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Pharmacokinetics of anti-TB drugs in children and adolescents with drug-resistant TB: a multicentre observational study from India

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Background: Drug-resistant tuberculosis (DR-TB) is one of the challenging forms of TB to treat, not only in adults but also in children and adolescents. Further, there is a void in the treatment strategy exclusively for children due to various reasons, including paucity of pharmacokinetic (PK) data on anti-TB drugs across the globe. In this context, the present study aimed at assessing the PK of some of the anti-TB drugs used in DR-TB treatment regimens.

Method: A multicentre observational study was conducted among DR-TB children and adolescents ($n=200$) aged 1–18 years (median: 12 years; IQR: 9–14) treated under programmatic settings in India. Steady-state PK (intensive: $n=89$; and sparse: $n=111$) evaluation of moxifloxacin, levofloxacin, cycloserine, ethionamide, rifampicin, isoniazid and pyrazinamide was carried out by measuring plasma levels using HPLC methods.

Results: In the study population, the frequency of achieving peak plasma concentrations ranged between 13% (for rifampicin) to 82% (for pyrazinamide), whereas the frequency of suboptimal peak concentration for pyrazinamide, cycloserine, moxifloxacin, levofloxacin and rifampicin was 15%, 19%, 29%, 41% and 74%, respectively. Further, the frequency of supratherapeutic levels among patients varied between 3% for pyrazinamide and 60% for isoniazid. In the below-12 years age category, the median plasma maximum concentration and 12 h exposure of moxifloxacin were significantly lower than that of the above-12 years category despite similar weight-adjusted dosing.

Conclusions: Age significantly impacted the plasma concentration and exposure of moxifloxacin. The observed frequencies of suboptimal and supratherapeutic concentrations underscore the necessity for dose optimization and therapeutic drug monitoring in children and adolescents undergoing DR-TB treatment.

Introduction

TB is the second leading cause of death from an infectious disease and is caused by the bacterium *Mycobacterium tuberculosis*. According to the WHO Global Tuberculosis Report 2023, there were approximately 7.5 million newly diagnosed TB cases worldwide, with children aged 0–14 years accounting for 12% of these cases. Additionally, around 1.3 million deaths from TB among HIV-negative individuals were recorded globally in 2022.[1] India contributes 27% of the global TB cases and accounts for 29% of TB deaths out of 81% of the global number of deaths occurred in WHO African and South-East regions among HIV-negative people. Although data on mortality among Indian children are limited, 16% of global TB deaths among HIV-negative individuals are in children aged under 15. Additionally, India represents a significant proportion of the global burden of drug-resistant tuberculosis (DR-TB) cases.[1] According to the India TB report, in the year 2022 in India there were 63 801 cases diagnosed with DR-TB, including MDR/rifampicin-resistant (RR)-TB, pre-extensively drug-resistant TB (Pre-XDR-TB) and isoniazid (H) mono/poly DR-TB; of these, 57 749 cases were receiving their respective treatment.[2] However, the number of cases involving children aged below 15 years is lacking. Further, due to the lack of prevalence studies in the paediatric population with DR-TB, it is difficult to ascertain the actual number in the Indian context.

According to the WHO Report of 2023, the treatment success rate of MDR/RR-TB was estimated to be 63%,[1] although a better treatment outcome is reported among children with DR-TB compared with adolescents and adults.[3,4] Nevertheless, a significant proportion of patients do not achieve successful treatment outcomes due to various factors. Among these, the attainment of therapeutic concentration and/or optimal exposure to anti-TB drugs upon treatment is one of the crucial determinants of treatment outcome and failure.[5,6] The pharmacokinetics (PK) of anti-TB drugs are influenced by several host factors, including age, sex, nutritional status, comorbidities and genetics, and this PK variability results in differences in attaining the target drug concentration and exposure for a given dose among individuals.[7] The current DR-TB treatment guidelines for children are extrapolated from the adult data, due to a lack of paediatric-specific regimens and dosing strategies compounded by limited PK data for anti-TB drugs in children.[3,8,9] Therefore, we conducted a multicentre observational study to describe the PK of selected anti-TB drugs in the DR-TB treatment regimen and identify predictors of PK variability in children and adolescents within programmatic settings in India.

Methods

Ethics

The institutional ethics committee (IEC) approvals were obtained before initiating the study from the respective participating institutes/sites [National Institute for Research in Tuberculosis (NIRT), NIRT-IEC No. 2019005; B.J. Medical College and Hospital (BJMCH), IEC-BJWHC/64/2019; Sir J J Group of Hospitals, No. IEC/Pharm/ICMR Project/713; and National Institute for Tuberculosis and Respiratory Diseases (NITRD), No. NITRD/EC/2021/3512].

