23,24] Anneke C. Hesseling,[5] Scott K. Heysell,[25] Misgana I. Idris,[26] Sushil K. Kabra,[27] Aarti Kinikar,[28] Agibothu K. Hemanth Kumar,[29] Awewura Kwara,[30] Rakesh Lodha,[27] Cecile Magis-Escurra,[31] Nilza Martinez,[32] Binu S. Mathew,[33] Vidya Mave,[28,34] Estomih Mduma,[35] Rachel Mlotha-Mitole,[36] Stellah G. Mpagama,[37] Aparna Mukherjee,[27] Heda M. Nataprawira,[38] Charles A. Peloquin,[39] Thomas Pouplin,[40] Geetha Ramachandran,[29] Jaya Ranjalkar,[33] Vandana Roy,[41] Rovina Ruslami,[42] Ira Shah,[43] Yatish Singh,[20] Marieke G. G. Sturkenboom,[44] Elin M. Svensson,[4,45] Soumya Swaminathan,[29,46] Urmilla Thatte,[47] Stephanie Thee,[48] Tania A. Thomas,[25] Tjokosela Tikiso,[2] Daan J. Touw,[44] Anna Turkova,[15] Thirumurthy Velpandian,[49] Lilly M. Verhagen,[50,51,52] Jana L. Winckler,[5] Hongmei Yang,[53] Vycke Yunivita,[42] Katja Taxis,[1] Jasper Stevens,[44,#] Jan-Willem C. Alffenaar,[7,54,55,#] for the Global Collaborative Group for Meta-Analysis of Paediatric Individual Patient Data in Pharmacokinetics of Anti-TB Drugs.

[#]Both authors contributed equally and shared senior authorship.

1. University of Groningen, Groningen Research Institute of Pharmacy, Unit of PharmacoTherapy, -Epidemiology and -Economics, Groningen, the Netherlands.
2. University of Cape Town, Department of Medicine, Division of Clinical Pharmacology, Cape Town, South Africa.

3. University of Cape Town, Institute of Infectious Disease and Molecular Medicine, Wellcome Centre for Infectious Diseases Research in Africa (CIDRI-Africa), Cape Town, South Africa.
4. Radboud University Medical Center, Radboud Institute of Health Sciences, Department of Pharmacy, Nijmegen, the Netherlands.
5. Stellenbosch University, Faculty of Medicine and Health Sciences, Department of Paediatrics and Child Health, Desmond Tutu Tuberculosis Centre, Tygerberg, South Africa.
6. The Children's Hospital at Westmead, Sydney, NSW, Australia.
7. The University of Sydney, Sydney Institute for Infectious Diseases, Sydney, NSW, Australia.
8. Ram Manohar Lohia Institute of Medical Sciences, Department of Paediatrics, Lucknow, Uttar Pradesh, India.
9. Komfo Anokye Teaching Hospital, Department of Child Health, Kumasi, Ghana.
10. Kwame Nkrumah University of Science and Technology, School of Medical Sciences, Department of Child Health, Kumasi, Ghana.
11. Pham Ngoc Thach Hospital, Ho Chi Minh City, Vietnam.
12. NHS Greater Glasgow and Clyde, Infectious Diseases Unit, United Kingdom.
13. University of Zambia, School of Medicine, Department of Paediatrics, Lusaka, Zambia.
14. University Teaching Hospitals - Children's Hospital, Lusaka, Zambia.
15. University College London, Medical Research Council Clinical Trials Unit, London, United Kingdom.
16. Malawi Liverpool Wellcome Clinical Research Programme, Clinical Department, Blantyre, Malawi.

17. University of Liverpool, Institute of Infection, Veterinary and Ecological Sciences, Liverpool, United Kingdom.
18. Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam
19. University of Oxford, Nuffield Department of Medicine, Centre for Tropical Medicine and Global Health, United Kingdom.
20. Sarojini Naidu Medical College, Department of Pediatrics, Agra, Uttar Pradesh, India.
21. Addis Ababa University, College of Health Sciences, School of Pharmacy, Department of Pharmacology and Clinical Pharmacy, Ethiopia.
22. University of Wisconsin-Madison, School of Medicine and Public Health, Department of Pediatrics, Wisconsin, United States.
23. University of Melbourne, Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia.
24. International Union Against Tuberculosis and Lung Disease, Paris, France.
25. University of Virginia, Division of Infectious Diseases and International Health, Charlottesville, Virginia, United States.
26. University of Alabama at Birmingham, Department of Biology, Birmingham, AL, United States.
27. All India Institute of Medical Sciences, Departments of Pediatrics, New Delhi, India.
28. Byramjee Jeejeebhoy Government Medical College - Johns Hopkins University Clinical Research Site, Pune, India.
29. Indian Council of Medical Research, National Institute for Research in Tuberculosis, Chennai, India.
30. University of Florida, Emerging Pathogens Institute, College of Medicine, Gainesville, United States.
31. Radboud University Medical Center – TB Expert Centre, Nijmegen, the Netherlands.

