



Pharmacokinetics and dosing of dispersible moxifloxacin formulation in children with rifampicin-resistance tuberculosis

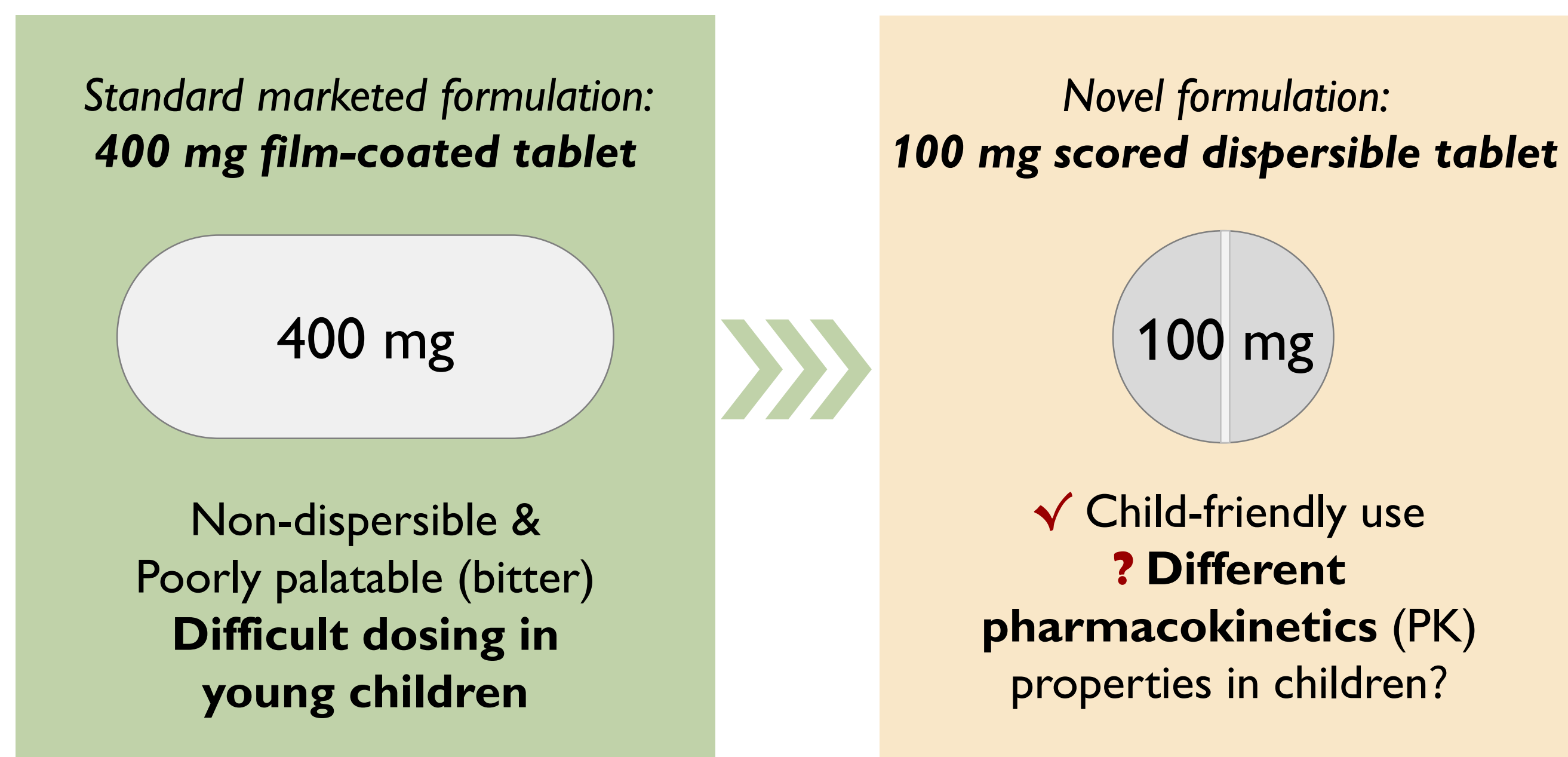
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Background

1. Moxifloxacin & formulations

- Fluoroquinolone antibiotic, priority drug for the treatment of rifampicin-resistant tuberculosis (RR-TB)



