EFFECTIVENESS AND PHARMACOKINETICS 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

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<tr>
<th>Database</th>
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<th>Results</th>
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<tbody>
<tr>
<td>PubMed</td>
<td>“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”</td>
<td>123</td>
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<tr>
<td>Cochrane Library</td>
<td>“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”</td>
<td>8400</td>
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<tr>
<td>Google Scholar</td>
<td>“Effectiveness” OR “Pharmacokinetics” AND “Anti TB Drugs” AND “Pediatrics”</td>
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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
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\textsuperscript{14,15,18}, INH\textsuperscript{14,19}, and PZA\textsuperscript{13}, as well as lower weight for age\textsuperscript{19}, poor social conditions\textsuperscript{21} and infection severity.\textsuperscript{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](image-url)

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<tr>
<th>Authors</th>
<th>Country &amp; study design</th>
<th>Dosing regimen</th>
<th>Type of TB</th>
<th>HIV Status</th>
<th>Age (y)</th>
<th>Body weight (kg)</th>
<th>Drugs pharmacokinetic parameter</th>
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<th>Factors affecting clinical outcome</th>
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<tr>
<td>Thee et al.\textsuperscript{23}</td>
<td>South Africa; prospective monocenter (n = 20)</td>
<td>5 and 10 mg/kg; RIF, 10 and 15 mg/kg; PZA, 25</td>
<td>PTB, n = 11; EPTB, n = 1; TBM, n = 8</td>
<td>5 HIV-1, 15 HIV-2</td>
<td>Mean (SD), 1.1 (0.5)</td>
<td>NR</td>
<td>H, RIF, and PZA Cmax and AUC \textsubscript{0-5}</td>
<td>Dosing regimen associated with Cmax and AUC for all drugs (P &lt; .001 for INH and PZA; P &lt; .006 for RIF) and NAT2 genotype with INH Cmax and AUC (P &lt; .05)</td>
<td>NR</td>
<td>NR</td>
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<td>Roy et al.\textsuperscript{24}</td>
<td>India; prospective monocenter (n = 20; G1, n = 7; G2, n = 13)</td>
<td>G1, PZA &gt; 30 mg/kg; G2, PZA &lt; 30–35 mg/kg</td>
<td>PTB; lymph node TB</td>
<td>NR</td>
<td>Mean (SEM), 5.6 (0.5) for G1 and 5.8 (0.2) for G2</td>
<td>PZA Cmax and AUC\textsubscript{0-24}</td>
<td>Dosing regimen associated with PZA Cmax and AUC (P &lt; .01)</td>
<td>NR</td>
<td>NR</td>
<td></td>
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<td>Ramachandran et al.\textsuperscript{25}</td>
<td>India; prospective multicenter (n = 84)</td>
<td>RNTCP guidelines</td>
<td>PTB, n = 19; EPTB, n = 63, PTB + EPTB, n = 2</td>
<td>84 HIV-</td>
<td>Mean (range), 7.1 (1.0–12.0)</td>
<td>NH, RIF, and PZA Cmax and AUC\textsubscript{0-8}</td>
<td>Age, NAT2 genotype, BMI, albumin, nutritional status, outcome</td>
<td>Younger age associated with lower Cmax and AUC for all drugs (P &lt; .01); malnutrition associated with decreased RIF Cmax and AUC (P &lt; .05); NAT2 genotype on INH Cmax and AUC (P = .001)</td>
<td>Favorable, n = 55; unfavorable, n = 15; LTFU, n = 14</td>
<td>RIF and INH Cmax lower in children with unfavorable outcomes (P &lt; .03); Rapid INH acetylator status associated with unfavorable outcomes (aOR 4.2; 95% CI, 1.1–15.4; P = .03)</td>
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Ramachandrman et al.\textsuperscript{11} 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\textsubscript{0–8} Age, sex, nutritional status, BMI, albumin, ART, NAT2 for INH, outcome Age <5 y with lower INH and PZA Cmax and AUC (P < 0.05); NAT2 genotype associated with INH Cmax and AUC (P < 0.02); 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 1.1–1.2; P = 0.01)