Study design and population

This was a prospective observational study, conducted in children and adolescents with DR-TB at different institutes/centres in India according to the following inclusion criteria: (i) aged 1–18 years, and (ii) diagnosed with isoniazid (H)-resistant mono/poly or rifampicin-resistant (RR) or MDR TB with or without any additional resistance. In addition, the patients included were clinically stable and interested in participating in the study irrespective of their treatment regimen duration; i.e. both longer and shorter regimens. However, HIV-positive children were not included in the study. The purpose of the study and the procedures involved were explained, and an informed written consent or assent was obtained for all participating individuals or guardians before inducting them into the study. The management of DR-TB was as per the latest guidelines of the National TB Elimination Program (NTEP), Government of India, followed from time to time, and all drugs supplied were through the Program.

Sample size calculation

The sample size was calculated based on a PK study reported in children with MDR-TB from Agra, India.[10] Considering the mean plasma cycloserine concentration (32.5 μg/mL) and SD (14.1) with an absolute precision of 2% and accounting for dropouts at the 5% level, the sample size required for this study was estimated as 200 children ($n = 200$).

Conduct of PK study

The PK study was conducted between 2019 and 2022 across multiple centres in India, under the supervision of experienced paediatricians. Initially, intensive PK assessments were completed for 89 patients. However, the onset of the COVID-19 pandemic halted recruitment, leading the Expert Committee on Project Monitoring and Evaluation to recommend revising the study protocol. To minimize hospitalization risks, the protocol was adapted to include sparse PK evaluations instead of intensive PK. Consequently, the study incorporated both intensive ($n = 89$) and sparse ($n = 111$) PK assessments ($N = 200$). Detailed clinical examinations were conducted, and demographic, disease, and treatment regimen data were systematically recorded.

The intensive PK study was conducted at the respective study sites, where the children were receiving treatment for a minimum period of 2 weeks. Eligible participants were admitted into the hospital at least 1 day before conducting the PK assessment. On the day of the PK study, under fasted conditions, blood (~3 mL) was collected in a heparin vacutainer tube ('0' h/pre-dose), followed by administration of appropriate anti-TB medications on an empty stomach under direct supervision. The time of drug administration was noted and then blood samples (~3 mL) were collected at 2, 4, 6, 8 and 12 h post-drug administration in heparin vacutainer tubes.

The sparse PK study was performed similarly to the intensive PK study without hospitalization and limited blood samples were collected at '0' h/pre-dose and 2 and 4 h post-dose administration in the eligible participants. Blood samples were centrifuged at 5000 rpm for 10 min and then plasma was separated, aliquoted and stored at −80°C. All the plasma samples collected at different sites were transported to the National Institute for Research in Tuberculosis (NIRT) under dry-ice shipping conditions for drug measurements.

Plasma drug measurement by reverse phase-HPLC

Plasma concentrations of moxifloxacin, levofloxacin, ethionamide, cycloserine, rifampicin, isoniazid and pyrazinamide were measured by using validated HPLC methods as reported.[11–16]

Statistical analysis

Values for continuous variables are presented as medians with IQRs, whereas categorical variables are reported as frequencies with percentages. The Shapiro–Wilk test was used to evaluate the normality of the PK data. Intensive PK data were analysed using a non-compartmental model in Stata 15.0 (StataCorp, College Station, TX, USA). The plasma C_{max} was determined from time-course drug concentration data, and the AUC_{0-12} was calculated using the linear trapezoidal method. Apparent clearance (CL/F) was calculated by dividing the dose by the AUC, whereas the elimination half-life ($t_{½}$) and volume of distribution (Vd/F) were determined using the natural log of 2 and clearance, respectively, divided by the elimination rate constant. For comparative analyses, the non-parametric Mann–Whitney *U* test was applied to evaluate drug-related continuous variables across age groups, whereas the Kruskal–Wallis test was employed for comparisons across different time periods. The proportion of patients achieving C_{max} within the therapeutic range for each anti-TB drug was calculated and compared between factors using Fisher's exact test. Associations between log-transformed PK parameters (C_{max} and AUC) and demographic factors such as age and body weight were assessed using the Pearson correlation test. Statistical significance was considered at $P \leq 0.05$ level.

Results

Demographic characteristics

Demographic details of the study participants are given in Table 1. Overall, the total study population ($N = 200$) had a median age of 12 years (IQR: 9–14) with a mean body weight of 30 kg (IQR: 22–38). Among them, 31% were males and 69% females, with pulmonary TB cases accounting for 57% and extrapulmonary TB cases for 43% (Table 1).

