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Moxifloxacin Pharmacokinetics, Cardiac Safety, and Dosing for the Treatment of Rifampicin-Resistant Tuberculosis in Children

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Background. Moxifloxacin is a recommended drug for rifampin-resistant tuberculosis (RR-TB) treatment, but there is limited pediatric pharmacokinetic and safety data, especially in young children. We characterize moxifloxacin population pharmacokinetics and QT interval prolongation and evaluate optimal dosing in children with RR-TB.

Methods. Pharmacokinetic data were pooled from 2 observational studies in South African children with RR-TB routinely treated with oral moxifloxacin once daily. The population pharmacokinetics and Fridericia-corrected QT (QTcF)-interval prolongation were characterized in NONMEM. Pharmacokinetic simulations were performed to predict expected exposure and optimal weight-banded dosing.

Results. Eighty-five children contributed pharmacokinetic data (median [range] age of 4.6 [0.8–15] years); 16 (19%) were aged <2 years, and 8 (9%) were living with human immunodeficiency virus (HIV). The median (range) moxifloxacin dose on pharmacokinetic sampling days was 11 mg/kg (6.1 to 17). Apparent clearance was 6.95 L/h for a typical 16-kg child. Stunting and HIV increased apparent clearance. Crushed or suspended tablets had faster absorption. The median (range) maximum change in QTcF after moxifloxacin administration was 16.3 (–27.7 to 61.3) ms. No child had QTcF ≥500 ms. The concentration–QTcF relationship was nonlinear, with a maximum drug effect (E_{max}) of 8.80 ms (interindividual variability = 9.75 ms). Clofazimine use increased E_{max} by 3.3-fold. Model-based simulations of moxifloxacin pharmacokinetics predicted that current dosing recommendations are too low in children.

Conclusions. Moxifloxacin doses above 10–15 mg/kg are likely required in young children to match adult exposures but require further safety assessment, especially when coadministered with other QT-prolonging agents.

Keywords. pharmacokinetics; tuberculosis; moxifloxacin; pediatrics.

Moxifloxacin is a high-priority drug for rifampicin-resistant tuberculosis (RR-TB) treatment [1]. It is recommended by the World Health Organization (WHO) for use in both short (9–11 month) and longer (≥18 months) regimens [1]. Moxifloxacin has higher potency and better penetration into and activity in lesions than levofloxacin [2–5]. It had demonstrated clinical efficacy in a phase 3 clinical trial of RR-TB and was associated with better TB treatment outcomes in a large individual participant data meta-analysis [6, 7]. Recently, moxifloxacin was a key component in the first shortened treatment regimen for drug-susceptible TB, which was noninferior to the standard 6-month regimen, further establishing its importance for TB treatment [8].

Despite its proven efficacy in adults, pediatric use of moxifloxacin has been limited, in part due to lack of pharmacokinetic and safety data, especially in young children with TB. Moxifloxacin is eliminated partly through metabolism (52%) by glucuronidation and sulfate conjugation with a half-life of 10–14 hours [9]. It has good bioavailability, and food minimally affects its absorption [9, 10]. One safety concern is prolongation of the QT interval [9]. Two pharmacokinetic and safety studies on moxifloxacin have been completed in children: 1 in South African children aged 7–15 years with RR-TB [11] and 1 in children aged 0.25–14 years from the United States with non-TB infections after a single intravenous dose [12]. These studies were small (<35 children), but neither identified significant safety concerns.

Poor palatability and the lack of a child-friendly formulation has also limited moxifloxacin use in children with TB, which still requires long treatment duration [13]. Until

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recently, oral moxifloxacin was only available as a 400-mg film-coated tablet, which does not support dosing for younger children. A new 100-mg dispersible tablet is becoming more widely available but has not yet been studied in children. Crushing or preparing an extemporaneous solution of the 400-mg tablet may facilitate its use, if tolerable, but requires pharmacokinetic assessment.

Moxifloxacin efficacy and the risk of QT interval prolongation are concentration-dependent [14–16]. Characterizing moxifloxacin pharmacokinetics and the concentration–QT relationship in children with TB is critical to support its safe and effective use. Our aim in this analysis was to describe moxifloxacin population pharmacokinetics, QT interval prolongation, and optimal dosing in a cohort of children aged 0 to <18 years routinely treated for RR-TB.

METHODS

Study Design, Patients, and Treatment

Data were collected from 2 prospective observational pharmacokinetic studies (MDR-PK1, MDR-PK2) in Cape Town, South Africa, that have been previously described in detail [17, 18]. MDR-PK1 enrolled children aged 0 to <15 years living with and without human immunodeficiency virus (HIV) routinely treated for probable or confirmed RR-TB from 2011 through 2015. MDR-PK2 enrolled children aged 0 to <18 years living with and without HIV routinely treated for RR-TB from 2016 through 2020, during which treatment guidelines recommended treatment with moxifloxacin (aged ≥8 years) or levofloxacin (aged <8 years) and at least 3 additional drugs for 9–18 months [19, 20]. In MDR-PK2, all children received both levofloxacin and moxifloxacin, separately, with at least 3 days of treatment before pharmacokinetic sampling (Supplementary Figure 1). All children with available moxifloxacin concentration data in MDR-PK1 and MDR-PK2 were included in this analysis.

