



Population pharmacokinetics of amikacin in Indian patients with multi-drug-resistant tuberculosis

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Background and objectives

India accounted for 27% of global multi-drug-resistant tuberculosis (MDR-TB) cases in 2023, ranking among the top 10 countries with the largest gap between cases and those enrolled for treatment.¹

Amikacin, a second-line injectable crucial for treatment of MDR-TB, is highly bioavailable via intramuscular (IM) administration, and almost entirely excreted unchanged via the kidneys, with a half-life of 2–3 hours in adults with normal renal function.^{2,3}

Due to risks of irreversible ototoxicity and nephrotoxicity, renal function monitoring is essential, prompting strategies such as intermittent dosing in patients with renal impairment.^{2,3}

Amikacin toxicity is driven by sustained exposure; desired trough levels should be below the toxicity threshold: trough concentration (C_{min}) > 5mg/L at 18–24 h post-dose.⁴ Efficacy is driven by the ratio of peak serum concentration (C_{max}) to bacterial minimum inhibitory concentration with a target C_{max} of 25–35 mg/L.⁵

Comprehensive pharmacokinetic (PK) data for amikacin in MDR-TB patients remain limited.² We characterized the PK of amikacin among Indian patients with MDR-TB.

Methods

This PK analysis was conducted as a sub study of an observational cohort study that evaluated drug levels obtained during susceptibility-guided treatment for MDR-TB.

Amikacin was administered IM in accordance with the Indian National Tuberculosis Elimination Programme (NTEP) guidelines. Doses : 500mg (16–29kg), 750mg (30–45.9kg) (46–70.9kg), 1000mg (>70 kg), 10mg/kg (60+ years).

Dosing intervals (II) were adjusted based on physician-assessed renal function

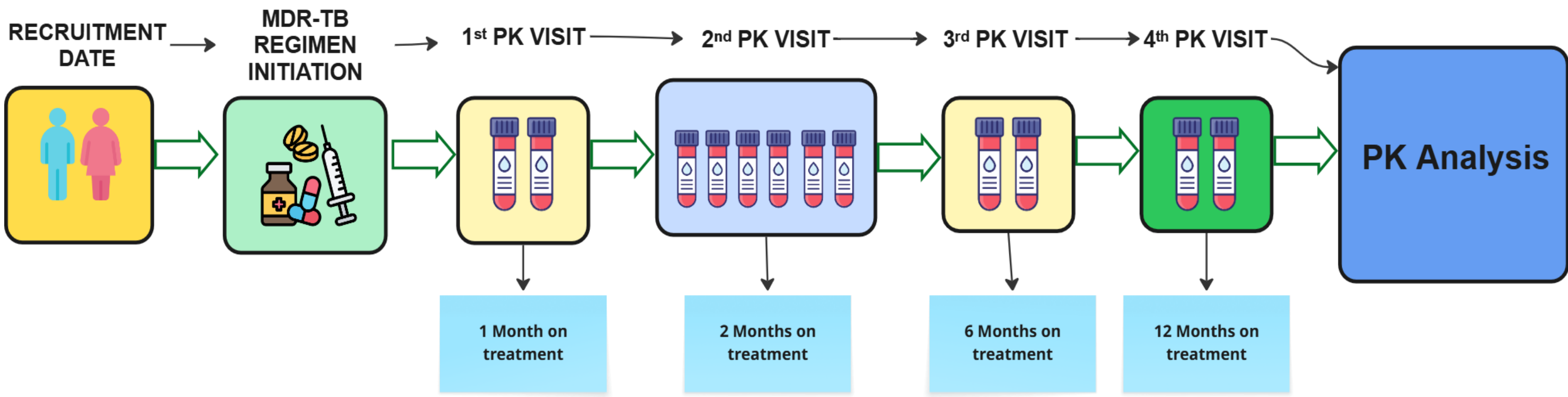


Figure 1: Pharmacokinetic protocol

Sparse sampling times: pre-dose, 2h post-dose; Intensive sampling times: pre-dose, 1, 2, 4, 6, 8 h post-dose.

Amikacin plasma concentrations were quantified using a homogenous enzyme immunoassay with a lower limit of quantification (LLOQ) of 2.5 mg/L. The PK analysis was performed using FOCE-I in NONMEM.

Samples below the LLOQ (BLQ) were handled using the M7* method⁶: imputed as a near zero value and the additive error inflated by the LLOQ.

Allometric scaling on disposition parameters was tested. Cockcroft-Gault derived creatinine clearance (CL_{cr}) was tested as a covariate on drug clearance in the model.