32. Instituto Nacional de Enfermedades Respiratorias y Del Ambiente, Asunción, Paraguay.
33. Christian Medical College and Hospital, Department of Pharmacology and Clinical Pharmacology, Vellore, Tamil Nadu, India.
34. Johns Hopkins University, Department of Medicine and Infectious Diseases, Baltimore, MD, United States.
35. Haydom Lutheran Hospital, Center for Global Health Research, Haydom, Tanzania.
36. Queen Elizabeth Central Hospital, Department of Paediatrics, Blantyre, Malawi.
37. Kibong'oto Infectious Diseases Hospital, Sanya Juu, Kilimanjaro, Tanzania.
38. Universitas Padjadjaran, Hasan Sadikin Hospital, Faculty of Medicine, Department of Child Health, Division of Paediatric Respirology, Bandung, Indonesia.
39. University of Florida College of Pharmacy, Gainesville, Florida, United States
40. Mahidol University, Faculty of Tropical Medicine, Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand.
41. Maulana Azad Medical College, Department of Pharmacology, New Delhi, India.
42. Universitas Padjadjaran, Faculty of Medicine, Department of Biomedical Sciences, Division of Pharmacology and Therapy, Bandung, Indonesia.
43. Bai Jerbai Wadia Hospital for Children, Department of Pediatric Infectious Diseases, Pediatric TB Clinic, Mumbai, India.
44. University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, the Netherlands.
45. Uppsala University, Department of Pharmacy, Uppsala, Sweden.
46. World Health Organization, Geneva, Public Health Division, Switzerland.
47. Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Department of Clinical Pharmacology, Mumbai, India.

48. Charité-Universitätsmedizin Berlin, coorporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Department of Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Berlin, Germany.

49. All India Institute of Medical Sciences, Ocular Pharmacology and Pharmacy Division, Dr. RP Centre, New Delhi-29, India.

50. Radboud University Medical Center, Radboud Center for Infectious Diseases, Laboratory of Medical Immunology, Section of Pediatric Infectious Diseases, Nijmegen, The Netherlands.

51. Radboud University Medical Center, Amalia Children's Hospital, Department of Paediatric Infectious Diseases and Immunology, Nijmegen, The Netherlands.

52. Stellenbosch University, Family Centre for Research with UBUNTU, Department of Paediatrics and Child Health, Cape Town, South Africa.

53. University of Rochester, School of Medicine and Dentistry, Department of Biostatistics and Computational Biology, Rochester, NY, United States.

54. The University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, NSW, Australia.

55. Westmead Hospital, Sydney, Australia.

*Corresponding author:

Fajri Gafar,

University of Groningen,

Groningen Research Institute of Pharmacy,

Unit of PharmacoTherapy, -Epidemiology and -Economics,

Antonius Deusinglaan 1 (room: 3214.0450),

9713 AV Groningen, The Netherlands,

Tel: +31 50 36 32476,

E-mail: f.gafar@rug.nl; or

fajri.gafar@gmail.com

Running title:

Pharmacokinetics of anti-TB drugs in children and adolescents

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

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

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ABSTRACT

Background

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

Methods

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

Results

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

Conclusion

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

Keywords

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

INTRODUCTION

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

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

To overcome these challenges, we aimed to summarize pharmacokinetic estimates of first-line anti-TB drugs (i.e., isoniazid, rifampicin, pyrazinamide, and ethambutol) in children and adolescents, stratified by study-level characteristics. Furthermore, we aimed to assess patient-level characteristics and key subpopulations in whom pharmacokinetic profiles may differ from the average observed in children with TB. This would identify the potential need for dose

adjustment in particular groups or individuals who are at risk of suboptimal drug exposure using currently WHO-recommended dosing strategies.