Children received approximately 7.5–15 mg/kg (max. = 400 mg) of moxifloxacin (Dr Reddy's Laboratories Ltd, Hyderabad, India) once daily. On the sampling day, exactly 10 mg/kg was administered in MDR-PK1; a weight-banded dosing approach was used in MDR-PK2 (Supplementary Table 1). Medications were given on an empty stomach after an overnight fast as whole tablets (400 mg), if possible; as an extemporaneously prepared suspension [21]; or as crushed tablets mixed in water. In MDR-PK2, older children able to swallow whole tablets had additional pharmacokinetic sampling after receiving crushed or suspended tablets to assess the formulation's bioequivalence (Supplementary Figure 1). Administration by nasogastric tube was only completed on sampling days if a child was unable to swallow. All children living with HIV were established on antiretroviral (ARV) treatment at study enrollment per standard of care and continued ARV treatment throughout RR-TB treatment. ARV medications were administered 1 hour after moxifloxacin on the sampling day.

Pharmacokinetic Sampling and Analysis

Pharmacokinetic sampling was performed after at least 4 daily doses (ie, steady state). Blood was drawn pre-dose and at 1, 2, 4, 8, and either 6 or 10 hours after the observed dose (MDR-PK1) or pre-dose and 1, 4, and 10 hours after the observed dose (MDR-PK2). Moxifloxacin plasma concentrations were determined with a validated liquid chromatography tandem mass spectrometry assay developed at the University of Cape Town, as previously described [11].

Moxifloxacin concentration data were pooled and analyzed using nonlinear mixed-effects modeling. Population pharmacokinetic parameters were estimated with first-order conditional estimation with interaction. Interindividual and interoccasion variability were modeled exponentially assuming a log-normal distribution. One and 2 compartment disposition models were evaluated with first-order absorption or absorption delay. Model building was guided by goodness-of-fit plots, objective function value, and simulation-based diagnostics. Stepwise covariate modeling ($P < .05$ forward selection; $P < .01$ backward deletion) was performed to identify predictors of volume, clearance, bioavailability, and absorption including body size (total body weight, fat-free mass [22], ideal body weight), formulation, administration route, age, nutritional status (weight-for-age, height-for-age, body mass index [BMI]-for-age z scores) [23, 24], HIV status, ARV regimen, gender, and study. Selection was informed by statistical and clinical significance and physiological plausibility.

QT Interval Prolongation and Safety Assessment

A 12-lead electrocardiogram (ECG) was performed in triplicate during pharmacokinetic sampling pre-dose and 1, 4, and 10 hours post-dose (MDR-PK2) or pre-dose and 2 hours post-dose (MDR-PK1). QT intervals were corrected using the Fridericia formula (QTcF). For descriptive analysis, triplicate mean was used. For modeling, all observations were used.

QTcF interval data were modeled sequentially with a population approach in NONMEM where individual pharmacokinetic parameters were used to generate plasma concentrations at the time of each QTcF measure. The population baseline QTcF and interindividual variability were estimated using pre-dose QTcF measures from 51 MDR-PK2 children during levofloxacin therapy (n = 252 measures) since pre-dose levofloxacin concentrations were near or below the lower limit of quantification (Supplementary Figure 1) and true baseline QTcF with moxifloxacin therapy was not available. Baseline QTcF was fixed and the effect of moxifloxacin concentration estimated during moxifloxacin treatment. Age, gender, use of concomitant QT-prolonging agents, and study were tested as covariates

on baseline and drug-effect parameters stepwise (as described above).

Simulations

Model-informed optimal doses were derived based on the target exposure in adults receiving 400 mg once-daily (median 24-hour area under the curve [AUC] at steady state [AUC_{24}] of 40 mg × h/L) [25, 26], prespecified WHO weight bands, and available formulations. Steady-state pharmacokinetics were simulated 500 times in a pediatric TB population (Supplementary Table 2) under current WHO dosing guidance [1] and model-informed dosing.

Statistics and Software

NONMEM 7.41 and Perl-speaks-NONMEM 4.7.0 were used for modeling and simulation. A change in objective function value of −3.84 was considered significant. Statistical differences in baseline characteristics were assessed in R 3.4.2 based on data normality: *t* test (normal) or Wilcoxon rank sum test (nonnormal) for continuous variables and χ^2 or Fisher exact test (n < 5) for categorical variables. Visual diagnostics were done with "Xpose" (0.4.4) and "vpc" (1.0.1) R packages.

Ethics

Written informed consent was provided by the parents or legal guardians, and written informed assent was provided by participants aged ≥7 years. The Stellenbosch University Health Research Ethics Committee and the local health departments and hospitals provided ethics approval.

RESULTS

Patients and Sampling

Pharmacokinetic data were collected from 33 children (n = 198 samples) in MDR-PK1 and 52 children (n = 242 samples) in MDR-PK2. Thirteen children had 2 sampling occasions. Nine samples below the lower limit of quantification (0.0628 mg/L) were excluded. Patient characteristics are summarized in Table 1. Children in MDR-PK2 were younger and fewer received a whole tablet. There were 16 children aged <2 years and 1 child aged <1 year.

Population Pharmacokinetics

Moxifloxacin pharmacokinetic profiles were similar between studies (Figure 1). The population pharmacokinetics were best described with 2 compartment distribution and 1 absorption transit compartment [27].

