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Effectiveness and Pharmacokinetic Exposures of First-Line Drugs Used to Treat Drug-Susceptible Tuberculosis in Children: A Systematic Review and Meta-Analysis

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Background. Optimal doses of first-line drugs for treatment of drug-susceptible tuberculosis in children and young adolescents remain uncertain. We aimed to determine whether children treated using World Health Organization–recommended or higher doses of first-line drugs achieve successful outcomes and sufficient pharmacokinetic (PK) exposures.

Methods. Titles, abstracts, and full-text articles were screened. We searched PubMed, EMBASE, CENTRAL, and trial registries from 2010 to 2021. We included studies in children aged <18 years being treated for drug-susceptible tuberculosis with rifampicin (RIF), pyrazinamide, isoniazid, and ethambutol. Outcomes were treatment success rates and drug exposures. The protocol for the systematic review was preregistered in PROSPERO (no. CRD42021274222).

Results. Of 304 studies identified, 46 were eligible for full-text review, and 12 and 18 articles were included for the efficacy and PK analyses, respectively. Of 1830 children included in the efficacy analysis, 82% had favorable outcomes (range, 25%–95%). At World Health Organization–recommended doses, exposures to RIF, pyrazinamide, and ethambutol were lower in children than in adults. Children ≤6 years old have 35% lower areas under the concentration-time curve (AUCs) than older children (mean of 14.4 [95% CI 9.9–18.8] vs 22.0 [13.8–30.1] μg·h/mL) and children with human immunodeficiency virus (HIV) had 35% lower RIF AUCs than HIV-negative children (17.3 [11.4–23.2] vs 26.5 [21.3–31.7] μg·h/mL). Heterogeneity and small sample sizes were major limitations.

Conclusions. There is large variability in outcomes, with an average of 82% favorable outcomes. Drug exposures are lower in children than in adults. Younger children and/or those with HIV are underexposed to RIF. Standardization of PK pediatric studies and individual patient data analysis with safety assessment are needed to inform optimal dosing.

Keywords. effectiveness; pediatric; World Health Organization dosing; drug-sensitive tuberculosis; pharmacokinetics.

In 2020, children <15 years old accounted for 11% of the estimated 10 million cases of tuberculosis (range, 8.9–11.0 million) and 16% of tuberculosis-related deaths (230 000 of 1.4 million) worldwide [1, 2]. Very young children (≤5 years old), children with human immunodeficiency virus (CWHIV), and malnourished children are at high risk of worse treatment outcomes [3]. Optimizing drug exposure for antituberculosis treatment is essential to increasing the likelihood of favorable outcomes [4, 5].

World Health Organization (WHO) recommendations on first-line antituberculosis drugs in children underwent reevaluation in 2014 [6] based on clinical pharmacokinetic (PK)–pharmacodynamic and safety data (Supplementary Material 1). However, the potential of inadequate dosing in children and the relationship with treatment outcomes has not been systematically quantified. Clinical trials in adults with tuberculosis have shown that higher drug exposures lead to improved culture conversion rates, improved efficacy and/or shorter treatment durations, while maintaining an acceptable safety profile [7–10].

A strategy recommended by regulatory bodies (the Food and Drug Administration and the European Medicines Agency) for defining pediatric doses is to use a child-adult exposure-matching approach [11, 12]. To define optimal dosing in children, these need to result in exposures that are similar to that achieved in adults. The main underlying assumption is that

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exposure-response relationships are comparable between adults and children for the same clinical context [12, 13]. If comparable exposures are achieved in children, similar treatment outcomes as in adults are expected, but safety should still be confirmed. However, different manifestations of the disease, ranging severity of tuberculosis by age group or nutritional status, and coinfection with other agents such as human immunodeficiency virus (HIV) are important factors that influence outcomes.

Newer PK studies in children have shown that exposures for first-line antituberculosis drugs (rifampicin [RIF], pyrazinamide [PZA], isoniazid [INH, ethambutol [EMB]) often remain lower than the observed exposures in adults receiving recommended doses [14–16]. Furthermore, pediatric exposures are consistently associated with larger between-child variability, which is often a consequence of imprecise dosing algorithms.

The aims of this systematic review and meta-analysis were to evaluate current evidence on clinical outcomes and exposure to first-line drugs among children, to synthesize knowledge on PK and other risk factors for unfavorable clinical outcomes, and to assess the maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) in children receiving current WHO-recommended or increased doses for treatment of drug-susceptible tuberculosis.

METHODS

Search Strategy and Selection Criteria

This systematic review and meta-analysis were done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [17]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; no. CRD42021274222).

We systematically searched PubMed, Embase, and Cochrane Library databases for observational, descriptive studies and randomized controlled trials from 2010 (date of update dosing recommendations [18]) to August 2021, regardless of language or publication status. A full list of the search terms used can be found in Supplementary Material 2. We identified studies involving children ≤18 years of age who were treated for confirmed or presumed drug-susceptible tuberculosis, considering all forms of tuberculosis.

All titles and abstracts were imported into the covidence software (Veritas Health Innovation). Two independent reviewers (A. B. and A. M.) screened titles and abstracts for relevance and appraised full text review for inclusion using prespecified selection criteria. Key articles were identified by consensus with a third and fourth reviewer (B. P. S. and K. R.). The methods used to assess quality and risk of bias and for data extraction and analysis are reported in Supplementary Material 3.

Clinical Outcomes

The outcome was considered favorable if children were smear or culture negative in the last month of treatment and on ≥1 previous occasion or if treatment was completed without evidence of failure. If the patient died, needed a treatment extension, had tuberculosis at the end of the treatment, had treatment failure within the follow-up period, or experienced a recurrence, the outcome was considered unfavorable.

Role of the Funding Source

The WHO funded the study and had a role in study design and data interpretation but had no role in data collection or data analysis.

RESULTS

Our search identified 304 studies, of which 104 were duplicated and 153 were ineligible based on selection criteria. A total of 47 studies met the inclusion criteria and were included for full text review; 12 and 18 studies were included for the efficacy and PK analyses, respectively (Figure 1). The included studies were conducted in 8 of the 30 countries with the highest tuberculosis burden [2], with the majority of the data collected in South Africa and India (10 and 4 studies, respectively) (Supplementary Material 4). All the studies were scored as very low quality, following the scoring method reported in Supplementary Material 5, except for 3 studies, 1 assessed as low [14] and 2 as moderate quality [19, 20].

Included studies are summarized in Table 1. Children in the studies ranged in age from infants to adolescents <18 years old. Eight studies included CWHIV (range, 4%–100%). Dosing regimens followed the WHO 2010 recommendations in most studies, but 5 studies [23–26] followed the Indian Revised National Tuberculosis Control Program, which used thrice-weekly dosing. One study assessed higher-than-WHO-recommended RIF doses (15.5–75 mg/kg) in combination with standard doses for all other drugs [31].