Rangari et al.\textsuperscript{13} India; prospective monocenter (n = 20; G1, n = 8; G2, n = 12) RNTCP guidelines; G1, INH >10 mg/kg; G2, INH = 1 mg/kg PTB; lymph node TB NR Median, 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\textsubscript{0–24} Dosing regimen Dosing regimen associated with RIF Cmax and AUC (P < 0.002) NR NR

Arya et al.\textsuperscript{15} India; prospective monocenter (n = 20) RNTCP guidelines; G1, INH >10 mg/kg; G2, RIF <10 mg/kg PTB; lymph node TB NR Median, 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\textsubscript{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 than 10 mg/kg and low Cmax and AUC; 5.8 μg/mL and 29.7 μg/h/mL, respectively

Mlotha et al.\textsuperscript{17} 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, and PZA, EMB Cmax<sub>0–24</sub> and Cmax<sub>0–60</sub> Age, dosing regimen Dosing regimen associated with RIF Cmax<sub>0–24</sub> (P = 0.03) NR NR

Hiruy et al.\textsuperscript{18} 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<sub>0–24</sub> and Cmax<sub>0–60</sub> Age, sex, nutritional status, HIV status HIV+ status associated with lower C2h INH (P = 0.04) NR NR

Mukherjee et al.\textsuperscript{19} India; prospective multicenter (n = 127; G1, n = 64; G2, n = 63) INH: G1, 5 (4.6) mg/kg; G2, 10 (7.5) 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+ Median, 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<sub>0–24</sub> and Cmax<sub>0–60</sub> Nutritional status, dosing regimen Dosing regimen associated with INH Cmax and AUC (P < 0.001) Favorable, n = 55 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 < 0.05). Confirmation of Mycobacterium tuberculosis associated with poor outcome (55.6% vs 16.4%; P = 0.01) G2 children with lower WAZ had poorer outcome

Bekker et al.\textsuperscript{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<sub>0–8</sub> Age, sex, nutritional status, premenstrual, HIV status, ethnicity mutation influenced RIF Cmax and AUC (P < 0.005); 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.\textsuperscript{23} 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+; Median (range), 32 HIV- Mean (SD), 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<sub>0–8</sub> Age, sex, nutritional status, NAT2 for INH, dosing regimen, HIV status Dosing regimen associated with lower C2h INH (P < 0.01); younger age associated with lower C2h INH (P = 0.04); HIV+ status associated with lower EMB Cmax (P < 0.05); NAT2 genotype associated with INH Cmax and AUC (P < 0.01) HIV+ favorable, n = 6; unfavorable, n = 17; LTFU, n = 1 HIV-: NR

Antwi et al.\textsuperscript{25} Ghana; prospective monocenter Median (IQR), INH, 11.2 (9.1–13) PTB, n = 85; EPTB, n = 28 54 HIV+; 59 HIV- Median (IQR), 3.0 (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