2. Currently available pediatric moxifloxacin dosing recommendations

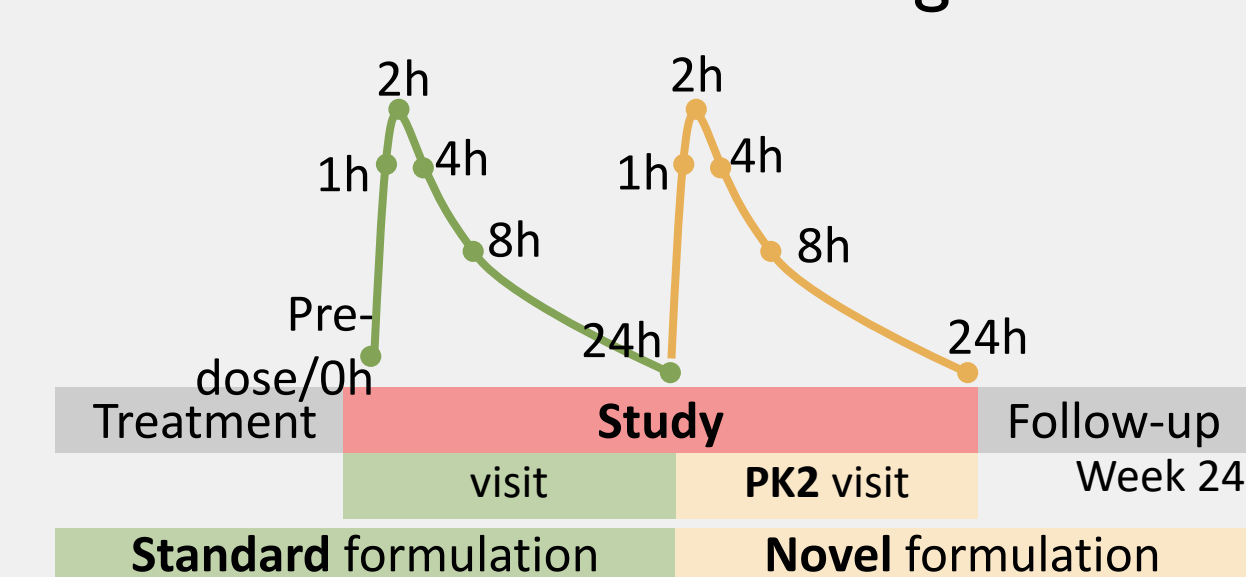
- Lower exposures were reported in children than adults.¹
- No consensus about adult exposure targets or reference.

AIM to assess 1) PK of the new formulation of moxifloxacin vs standard formulation in children treated for RR-TB; 2) current moxifloxacin dosing tables in children based on the proposed reference exposure.

Methods

1. CATALYST: phase III multisite trial of PK, safety, and acceptability of new child-friendly formulations of TB drugs including moxifloxacin

- One-sequence crossover.
- Dosed with WHO dosing table.²



2. Population (pop) PK modelling

- Starting model:** published popPK model of moxifloxacin.³
- Model components re-evaluation:**
 - structures & variabilities
- Covariate testing:** formulation (on absorption), age, country, WAZ, HAZ, HIV.
- Evaluation:**
 - Formulation effect:** 90% confidence interval (CI) with log-likelihood profiling (LLP).
 - Final model:** visual predictive checks (VPC) & sampling importance resampling (SIR)

3. Dosing simulation

1000 children (uniform WT distribution) simulated per dosing WT band, dosed per:

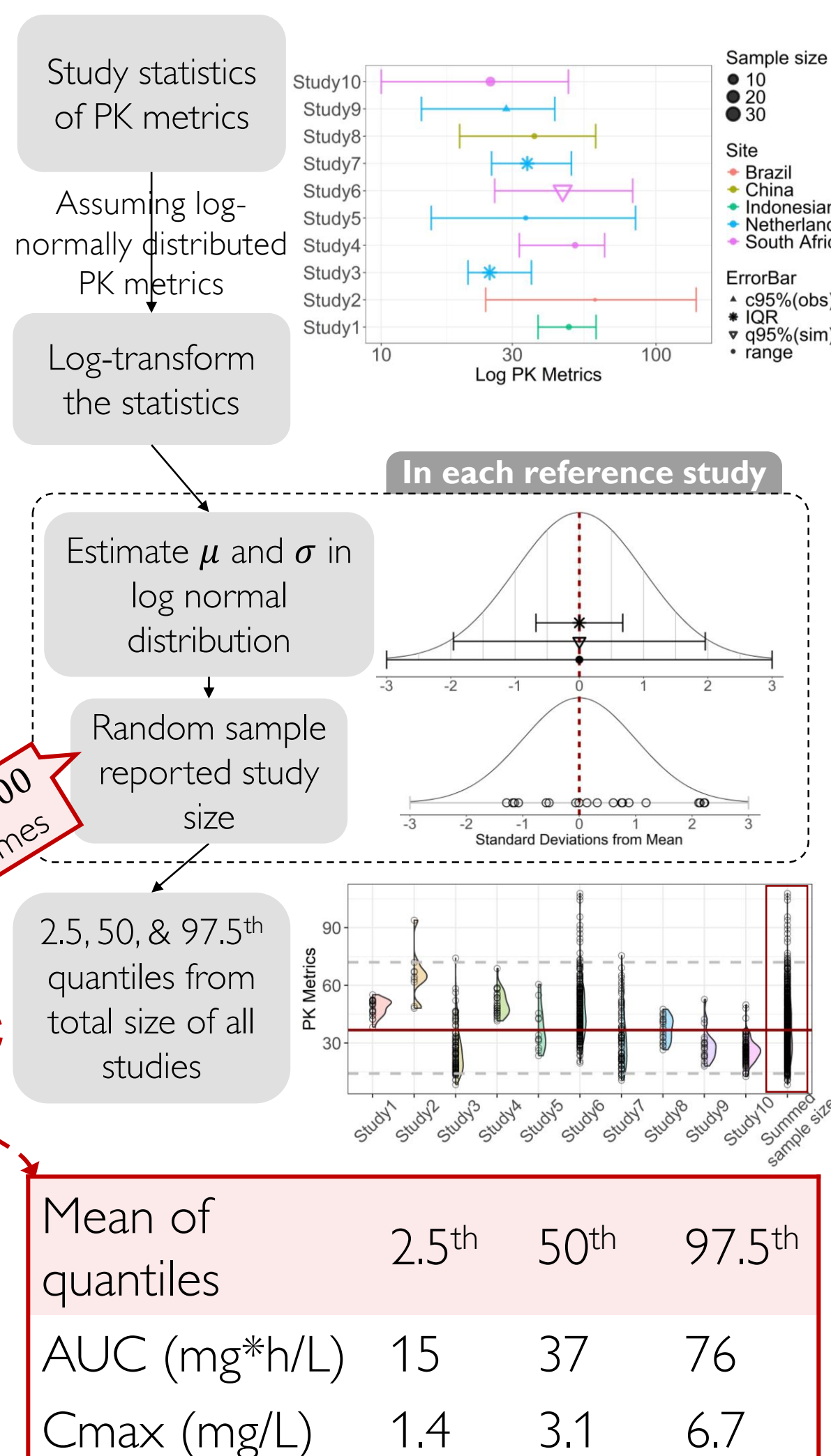
- WHO-guided.²
- Previous model-suggested doses (Radtke et al).³

4. Reference exposure

To evaluate doses, strategy matching adult exposure was used:

- AUC₀₋₂₄ matching for efficacy
- C_{max} comparison for safety

Reference levels were derived from 10 relevant adult studies, yielding weighted median and 95% population coverage:



Results

Patient Characteristics	All participants (n=36; obs=384)	South Africa (n=20)	India (n=6)	The Philippines (n=10)
Male	14 (39%)	9 (45%)	1 (17%)	4 (40%)
Age (years)	4.8 (0.4, 15)	4.1 (0.4, 11.2)	7.8 (0.7, 15)	8.1 (0.8, 14.8)
WT (kg)	15.6 (6.9, 42.1)	15.3 (6.9, 26.6)	18.4 (8.0, 42.1)	19.1 (8.0, 30.0)
HT (cm)	101 (60, 163)	99 (60, 142)	118 (64, 163)	114 (69, 147)
HAZ	-1.1 (-4.1, 0.46)	-0.55 (-4.1, 0.46)	-1.6 (-3.4, 0.11)	-2.3 (-3.7, -0.69)
WAZ	-1.6 (-4.7, 1.2)	-0.70 (-3.7, 1.1)	-1.9 (-3.9, -0.03)	-2.4 (-4.7, 1.2)
HIV-positive	1 (3%)	1 (5%)	0	0