Clinical Outcomes

Twelve studies reported clinical outcomes (Figure 2). Of the total 1862 patients included in these studies, outcomes were reported in 1830 (98%). The median percentage of favorable outcomes was 82% (range, 25%–97%), lower than the WHO target of 90% treatment success [2] and the global average (88%). The majority of the data came from a large phase 3 trial in children with minimal disease (n = 1024; 97% favorable outcomes) [34]. Only 3 other studies reported >90% favorable outcomes, including 20 [23], 27 [29], and 37 children [33]. Studies using daily WHO-recommended doses reported 81% of favorable outcomes. The study that reported the highest percentage of unfavorable outcomes (75%) included 24 CWHIV [34], of whom 17 had an unfavorable outcome and 1 was lost to follow-up.

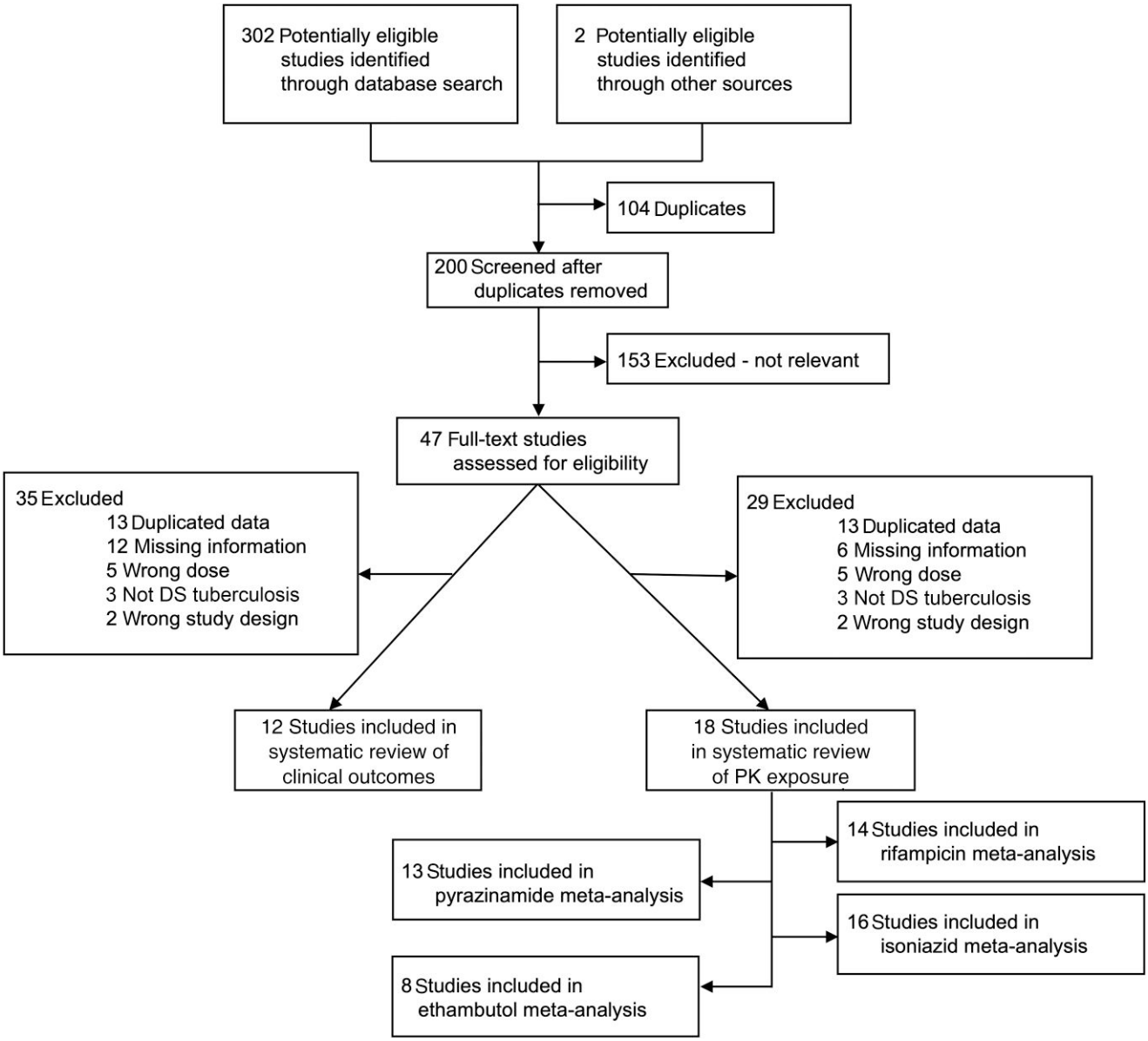

Figure 1. Study selection. Abbreviations: DS, drug-susceptible; PK, pharmacokinetic.

Table 1 shows the breakdown between favorable and unfavorable outcomes and loss to follow-up, as reported by the individual studies. Reported risk factors for unfavorable outcomes included lower drug exposures, including for RIF [23, 26, 29], INH [19, 23], and PZA [24], as well as lower weight for age [19] or severe malnutrition [36], poor social circumstances [15], and severity of infection [33].

Drug Exposure

In the exposure review and meta-analysis, 963 patients were included. Among this cohort, INH, RIF, PZA, and EMB PK parameters were evaluated in 16 (89%), 14 (78%), 13 (72%), and 8 (44%) studies, respectively. All studies reported C_{max}, and 17 (94%) reported AUC. Target exposure attainment was reported in 8 studies, with variable study-defined targets in each of the publications. The C_{max} target was achieved in 45%, 71%, 52%, and 37% of children for RIF, INH, PZA, and EMB, respectively, and the AUC target was achieved in 50%, 67%, 19% of children for RIF, INH, and PZA. One study found that 67% of children had simultaneously low concentrations of all drugs [16].

PK parameters were reported differently across studies; 11 (73%), 10 (67%), 9 (69%), and 6 (67%) studies reported AUCs for the full cohort for RIF, INH, PZA and EMB, respectively. The remaining studies reported AUCs and C_{max} only by subgroups. PK data are summarized in Supplementary Material 6.