CL_{cr} was size standardised to that of a 55kg typical individual, used to estimate renal function factor (RF) which was then used to scale the renal component of drug clearance.⁷

Results

Table 1. Participants characteristics

Baseline (First visit) (N = 52)	
Female	39.0 (75.0)
Weight (kg)	55.0 (32.0–99.0)
Height (m)	1.58 (1.43–1.88)
Fat-free mass (kg)	36.8 (24.6–72.1)
Age (years)	26.0 (15.0–61.0)
Serum creatinine (mg/dL)	0.60 (0.40–1.10)
Creatinine clearance (mL/min) ^b	129 (52.2–296)

Data is presented as median (range) for continuous variables or n (%) for categorical variables.

^b Creatinine clearance was calculated using the Cockcroft-Gault formula, assuming a standard male for all, then Fat-free mass (FFM) allometry was applied.

A two-compartment model with first-order absorption and elimination best described the data

320 samples were analyzed of which, 110 (34.4%) were BLQ with 108 being predose samples and 2 8h post-dose samples (Desired; low risk of sustained exposure due to dose stacking).

Table 2. Final parameter estimates

Parameter	Typical value (95% CI) ^a	Variability (%) (95% CI) ^a
Clearance (L/h) ^{b, c}	3.12 (2.88–3.37)	Between subject: 24.3 (18.96–31.44)
Central volume of distribution (L) ^b	13.9 (12.63–15.21)	Between subject: 23.8 (16.97–32.35)
Intercompartmental clearance (L/h) ^b	1.17 (0.88–1.51)	
Peripheral volume of distribution (L) ^b	15.9 (8.53–31.72)	
Bioavailability	1 FIXED	Between occasion: 17 (14.14–19.87)
First-order absorption rate constant (h ⁻¹)	1.78 (1.44–2.22)	Between occasion: 49.2 (34.06–72.11)
Proportional error (%)	4.45 (3.12–6.42)	
Additive error (mg/L) ^d	0.5 FIXED	

^a 95% confidence intervals (CI) were obtained using sampling-importance resampling.

^b Parameters allometrically scaled by fat-free mass. The reported typical values refer to the typical individual in the cohort with fat-free mass of 38 kg.

^c Size-standardising; RF calculation; Clearance equation: $CL_{cr, standardised} = CL_{cr,i} \times \frac{55kg}{Weight_i}$; $RF =$

$\frac{CL_{cr, standardised}}{108 mL/min}$; $CL_i = ((CL_{renal} \times RF) + CL_{non-renal}) \times \frac{FFM_i}{FFM_{reference}}^{0.75} \times \eta_{CL_i}$, $CL_{non-renal} = 0 (FIXED)$

^d Estimate of additive component of residual unexplained variability fixed at 20% of LLOQ

Results

There was statistically significant effect of creatinine clearance on drug clearance ($\Delta_{ofv} = -7.9$, $pvalue < 0.005$). CL increased with CL_{cr} above the median 108 mL/min, and decreased below it.

Allometric scaling by fat-free mass best described the effect of body size and improved the model fit. ($\Delta_{ofv} = -37.2$).