Allometric scaling by fat-free mass resulted in a similar fit to body weight; thus, body weight was chosen. Children living with HIV had 44% higher clearance (CL/F). Height-for-age *z* score (HAZ) influenced CL/F: 9.8% increase per unit decrease in HAZ (Table 2). These effects remained

Table 1. Demographic and Clinical Characteristics of Children Treated for Rifampicin-Resistant Tuberculosis in the MDR-PK1 and MDR-PK2 Studies

	"MDR-PK1" Study	"MDR-PK2" Study	Combined	
Description	N = 33	N = 52	N = 85	*P* Value [a]
Male, n (%)	13 (39.4)	24 (46.2)	37 (43.5)	.540
Age, median (IQR) [min, max], years	9.6 (4.6 to 12.3) [1.0, 15.0]	3.0 (2.1 to 6.0) [0.90, 14.6]	4.6 (2.5 to 9.9) [0.90, 15.0]	<.001
Weight, median (IQR) [min, max], kg	25.1 (16.0 to 36.3) [10.7, 66]	12.8 (10.9 to 18.1) [7.66, 46.6]	16.0 (11.4 to 27.9) [7.66, 66.0]	<.001
Height, median (IQR) [min, max], cm	130 (103 to 144) [76.0, 172]	90.0 (81.6 to 112) [71.4, 158]	102 (84.0 to 132) [71.4, 172]	<.001
Human immunodeficiency virus positive, n (%)	7 (21.2)	1 (1.9)	8 (9.4)	.005
Antiretroviral therapy,[b] n (%)				
Efavirenz-based	3 (43)	1 (100)	4 (50)	
Lopinavir/ritonavir-based	4 (57)	0 (0)	4 (50)	1.000
Weight-for-age *z* score,[c] mean (SD) [min, max]	−0.358 (0.924) [−2.28, 1.53]	−0.95 (1.22) [−4.08, 1.37]	−0.777 (1.16) [−4.08, 1.53]	.062
Height-for-age *z* score, mean (SD) [min, max]	−0.905 (1.20) [−3.76, 1.43]	−1.26 (1.23) [−4.02, 1.79]	−1.12 (1.22) [−4.02, 1.79]	.189
Body mass index-for-age *z* score, mean (SD) [min, max]	−0.009 (1.21) [−2.41, 2.89]	−0.236 (1.24) [−3.98, 1.88]	−0.148 (1.23) [−3.98, 2.89]	.411
Route of administration,[d] n (%)				
Oral	25 (75.8)	46 (88.5)	71 (83.5)	
Nasogastric tube	8 (24.2)	6 (11.5)	14 (16.5)	.124
Moxifloxacin dose,[d] median (IQR) [min, max], mg/kg	9.99 (9.88 to 10.0) [6.06, 14.9]	12.4 (11.3 to 14.2) [8.58, 19.1]	10.9 (10.0 to 13.1) [6.06, 19.1]	<.001
Formulation administered,[d] n (%)				
Whole tablet	20 (60.6)	8 (15.4)	28 (32.9)	
Crushed tablet	7 (21.2)	2 (3.8)	9 (10.6)	
Extemporaneous suspension	6 (18.2)	42 (80.8)	48 (56.5)	<.001

Abbreviations: IQR, interquartile range; SD, standard deviation.

[a]For continuous variables not normally distributed, medians were compared using the Wilcoxon rank sum test and means were compared using *t* tests for variables normally distributed. Proportions were compared using the χ^2 or Fisher exact test (n <5) as appropriate for categorical variables.

[b]Percentage reflects percent of children living with human immunodeficiency virus.

[c]Children aged <10 years only, [n = 19] for "MDR-PK1" study and [n = 46] for "MDR-PK2" study.

[d]Values are based on the first pharmacokinetic sampling occasion.

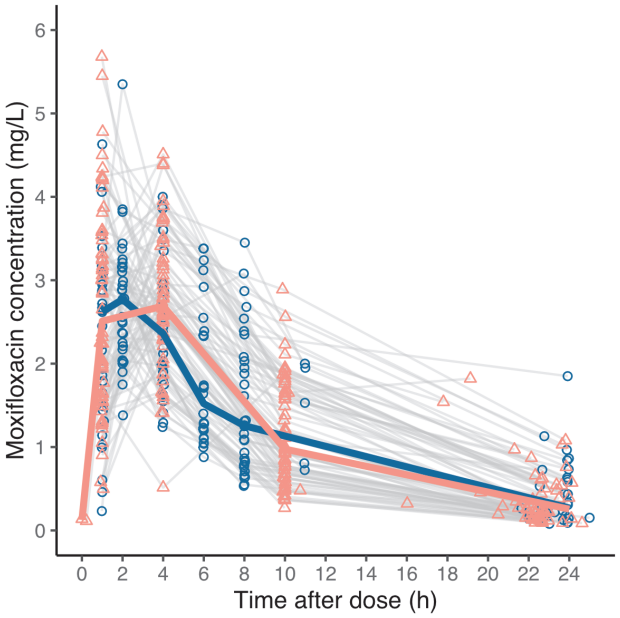

Figure 1. Moxifloxacin pharmacokinetic profiles in children treated for rifampicin-resistant tuberculosis. Gray lines connect individual observed concentrations (circle = MDR-PK1; triangle = MDR-PK2) over time at unique sampling occasions. Mean concentrations over time are shown with bold lines (blue = MDR-PK1; pink = MDR-PK2). Trough concentrations are shown as the actual time after the previous recorded dose.

whether allometric scaling by fat-free mass or total body weight. Crushed or suspended moxifloxacin tablets had faster absorption. Relative bioavailability was not different by formulation in the bioequivalence group (n = 8, MDR-PK2; Supplementary Figure 3).

