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EFFECTIVENESS AND PHARMCOKINETICS OF FIRST-LINE ANTI TUBERCULOSIS DRUGS IN CHILDREN: A SYSTEMATIC REVIEW

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Abstract

Background: *The optimal doses of first-line drugs for treating drug-susceptible tuberculosis in children and adolescents are still uncertain.*

Aim: *The purpose of this study was to determine whether children treated with recommended or increased doses of first-line drugs achieve successful outcomes and adequate pharmacokinetic (PK) exposures.*

Methods: *A systematic search strategy was conducted across several electronic reference databases (PubMed, Cochrane Library, Google Scholar) and included articles published between 2010–2023. Duplicate publications, review articles, editorials, and incomplete articles were excluded.*

Results: *Database searches identified a total of 59.123 articles. Of these, 300 articles passed the screening process, resulting in 47 articles for full-text assessment. Among them, 28 articles did not evaluate the outcome of interest. Hence, we found 19 appropriate studies included.*

Conclusion: *The outcomes are highly variable. Children have lower drug exposures than adults. Rifampicin exposure is inadequate for younger infants and/or those with HIV. For optimal administration, standardisation of pharmacokinetic paediatric studies and individual patient data analysis with safety assessment are required.*

Keywords: *Anti-tuberculosis drugs, Effectiveness, Pharmacokinetics, and Pediatrics*

INTRODUCTION

Children under the age of 15 accounted for 11% of the predicted 10 million tuberculosis cases (range, 8.9-11.0 million) and 16% of tuberculosis-related fatalities (230 000 of 1.4 million) worldwide in 2020.[1,2] Children under the age of five, children infected with human immunodeficiency virus (CWHIV), and underweight children are at a higher risk of poor treatment outcomes.[3] Increasing the chance of favourable outcomes requires optimising drug exposure for antituberculosis treatment.[4,5]

In 2014, the World Health Organisation (WHO) reevaluated its guidelines for first-line antituberculosis medications in children based on clinical pharmacokinetic (PK)-pharmacodynamic and safety data.[6] However, the possibility of inadequate dosage in children and its relationship to treatment results has not been evaluated extensively. Clinical trials in people with tuberculosis have demonstrated that increased medication exposure leads to better culture conversion rates, efficacy, and/or shorter treatment durations while retaining an acceptable safety profile.[7]

For defining paediatric doses, the Food and Drug Administration and the European Medicines Agency recommend a child-adult exposure matching approach.[8,9] In order to determine the optimal dosage for children, these must result in exposures comparable to those attained in adults. The fundamental underlying assumption is that adult and paediatric exposure-response relationships are comparable in the same clinical context.[9,10] If comparable exposures are obtained in children, it is anticipated that treatment outcomes will be similar to those in adults; however, safety should still be confirmed. However, various manifestations of the disease, varying severity of tuberculosis by age group or nutritional status, and coinfection with other agents such as the human immunodeficiency virus (HIV) are significant factors that affect outcomes.

Newer PK investigations on children have revealed that exposures to first-line antituberculosis drugs (rifampicin [RIF], pyrazinamide [PZA], isoniazid [INH, ethambutol [EMB]) are frequently lower than those observed in adults receiving the recommended doses.[11,12] In addition, paediatric exposures are invariably associated with greater inter-child variability, which is frequently the result of imprecise dosage algorithms.

This systematic review aimed to evaluate current evidence on clinical outcomes and exposure to first-line drugs among children, to synthesise knowledge on PK and other risk factors for adverse clinical outcomes, and to assess the maximum plasma concentration (Cmax) and area under the concentration-time curve (AUC) in children receiving current WHO-recommended or increased doses for treatment of drug-susceptible tuberculosis.

Method

Search Strategy

This study is a qualitative systematic review. The data is obtained through electronic database search in Medline (PubMed), Cochrane Library, and Google Scholar. The keywords used are “Aspirin” AND “Preeclampsia” AND “Prophylaxis” OR “Prevention”. The selected articles are based on inclusion and exclusion criteria.

Table 1. Literature search strategy

Database	Keywords	Results
PubMed	“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”	123
Cochrane Library	“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”	8400
Google Scholar	“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”	50.600

Eligibility Criteria

All studies were assessed for eligibility. The inclusion criteria of the included studies were original articles (observational studies including cohort, case control, cross-sectional, or randomized clinical trials), full-text articles available published from 2010 to 2023, published in English, and studied the effectiveness and pharmacokinetics of anti TB drugs in children. The exclusion criteria of the studies are articles that are not indexed by Scopus, editorials, reviews, and articles that did not evaluate the focus of interest of this study. The research selection was carried out in three successive phases. The titles and abstracts of all search results were initially screened and evaluated for relevance. Second, complete access was gained to all potentially eligible studies. Finally, the systematic review included only those studies that met our inclusion criteria. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline is used for the selection.