Table 1. Demographics of the study participants[a]

	Intensive PK (n=89)	Sparse PK (n=111)	Combined (n=200)
Age (y)	11.5 (9–14)	12 (9–14)	12 (9–14)
≤12 y	55 (61%)	59 (53%)	114 (57%)
>12 y	34 (39%)	52 (47%)	86 (43%)
Weight (kg)	30.5 (22–38)	30.0 (23–38)	30 (22–38)
Gender			
Male	35 (39%)	28 (25%)	63 (31%)
Female	54 (61%)	83 (75%)	137 (69%)
Pulmonary TB	54 (61%)	59 (53%)	113 (57%)
Extra-pulmonary TB	35 (39%)	52 (47%)	87 (43%)

[a]Values are median with interquartile range or frequency with percentage.

PK of anti-TB drugs

From the PK data (combining intensive and sparse PK), the frequencies and percentages of the study population who achieved the target concentration or suboptimal or supratherapeutic levels of various anti-TB drugs are given in Table 2, based on the therapeutic ranges as reported earlier.[17–19] Among fluoroquinolones, the target plasma concentration of moxifloxacin (3–5 μg/mL) and levofloxacin (8–12 μg/mL) was achieved among 34% and 32% of the study population, respectively. From the samples analysed for cycloserine and ethionamide, the respective target concentrations of 20–35 μg/mL and 1–5 μg/mL achieved among DR-TB were 44% and 76%. For the first-line anti-TB drugs, the target concentrations of rifampicin (8–24 μg/mL), isoniazid (3–6 μg/mL) and pyrazinamide (20–50 μg/mL) were achieved among 13%, 40% and 82% of the study participants, respectively.

Non-compartmental PK evaluation of moxifloxacin, levofloxacin, ethionamide, cycloserine, rifampicin, isoniazid and pyrazinamide was carried out for the intensive PK samples and is presented in Table 3. From the sparse PK samples, plasma C_{max} and time to reach plasma maximum concentration (T_{max}) were calculated and are given in Table 4. The plasma concentrations of various anti-TB drugs at various time intervals during PK evaluation (both intensive and sparse) are presented as violin plots (Figure S1, available as Supplementary data at *JAC* Online) and they show the pattern of drug absorption, peak concentration and declining/elimination phase over a period of time (i.e. 0 to 12 h). In addition, the C_{max} of different age groups is given in a violin plot diagram (Figure S2, available as Supplementary data at *JAC* online).

Factors influencing the PK of anti-TB drugs

Due to the limited sample size, the PK data were not stratified for all the anti-TB drugs measured according to different age or by sex, except for a few antibiotics by categorizing the age into two, i.e. below-12 years age and above-12 years age (based on the median age of this study population), and compared (Table 5). Accordingly, the median dose administered for moxifloxacin, cycloserine, rifampicin and pyrazinamide in the above-12 years age group was significantly higher than in the

Table 2. Frequency and percentage—based on therapeutic range/target concentration[a]

Anti-TB drugs	Therapeutic range, μg/mL	Subtherapeutic	Therapeutic	Supratherapeutic
Moxifloxacin (n=102)	3–5	29 (29%)	35 (34%)	38 (37%)
Levofloxacin (n=34)	8–13	14 (41%)	11 (32%)	9 (27%)
Cycloserine (n=147)	20–35	28 (19%)	64 (44%)	55 (37%)
Ethionamide (n=25)	1–5	—	19 (76%)	6 (24%)
Rifampicin (n=15)	8–24	11 (74%)	2 (13)%	2 (13%)
Isoniazid (n=10)	3–6	—	4 (40%)	6 (60%)
Pyrazinamide (n=34)	20–50	5 (15%)	28 (82%)	1 (3%)

[a]The data represent the frequency and percentage of the study participants based on their plasma drug concentration from intensive and sparse PK according to the therapeutic range.

below-12 years age group. After adjusting the dose for body weight, the median dose of cycloserine and rifampicin was found to be significantly lower (15.0 versus 13.2 mg/kg and 14.9 versus10.9 mg/kg, respectively) than that of the below-12 years category. However, the median C_{max} of the cycloserine was significantly higher than the below-12 years category, whereas rifampicin C_{max} showed no such differences. On the contrary, the median C_{max} and exposure (or AUC_{0-12}) of moxifloxacin for the above-12 years category were significantly higher than for the below-12 years category. Similarly, the exposure of pyrazinamide was also high in the above-12 years category. Notably, compared to the below-12 years category, the median elimination $t_{½}$ for rifampicin and pyrazinamide, and the apparent *V*d/F for rifampicin were significantly higher in the above-12 years age category.