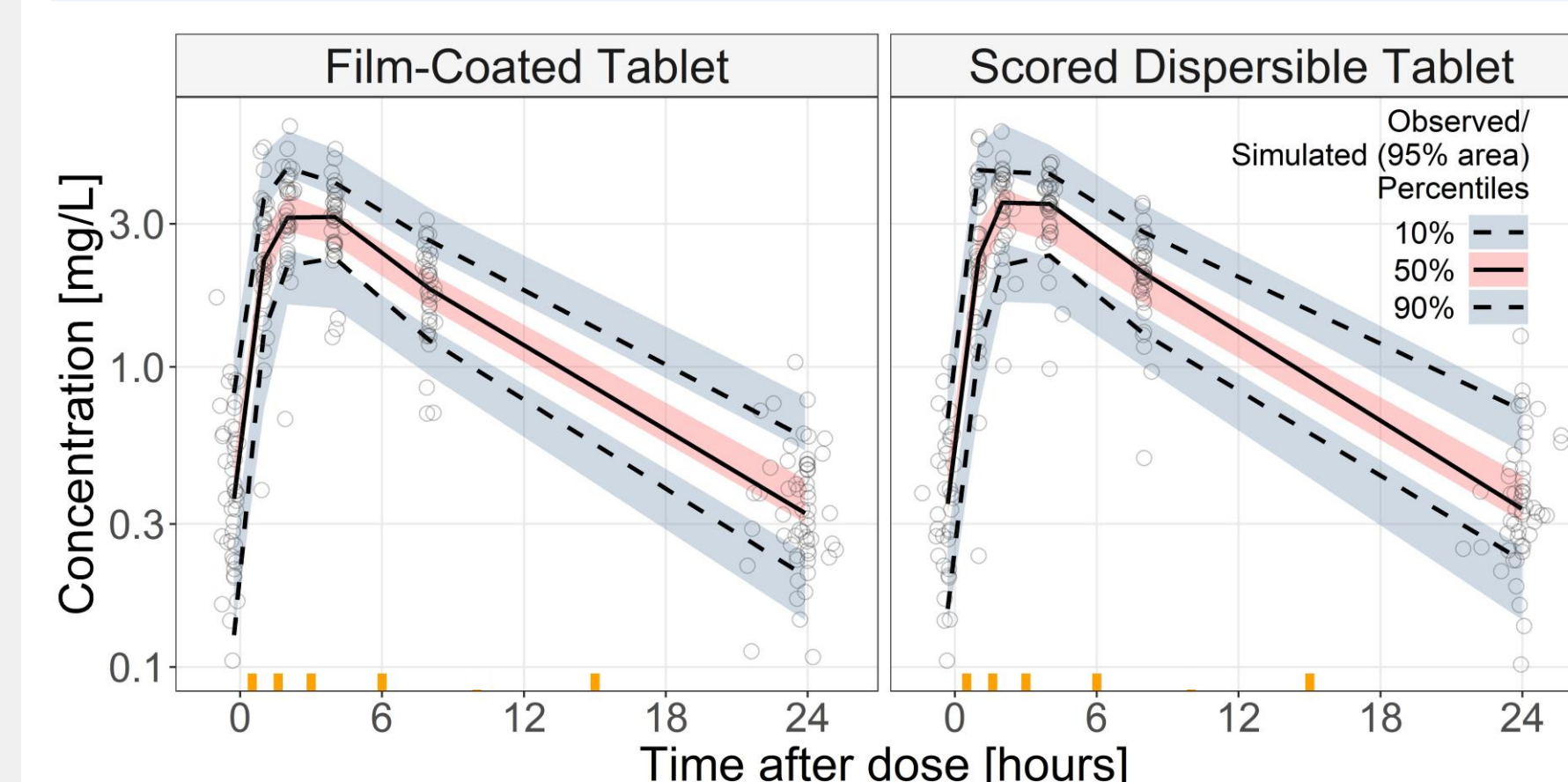
N (%) or Median (range). WT, weight; HT, height; HAZ&WAZ, HT&WT-Age-Z scores

* HIV treatment: abacavir (ABC), lamivudine(3TC), Lopinavir/ritonavir (LPV/r)