Table 2 summarises the included investigations. The ages of the children in the studies ranged from neonates to adolescents younger than 18 years. In the majority of studies, dosing regimens adhered to the WHO 2010 recommendations; however, four studies followed the Indian Revised National Tuberculosis Control Programme, which employed thrice-weekly administration.[13–16] One study evaluated RIF concentrations greater than those recommended by the World Health Organisation (15.5–75 mg/kg) in combination with standard doses for all other medications.[17]

Data Extraction

All the authors extracted the data from the articles. According to the individual studies, Table 1 displays the division between favourable and unfavourable outcomes and loss to follow-up. Risk factors for unfavourable outcomes included lower drug exposures, including for RIF[14,15,18], INH[14,19], and PZA[13], as well as lower weight for age[19] or severe malnutrition[20], poor social conditions[21] and infection severity.[22] The PK parameters of INH, RIF, PZA, and EMB were evaluated, and all investigations reported Cmax and AUC.

Results

The databases search identified a total of 59.123 articles (Table 1). Of these, 300 articles passed the screening process, resulting in 47 articles for full-text assessment. Among them, 28 articles did not evaluate the focus of interest. Hence, we found 19 appropriate studies included (Figure 1). The summary of the main findings of the selected studies is presented in Table 2.

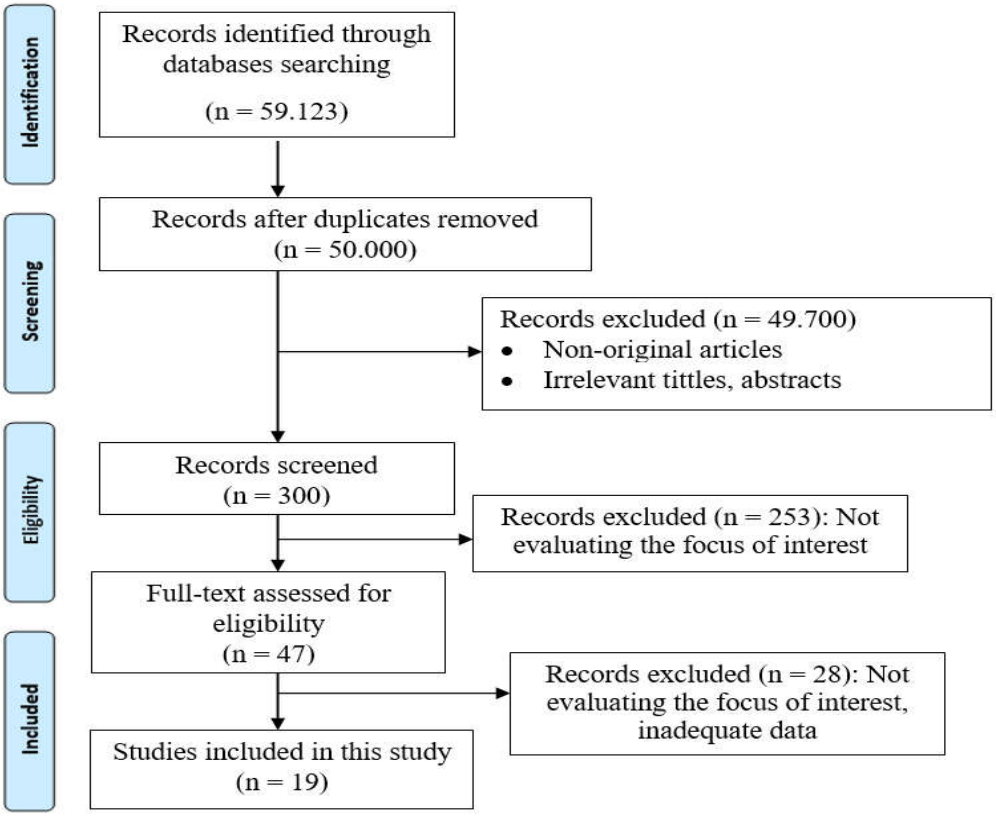

Figure 1. PRISMA flow diagram

Table 2. Summary of included studies

Authors	Country & study design	Dosing regimen	Type of TB	HIV Status	Age (y)	Body weight (kg)	Drugs pharmacokinetic parameter	Covariate	Factors affecting PK parameters	Clinical outcome	Factors affecting clinical outcome
Thee et al.[23]	South Africa; prospective monocenter (n = 20)	5 and 10 mg/kg; RIF, 10 and 15 mg/kg; PZA, 25	PTB, n = 11; EPTB, n = 1; TBM, n = 8	5 HIV+; 15HIV -	Mean (SD), 1.1 (0.5)	NR	H, RIF, and PZA Cmax 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 Cmax and AUC (P <0.05	NR	NR
Roy et al.[24]	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 TB	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	PZA Cmax and AUC_{0-24}	Dosing regimen	Dosing regimen associated with PZA Cmax and AUC (P <0.01)	NR	NR
Ramachandran et al.[14]	India; prospective multicenter (n = 84)	RNTCP guidelines	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)	NH, RIF, and PZA Cmax and AUC_{0-8}	Age, NAT2 for INH, BMI, albumin, nutritional status, outcome	Younger age associated with lower Cmax and AUC for all drugs (P < .01); malnutrition associated with decreased RIF Cmax and AUC (P < .05); NAT2 genotype on INH Cmax and AUC (P<0.001)	Favorable, n = 55; unfavorable, n = 15; LTFU, n = 14	RIF and INH AUC and Cmax 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 = 0.03