Fisher's exact test was performed to assess the association of age with the target concentration/therapeutic range, according to different age categories, and revealed that moxifloxacin alone showed a significant association ($P < 0.03$), whereas no such association was found with other drugs in this study population (Table 6). Further, Pearson correlation analysis showed that age and body weight significantly correlated with C_{max} ($P < 0.0007$ and $P < 0.0498$, respectively) and drug exposure (AUC_{0-12}) ($P < 0.0004$ and $P < 0.0253$, respectively) of moxifloxacin alone (Figure 1a and b).

Discussion

The present observational study provides the PK of some of the anti-TB drugs, namely moxifloxacin, levofloxacin, ethionamide, cycloserine, rifampicin, isoniazid and pyrazinamide, that were used in the treatment of DR-TB in children and adolescents within the programmatic settings. It found that most of the PK parameters of these anti-TB drugs were within the expected range reported for the WHO-recommended dosage. However, the discussion primarily emphasizes age-based differences in the PK of these anti-TB drugs.

Fluoroquinolones, particularly moxifloxacin and levofloxacin, the broad-spectrum repurposed antibiotics, are among the key constituents of drug regimens for DR-TB. The median C_{max} obtained for the moxifloxacin dose administered was within the expected range of 3–5 µg/mL in the below- and above-12 year categories. Previously, Thee *et al.*[20] reported a median C_{max} of 3.08 µg/mL (IQR: 2.85–3.82) for moxifloxacin in South African MDR-TB children with a median age of 11 years (IQR: 9.2–12.0). Notably, most of these PK parameters (particularly in HIV-uninfected children) were similar and comparable to our current study for the below-12 years age category . However, the overall frequency of supratherapeutic level was 37% among the study participants. Earlier safety studies have shown moxifloxacin to be a well-tolerated antibiotic even at higher doses (ranging between 600 and 800 mg)[21,22] and thus the median dose of 300 mg (IQR: 300–400) and 450 mg (IQR: 400–600) for the below- and above-12 years age categories, respectively, indicates they were within the tolerable limit. Conversely, the suboptimal concentration of moxifloxacin (29%) observed in this study is another key concern. Nijland *et al.*[23] reported a reduction in plasma moxifloxacin concentration due to rifampicin co-administration, which resulted in the induction of

Table 3. Basic characteristics of intensive pharmacokinetic data[a]

Intensive PK parameters ($N = 89$)	Moxifloxacin ($n = 59$)	Levofloxacin ($n = 12$)	Cycloserine ($n = 52$)	Ethionamide ($n = 6$)	Rifampicin ($n = 15$)	Isoniazid ($n = 9$)	Pyrazinamide ($n = 26$)
Dose, mg	400 (300–400)	750 (750–750)	375 (275–500)	500 (400–500)	450 (300–450)	300 (200–600)	1250 (750–1250)
Dose, mg/kg	12.6 (11.8–14.3)	20.2 (16.3–21.9)	14.7 (13.3–16.4)	12.7 (12.5–12.8)	12.5 (10.0–13.2)	11.5 (9.4–15.1)	32.6 (27.8–35.7)
C_{max}, mg/L	4.1 (3.0–5.5)	8.6 (6.9–11.0)	33.6 (24.7–43.9)	4.2 (2.2–5.2)	4.7 (3.5–9.0)	6.47 (5.29–7.0)	38.2 (32.6–46.4)
T_{max}, h	2.0 (2.0–4.0)	4.0 (3.0–4.0)	4.0 (2.0–4.0)	2.0 (2.0–2.0)	4.0 (2.0–6.0)	2.0 (2.0–2.0)	4.0 (2.0–4.0)
AUC_{0-12}, mg·h/L	28.6 (19.0–41.3)	66.2 (53.8–82.4)	296.5 (207.6–372.0)	21.7 (14.6–40.1)	33.3 (16.8–44.2)	33.7 (27.0–41.5)	328.5 (275.2–381.2)
$t_{½}$, h	5.7 (4.0–7.4)	7.5 (6.3–10.5)	11.7 (7.7–16.0)	5.5 (3.4–7.6)	3.4 (2.1–5.3)	4.4 (2.7–5.3)	11.33 (8.2–13.6)
*V*d/F, L	72.6 (45.4–102)	76.8 (51.1–126)	10.9 (7.8–14.4)	121.1 (89–194)	61.5 (25.7–139)	37.9 (30.9–73.8)	26.4 (18.8–37.8)
Clearance, L/h	8.0 (5.8–14.2)	6.6 (5.2–9.4)	0.63 (0.42–1.12)	16.6 (10.4–27.0)	10.8 (6.6–26.9)	7.2 (5.8–13.7)	1.9 (1.5–2.7)

[a]Non-compartmental pharmacokinetic evaluation of anti-TB drugs. Values are expressed as median with IQR.