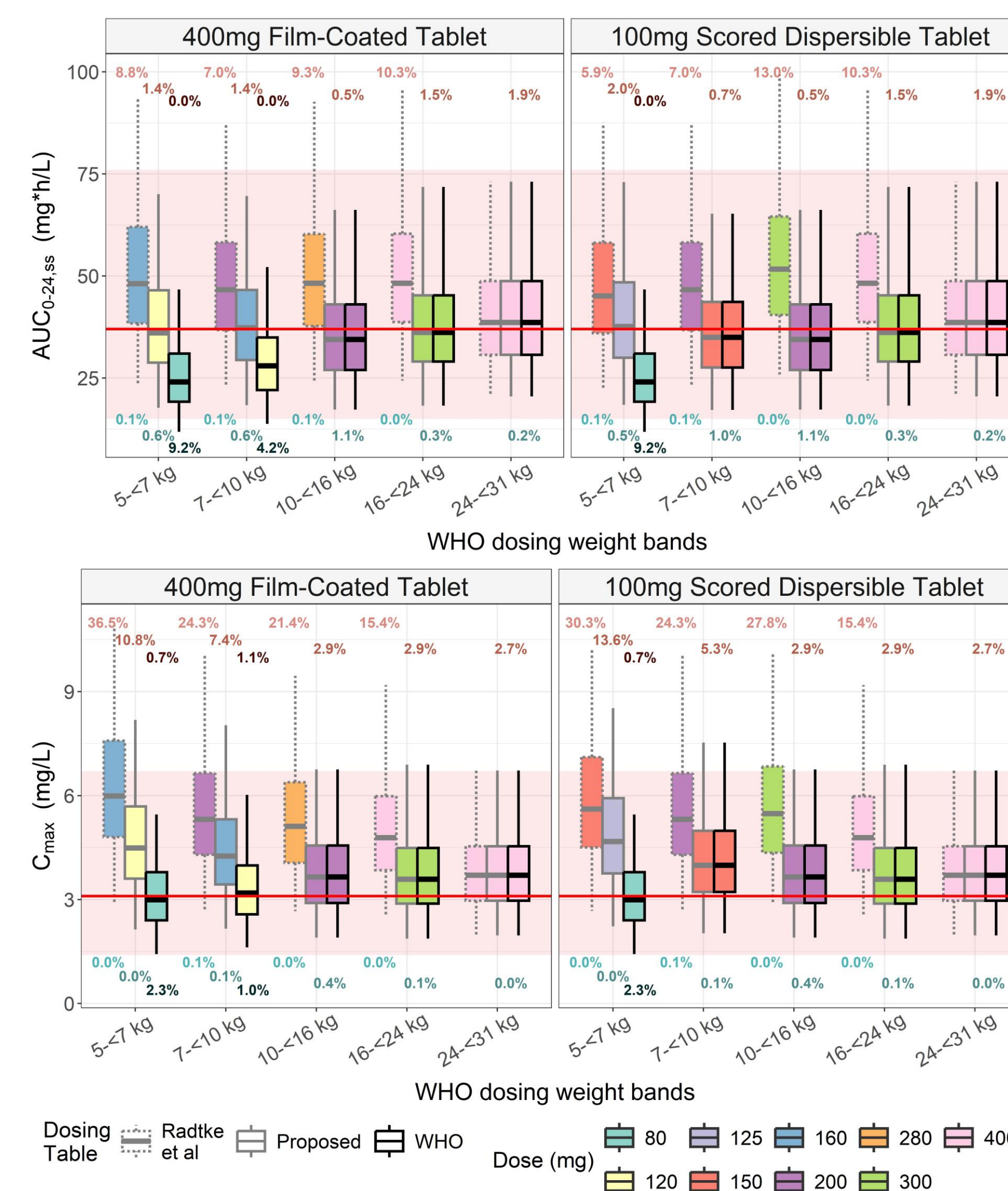
Model Parameter (Refer to 16kg)	Estimate	%RSE (SIR)
CL/F (L/h)	6.90	4.0
Vc/F (L)	61.1	4.2
Q/F (L/h)	0.860	19
Vp/F (L)	44.5	36
MAT (h)	1.01	5.6
F	1 (fixed)	-
Scaling factor on pre-dose IOVs	1.70	25
IIV_CL (%CV)	13.6	13
IOV_F (%CV)	30.8	9
IOV_MAT (%CV)	42.2	12
Prop (%CV)	13.6	12
Add (mg/L)	0.0435	14

Final popPK model: two-compartment model with first-order elimination and 3-transit delayed absorption; allometric scaling with WT. None of tested covariates were found significant.

The F of dispersible tablets was estimated as 105% (90% CI: 95-115%) compared to film-coated tablets, fulfilling standard criterion of 80-125% for bioequivalence.



RSE, relative standard error; CL, clearance; Vc&Vp, central&peripheral volume; Q, intercompartment clearance; MAT, mean absorption time; F, bioavailability; IIV&IOV, inter-individual&occasion variability; CV, coefficient variation; prop, proportional residual error; Add, additive residual error



Conclusion

- Similar PK was found between the new and standard moxifloxacin formulation in children with RR-TB across three countries.
- Previous model-based dosing (Radtke et al) produced higher exposures than proposed reference exposure.
- Current WHO-guided moxifloxacin doses for children with RR-TB provide exposures similar to adult level for most children, but those <10 kg may benefit from increased doses.

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- Thee S, et al. Clinical Infectious Diseases. 2015;60(4):549-556.
- World Health Organization (WHO). Operational Handbook on Tuberculosis - Module 5: Management of Tuberculosis in Children and Adolescents.; 2022.
- Radtke KK, et al. Clinical Infectious Diseases. 2022;74(8):1372-1381.