CL/F maturation with age was not supported. Conversely, a statistically significant decrease in CL/F with age (–2.5% per year) was observed after adjusting for weight, which was driven by 14 children aged >12 years. Given the small effect size and no physiological explanation, it was excluded from the final model.

Table 2 shows the final pharmacokinetic parameter estimates. The pharmacokinetic model predicted the observed data well (Supplementary Figure 2). The median (2.5th, 97.5th percentiles) individual Bayesian estimates of maximum concentration (C_{max}) were 3.05 (1.81, 4.43) mg/L and of AUC_{24} were 25.9 (13.6, 51.5) mg × h/L. Stunting (HAZ < –2) and low weight (<24 kg) had lower dose-adjusted AUC_{24} and higher weight-adjusted CL/F (Figure 2).

Cardiac Safety

Fifty-seven children (n = 45 aged < 7 years) contributed 711 ECG measurements after repeated oral dosing of moxifloxacin. Ten children contributed ECG data on 2 occasions (n = 67 total occasions). Clofazimine was the major concomitantly used QT-prolonging TB drug: clofazimine (n = 3, MDR-PK1; n = 26, MDR-PK2), delamanid (n = 1), bedaquiline (n = 0). The median (interquartile range) time on clofazimine at ECG sampling was 79 (63–88) days.

The median (range) maximum QTcF interval was 409 (325–491) ms and time of peak QTcF was 1.88 (0–10) hours. High intraindividual variability was observed among triplicate QTcF measures at the same time point and occasion (mean ± standard deviation absolute difference, 20.2 ± 15.8 ms). No child had a QTcF interval >500 ms or clinical cardiac adverse event. There were 3 (4.5%) of 67 occasions with QTcF ≥450 to <480 ms and 2 (2.9%) ≥480 to <500 ms; 4 of 5 occasions with QTcF ≥450 ms occurred in children receiving clofazimine. The median (range) maximum change in QTcF (ΔQTcF) was 16.3 (–27.7, 61.3) ms: 13.7 (–27.7 to 47.0) ms in children not receiving clofazimine and 23.3 (–11.8 to 61.3) ms in children receiving clofazimine (Figure 3). There were 11 (19%) children with maximum ΔQTcF ≥30 to <60 ms, and 1 (1.7%) of ΔQTcF ≥ 60 ms.

Concentration–QTcF Relationship

The pharmacokinetic–QTcF model estimates are shown in Table 2. Moxifloxacin-induced QTcF prolongation was best characterized with a direct concentration-response model and maximum effect (E_{max}) relationship. An effect compartment model (time delay) was evaluated to explain sustained QTcF prolongation after 4 hours post-dose (ie, time of moxifloxacin C_{max}). The models had similar fit, so the direct model (simplest) was chosen. Younger children had lower baseline QTcF, which increased linearly up to age 2.6 years with no effect thereafter. Clofazimine use increased E_{max} from 8.8 ms to 28 ms but did not increase baseline QTcF. Visual diagnostics show that QTcF interval data were well predicted by the model (Supplementary Figure 2).

Optimal Dosing Simulations

Model-informed optimized doses were 10%–50% higher than currently recommended by WHO (Table 3). In children who weighed 24 kg or more, model-informed doses exceeded 400 mg. Up to 600 mg was required to match exposures in adults receiving the current standard 400-mg dose. Simulated AUC_{24} were below target with current WHO dosing for all weight bands (Figure 4). Target attainment by AUC_{24} and free AUC_{24}/minimum inhibitory concentration (MIC) at MICs 0.25–0.5 mg/L [28] improved with model-informed dosing (Figure 4, Supplementary Figure 7).

DISCUSSION

This is the first report of moxifloxacin population pharmacokinetics and cardiac safety in young children with TB. We show that moxifloxacin did not prolong the QTcF interval to ≥500 ms with 10–15 mg/kg daily in children. However, moxifloxacin concentrations were below target at the evaluated doses. Suboptimal exposures were predicted in all weight bands under current WHO dosing [1]. The proposed model-informed

Table 2. Population Pharmacokinetic and Fridericia-Corrected QT Parameter Estimates in Children Treated With Moxifloxacin for Rifampicin-Resistant Tuberculosis

Parameter	Population Estimate [90% CI], (% RSE)	Interindividual Variability %CV [a] [90% CI], (% RSE)
Pharmacokinetic model		
CL/F [b,c] (L/h)	6.95 [6.53 to 7.41], (3.59)	29.1 [24.8 to 32.2], (7.92)
V/F [b] (L)	40.7 [36.8 to 44.3], (9.54)	-
MTT (h) [d]	1.44 [1.18 to 1.69], (12.7)	51.5 [45.0 to 58.9], (8.2)
Q/F [b] (L/h)	1.98 [1.26 to 3.28][e], (50.0)	-
VP/F [b] (L)	24.1 [17.5 to 3464][e], (68.0)	-
Effect of human immunodeficiency virus on CL/F (%)	44.0 [20.3 to 68.9], (32.3)	-
Effect of HAZ on CL/F (% per HAZ)	–9.83 [–3.80 to –16.0], (56.8)	-
Effect of formulation on MTT (%)		
Whole tablet	Reference	-
Crushed tablet	–39.6 [–5.42 to –79.2], (44.2)	-
Extemporaneous suspension	–22.5 [–4.62 to –35.3], (41.8)	-
Residual error, proportional (%)	20.4 [16.9 to 23.9], (12.1)	-
Residual error, additive (mg/L)	0.046 [0.0004 to 0.072], (43.4)	-
Fridericia-corrected QT model [f]		
Baseline QTcF (ms)[g]		26.5 [20.6 to 31.4], (12.6)
MDR-PK2	381 [374 to 387], (1.01)	-
MDR-PK1	354 [338 to 366], (32.1)	-
E_{max} (ms)		9.75 [4.44 to 15.4], (31.3) [h]
Moxifloxacin alone	8.80 [1.06 to 18.2], (64.3)	-
Moxifloxacin +Clofazimine	28.4 [4.37 to 220], (91.6)	-
EC_{50} (mg/L)	0.293 [0.126 to 0.922], (55.4)	-
Effect of age ≤2.6 years on baseline (% per year)	7.05 [5.11 to 9.48], (17.6)	-
Effect of age >2.6 years on baseline (% per year)	0[i]	-
Residual error (ms)	17.8 [16.3 to 19.3], (5.20)	-