Table 1. Characteristics of Included Studies in Both Reviews

Authors	Country and Study Design	Dosing Regimen[a]	Type of Tuberculosis	HIV Status	Age, y	Body Weight, kg	Nutritional Status	Drug PK Parameters	Covariate	Factors Affecting PK Parameters	Clinical Outcome[b]	Factors Affecting Clinical Outcomes
Thee et al [21]	South Africa; prospective monocenter (n = 20)	INH, 5 and 10 mg/kg; RIF, 10 and 15 mg/kg; PZA, 25 and 35 mg/kg	PTB, n = 11; EPTB, n = 1; TBM, n = 8	5 HIV+; 15 HIV−	Mean (SD), 1.1 (0.5)	NR	Mean WAZ (SD), −1.7 (1.8)	INH, RIF, and PZA C_{max} and $AUC_{0–5}$	Age, sex, type of tuberculosis, nutritional status, HIV status, *NAT2* for INH	Dosing regimen associated with C_{max} and AUC for all drugs (P < .001 for INH and PZA; P < .006 for RIF) and *NAT2* genotype with INH C_{max} and AUC (P < .05)	NR	NR
Roy et al [22]	India; prospective monocenter (n = 20; G1, n = 7; G2, n = 13)	G1, PZA >30–35 mg/kg; G2, PZA <30–35 mg/kg	PTB; lymph node tuberculosis	NR	Range, 5–12; mean (SEM), 5.6 (0.3) for G1 and 5.8 (0.2) for G2	Mean (SEM), 15.7 (0.4) for G1 and 16.3 (0.8) for G2	NR	PZA C_{max} and $AUC_{0–24}$	Dosing regimen	Dosing regimen associated with PZA C_{max} and AUC (P < .01)	NR	NR
Ramachandran et al [23]	India; prospective multicenter (n = 84)	RNTCP guidelines[c]	PTB, n = 19; EPTB, n = 63; PTB + EPTB, n = 2	84 HIV−	Mean (range), 7.1 (1.0–12.0)	Median (IQR), 18 (13–23)	Stunted, n = 22; underweight, n = 31; wasted, n = 16; median HAZ (IQR), −1.2 (−2.1 to −0.3); median WAZ, −1.8 (−2.4 to −1.1); WHZ, −1.2 (−1.9 to −0.3)	INH, RIF, and PZA C_{max} and $AUC_{0–8}$	Age, *NAT2* for INH, BMI, albumin, nutritional status, outcome	Younger age associated with lower C_{max} and AUC for all drugs (P < .01); malnutrition associated with decreased RIF C_{max} and AUC (P < .05); *NAT2* genotype on INH C_{max} and AUC (P < .001)	Favorable, n = 55; unfavorable, n = 15; LTFU, n = 14	RIF and INH AUC and C_{max} lower in children with unfavorable outcomes (P < .03) Rapid INH acetylator status associated with unfavorable outcomes (aOR 4.2; 95% CI, 1.1–15.4; P = .03)
Ramachandran et al [24]	India; prospective multicenter (n = 77)	RNTCP guidelines[c]	PTB, n = 49; EPTB, n = 28	77 HIV+	Median (range), 9 (1–15)	Median (IQR), 17.0 (14.1–22.5)	Stunted, n = 59; underweight, n = 56; wasted, n = 15; median HAZ (IQR), −3.0 (−4.1 to −2.0); median WAZ, −2.7 (−3.4 to −1.9); median WHZ, −1.1 (−1.7 to −0.02)	INH, RIF, and PZA C_{max} and $AUC_{0–8}$	Age, sex, nutritional status, BMI, albumin, ART, *NAT2* for INH, outcome	Age <5 y associated with lower INH and PZA C_{max} and AUC (P < .05); *NAT2* genotype associated with INH C_{max} and AUC (P < .02); low albumin level associated with decreased RIF C_{max} (P = .04)	Favorable, n = 54; unfavorable, n = 18; LTFU, n = 5	PZA C_{max} had an impact on outcome (aOR, 1.1; 95% CI 1–1.2; P = .01)
Rangari et al [25]	India; prospective monocenter (n = 20; G1, n = 8; G2, n = 12)	RNTCP guidelines[c]; G1, INH >10 mg/kg; G2, INH <10 mg/kg	PTB; lymph node tuberculosis	NR	Range, 5–12; mean (SEM), 8.8 (0.4) for G1 and 10.8 (0.3) for G2	Mean (SEM), 21.5 (0.3) for G1 and 22.6 (0.7) for G2	NR	INH C_{max} and $AUC_{0–24}$	Dosing regimen	Dosing regimen associated with INH AUC (P = .002)	NR	NR

Table 1. Continued

Authors	Country and Study Design	Dosing Regimen[a]	Type of Tuberculosis	HIV Status	Age, y	Body Weight, kg	Nutritional Status	Drug PK Parameters	Covariate	Factors Affecting PK Parameters	Clinical Outcome[b]	Factors Affecting Clinical Outcomes
Arya et al [26]	India; prospective monocenter (n = 20)	RNTCP guidelines[c]; G1, RIF >10 mg/kg; G2, RIF <10 mg/kg	PTB; lymph node tuberculosis	NR	Median (range), 9 (6–10) for G1 and 12 (6–12) for G2	Median (range), 20.6 (15–22.4) for G1 and 24.2 (15.2–25.0) for G2; mean (range), 21.6 (15.0–25.0)	NR	RIF C_{max} and AUC_{0-12}	Age, dosing regimen	Dosing regimen associated with RIF C_{max} and AUC ($P < .05$)	At 6 mo: favorable, n = 19; unfavorable, n = 1	One unfavorable outcome with RIF less than10 mg/kg and low C_{max} and (AUC, 5.8 μg/mL and 29.7 μg·h/mL, respectively)
Mlotha et al [27]	Malawi; prospective monocenter (n = 30)	INH, 5 mg/kg; RIF, 10 mg/kg; PZA, 25 mg/kg; EMB, 20 mg/kg	PTB, n = 21; EPTB, n = 9	20 HIV+; 10 HIV–	Median (range), 7.5 (0.5–15.6)	Median (range), 18.0 (4.8–45.0)	NR	INH, RIF, PZA, and EMB C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$	Age, dosing regimen, HIV status	Dosing regimen associated with RIF $AUC_{0-max\infty}$ ($P = .03$)	NR	NR
Hiruy et al [28]	South Africa; prospective monocenter (n = 31)	INH, 10–15 mg/kg; RIF, 10–15 mg/kg; PZA, 30–40 mg/kg EMB 15–25 mg/kg	PTB, n = 22; EPTB, n = 9	7 HIV+; 24 HIV–	Median (range), 2.29 (0.25–10.5)	Median (range), 11.5 (6.1–19.0)	Malnourished, n = 20	INH, RIF, PZA, EMB C_{max}, AUC_{0-24}, and C2h	Age, sex, nutritional status, HIV status	HIV+ status associated with lower C2h INH ($P = .04$)	NR	NR
Mukherjee et al [19]	India; prospective multicenter (n = 127; G1, n = 64; G2, n = 63)	INH: G1, 5 (4–6) mg/kg; G2, 10 (7–15) mg/kg; RIF: G1, 10 (8–12) mg/kg; G2, 15 (10–20) mg/kg; PZA, 30–35 mg/kg; EMB, 20–25 mg/kg. Showing median and range	PTB, n = 63; EPTB, n = 64	127 HIV–	Range, 0.5–15.0; mean (SD) for G1, 8.8 (3.6) in malnourished and 8.1 (3.7) in normal children; mean (SD) in G2, 7.6 (3.2) in malnourished and 10.5 (2.4) in normal children	NR	Malnourished, n = 58	INH, RIF, PZA, and EMB C_{max}, AUC_{0-4}, and C2h	Nutritional status, dosing regimen	Dosing regimen associated with INH C_{max} and AUC ($P < .001$)	Favorable, n = 53 for G1 and n = 44 for G2; unfavorable, n = 9 for G1 and n = 17 for G2; LTFU, n = 2 for both G1 and G2	INH C_{max} lower in children with unfavorable outcome (1.3 [0.7–1.5] vs 3.4 [1.8–5.0] μg/mL; $P = .05$) Confirmation of *Mycobacterium tuberculosis* associated with poor outcome (55.6% vs 16.4%; $P = .01$) G2: children with lower WAZ had poorer outcome
Bekker et al [15]	South Africa; prospective multicenter (n = 39)	INH, 14 (9–20) mg/kg RIF, 14 (9–20) mg/kg PZA, 32 (19–45) mg/kg; EMB, 20 (13–29) mg/kg. Showing median and range	PTB, n = 36; TBM, n = 1; PTB + EPTB, n = 2	5 HIV+; 34 HIV–	Mean (range), 0.55 (0–1)	Mean (SD), 6.45 (1.67)	Mean WAZ (SD), –1.62 (1.53); mean WHZ, –0.40 (1.26)	INH, RIF, PZA, and EMB C_{max} and AUC_{0-8}	Age, sex, nutritional status, prematurity, HIV status, ethnicity	Formulation influenced RIF C_{max} and AUC ($P < .005$); HIV status associated with lower PZA and EMB C_{max} and AUC ($P < .02$)	Favorable, n = 33; unfavorable, n = 6	All unfavorable outcomes were in children with poor social circumstances