Ramachandran et al.[13]	India; prospective multicenter (n = 7)	RNTCP guidelines	PTB, n = 49; EPTB; n = 28	77 HIV+	Median (range), 9 (1–15)	Median (IQR), 17.0 (14.1–22.5)	INH, RIF, and PZA Cmax and AUC_{0-8}	Age, sex, nutritional status, BMI, albumin, ART, NAT2 for INH, outcome	ge <5 y associated with lower INH and PZA Cmax and AUC (P < .05); NAT2 genotype associated with INH Cmax and AUC (P < .02); low albumin level associated with decreased RIF Cmax	Favorable, n = 54; unfavorable, n = 18; LTFU, n = 5	PZA Cmax had an impact on outcome (aOR, 1.1; 95% CI 1–1.2; P = 0.01)
Rangari et al.[16]	India; prospective monocenter (n = 20; G1, n = 8; G2, n = 12	RNTCP guidelinesc; G1, INH >10 mg/kg; G2, INH <1 mg/kg	PTB; lymph node TB	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	Cmax and AUC_{0-24}	Dosing regimen	Dosing regimen associated with INH AUC (P = 0.002)	NR	NR
Arya et al.[15]	India; prospective monocenter (n = 20)	RNTCP guidelinesc; G1, RIF >10 mg/kg; G2, RIF <10 mg/kg	PTB; lymph node TB	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)	RIF Cmax and AUC_{0-12}	Age, dosing regimen	Dosing regimen associated with RIF Cmax and AUC (P<0.05)	At 6 mo: favorable, n = 19; unfavorable, n = 1	One unfavorable outcome with RIF less than10 mg/kg and low Cmax and (AUC, 5.8 μg/mL and 29.7 μg·h/mL, respectively
Mlotha et al.[25]	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 (10.5 – 15.6)	Median (range), 18.0 (14.8–45.0)	INH, RIF, PZA, and EMB Cmax, AUC0–last, and $AUC_{0-\infty}$	Age, dosing regimen, HIV status	Dosing regimen associated with RIF AUC0–max∞ (P = 0.03)	NR	NR
Hiruy et al.[26]	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 (16.1–19.0)	INH, RIF, PZA, EMB Cmax, AUC0–24, and C2h	Age, sex, nutritional status, HIV status	HIV+ status associated with lower C2h INH (P = 0.04)	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	INH, RIF, PZA, and EMB Cmax, AUC0–4, and C2h	Nutritional status, dosing regimen	Dosing regimen associated with INH Cmax and AUC (P < 0.001)	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	H Cmax 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.[21]	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)	INH, RIF, PZA, and EMB Cmax and AUC0–8	Age, sex, nutritional status, prematurity, HIV status, ethnicity	mulation influenced RIF Cmax and AUC (P < .005); HIV status associated with lower PZA and EMB Cmax and AUC (P<0.02)	Favorable, n = 33; unfavorable, n = 6	All unfavorable outcomes were in children with poor social circumstances
Mukherjee et al.[27]	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	INH, RIF, PZA, and EMB Cmax, AUC0–4, 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 Cmax and AUC (P<0.01)	HIV+: favorable, n = 6; unfavorable, n = 17; LTFU, n = 1 HIV-: NR	No retrieved association
Antwi et al.[11]	Ghana; prospective monocenter	Median (IQR): INH, 11.2 (9.1–	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)	INH, RIF, PZA, and EMB Cmax	Sex, NAT2 for INH, dosing	HIV+ status associated with lower RIF and	Favorable, n = 99;	NR