Table 4. Basic characteristics of sparse pharmacokinetic data[a]

Sparse PK parameters ($N=111$)	Moxifloxacin ($n=43$)	Levofloxacin ($n=22$)	Cycloserine ($n=95$)	Ethionamide ($n=19$)	Pyrazinamide ($n=8$)
Dose, mg	400 (400–400)	500 (250–500)	250 (250–500)	500 (250–500)	875 (375–1225)
Dose, mg/kg	13.6 (10.3–16.7)	20.8 (15.2–22.9)	11.1 (7.8–16.1)	13.5 (9.4–16.7)	29.0 (23.7–34.0)
C_{max}, mg/L	4.6 (2.9–5.7)	8.1 (6.6–12.8)	30.7 (20.7–38.7)	2.9 (1.4–4.8)	28.9 (18.2–40.5)
T_{max}, h	2.0 (2.0–4.0)	4.0 (2.0–4.0)	4.0 (2.0–4.0)	4.0 (2.0–4.0)	2.0 (1.0–4.0)

[a]Non-compartmental pharmacokinetic evaluation of anti-TB drugs. Values are expressed as median with IQR.

glucuronidation and sulphation of moxifloxacin. However, the interactions of other co-administered drugs with moxifloxacin may not be ruled out in this study. Although the exact cause is not known, and it warrants further investigations, the age-dependent PK variability and suboptimal concentration of moxifloxacin have been reported among DR-TB patients, including in India.[10,20,21] Besides, the frequency of suboptimal plasma peak concentration of levofloxacin was 41% for the dose of 20 mg/kg. Previously, some of the studies including individual patient data meta-analysis in children have reported inadequate drug exposure of levofloxacin for the dose 20 mg/kg and indicated a need for revision of dosage in the paediatric population.[24–26] The current study reiterates that age influences the C_{max} and drug exposure of moxifloxacin. Being potent sterilizing agents, the fluoroquinolones moxifloxacin and levofloxacin are used not only in the treatment regimen for DR-TB but also in drug-susceptible TB (DS-TB), particularly the former one. Therefore, there is a need to revisit the dosage of moxifloxacin and levofloxacin in the treatment regimen for DR-TB in children.

The target plasma concentration of cycloserine is expected to be 20–35 µg/mL for the administered dose of 250–500 mg, whereas the median C_{max} of the above-12 years age category was at supratherapeutic levels, despite the median dose administered being 500 mg (IQR: 375–500). On the other hand, the median C_{max} observed in the below-12 years category was comparable to a previous study from India, where a median C_{max} of 31.8 µg/mL (IQR: 10.6–63.0) for cycloserine was reported among DR-TB children with a median age of 16 years (IQR: 5–18).[10] However, the overall frequency of suboptimal level (19%) of cycloserine was lower than that of earlier reports, in which the frequency ranged between 44% and 71%.[22,27,28] On the contrary, the frequency of supratherapeutic levels (37%) was almost similar to that of a previous study by Hemanth Kumar *et al.*,[10] in which 40% of the children treated for DR-TB showed high levels of cycloserine (i.e. >35 µg/mL). Importantly, the peak plasma concentration (1–5 µg/mL) of ethionamide was attained among 76% of the population studied, whereas 24% had supratherapeutic levels. Similarly, plasma peak concentration (3–6 µg/mL) of isoniazid, an important first-line drug, was attained in all the study participants; however, 60% of them had supratherapeutic levels. Chirehwa *et al.*[29] reported a novel drug–drug interaction of ethionamide and isoniazid resulting in increased exposure of the former in South African patients with MDR-TB. However, due to limited sample size and varied combination of drugs among individuals treated for DR-TB, drug–drug interactions were not addressed in this study's data and it is one of the major limitations.