Table 1. Continued

Authors	Country and Study Design	Dosing Regimen[a]	Type of Tuberculosis	HIV Status	Age, y	Body Weight, kg	Nutritional Status	Drug PK Parameters	Covariate	Factors Affecting PK Parameters	Clinical Outcome[b]	Factors Affecting Clinical Outcomes
Mukherjee et al [20]	India; prospective monocenter (n = 56)	INH, 4–6 mg/kg; RIF, 8–12 mg/kg; PZA, 30–35 mg/kg; EMB, 20–25 mg/kg	PTB, n = 52; pleural tuberculosis, n = 4; associated EPTB, n = 19	24 HIV+; 32 HIV−	Range, 0.5–15; mean (SD), 8.8 (3.6) for HIV+ and 8.1 (3.7) for HIV−	NR	HIV+: median HAZ (IQR), −2.5 (−4.2 to −1.6); median WAZ −3.2 (−4.5 to −2.1) HIV−: median HAZ −1.4 (−2.3 to 0.0); median WAZ, −1.4 (−2 to −0.7)	INH, RIF, PZA, and EMB C_{max}, $AUC_{0–4}$, and C2h	Age, sex, nutritional status, *NAT2* for INH, dosing regimen, HIV status	Dosing regimen associated with lower C2h INH ($P = .01$); younger age associated with lower C2h INH ($P = .04$); HIV+ status associated with lower EMB AUC ($P < .05$); *NAT2* genotype associated with INH C_{max} and AUC ($P < .01$)	HIV+: favorable, n = 6; unfavorable, n = 17; LTFU, n = 1 HIV−: NR	No retrieved association
Antwi et al [14]	Ghana; prospective monocenter (n = 113)	Median (IQR): INH, 11.2 (9.1–12.8) mg/kg RIF 15.8 (13.6–18.8) mg/kg; PYR, 24.8 (22.6–30.0) mg/kg; EMB, 16.9 (15.0–20.6) mg/kg	PTB, n = 85; EPTB, n = 28	54 HIV+; 59 HIV−	Median (IQR), 5.0 (2.2–8.3)	Median (IQR), 14.0 (8.8–19.5)	Median HAZ (IQR), −2.0 (−3.2 to −1.1); median WAZ, −2.5 (−3.8 to −1.4)	INH, RIF, PZA, and EMB C_{max} and $AUC_{0–8}$	Sex, *NAT2* for INH, dosing regimen, HIV status	HIV+ status associated with lower RIF and EMB C_{max} and AUC and PZA AUC ($P < .03$); *NAT2* genotype associated with INH C_{max} and AUC ($P < .02$)	Favorable, n = 99; unfavorable, n = 6; LTFU, n = 4	NR
Ranjalkar et al [29]	India; prospective multicenter (n = 41; G1, n = 27; G2, n = 14)	Median (IQR) for G1 (thrice-weekly): INH, 10 (8–12) mg/kg; RIF, 10 (9–12) mg/kg; G2 (daily): INH, 8 (7–9) mg/kg; RIF, 11 (10–12) mg/kg	PTB, n = 36 (G1, n = 24; G2, n = 12); lymph node tuberculosis, n = 5(G1, n = 3; G2, n = 2)	NR	Range, 2–16	Median (IQR), 14.7 (12–24) for G1 and 37.0 (21–41) for G2	Median HAZ (IQR), −1.41 [−2.00 to −0.56) for G1 and −0.32 (−1.15 to 0.22) for G2	INH and RIF C_{max}, $AUC_{0–6}$, and C2h	Age, group (G1 vs G2)	No retrieved association	Favorable, n = 25 for G1 and n = 11 for G2; unfavorable, n = 2 for G1 and n = 3 for G2	G1: both patients with an unfavorable outcome had RIF C_{max} less than8 μg/mL
Dayal et al [30]	India; prospective monocenter (n = 37)	INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg	PTB, n = 18; EPTB, n = 19	37 HIV−	Median (IQR), 8 (3–10)	NR	Stunted, n = 14/21 (age <6 y); underweight, n = 14/37; wasted, n = 16/21 (age <6 y)	INH and PZA C_{max} and $AUC_{0–8}$	Age, type of tuberculosis, BMI	EPTB associated with lower INH AUC compared with PTB ($P = .05$); Age >3 y associated with higher PZA AUC ($P = .001$)	Favorable, n = 35; LTFU, n = 2	NR
Garcia-Prats et al [31]	South Africa; prospective multicenter (n = 62)	RIF: G1, 15–20, then 35 mg/kg; G2, 35, then 50 mg/kg; G3, 60, then 75 mg/kg	PTB, n = 45; EPTB, n = 2; PTB + EPTB, n = 15	62 HIV−	Median (range), 2.0 (1.2–3.4) for G1, 2.0 (1.1–3.9) for G2, and 2.8 (1.0–5.5) for G3	Median (range), 10.6 (8.7–14.2) for G1, 10.9 (9.3–14.1) for G2, and 12.5 (8.0–17.4) for G3	Underweight, n = 18	RIF C_{max} and $AUC_{0–24}$	Dosing regimen	Analysis not published	NR	NR