	(n = 113)	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					and AUC0–8	regimen, HIV status	EMB Cmax and AUC and PZA AUC (P < .03); NAT2 genotype associated with INH Cmax and AUC (P<0.02)	unfavorable, n = 6; LTFU, n = 4	
Ranjalkar et al.[18]	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	INH and RIF Cmax, AUC0–6, 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 Cmax less than 8ug/ml
Dayal et al.[28]	India; prospective monocenter (n = 37)	NH, 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	INH and PZA Cmax and AUC0–8	Age, type of tuberculosis, BMI	PTB associated with lower INH AUC compared with PTB (P = .05); Age >3 y associated with higher PZA AUC (P = 0.001)	Favorable, n = 35; LTFU, n = 2	NR
Garcia-Prats et al.[17]	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	RIF Cmax and AUC_{0-24}	Dosing regimen	Analysis not published	NR	NR
Shah et al.[29]	India; prospective monocenter (n = 35)	INH, 10 mg/kg daily	PTB, n = 12; EPTB, n = 22	NR	Range 1–15	NR	INH Cmax and AUC_{0-24}	Age, sex, tuberculosis type, formulation, nutritional status	No retrieved association	NR	NR
Panjasawatwong et al.[22]	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 (0.2–12)	Median (range), 10.9 (4–43)	INH, RIF, PZA, and EMB Cmax 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
Justine et al.[22]	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	INH, RIF, PZA, and EMB C_{max}	Age, sex, dosing regimen, nutritional status	Dosing regimen associated with RIF and PZA Cmax (P = .005); malnutrition associated with decreased INH and RIF Cmax (P = 0.001)	NR	NR
Wobudeya et al.[30]	India, South Africa, Uganda, and Zambia; randomized, open label multicenter (n = 1024)	NH, 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	Unfavorable and LTFU, n = 16 for G1 and n = 18 for G2	No retrieved association
Nansumba et al.[31]	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	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

Discussion

We discovered that clinical outcomes in children treated for drug-susceptible tuberculosis are variable at WHO-recommended doses, with the majority achieving a favourable outcome, and that RIF, PZA, and EMB exposures are routinely lower in children than in adults and have been identified as risk factors for unfavourable outcomes.

Low RIF, INH, and PZA exposures have already been reported as predictors of unfavourable outcomes in studies. A higher clearance of medicines per kilogramme in younger children has also been identified as a factor. Malnutrition was identified as a significant risk factor for poor outcomes in two investigations. In 127 children from India, Mukherjee et al.[19] found 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 favourable and unfavourable outcomes, respectively ($p = 0.007$). Nansumba et al. found that severe malnutrition was a predictor of death in 144 Ugandan children, with a hazard ratio of 8.8 (95% CI 1.6-48.3).[31] Undernutrition is responsible for approximately 45% of global fatalities in children under the age of five, primarily in low- and middle-income countries, where more than a third of children under the age of five are stunted.[32,33] As a result, malnutrition is a major cause of death, and more research with an accurate assessment of nutritional status is required.

Higher RIF doses (in mg/kg) resulted in higher exposures but were still lower than the adult median AUC, implying that daily RIF doses >15 mg/kg in children >6 years old are required to match exposures in adults treated with 10 mg/kg. Modelling and simulation studies estimate that 25 mg/kg may be required to guarantee appropriate PK target exposure in children, and larger PK exposures may result in a higher proportion of favourable clinical outcomes.[14,34–36] One included study looked at doses that were higher than the current WHO recommendations and discovered larger exposures with a safe profile.[17] The current INH doses (7.5-15 mg/kg) appeared to be adequate overall. The key factor leading to exposure variability was NAT2 metabolizer status, which was much lower in quick metabolizers. NAT2 genotyping has been proposed[37,38], and a trial of genotype-based dosage in adults revealed improved clinical results and safety.[39]

Our study was constrained by inconsistent reporting of PK parameters, heterogeneous populations, disease status, and small sample sizes among studies. Due to the short half-life of the majority of drugs (approximately 3–4 hours), this has a minimal impact on the results, but it introduces uncertainty. Overall, PK variability and heterogeneity were substantial across all studies. We also found that CWHIV tend to have lower RIF AUCs than HIV-negative adolescents.

Conclusion

There is a scarcity of research data on paediatric dose of tuberculosis medications, reporting of PK parameters is inconsistent, and the populations are diverse. Drug exposure to RIF, PZA, and EMB in children is consistently lower than in adults at WHO recommended doses. The limits of available data suggest that paediatric dosing might benefit from additional research that is standardised in the measurement of PK parameters and incorporates assessments of safety, in conjunction with strong analytic methodologies, such as PK modelling.

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