Administration of a rifampicin dose at 10 mg/kg is expected to produce the target plasma concentration of 8–24 µg/mL, although studies have reported C_{max} ranging from 5.79 to 6.6 µg/mL.[19,30,31] In the current study, the PK data of rifampicin were from a very limited number of patients (i.e. $n=15$) and thus were inconclusive. However, the low median C_{max} of rifampicin observed for the above-12 years age category (3.9 µg/mL; IQR: 3.1–6.0) was similar to a study by Seth *et al.*,[32] who reported a C_{max} range of 3.3–3.8 µg/mL. In this study, 11 of 15 subjects (74%) had low plasma rifampicin levels (<8 µg/mL). Ramachandran *et al.*[33] reported a frequency of 90% low plasma rifampicin among children treated for TB in India. Several factors, including nutritional status and other clinical conditions, are associated with low drug levels; however, the exact cause for low rifampicin is yet to be ascertained.[31]

The PK data of another first-line anti-TB drug, pyrazinamide, showed a high drug exposure in the above-12 years age category, possibly due to a long half-life, compared with the below-12 years category. However, there were no changes in the clearance rate or apparent volume of distribution. Notably, nearly 82% of the study population attained the expected plasma concentration of pyrazinamide (i.e. 20–50 µg/mL), whereas the sub- and supratherapeutic levels were found to be 15% and 3%, respectively. Previously, studies have reported a frequency of 8.7% for low plasma pyrazinamide level, and age, sex and delayed absorption have been identified as affecting the plasma drug concentrations.[18,34–36]

The study's primary focus on assessing the PK of selected anti-TB drugs limited the collection of data on treatment outcomes and adverse events, precluding any analysis of their relationship with plasma drug levels or exposure—a major limitation of this study. Additionally, the variability in treatment regimens across centres, involving different combinations of anti-TB drugs tailored by treating physicians based on treatment outcomes/responses, comorbidities and adverse events, hindered the ability to analyse potential drug–drug interactions. This represents another significant limitation in explaining the observed PK variability of these drugs. Furthermore, the revised study protocol necessitated by the COVID-19 pandemic resulted in a reduced sample size for the intensive PK analysis. This limitation restricted data stratification by weight, age and sex, thereby constraining the statistical analysis, interpretation and conclusions for most of the anti-TB drugs. As a result, the clinical implications of the study's findings remain uncertain. Despite these limitations, the study has merit as one of the few multicentre observational studies from India that provides evidence on plasma anti-TB drug levels in children and adolescents treated for DR-TB in programmatic settings.

Table 5. Intensive pharmacokinetic data analysis based on age[a]

PK parameters	Moxifloxacin ($n=59$)			Cycloserine ($n=52$)			Rifampicin ($n=15$)			Pyrazinamide ($n=52$)		
	≤12 y ($n=41$)	>12 y ($n=18$)	*P* value	≤12 y ($n=39$)	>12 y ($n=13$)	*P* value	≤12 y ($n=5$)	>12 y ($n=10$)	*P* value	≤12 y ($n=39$)	>12 y ($n=13$)	*P* value
Dose, mg	300 (300–400)	450 (400–600)	**<0.001**	375 (250–500)	500 (375–500)	**0.038**	300 (300–300)	450 (450–450)	**0.031**	750 (600–1200)	1250 (1200–1250)	**0.002**
Dose, mg/kg	12.5 (11.8–13.5)	12.9 (11.2–15.3)	0.711	15.0 (13.9–16.7)	13.2 (10.5–14.7)	**0.029**	14.9 (13.7–21.9)	10.9 (9.8–12.5)	**0.011**	36.6 (30.6–37.5)	32.5 (27.2–34.7)	0.203
C_{max}, mg/L	3.8 (2.9–4.8)	5.4 (3.9–7.5)	**0.006**	31.9 (22.9–38.3)	42.3 (33.4–51.8)	**0.02**	7.6 (7.0–9.0)	3.9 (3.1–6.0)	0.066	35.5 (8.3–48.7)	38.9 (32.7–46.4)	0.26
T_{max}, h	4 (2–4)	2 (2–4)	0.32	4 (2–4)	2 (2–4)	0.358	2 (2–2)	6 (4–6)	**0.033**	4 (2–6)	4 (2–4)	0.901
AUC_{0-12}, mg·h/L	24.9 (17.9–33.3)	39.2 (28.6–51.3)	**0.003**	279.7 (176.0–368.6)	327.4 (268.8–478.1)	0.097	39.7 (27.2–44.2)	30.7 (14.5–35.2)	0.391	247.4 (63.0–327.9)	344.2 (299.7–391.0)	**0.026**
$t_{½}$, h	5.5 (4.1–6.6)	6.6 (3.7–8.1)	0.41	12.0 (8.2–16.4)	9.9 (7.4–11.8)	0.101	1.91 (1.6–2.1)	4.7 (3.4–8.4)	**0.002**	6.3 (3.8–11.4)	11.6 (9.7–14.0)	**0.019**
Clearance, L/h	8.0 (5.81–14.3)	8.2 (6.4–11.7)	0.947	0.62 (0.39–1.42)	0.72 (0.58–1.1)	0.824	7.39 (6.6–10.9)	12.3 (7.1–28.1)	0.391	1.7 (1.5–15.3)	1.9 (1.5–2.5)	0.623
Vd/F, L	75.2 (45.1–107.0)	70.2 (57.7–84.9)	0.961	11.4 (7.8–16.8)	10.4 (8.4–12.2)	0.369	22.9 (22.4.-25.7)	101.1 (51.0–154.0)	**0.007**	16.8 (15.0–74.4)	27.9 (25.0–37.8)	0.156