METHODS

Search strategy and selection criteria

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

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

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

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

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

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

Data management

Authors of eligible studies were asked to provide anonymized patient-level information on demographics (age, sex, weight, and height), clinical/laboratory characteristics (type of TB, HIV status, serum creatinine and albumin, arylamine N-acetyltransferase 2 [*NAT2*] genotypes, and solute carrier organic anion transporter family member 1B1 [*SLCO1B1*] genotypes),

medication characteristics (drug dose, drug formulation and administration, dosing time, and dosing interval), and pharmacokinetic characteristics (sampling time and observed plasma concentrations) (Appendix 3).

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

Study definitions

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

Data analysis

Our primary pharmacokinetic measures were total/extrapolated area under the plasma concentration-time curve from 0-24 hours post-dose (AUC_{0-24}) and peak plasma concentration

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

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

The effects of patient-level characteristics on log-transformed AUC_{0-24} and C_{max} were assessed with linear mixed-effects analyses using the *lme4* package in R (version 1.1.28), with study-level random effects estimated via restricted maximum likelihood. For these mixed-effects analyses, AUC_{0-24} and C_{max} were not dose-normalized to allow adjustment of the models for drug dose, among other variables. To identify the most relevant variables, base models (adjusted for drug dose only) were developed for each patient characteristic; in each model, observations

missing a certain variable were excluded. Next, we adjusted our multivariate models for drug dose, age, sex, severity of malnutrition, and HIV status, and completed with variables showing a trend toward association ($p<0.1$) in the base models. Variance components of a mixed-effects model were estimated, including residual variance, random intercept variance, random slope variance for drug dose, random slope-intercept correlation, and intraclass correlation coefficient. The final multivariate models were selected based on the highest total explained variance, the lowest Akaike or Bayesian information criterion value, and the largest number of observations included in the models. Fixed-effects regression coefficients (βs) were used to assess the degree of change in log-transformed $AUC_{0\text{-}24}$ and C_{max} for every 1-unit change in the predictor variable. Statistical significance was accepted at $p<0.05$.

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

RESULTS

From the 3620 individual articles identified in our search on February 2, 2021, we read titles and abstracts and subsequently screened the full text of 163 studies, including two full-text studies added through an updated search on December 31, 2021 (Figure 1). This led to the inclusion of 55 eligible studies, and the exclusion of 108 studies of which 21 had identical or overlapping cohorts with eligible studies (Table E1). Individual patient data were provided for 39 (71%) of 55 eligible studies (Table E2) [16–54], of which 26 (67%) were of high quality and 13 (33%) of moderate quality (Table E3). Of the 16 studies for which individual patient data were not provided, 13 (81%) were conducted in/before the 1990s, when most of the investigators no longer had access to the data (Table E4).

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

For isoniazid, dose-normalized estimates were summarized for $AUC_{0\text{-}24}$ (geometric mean: 18.7 [95% CI: 15.5−22.6] h·mg/L; Figure 2A) and C_{max} (geometric mean: 4.9 [95% CI: 4.1−5.8] mg/L; Figure 3A) in patients with steady-state concentrations, and in other study-level groups (Table 2; Figures E1-E2). In multivariate mixed-effects analysis (table 3), lower log-$AUC_{0\text{-}24}$ values were associated with younger age <2 years (fixed-effects coefficient (β): -0.28 [95% CI -0.40 to -0.16]), moderate malnutrition (β: -0.10 [95% CI: -0.19 to -0.01]), severe malnutrition (β: -0.15 [95% CI: -0.24 to -0.06]), HIV-positive status (β: -0.15 [95% CI: -0.25 to -0.04]), and half-life rapid acetylator phenotype (β: -0.39 [95% CI: -0.50 to -0.28]); while higher log-$AUC_{0\text{-}24}$ values were associated with higher mg/kg doses (β: 0.42 [95% CI: 0.34−0.51]), and half-life slow acetylator phenotype (β: 0.70 [95% CI: 0.62−0.77]). Based on *NAT2* genotyping, rapid acetylators had lower log-$AUC_{0\text{-}24}$ values (β: -0.30 [95% CI: -0.46 to -0.15]), whereas slow acetylators had higher log-$AUC_{0\text{-}24}$ values (β: 0.71 [95% CI: 0.58−0.83]) compared with

intermediate acetylators (Table E6). Determinants of isoniazid C_{max} were similar to those for AUC_{0-24}, except for moderate malnutrition which had no significant effect on C_{max} (Table 4).

