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

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Link to published version: https://doi.org/10.1183/13993003.01596-2022

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**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** https://bit.ly/3Vzw4f0

**Cite this article as:** Gafar F, Wasmann RE, McIlleron HM, *et al*. Global estimates and determinants of antituberculosis drug pharmacokinetics in children and adolescents: a systematic review and individual patient data meta-analysis. *Eur Respir J* 2023; 61: 2201596 [DOI: 10.1183/13993003.01596-2022].

This single-page version can be shared freely online.



This article has an editorial commentary: https://doi.org/10.1183/13993003.02003-2022

Received: 12 Aug 2022
Accepted: 10 Oct 2022

## Abstract

***Background*** Suboptimal exposure to antituberculosis (anti-TB) drugs has been associated with unfavourable treatment outcomes. We aimed to investigate estimates and determinants of first-line anti-TB 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 anti-TB 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 from 0 to 24 h post-dose ($AUC_{0–24}$) and peak plasma concentration ($C_{max}$) were assessed with random-effects models, normalised with current World Health Organization-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 of steady-state $AUC_{0–24}$ were summarised for isoniazid (18.7 (95% CI 15.5–22.6) $h \cdot mg \cdot L^{-1}$), rifampicin (34.4 (95% CI 29.4–40.3) $h \cdot mg \cdot L^{-1}$), pyrazinamide (375.0 (95% CI 339.9–413.7) $h \cdot mg \cdot L^{-1}$) and ethambutol (8.0 (95% CI 6.4–10.0) $h \cdot mg \cdot L^{-1}$). Our multivariate models indicated that younger age (especially <2 years) and HIV-positive status were associated with lower $AUC_{0–24}$ for all first-line anti-TB 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 $AUC_{0–24}$.

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