Bold values denote statistically significant at $P < 0.05$ level.
[a]Non-compartmental pharmacokinetic evaluation of anti-TB drugs. Values are median with IQR. Non-parametric Mann–Whitney *U* test was performed and $P<0.05$ considered significant.

Table 6. Peak plasma concentration of drugs based on target concentration with age group[a]

Drug levels, µg/mL	Age group			Total	*P* value
	1 to 5 y	6 to 12 y	13 to 18 y		
Moxifloxacin ($n=102$)					
Subtherapeutic (<3)	3 (30)	13 (24)	13 (34)	29 (29)	**0.030**
Therapeutic (3–5)	5 (50)	24 (44)	6 (16)	35 (34)	
Supratherapeutic (>5)	2 (20)	17 (32)	19 (50)	38 (37)	
Levofloxacin ($n=34$)					
Subtherapeutic (<8)	3 (50)	6 (60)	5 (28)	14 (41)	0.494
Therapeutic (8–13)	1 (17)	2 (20)	8 (44)	11 (32)	
Supratherapeutic (>13)	2 (33)	2 (20)	5 (28)	9 (27)	
Cycloserine ($n=147$)					
Subtherapeutic (<20)	1 (6)	15 (20)	12 (21)	28 (19)	0.542
Therapeutic (20–35)	10 (55)	29 (40)	25 (45)	64 (44)	
Supratherapeutic (>35)	7 (39)	29 (40)	19 (34)	55 (37)	
Ethionamide ($n=25$)					
Subtherapeutic (<1)	—	—	—	—	0.659
Therapeutic (1–5)	1 (50)	3 (75)	15 (79)	19 (76)	
Supratherapeutic (>5)	1 (50)	1 (25)	4 (21)	6 (24)	
Rifampicin ($n=15$)					
Subtherapeutic (<8)	1 (100)	2 (50)	8 (80)	11 (73)	0.416
Therapeutic (8–24)	—	2 (50)	2 (20)	4 (27)	
Supratherapeutic (>24)	—	—	—	—	
Isoniazid ($n=10$)					
Subtherapeutic (<3)	—	—	—	—	0.190
Therapeutic (3–6)	—	3 (75)	1 (17)	4 (40)	
Supratherapeutic (>6)	—	1 (25)	5 (83)	6 (60)	
Pyrazinamide ($n=34$)					
Sub-therapeutic (<20)	—	4 (40)	1 (5)	5 (15)	0.064
Therapeutic (20–50)	2 (100)	6 (60)	20 (90)	28 (82)	
Supratherapeutic (>50)	—	—	1 (5)	1 (3)	

Bold value denotes statistically significant at $P < 0.05$ level.
[a]Values are expressed in frequency and percentage. Fisher's exact test was performed to assess the association of age with plasma drug concentration, and $P<0.05$ level was considered significant.

In conclusion, age and body weight significantly impacted the plasma maximum concentration and exposure of moxifloxacin in children and adolescents undergoing DR-TB treatment. Among this study population, the frequency of target concentration achieved for the WHO-recommended dosage of rifampicin, levofloxacin, moxifloxacin, isoniazid, cycloserine, ethionamide and pyrazinamide ranged between 13% and 82%, whereas the frequency of supratherapeutic levels varied between 3% and 60%. Except for ethionamide and isoniazid, the frequency of suboptimal concentrations of other anti-TB drugs ranged between 15% and 74%. Overall, this study highlights the critical need for dose optimization and therapeutic drug monitoring of anti-TB drugs within programmatic settings in India, particularly in paediatric and adolescent populations treated for DR-TB. Therefore, implementing these strategies is essential not only for enhancing drug efficacy and minimizing adverse events but also for advancing TB elimination efforts.