Abbreviations: 90% CI, 90% confidence interval based on nonparametric bootstrap (n = 1000); CL/F, apparent clearance; ε, residual error; E_{max}, maximum drug effect; EC_{50}, concentration at 50% maximum effect; MTT, mean transit time; Q/F, apparent intercompartmental clearance; RSE, relative standard error; V/F, apparent volume of distribution; VP/F, apparent peripheral volume of distribution.

[a]Interindividual variability was modeled exponentially for pharmacokinetic parameters and additively for QT interval corrected by Fridericia formula parameters.

[b]Allometrically scaled to median weight of population (16 kg) with exponent of 0.75 for CL/F and Q/F and 1 for V/F and VP/F.

The following definitions apply to footnotes c, d, and f: θ_{age}, fractional effect of age on baseline QTcF, centered at the population median of 2.6 years; θ_{form}, fractional effect of formulation (crushed or suspended tablet) on MTT; θ_{HAZ}, fractional effect of height for age z-score (HAZ) on CL/F, centered at the population median HAZ of -1.06; θ_{HIV}, fractional effect of HIV positive status on CL/F; θ_{pop}, population estimate; C_p, concentration of moxifloxacin in plasma; E_{max}, maximum drug effect; EC_{50}, concentration at 50% maximum effect; MTT, mean transit time; QTcF, QT interval corrected by Fridericia formula; WT, body weight (kg);

[c]$CL/F = \theta_{pop} \times (WT/16)^{0.75} \times (1 + \theta_{HIV}) \times (1 + \theta_{HAZ} \times (HAZ + 1.06))$.

[d]$MTT = \theta_{pop} \times (1 + \theta_{form})$.

[e]Confidence interval based on base model without covariates.

[f]$QTcF = \text{baseline QTcF} \times (1 + \theta_{age} \times (\text{age} - 2.6 \text{ years})) + E_{max} \times C_p/(EC_{50} + C_p) + \varepsilon$.

[g]Baseline was modeled based on pre-dose QTcF data from MDR-PK2 during levofloxacin treatment. The estimate was adjusted for MDR-PK1 children.

[h]Modeled as intraindividual variability.

[i]Estimate was approximately 0 and therefore fixed.

optimized doses ensure adequate exposures in all children, align with WHO weight bands, and can be practically implemented with available oral formulations.

We observed comparatively high moxifloxacin CL/F in this pediatric population. In adults with TB, moxifloxacin CL/F was 6.66–8.50 L/h, which scales to 2–3 L/h for a 16-kg child [26, 28, 29]. This difference may be partly explained by our observation of decreased CL/F in children aged >12 years, after applied allometric scaling, suggesting CL/F changes minimally with weight after childhood. However, pediatric analyses have quantified moxifloxacin CL/F as 5.48 L/h [12] (adjusting for bioavailability [9]) and 0.45 L/h/kg$^{0.75}$ [30], which are similar to our estimates. Our data did not support clearance maturation with age, agreeing with Willmann et al; however, both studies included few children aged <1 year [30]. Further evaluation of moxifloxacin pharmacokinetics in children aged <2 years and adolescents aged 12–18 years are needed to reconcile these questions.

Stunted children (HAZ < –2) had higher moxifloxacin CL/F and lower AUC compared with children with normal HAZ. No association was found with weight-for-age or BMI-for-age *z* scores. Stunting, typically representing chronic undernutrition, has been associated with low first-line TB drug exposures in children [31, 32]. Higher CL/F with lower HAZ may reflect underprediction of CL/F by total body weight alone. Interestingly, the effect remained significant when scaling by fat-free mass. While total body weight is lower in malnourished children, liver size may not differ [33]. Another possible