Table 1. Continued

Authors	Country and Study Design	Dosing Regimen[a]	Type of Tuberculosis	HIV Status	Age, y	Body Weight, kg	Nutritional Status	Drug PK Parameters	Covariate	Factors Affecting PK Parameters	Clinical Outcome[b]	Factors Affecting Clinical Outcomes
Shah et al [32]	India; prospective monocenter (n = 35)	INH, 10 mg/kg daily	PTB, n = 12; EPTB, n = 22	NR	Range, 1–15	NR	Underweight, n = 11	INH C_{max} and AUC_{0-24}	Age, sex, tuberculosis type, formulation, nutritional status	No retrieved association	NR	NR
Panjasawatwong et al [33]	Vietnam; prospective monocenter (n = 100)	INH, 5 mg/kg; RIF, 10 mg/kg; PZA, 25 mg/kg; EMB, 15 mg/kg	TBM, n = 100	4 HIV+; 92 HIV−; 4 NA	Median (range) 3 (0.2–15)	Median (range), 10.9 (4–43)	Median HAZ (range), −1.64 (−9.17 to 2.21); median WAZ, −1.93 (−5.52 to 2)	INH, RIF, PZA, and EMB C_{max} and AUC_{0-24}	None	No retrieved association	At 8 mo: favorable, n = 81; unfavorable, n = 15; LTFU, n = 4	Severity of infection associated with outcome[d]
Justine et al [16]	Tanzania; prospective monocenter (n = 51)	INH, 2–10 mg/kg; RIF, 5–20 mg/kg; PZA, 10–40 mg/kg; EMB, 7.5–35 mg/kg	PTB, n = 18; EPTB, n = 17; PTB + EPTB, n = 16	51 HIV−	Median (range), 5.3 (0.75–14)	NR	Stunted, n = 16/23; underweight, n = 16/23	INH, RIF, PZA, and EMB C_{max}	Age, sex, dosing regimen, nutritional status	Dosing regimen associated with RIF and PZA C_{max} ($P = .005$); malnutrition associated with decreased INH and RIF C_{max} ($P = 0.001$)	NR	NR
Wobudeya et al [34]	India, South Africa, Uganda, and Zambia; randomized, open label multicenter (n = 1024)	INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg; G1, 4 mo; G2, 6 mo	NR	127 HIV+; 897 HIV−	Range, 0.4–15	NR	NR	NR	NR	NR	Unfavorable and LTFU, n = 16 for G1 and n = 18 for G2	No retrieved association
Nansumba et al [35]	Uganda; prospective monocenter (n = 144)	INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg	NR	48 HIV+; 94 HIV−; 2 NR	Range, 0.08–14; <2, 44.4%; 2–5, 29.2%; ≥5, 26.4%	NR	WHZ ≤−1, 41.6%; ≤−2, 24.7%; <−2 to ≤−3, 12.7%; ≤−3, 21.1%	NR	NR	NR	End of treatment Favorable, n = 117; unfavorable, n = 22; LTFU, n = 5	Severe malnutrition (WHZ less than or equal to −2) was a predictor of death (adjusted HR, 8.8; 95% CI) 1.6–48.3 Interaction between younger age and malnutrition

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; AUC, area under the concentration-time curve; AUC_{0-4}, AUC at 0–4 hours; $AUC_{0-\infty}$, AUC at 0 to infinite; AUC_{0-last}, AUC at 0 to the last measured time; BMI, body mass index; C_{2h}, concentration at 2h; CI, confidence interval; C_{max}, maximum plasma concentration; EMB, ethambutol; EPTB, extrapulmonary tuberculosis; G1, group 1; G2, group 2; G3, group 3; HAZ, height-for-age *z* score (stunted if ≤−2 SD); HIV, human immunodeficiency virus; HR, hazard ratio; INH, isoniazid; IQR, interquartile range; LTFU, lost to follow-up; NA, non-available; *NAT2,* N-acetyltransferase; NR, not reported; PK, pharmacokinetic; PTB, pulmonary tuberculosis; PZA, pyrazinamide; RIF, rifampicin; RNTCP, Revised National Tuberculosis Control Program; SD, standard deviation; SEM, standard error of the mean; TBM, tuberculous meningitis; WAZ, weight-for-age *z* score (underweight if ≤−2 SD); WHZ, weight-for-age *z* score (wasted if ≤−2 SD).

[a]Dosing regimen expressed per day, unless otherwise specified.

[b]Treatment success was defined as: cured/treatment completed. Unfavorable outcome was defined as failure or death.

[c]RNTCP guidelines were as follows: INH, 10 mg/kg; RIF, 10 mg/kg; PZA, 30–35 mg/kg; EMB 30 mg/kg; all given thrice weekly.

[d]Disease severity was based on the Blantyre coma score (BCS) for children <5 years old and the Glasgow coma score (GCS) for those ≥5 years old. Grade I was defined as BCS 4–5 with no focal neurological signs or GCS 15 with no focal neurological signs; grade II, as BCS 2–3 or BCS 4–5 with focal neurological signs or GCS 11–14 or GCS 15 with focal neurological signs; and grade III, as BCS <1 or GCS <10.