Journal of Advance Research in Medical & Health Science
ISSN: 2208-2425

Volume-9 | Issue-7 | July, 2023
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<td>Ranjalkar et al.</td>
<td>India; prospective multicenter (n = 41; G1, n = 27; G2, n = 14)</td>
<td>Median (IQR) for G1 (three-weekly): INH, 10 (8–12) mg/kg; RIF, 10 (9–12) mg/kg; EMB, 15–25 mg/kg</td>
<td>PTB, n = 36 (G1, n = 24; G2, n = 12); lymph node tuberculosis, n = 5 (G1, n = 3; G2, n = 2)</td>
<td>Median (IQR), 14–17 (12–24) for G1 and 37–41 (21–41) for G2</td>
<td>INH and RIF</td>
<td>Cmax and AUC</td>
<td>Favorable, n = 25 for G1 and n = 11 for G2; unfavorable, n = 2 for G1 and n = 3 for G2</td>
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<tr>
<td>Dayal et al.</td>
<td>India; prospective monocenter (n = 37)</td>
<td>INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg</td>
<td>PTB, n = 18 EPTB, n = 19</td>
<td>Median (IQR), 8 (3–10)</td>
<td>INH and PZA Cmax and AUC</td>
<td>No retrieved association</td>
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<tr>
<td>Garcia-Prats et al.</td>
<td>South Africa; prospective multicenter (n = 62)</td>
<td>RIF, G1, 15 20, then 35 mg/kg; G2, 35; then 50 mg/kg; G3, 60, then 75 mg/kg</td>
<td>PTB, n = 45 EPTB, n = 2; PTB + EPTB, n = 15</td>
<td>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</td>
<td>RIF Cmax</td>
<td>and AUC</td>
<td>Dosing regimen published</td>
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<tr>
<td>Shah et al.</td>
<td>India; prospective monocenter (n = 35)</td>
<td>INH, 10 mg/kg daily</td>
<td>PTB, n = 12 EPTB, n = 22</td>
<td>Range 1–15</td>
<td>INH Cmax and AUC</td>
<td>No retrieved association</td>
<td></td>
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<tr>
<td>Panjasawat et al.</td>
<td>Vietnam; prospective monocenter (n = 100)</td>
<td>INH, 5 mg/kg; RIF, 10 mg/kg; PZA, 25 mg/kg; EMB, 15 mg/kg</td>
<td>TBIM, n = 100</td>
<td>4 HIV+; 92 HIV−</td>
<td>INH, RIF, PZA, and EMB Cmax and AUC</td>
<td>None</td>
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<tr>
<td>Justine et al.</td>
<td>Tanzania; prospective monocenter (n = 51)</td>
<td>INH, 2–10 mg/kg; RIF, 5–20 mg/kg; PZA, 10–40 mg/kg; EMB, 7.5–35 mg/kg</td>
<td>PTB, n = 18 EPTB, n = 17; PTB + EPTB, n = 16</td>
<td>Median (range), 5.3 (0.75–14)</td>
<td>INH, RIF, PZA, and EMB Cmax</td>
<td>None</td>
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<tr>
<td>Wobudeya et al.</td>
<td>India, South Africa, Uganda, and Zambia; randomized, open label multicenter (n = 1024)</td>
<td>INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg; G1, 4 mg; G2, 6 mg</td>
<td>NR</td>
<td>127 HIV+; 897 HIV−</td>
<td>Range, 0.4–15</td>
<td>None</td>
<td>Unfavorable and LTFU, n = 16 for G1 and n = 18 for G2</td>
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<tr>
<td>Nansumba et al.</td>
<td>Uganda; prospective monocenter (n = 144)</td>
<td>INH, 10–15 mg/kg; RIF, 10–20 mg/kg; PZA, 30–40 mg/kg; EMB, 15–25 mg/kg</td>
<td>NR</td>
<td>48 HIV+; 94 HIV−</td>
<td>Range, 0.08–14; &lt;2, 44.4%; 2–5, 29.2%; ≥5, 26.4%</td>
<td>None</td>
<td>End of treatment</td>
</tr>
</tbody>
</table>

G1: both patients with an unfavorable outcome had RIF Cmax less than 8ug/ml

NR: not retrieved

*P<0.05, **P<0.01, ***P<0.001

Variance in nutritional status for INH Cmax and associated with INH Cmax and AUC

INH, RIF, PZA, and EMB Cmax and AUC

None

Infection associated with outcome

Severe malnutrition (WHZ less than or equal to -2) was a predictor of death (adjusted HR, 8.8; 95% CI 1.6–48.3)
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. 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). 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. 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. One included study looked at doses that were higher than the current WHO recommendations and discovered larger exposures with a safe profile. 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, and a trial of genotype-based dosage in adults revealed improved clinical results and safety.

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.

References


2018;57(5).