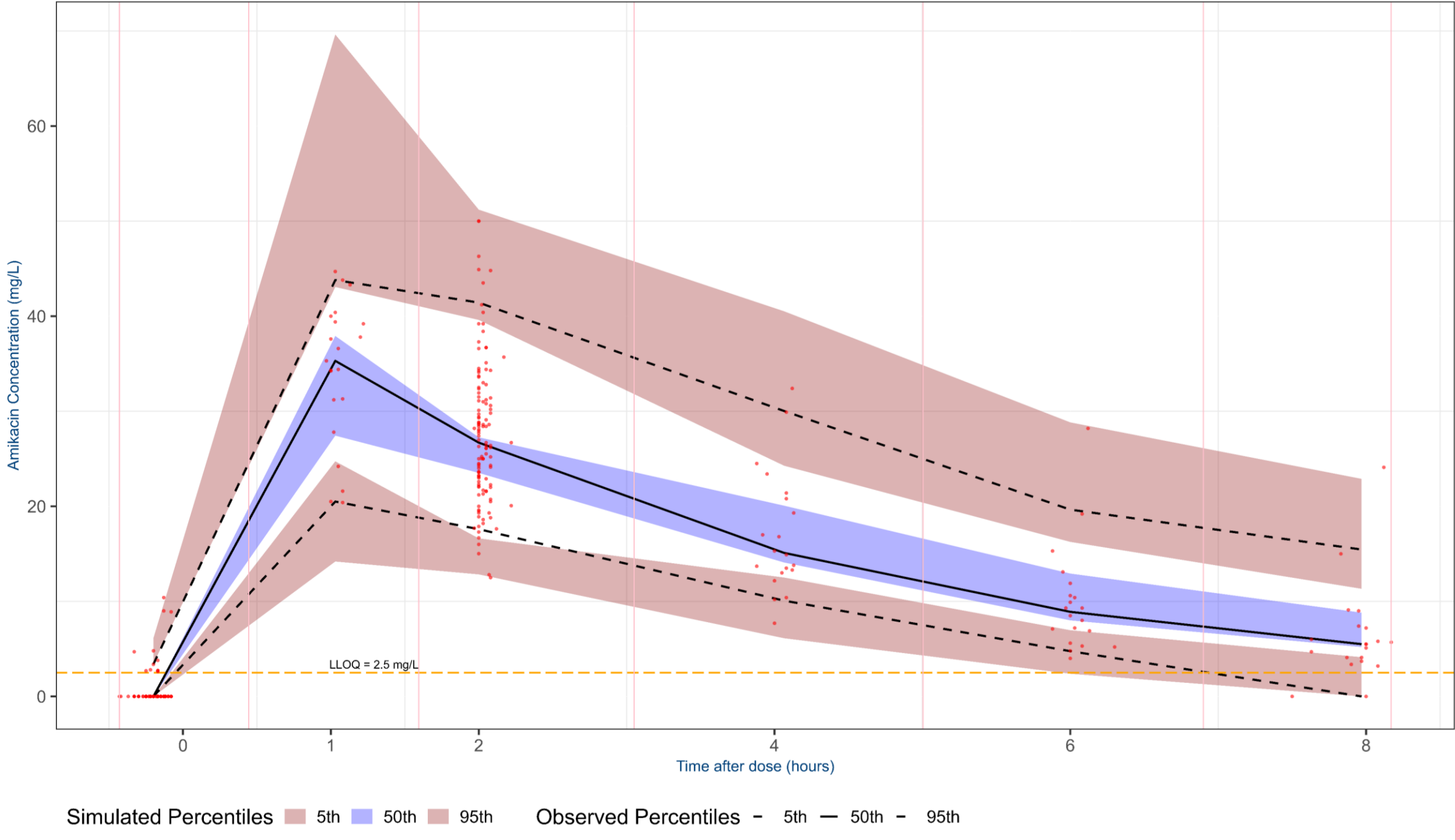
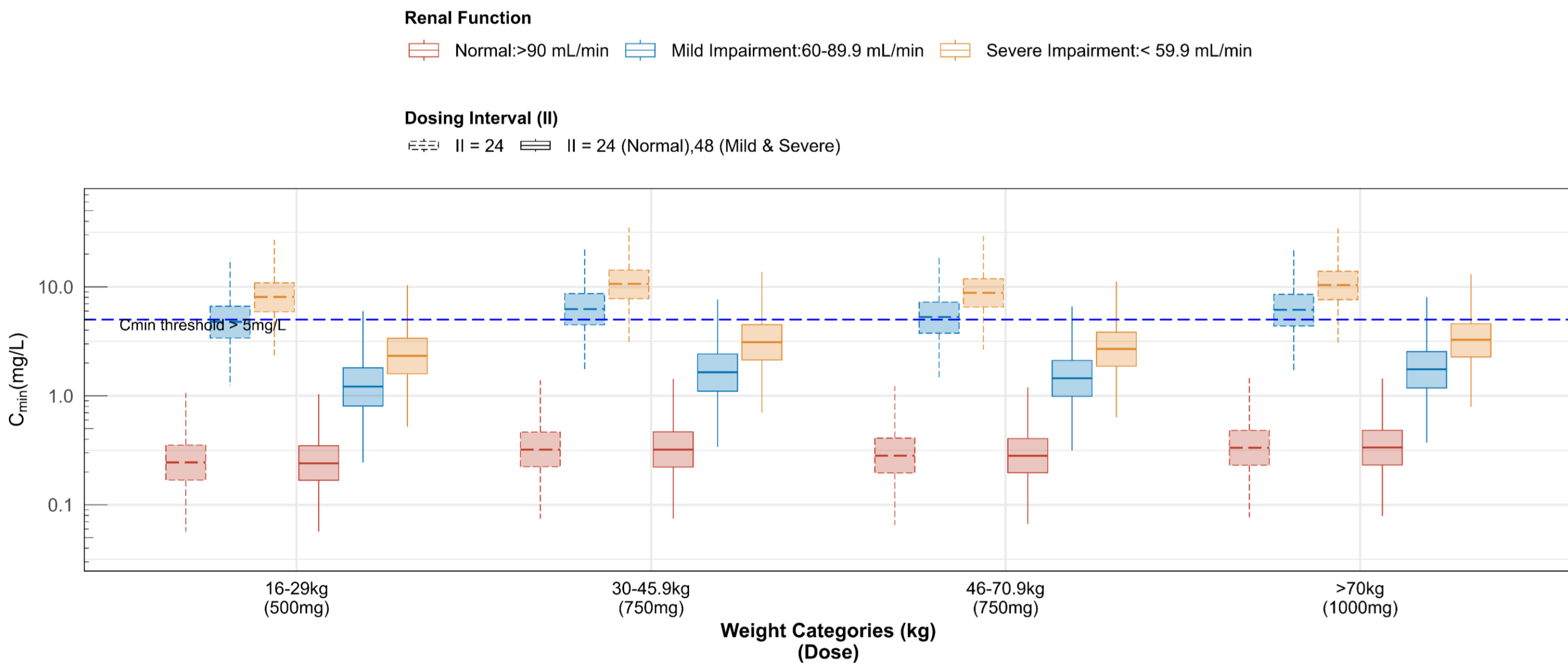