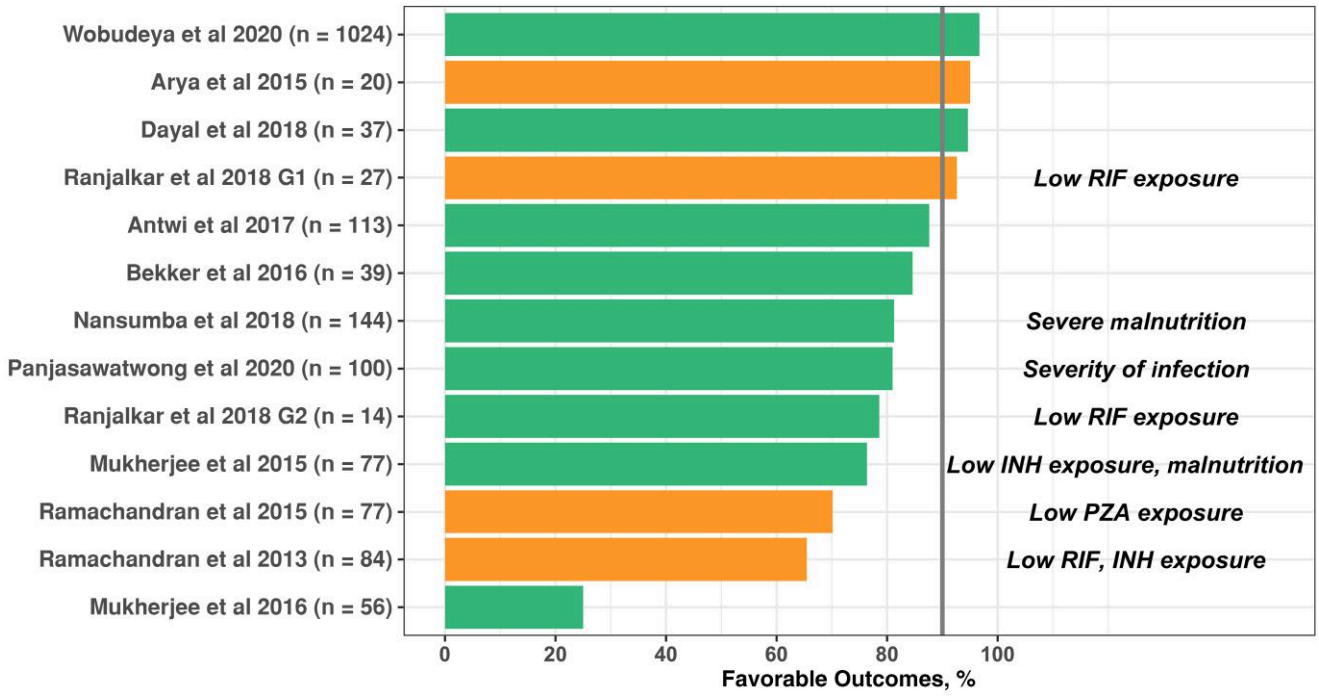

Figure 2. Percentage of reported favorable outcomes per study, with the risk factors identified in the listed publications [14, 15, 19, 20, 23, 24, 26, 29, 30, 33–35]. Colors indicate whether children in the study received World Health Organization (WHO)–recommended doses of first-line antituberculosis agents or doses based on Revised National Tuberculosis Control Program guidelines. Vertical line represents the WHO target of 90% treatment success [2]. Abbreviations: G1, group 1; G2, group 2; INH, isoniazid; PZA, pyrazinamide; RIF, rifampicin.

For RIF, the median summary estimates for the AUC and C_{max} were 23.4 μg·h/mL and 6 μg/mL, respectively, lower than the median adult exposure targets of 38.7 μg·h/mL and 8 μg/mL (Figure 3*A* and Supplementary Material 7*A*). In meta-analysis, children <6 years old had significantly lower RIF AUCs, showing median and 95%CI: (14.4 [9.9–18.8]) μg·h/mL) than older children (22.0 [13.8–30.1] μg·h/mL), and a trend toward lower RIF AUCs in CWHIV was identified (17.3 [11.4–23.2] vs 26.5 [21.3–31.7] μg·h/mL in HIV-negative children) (Figure 4*A*). Younger age was associated with lower exposures in 1 study [29], and CWHIV were reported to have lower exposures in another study [14] (Table 1). Higher RIF doses were associated with statistically significant increased PK levels in 4 studies [16, 21, 26, 27] (Table 1). Within-study dose comparison in 2 studies showed higher C_{max} and AUC at 0–12 hours with doses >10 mg/kg [21, 26], confirmed by additional studies reporting an increase of 0.12 μg·h/mL in AUC_{0-last} (AUC at 0 to the last measured time) ($P = .03$) and 0.2 (95% confidence interval [CI], .1–.4) μg/mL in C_{max} for each additional milligram per kilogram ($P = .005$) [16, 27]. The study using doses higher than those recommended by WHO showed a steady-state median (range) AUC at 0–24 hours of 39.5 (11.7–76.1) μg·h/mL at 15–20 mg/kg, 68.4 (18.9–169) μg·h/mL at 35 mg/kg, and 192.8 (17.2–415.6) μg·h/mL at 60 mg/kg [31].

For INH, the summary estimate for the AUC was 23.4 μg·h/mL, equal to the median adult exposure target (Figure 3*B*). The summary estimate for C_{max} was 5.6 μg/mL, compared with the target of 3–5 μg/mL (Supplementary Material 7*B*). Subgroup meta-analysis resulted in 40% lower AUCs in fast than in slow metabolizers, showing median and 95% CI (14.2 [9.2–19.1] vs 35.3 [17.6–53.0], respectively) (Supplementary Material 8). In the meta-analysis, younger children had lower AUCs than older children, but this difference was not statistically significant. Similarly, CWHIV had lower AUCs as than children without HIV (summary estimates, showing median and AUC 18.7 [13.9–23.5] and 20.0 [15.4–24.4] μg·h/mL, respectively), but this difference was not statistically significant. The influence of N-acetyltransferase (*NAT2*) genotype was reported in 5 studies [14, 20, 21, 23, 24], and age was reported as a significant covariate for INH exposure in 3 [20, 23, 24] (Table 1 and Supplementary Material 6.2). Ramachandran et al [23] found an increase in INH C_{max} of 0.4 (95% CI, .19–.62) μg/mL per year ($P < .001$) and an increase in the AUC at 0–8 hours (AUC_{0-8}) of 1.3 (.43–2.2) μg·h/mL per year ($P < .01$). Similarly, Mukherjee et al [20] identified young age as a significant predictor of INH C2h in multivariate regression ($P = .04$). Children <5 were reported by Ramachandran et al [24] to have lower exposure ($P < .05$). Only Hiruy