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

For pyrazinamide, dose-normalized estimates were summarized for AUC_{0-24} (geometric mean: 375.0 [95% CI: 339.9−413.7] h·mg/L; Figure 2C) and C_{max} (geometric mean: 41.5 [95% CI: 38.1−45.2] mg/L; Figure 3C) in patients with steady-state concentrations, and in other study-level groups (Table 2; Figures E5-E6). In multivariate mixed-effects analysis (Table 3), lower log-AUC_{0-24} values were associated with younger age, including ages <2 years (β: -0.28 [95% CI: -0.38 to -0.17]), 2−4 years (β: -0.24 [95% CI: -0.34 to -0.14]), and 5−9 years (β: -0.12 [95% CI: -0.21 to -0.03]). Furthermore, lower log-AUC_{0-24} values were associated with male sex (β: -0.08 [95% CI: -0.14 to -0.02]), severe malnutrition (β: -0.08 [95% CI: -0.16 to -0.005]), and HIV-positive status (β: -0.19 [95% CI: -0.29 to -0.10]); whereas higher log-AUC_{0-24} values were associated with higher mg/kg doses (β: 0.17 [95% CI: 0.10−0.23]). Determinants of

pyrazinamide C_{max} were similar to those for AUC_{0-24}, except for male sex which had no significant effect on C_{max} (Table 4).

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

In dose-adjusted mixed-effects analyses, we identified additional determinants of lower log-AUC_{0-24} values, including severe stunting (i.e., height-for-age Z-score <-3) for isoniazid (β: -0.13 [95% CI: -0.24 to -0.02]), rifampicin (β: -0.13 [95% CI: -0.25 to -0.01]), pyrazinamide (β: -0.16 [95% CI: -0.24 to -0.07]), and ethambutol (β: -0.19 [95% CI: -0.37 to -0.02]); moderate stunting (i.e., height-for-age Z-score ≥-3 but <-2) for pyrazinamide (β: -0.09 [95% CI: -0.17 to -0.02]); severe underweight (i.e., weight-for-age Z-score <-3) for pyrazinamide (β: -0.10 [95% CI: -0.19 to -0.01]); and *SLCO1B1* (rs4149032) TT genotype for rifampicin (β: -0.34 [95% CI: -0.61 to -0.08]). Detailed results of the dose-adjusted analyses for AUC_{0-24} and C_{max} are presented in Tables E7-E14.

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

DISCUSSION

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

Compared with adult data, our summary estimates for steady-state AUC_{0-24} were comparable for isoniazid (geometric mean: 18.7 [95% CI: 15.5−22.6] *vs* median range: 11.6−26.3 h·mg/L) [56], pyrazinamide (geometric mean: 375.0 [95% CI: 339.9−413.7] *vs* median range: 233−429 h·mg/L) [56], and rifampicin (geometric mean: 34.4 [95% CI: 29.4−40.3] *vs* mean: 38.7 [95% CI: 34.4−43.0] h·mg/L) [57], but were lower for ethambutol (geometric mean: 8.0 [95% CI: 6.4−10.0] *vs* median range 16−28 h·mg/L) [56], regardless of significant methodological heterogeneities among studies included in two systematic reviews assessing these estimates for adult patients [56, 57]. Ideally, target AUC_{0-24} and C_{max} values are established based on pharmacokinetic/pharmacodynamic knowledge, taking drug efficacy, safety and tolerability

into account [14]. However, unlike pharmacokinetic studies in adults, most paediatric studies lack data on clinical and bacteriological responses to TB treatment, probably due to the paucibacillary disease and the difficulty in obtaining microbiological specimens. This has resulted in a significant challenge in establishing target AUC_{0-24} and C_{max} values based on pharmacokinetic/pharmacodynamic analyses. Until these pharmacokinetic/pharmacodynamic targets are available, our summary AUC_{0-24} and C_{max} estimates can serve as real-life reference values for clinicians and researchers working on dosing of first-line anti-TB drugs in children and adolescents.