Figure 2. Visual predictive check. The red circles represent the original data, the black dashed lines are the 5th, 95th and solid line: 50th percentiles of the observed data, while the shaded areas represent the corresponding model-predicted 95% confidence intervals. Pink gridlines are the bins.

Simulations

Trough concentrations (C_{min}) -Toxicity



Peak concentrations (C_{max}) – Efficacy

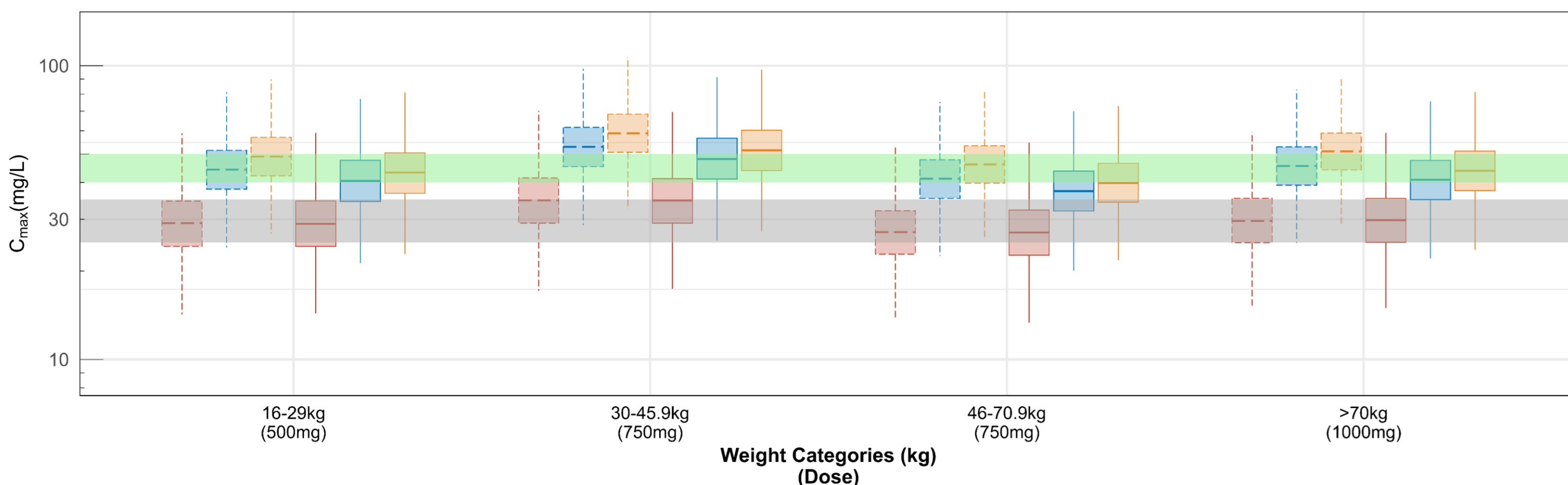


Figure 3: Simulated trough concentration analysis (top): Blue line is the toxicity threshold (>5mg/L), simulated peak concentration analysis (bottom): green band: C_{max} range 40–50mg/L (Queensland, Australia guidelines); gray band: 25–35 mg/L (Sabur et al, 2021).

Simulations showed that the mildly impaired (60–89.9 mL/min) and severely impaired (<60 mL/min) achieved lower trough concentrations when their interval was adjusted to 48 h rather than 24 h.

Current dosing in India was sufficient to attain the desired C_{max} targets irrespective of renal function.

Conclusions

We developed a two-compartment model that characterized PK of amikacin in MDR-TB patients from India and included the effect of renal function and body size. It aligns with findings from Kato et al⁸ who also reported similar values of CL and model structure in patients admitted for various types of infections.

Our model can be used to adjust dose based on renal function. Patients with mild and severe renal impairment should be dosed 48 hourly to limit toxicity.

Our model can be used to improve safety of amikacin dosing in settings with limited access to regular drug level monitoring

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