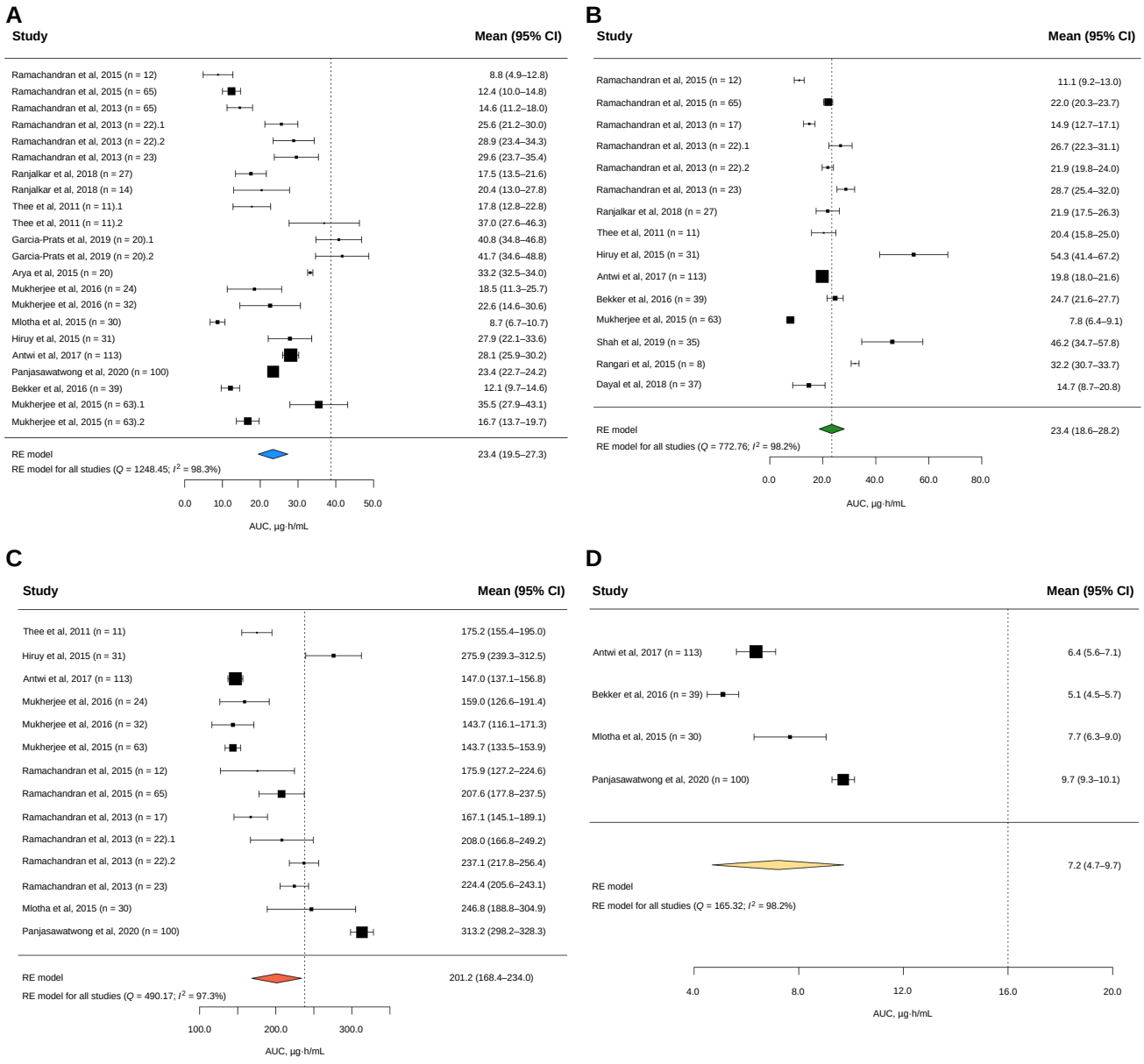

Figure 3. Forest plots displaying summary estimates for rifampicin (*A*), isoniazid (*B*), pyrazinamide (*C*), and ethambutol (*D*) area under the concentration-time curves (AUCs), based on published studies [14, 15, 19–21, 23–33]. Dashed lines represent median adult AUCs of 38.7, 23.4, 238–428, and 16–28 µg·h/mL, respectively. Square size is proportional to sample size, which is shown in parentheses; when different arms of the same study had the same sample size, a number is added after the sample size. Abbreviations: CI, confidence interval; RE, random effects.

et al [28] reported a significantly lower INH C_{max} in CWHIV ($P < .04$). In addition, higher doses (in milligrams per kilogram) were associated with increased INH PK levels in 5 studies [16, 19, 21, 26, 27] (Table 1).

For PZA, the summary estimate for the AUC in children was 201.2 µg·h/mL, lower than the target of 238–428 µg·h/mL (Figure 3C). The summary estimate for C_{max} was 39.6 µg/mL (target, 35–60 µg/mL) (Supplementary Material 7C). No differences in AUC or C_{max} were found by subgroup. The C_{max} and the AUC at 0–5 hours (AUC_{0-5}) increased significantly with dose, with a C_{max} of 30.0 (26.2–33.7, showing median and 95% CI) versus 47.1 (42.6–51.6) µg/mL ($P < .001$), and an AUC_{0-5} of 118.0 (101.3–134.7) versus 175.2 (155.5–195) µg·h/mL ($P < .001$) for 25 and 35 mg/kg, respectively [21]. Two studies compared doses <30 and 30–35 mg/kg, showing a significant increase in C_{max} with higher doses ($P < .05$) [16, 22]. The AUC_{0-8} for PZA was lower in CWHIV in 1 study [14] ($P = .03$), and a significant association was reported by Bekker et al [15] but not in any other study. Age was reported as a significant covariate for PZA in 3 studies [23, 24, 30].

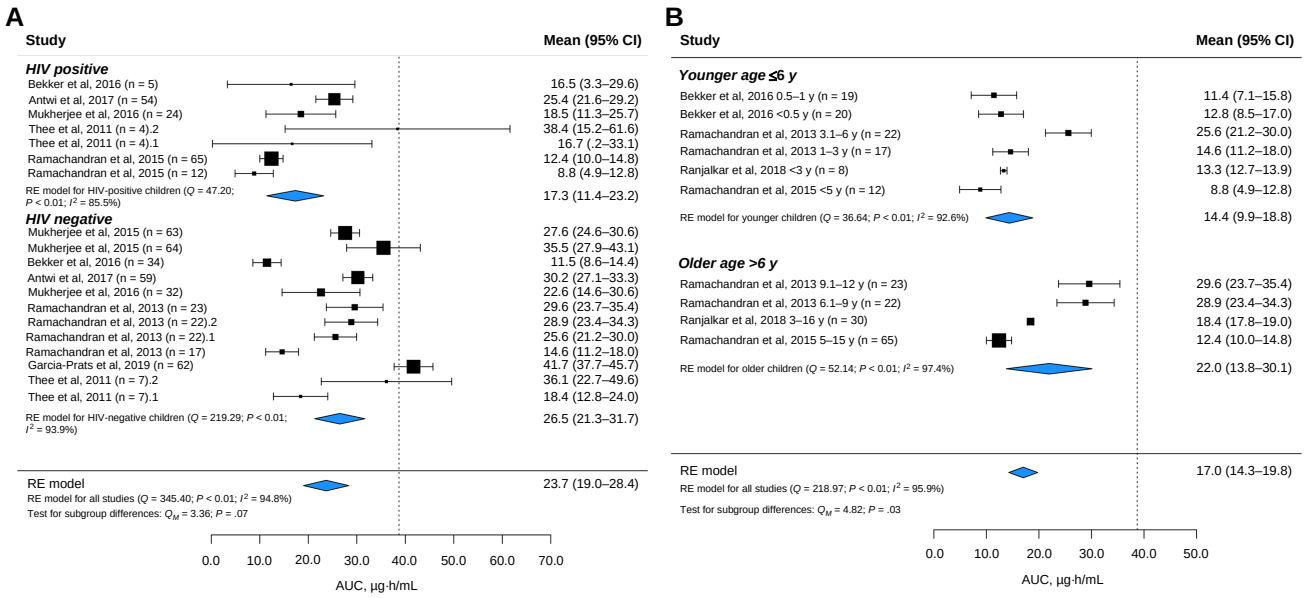

Figure 4. Forest plot displaying summary estimates for rifampicin area under the concentration-time curve (AUC) stratified based on human immunodeficiency virus (HIV) status (*A*) and age (*B*), based on published studies [14, 15, 19, 20, 21, 23, 24, 29, 31]. Dashed lines represent the median adult AUC of 38.7 µg·h/mL. Square size is proportional to sample size, which is shown in parentheses; when different arms of the same study had the same sample size, a number is added after the sample size. Abbreviations: CI, confidence interval; RE, random effects.