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

Young children are most vulnerable to severe forms of disease, including miliary TB and TB meningitis. Lower drug exposures in young children, especially those <2 years of age, are likely attributed to the non-linear effect of weight on clearance due to allometric scaling, which result in reduced exposures in smaller children when dosed at the same mg/kg as bigger children and adolescents [64]. Additionally, these could be due to lower bioavailability of isoniazid and rifampicin in children <2-3 years of age [50]. For TB meningitis, these low plasma exposures could lead to extremely low exposures at the site of infection in the meninges, especially for

rifampicin and ethambutol which have poor cerebrospinal fluid penetration [26, 36]. Higher rifampicin doses can be considered for paediatric TB meningitis [65], and for paediatric TB in general [16], with good safety profiles [16]. However, higher ethambutol doses may increase the risk of ocular toxicity [66], highlighting the importance of exploring substitutes for ethambutol such as ethionamide or fluoroquinolones (e.g., levofloxacin).

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

Different levels of low exposures to first-line anti-TB drugs in children and adults living with HIV have been reported in two systematic reviews, but the estimates were not adjusted for confounders, and consistent results could not be obtained due to methodological and statistical heterogeneities among the included studies [56, 67]. The impact of HIV on reducing exposures to first-line anti-TB drugs has been hypothesized to be due to malabsorption of the drugs in patients with advanced HIV coinfection [68]. However, as antiretroviral data were unavailable in our dataset, further research is needed to assess the potential impact of antiretroviral therapy on anti-TB drug pharmacokinetics in children and adolescents living with HIV.

Severe malnutrition was found to have small but significant negative effects on isoniazid and pyrazinamide exposures. For highly protein-bound rifampicin [69], the protein-unbound fraction may be higher in patients with severe protein-energy malnutrition, which may have

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

The potential benefits of *NAT2* genotype-guided isoniazid dosing in reducing toxicity and treatment failure have been reported in adult patients [72]. In resource-limited settings where genotyping is rarely available, an automated assay on the GeneXpert platform can be used as an alternative option to detect *NAT2* polymorphisms and guide isoniazid dosing [73]. Next, our results showed that *SLCO1B1* polymorphisms had moderate negative effects on rifampicin exposures, although these results were only obtained from two studies among African children [17, 50]. *SLCO1B1* polymorphisms associated with lower rifampicin exposures have been reported to be more common in African adult patients [74], and these might partly explain the lower rifampicin exposures in our patients from African versus non-African regions.

There has been growing interest in the use of shorter TB treatment regimens. Recent clinical trials have shown that four months of anti-TB treatment with a rifapentine-based regimen containing moxifloxacin in adults with pulmonary TB [75], and with a standard first-line anti-TB drug regimen in children with non-severe TB [59], were non-inferior to the standard six-month regimen and showed excellent treatment outcomes. High-yield opportunities for stratified and personalized medicine approaches, including differential dosing for key

subpopulations, should be explored as potential alternatives to the traditional one-size-fits-all strategy [76]. Although programmatic TB treatment may be suitable for most patients, stratification of treatment and a more person-centred approach in certain groups is necessary to ensure high-quality care, such as in patients at risk of suboptimal exposure to anti-TB drugs, patients at risk of developing drug-related toxicity, and patients who could benefit from therapeutic drug monitoring (TDM) [63]. In addition, less invasive TDM methods using saliva, hair, and dried blood spot samples should be explored in further studies to reduce the burden of venous blood sampling in this population [14, 63, 77].

This study has limitations that should be acknowledged. First, summary pharmacokinetic estimates in study-level groups showed high heterogeneities, although we were able to correct these estimates by individual-level covariates and variance components in mixed-effects models. Second, although dose-normalized exposures for high-dose rifampicin >35 mg/kg were not estimated due to saturation of hepatic clearance (4% of all observations) [16], the effect on standard doses cannot be ruled out [50], and therefore the rifampicin estimates should be interpreted carefully. Third, we were unable to reliably assess $AUC_{0\text{-}24}$ and C_{max} on sparse sampling data [23, 26, 40, 54]. Further studies using pharmacokinetic/pharmacodynamic modelling and Monte Carlo simulations are needed to better characterize the relationships of physiologically sensible covariates with pharmacokinetic parameters (e.g., drug clearance and volume of distribution) and to design more optimal dosing strategies [14], by including both intensive and sparse sampling data. In addition, given that only protein-unbound concentrations are generally considered to exhibit pharmacological effects, the inclusion of protein binding parameter in future pharmacokinetic/pharmacodynamic models is important, especially for rifampicin, as only about 10-20% of the total drug concentration can freely penetrate to the site of infection [69, 78]. Fourth, none of the included studies were from European countries, and

there was a lack of data in children aged <3 months and adolescents aged 15−18 years. The latter is likely due to the historically fragmented approach of only classifying persons aged <15 years as children, excluding those aged 15−18 years from both paediatric and adult studies [79]. Despite these limitations, our findings provide the most comprehensive study-level estimates of plasma exposures to first-line anti-TB drugs by including ~30 years of available data worldwide, and therefore the results can be generalized to the global population of children aged >3 months to 14 years. Additionally, our mixed-effects models include a wide range of variables, and our results are consistent in various subgroup analyses.