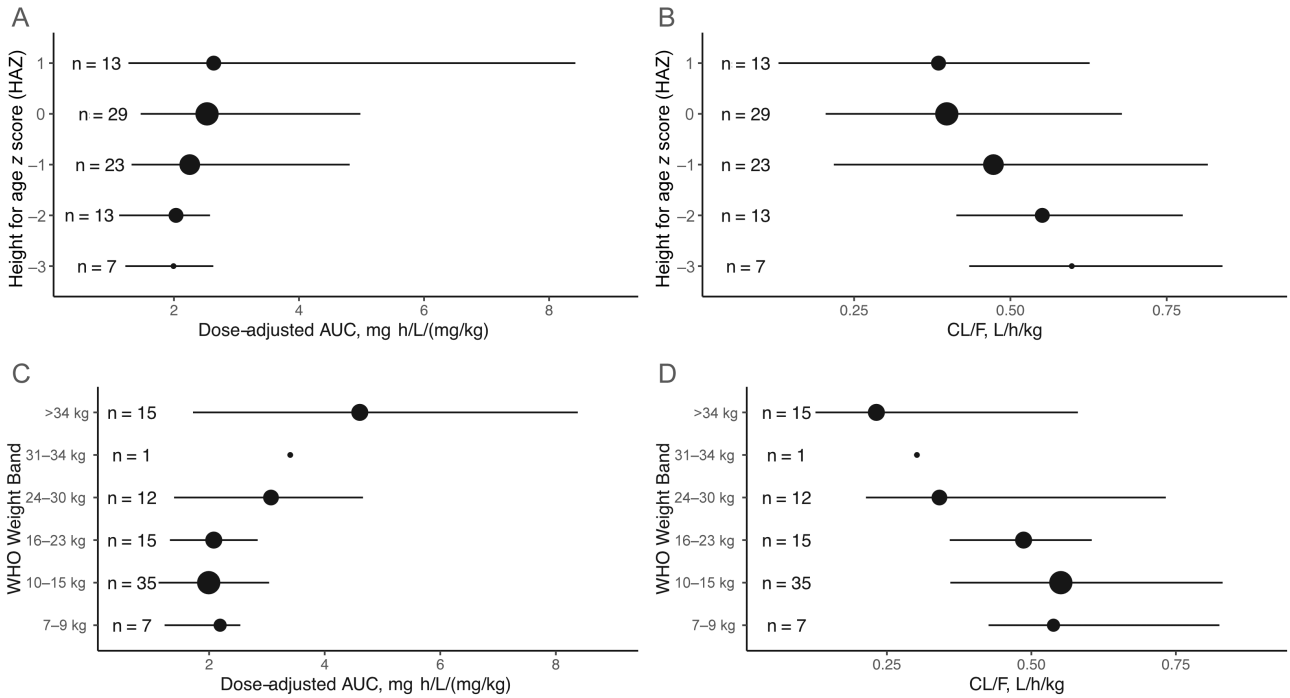

Figure 2. Moxifloxacin AUC_{24} *(A, C)* and apparent clearance *(B, D)* by nutritional status and body weight. Nutritional status is shown by HAZ and body weight by WHO weight band. AUC_{24} is adjusted for the milligram per kilogram dose. CL/F is adjusted for body weight. The sample size (n) of each group is displayed in text, and the size of the center point represents the relative sample size. Center points represent the median. Lines represent the 2.5th to 97.5th percentile range. Abbreviations: AUC, area under the curve; CL/F, moxifloxacin oral clearance; HAZ, height-for-age *z* score; WHO, World Health Organization.

explanation could be compromised drug absorption with malnutrition, thereby increasing apparent CL/F [34]. Since stunting is highly prevalent in countries with a high TB burden, it is important to assess TB drugs' pharmacokinetics and dosing in representative populations [35].

Efavirenz induces UDP-glucuronosyltransferase activity [36]. Naidoo and colleagues reported 42% higher moxifloxacin clearance in adults with TB and HIV receiving efavirenz, similar to the 44% increase we observed in children living with HIV [37]. Distinguishing HIV from efavirenz was impossible in this study due to small sample size. More data in children with TB and HIV receiving efavirenz is required to understand whether dose adjustments are needed.

The median maximum ΔQTcF observed among children in our study was similar to that observed in adults receiving 400 mg moxifloxacin; however, we estimated a weaker concentration-QTcF response [16, 38–41]. In healthy adults, reported E_{max} was 34 ms and concentration at 50% E_{max} (EC_{50}) was 3.9 mg/L compared with 8.4 ms (E_{max}) and 0.28 mg/L (EC_{50}) in our study [40]. Other adult studies report 2.3–4.1 ms increase in QTcF per milligram per liter of moxifloxacin [16, 38, 41]. We observed high intraindividual variability in QTcF, potentially limiting estimation of a strong moxifloxacin effect. Therefore, our model cannot confidently predict QTcF intervals at higher concentrations. Nonetheless, simulated C_{max} distributions with optimized dosing do not exceed limits observed after intravenous infusion (up to 10 mg/L), which was safe from severe QTcF prolongation [9, 12]. Future QTcF studies in children should ideally include pre-drug ECGs collected under the same conditions and time of day as during pharmacokinetic sampling to improve estimation of concentration-QTcF response.

At the population level, QTcF prolongation appeared sustained after the moxifloxacin C_{max}, but individual QTcF profiles were highly heterogeneous. The data were equally well described with direct and delayed drug-effect models, so the direct (simplest) model was chosen. Sustained QT interval prolongation with moxifloxacin has been reported [39]. Without a control arm, we could not account for normal fluctuations in QTcF. Additionally, most QTcF sampling occurred near the bounds of moxifloxacin C_{max} (1 and 4 hours after dose). ECGs at 2–3 hours after dose and before drug initiation in future studies may help in characterizing the time profile of moxifloxacin-induced QTcF prolongation in children.