Ramachandran et al [24] found significantly lower exposure in children ≤5 years old than in older children. Separately, in a multiple regression analysis, C_{max} increased by 1.2 (95% CI, .23–2.18) µg/mL per year of age ($P < .05$), and the AUC_{0-8} increased by 7.46 (1.97–12.94) µg·h/mL ($P < .01$) [23]. Dayal et al [30] found similar results, with an increase in the PZA AUC_{0-8} of 8.4 (95% CI, 3.6–13.1) µg·h/mL per year of age ($P = .001$).

For EMB, the summary estimate was 7.2 µg·h/mL for the AUC and 1.4 µg/mL for C_{max}, compared with the targets of 16–28 µg·h/mL and 2–6 µg/mL, respectively (Figure 3*D*). Subgroups of interest were rarely studied, and no subgroup meta-analysis was conducted for EMB. All reported EMB exposure values by subgroups are in Supplementary Material 6.4. The only significant association retrieved in the original publications was lower exposure in CWHIV [15, 20, 37].

DISCUSSION

In this work we found that, at WHO-recommended doses, clinical outcomes in children treated for drug-susceptible tuberculosis are variable, with an average of 82% achieving a favorable outcome, and that RIF, PZA, and EMB exposures are routinely lower in children than in adults and have been identified as risk factors for unfavorable outcomes.

Studies have previously identified low exposures to RIF, INH, and PZA [19, 23, 24, 26, 29] as predictors of unfavorable outcomes. Higher clearance of drugs per kilogram in younger children has also been noted as a contributing factor [38]. Malnutrition was reported as an important factor for unfavorable outcomes in 2 studies [19, 35]. Mukherjee et al [19] reported a median (interquartile range) weight-for-age *z* score of −1.3 (−1.9 to −0.6) and −1.9 (−2.3 to −1.8) for favorable and unfavorable outcomes, respectively ($P = .007$), in 127 children from India. Nansumba et al [35], reported 81% favorable outcomes in 144 children from Uganda, and severe malnutrition was identified as a predictor of death, with a hazard ratio of 8.8 (95% CI 1.6–48.3). Approximately 45% of global deaths in children <5 years old are attributable to undernutrition, mainly in low- and middle-income countries, where more than a third of children <5 years old are stunted [39, 40]. Therefore, malnutrition is a predominant death risk factor, and more studies with adequate assessment of nutritional status are needed.

Malnourished children are expected to have lower PK levels [38], which could partially explain why malnourished kids are at a higher risk of treatment failure. Modeling and simulation suggest that malnourished children have lower exposures because lower doses are administered in lower weight bands [38]. The current science of pediatric pharmacology proposes higher doses (in milligrams per kilogram) in lower weight bands or younger children [9, 41] or dosing according to ideal body weight [38]. Low-weight children may benefit from higher doses given the higher risk for severe tuberculosis disease and death [42]. This review could not draw definitive conclusions regarding malnutrition or merits and risks of weight-band approaches to dosing. However, large pediatric PK studies

in populations of children with infectious diseases such as malaria [43], HIV [44], and tuberculosis [36] have shown that weight-based dosing is not optimal for malnourished children and more adequate dosing needs to be developed.

In the current study, we found that higher RIF doses (in milligrams per kilogram) resulted in higher exposures but were still lower than the adult median AUC, suggesting that, at minimum, daily RIF doses >15 mg/kg in children >6 years old are required to match exposures in adults treated with 10 mg/kg. Modeling and simulation studies predict that it may require ≥25 mg/kg to ensure adequate PK target exposure in children and suggest that higher PK exposures could lead to higher proportions of favorable clinical outcomes [23, 41, 45, 46]. One included study evaluated doses higher than the current WHO recommendations, finding higher exposures with a safe profile [31]. Current INH doses (7.5–15 mg/kg) appeared sufficient overall. *NAT2* metabolizer status was the main factor contributing to variability in exposure, being significantly lower in fast metabolizers. *NAT2* genotype testing has been proposed [47, 48], and a trial of genotype-based dosing reported improved clinical outcomes and safety in adults [49].

Our work was limited by inconsistent reporting of PK parameters, heterogenous populations, disease status, and small sample sizes across studies. Only 4 of 14 studies reported RIF PK by age, and none reported by the same age groups. Only 5 studies had a samples including >100 patients. The different sample sizes can also affect the pooled point estimate of the meta-analysis, so the studies with larger samples would influence these results. Studies with larger samples are needed to identify significant predictors of unfavorable outcomes, especially in children. In addition, assumptions were made to support the meta-analysis: reported AUCs varied from 0–4 to 0–24 hours but were considered equivalent. Given the short half-life of most drugs (approximately 3–4 hours) this minimally affects the results, but it adds uncertainty. C_{max} values were also considered to be the 2-hour concentrations, which may not account for delayed absorption and may make it appear that the target was not achieved.

Such assumptions could be better handled through the analysis of raw PK data and individual participant data meta-analysis approaches, which should be pursued to inform the appropriate dosing algorithm in children. These approaches have been successful in determining optimal doses for general populations as well as high-risk subgroups [50–52]. Given the large number of PK studies that have already been conducted, this approach would be feasible and preferred over a new PK study, even though safety would still need to be assessed. Finally, the PK report of the SHINE trial evaluating shorter 4-month tuberculosis treatment schedule was published after our search was concluded [53], and their PK results were not included in our meta-analysis. Our results align well with their report of low RIF exposure. Their results suggest that higher doses (in milligrams per kilogram) should be used in smaller children to achieve adult exposure targets. While lower exposures may have been sufficient for children with minimal disease, optimal and higher levels are needed for those with more severe tuberculosis.

Overall, there was high PK variability and heterogeneity across all studies. Two significant associations were found in the subgroup analyses: children <6 years had lower RIF AUCs, and those categorized as *NAT2* fast metabolizers had lower INH exposure. However, these results need to be interpreted with caution owing to the scarcity of studies and inconsistent stratifications. We also observed that CWHIV tended to have lower RIF AUCs than children without HIV infection.

In conclusion, there are scarce research data on pediatric dosing of tuberculosis medicines, the reporting of PK parameters is inconsistent, and the populations are heterogeneous. At WHO-recommended doses, drug exposures to RIF, PZA, and EMB in children are consistently lower than those reported in adults. The limitations of available data suggest that pediatric dosing would benefit from new research that is standardized in the assessment of PK parameters and includes measures of safety, in conjunction with robust analytic methods, such as PK modeling.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. B. P. S, K. R, P. N., and R. M. S. wrote the protocol and conceptualized the review. B. P. S., A. B, K. R., and A. M. screened the studies, performed the quality assessment, and extracted the data. B. P. S., A. B., and K. R. accessed and verified the data. B. P. S., A. B., and K. R. performed the statistical analysis and wrote the first draft of the report, with input from P. N. and R. M. S. All authors reviewed the manuscript and approved the final version, had full access to all the data collected in the systematic review, and had final responsibility for the decision to submit for publication.

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Potential conflicts of interest. K. R. reports a role as chair of the Global Health Community, American Society of Clinical Pharmacology and Therapeutics. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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