In conclusion, our individual patient data meta-analysis summarized pharmacokinetic estimates of first-line anti-TB drugs in children and adolescents using a large amount of globally available data. Although children and adolescents with TB generally have good treatment outcomes with standardized treatment approaches in previous reports, certain subgroups at risk of suboptimal drug exposures, especially children under two years of age and those with severe malnutrition or HIV, may require population-specific dose adjustment or individualized TDM. Designing more optimal dosing strategies using pharmacokinetic/pharmacodynamic modeling and simulations is warranted in these vulnerable groups. This is important for policymakers and TB programs to ensure the best treatment outcome in children and adolescents with TB.

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Author contributions:

FG, BW,† and JWCA designed the study and protocol. FG, REW, HMM, REA, HSS, DA, SA, NDB, AB, DJB, CC, LC, GRD, JND, RD, PD, PRD, EE, AJGP, DG, SMG, ACH, SKH, MII, SKK, AK(1), AKHK, AK(2), RL, CME, NM, BSM, VM, EM, RMM, SGM, AM, HMN, CAP, TP, GR, JR, VR, RR, IR, YS, EMS, SS, UT, ST, TAT, TT, AT, TV, LMV, JLW, HY, and VY contributed individual patient data. FG analysed the data and created tables and figures under the supervision of JS and JWCA. FG wrote the initial draft of the manuscript under the supervision of KT, JS and JWCA. REW, HMM, REA, HSS, and BJM were members of the writing committee, and helped revise the drafted version of the manuscript before and after circulation to all co-authors. All authors provided critical input and revisions to manuscript drafts and approved the final version of the manuscript before submission for publication.

Conflict of interest:

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

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

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

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

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

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

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

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

Data are presented as fixed-effects estimates (beta coefficients) and 95% confidence intervals (CI), unless stated otherwise: §mean and standard deviation. AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours after dosing; HIV: human immunodeficiency virus; σ^2: residual variance, τ_{00}: random intercept variance, τ_{11}: random slope variance, ρ_{01}: random slope-intercept correlation, ICC: interclass correlation estimate, N: number of included studies (studies or study occasions), conditional R^2: the proportion of variance explained by both the fixed and random effects. ‡Percentage change was calculated with the following equation: $e^{\text{fixed-effects coefficient}} - 1 \times 100\%$. ¶Dose was mean-centred by subtracting the mean from each data point, then standardized by dividing each point by the standard deviation. †Among children <2 years of age, AUC_{0-24} values were significantly higher in patients aged 3−11 months compared with those aged 12−23 months for pyrazinamide ($p<0.001$), but no significant differences were found for isoniazid, rifampicin, and ethambutol; the results were adjusted for drug dose in mg/kg, sex, nutritional status, and HIV status. ††We used children aged 10−14 years as a reference group, assuming that they were the most adult-like among children under <15 years of age, and also to assess the statistical difference with older adolescents aged 15−18 years. §§Moderate malnutrition was defined as weight-for age or height-for-age Z-score ≥-3 but <-2 in children aged <5 years, and height-for-age or body mass index-for-age Z-score ≥-3 but <-2in children aged ≥5 years; and severe malnutrition was defined as weight-for age or height-for-age Z-score <-3 in children aged <5 years, and height-for-age or body mass index-for-age Z-score <-3 in children aged ≥5 years. ¶¶Acetylator phenotypes of isoniazid were rapid (elimination half-life [$t_{1/2}$] <1.25 h), intermediate (1.25 h ≤ $t_{1/2}$ ≤2 h), and slow ($t_{1/2}$ >2 h). ***p<0.001, **p<0.01, *p<0.05, #p<0.1.

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

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

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

Figure legends

Figure 1. Study selection.

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

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

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

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

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