WHO recommends clofazimine and fluoroquinolones, potentially also in combination with bedaquiline or delamanid, for RR-TB treatment [1]. These drugs can prolong the QT interval [42]. The change in QTcF was higher with concomitant moxifloxacin and clofazimine use, suggesting clofazimine further prolongs the QTcF interval. These findings closely represent steady-state clofazimine conditions, assuming a half-life of approximately 30 days [43]. Despite higher ΔQTcF, there were no clinical cardiac events or QTcF >500 ms. Similarly, no

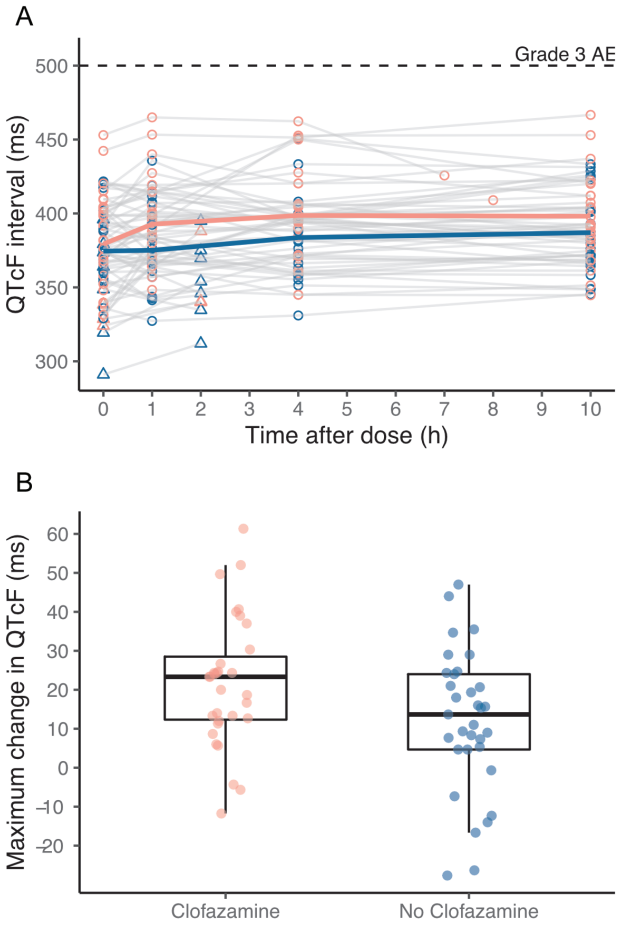

Figure 3. QTcF profiles in children treated with moxifloxacin for rifampicin-resistant tuberculosis as *(A)* QTcF interval over time and *(B)* maximum change in QTcF during the dosing interval in children receiving clofazimine (n = 29) and not (n = 27). *(A)* Gray lines represent distinct children and sampling occasions with individual observations as triangles (MDR-PK1) or circles (MDR-PK2). The bold line (pink = clofazimine group; blue = no clofazimine group) is the population mean. *(B)* Box plots represent the median, interquartile range, and whiskers show 95th and 5th percentile. Abbreviations: AE, adverse event; QTcF, Fridericia-corrected QT interval.

significant QT prolongation occurred in 27 children receiving clofazimine for *Mycobacterium abscessus* infection [44]. The effect of bedaquiline or delamanid together with moxifloxacin (± clofazimine) could not be assessed because there were not enough children who received these drug combinations. Considering current guidelines, these data are urgently needed in children. ECGs should be monitored in children on moxifloxacin and other QT-prolonging agents, especially longitudinally for drugs with long half-lives (eg, bedaquiline, clofazimine).

Although most children treated for RR-TB have good outcomes, children with HIV, poor nutritional status, or severe TB, including adolescents, have worse outcomes [45]. These groups had suboptimal moxifloxacin exposure in this study. When no dose limit was applied, model-informed doses ensured target exposure attainment for all weight bands. However, doses above 400 mg were required in children who weighed >30 kg to match expected adult exposures. This should be interpreted with caution as no safety data exist for children and adolescents at higher doses. While 600–800 mg moxifloxacin has been safely used in adults, more QT prolongation events occurred with high dose vs standard dose, though not statistically significant [6]. Pharmacokinetic data in adolescents are needed to understand how moxifloxacin CL/F scales with growth into adulthood as well as safety assessment at higher doses. Similarly, proposed doses for children who weigh <10 kg require cautious interpretation as few data were available in these children.

This work has important implications for RR-TB treatment, as fluoroquinolones have higher bactericidal activity than other second-line medications [46] and multiple shortened regimens for RR-TB under evaluation include moxifloxacin. Furthermore, a 4-month regimen with moxifloxacin recently demonstrated noninferiority to the standard 6-month regimen without moxifloxacin in adults with drug-susceptible TB [8]. Appropriate dosing may be even more important for efficacy of novel regimens that contain fewer drugs and/or

Table 3. Currently Recommended and Optimized Pediatric Weight Band Dosing for Moxifloxacin

	Current World Health Organization Dosing				Model-Informed Optimized Dosing (Max. 400 mg)				Model-Informed Optimized Dosing (No Limit)			
	100-mg Dispersible Tablet		400-mg Tablet		100-mg Dispersible Tablet		400-mg Tablet		100-mg Dispersible Tablet		400-mg Tablet	
Weight Band	Tablets	Dose, mg	Tablets	Dose, mg	Tablets	Dose, mg	Tablets	Dose, mg	Tablets	Dose, mg	Tablets	Dose, mg
5–6 kg	0.8	80	2 mL[a]	80	1.5	150	4 mL[a]	160	1.5	150	4 mL[a]	160
7–9 kg	1.5	150	3 mL[a]	120	2	200	5 mL[a]	200	2	200	5 mL[a]	200
10–15 kg	2	200	5 mL[a]	200	3	300	7 mL[a]	280	3	300	7 mL[a]	280
16–23 kg	3	300	0.5	200	4	400	1	400	4	400	1	400
24–30 kg	4	400	4	400	4	400	1	400	4	400	1	400
31–34 kg	4	400	4	400	4	400	1	400	5	500	1	400
>34 kg	4	400	4	400	4	400	1	400	6	600	1.5	600

[a]400-mg tablet dissolved in 10 mL water (40 mg/mL).