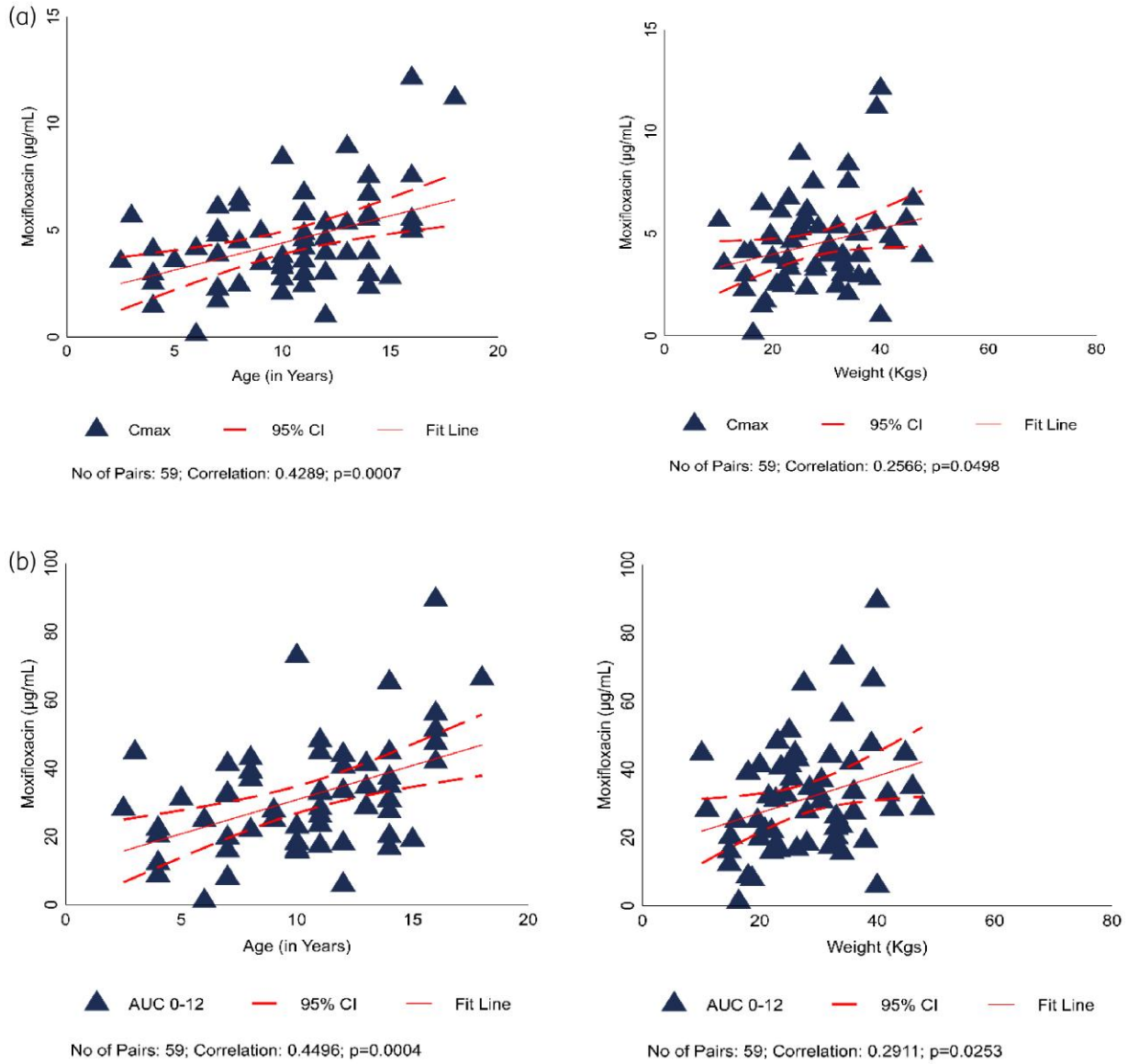

Figure 1. Pearson correlation analysis for moxifloxacin. (a) Plasma maximum concentration (C_{max}) and (b) drug exposure (AUC_{0-12}) with age and body weight. Statistical significance was considered at $P < 0.05$ level. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

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Transparency declarations

None to declare.

Author contributions

H.K.A.K.: conceptualization, study design and funding. I.S., S. Mane, S.S., P.G., S.G., V.P., Z.N., V.O., P.G., S.B.B., S.R. and A.F.: enrolment and management of participants. P.C.: recruitment and co-ordination of sites and critical review of the manuscript. B.R.T., S.V., V.A., S.M.M.: sample analysis. K.T.: data analysis. S.M.J.: analysis, data interpretation and manuscript preparation. All the authors read and approved the final version of the manuscript for submission.

Supplementary data

Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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