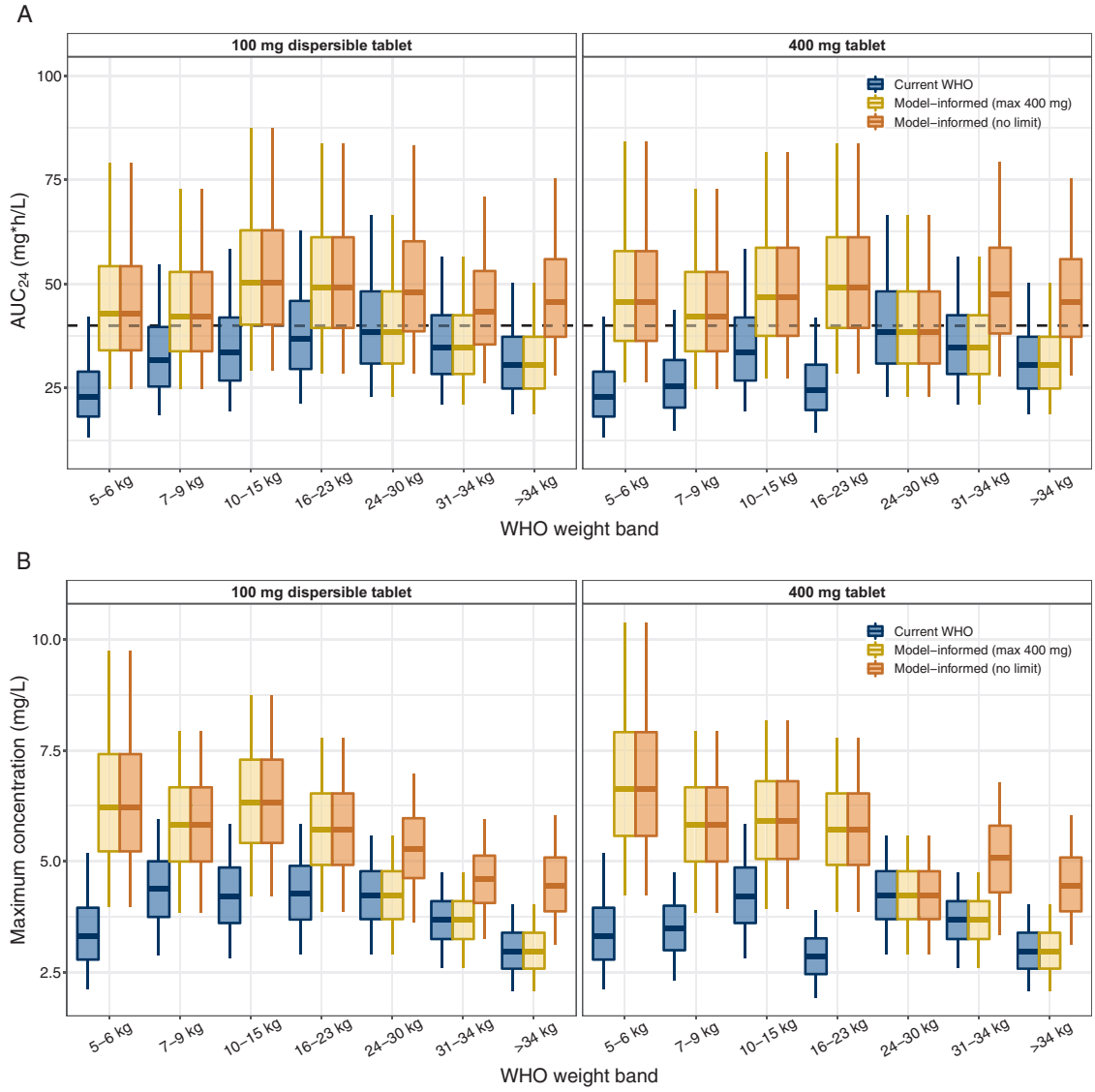

Figure 4. Simulated moxifloxacin *(A)* AUC_{24} and *(B)* maximum concentration at steady state with weight band dosing according to current WHO recommendations (blue) and model-informed optimized doses (yellow, 400 mg maximum dose; orange, no maximum dose). Data are based on 500 simulations. Weight band doses are shown in Table 3. Dashed line in *(A)* represents the target AUC_{24}. Abbreviations: AUC_{24}, area under the curve at steady state over 24-hours; WHO, World Health Organization.

are of shortened durations. Our findings have broader relevance for pediatric TB treatment given higher incidence of drug-susceptible TB (1.19 million) compared with RR-TB (approximately 26 000–30 000) [47].

In conclusion, up to 15 mg/kg of moxifloxacin was safe in children with RR-TB. Higher doses are needed in children to match adult exposures but requires safety assessment, especially when concomitantly used with other QT-prolonging agents.

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

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