

Background and Objectives

Multidrug-resistant tuberculosis (MDR-TB) is an emerging problem, increasingly affecting children.

Ofloxacin is a fluoroquinolone used in the treatment and prophylaxis of MDR-TB.

Objective: describe ofloxacin PK in paediatrics, investigate the effect of weight, age, and dosing procedure (see below), and optimise future dosing regimens.

Methods

88 South African children routinely receiving daily ofloxacin as part of MDR-TB treatment or prophylaxis.

Blood samples collected pre-dose, and at 1, 2, 4, and 6-8 or 8-11 hr post-dose.

Table 1 Patient info		
Covariate	Median (range)	
Sex	M = 49 / F = 39	
Age (years)	3.5 (0.5 to 15)	
Weight (kg)	15 (7 to 66)	
Total Dose (mg)	300 (134 to 800)	
Treatmt/Prophlxs	T = 58 / P = 30	
HIV status	P = 11 / N = 77	

Dosing time on the day before PK sampling was unknown, so it was estimated in the model, as shown in **Figure 1**

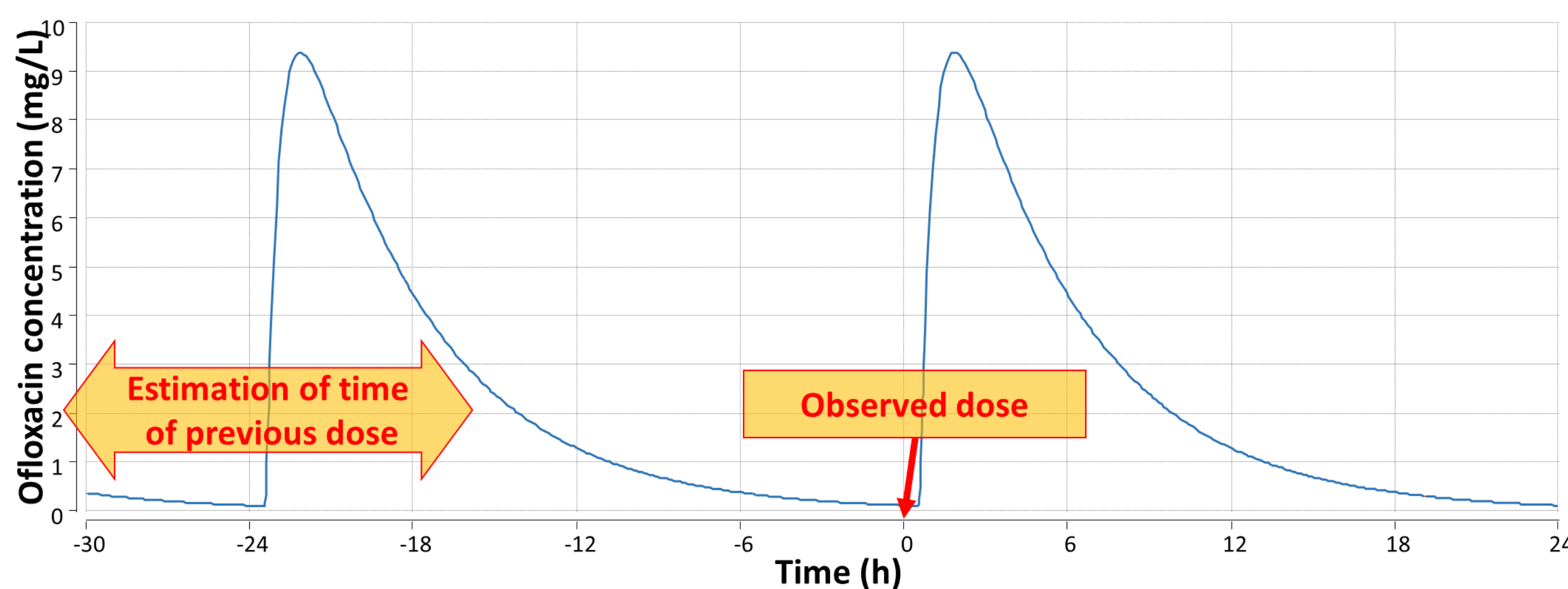


Figure 1 Estimation of time of previous dose

The data was modelled in Monolix 4.3.3

Results

1-compartment model

1st-order elimination and 1st-order absorption with lag time.

Allometric scaling [1] on CL and V.

Estimation of time of previous dose significantly improved the fit and addressed few “larger than expected” pre-dose concentrations.

Crushing tablets or use of naso-gastric tube affected the speed of absorption, but not bioavailability.

Age, HIV status, and treatment vs. prophylaxis did not significantly affect PK.

Table 2 Final parameter estimates (%RSE)

Parameter	Estimate (%RSE)	BSV (%RSE)
F ()	1 Fixed	25.8% (9%)
V (L)	24.8 (2%)	-
CL (L/h)	5.14 (2%)	15.7% (13%)
Tlag - whole tablet (h)	0.553 (20%)	56.6% (30%)
Tlag - crushed tablet (h)	0.153 (32%)	
ka - normal oral dose (1/h)	2.03 (11%)	58.2% (11%)
ka - naso-gastric tube (1/h)	1.28 (11%)	
Time since previous dose (h)	20.5 (4%)	5.04 h (11%)
Additive error (mg/ L)	0.113 (38%)	-
Proportional error (%)	9.55 % (6%)	-

CL and V parameters reported for a 15 kg child, precision estimates from stochastic approximation

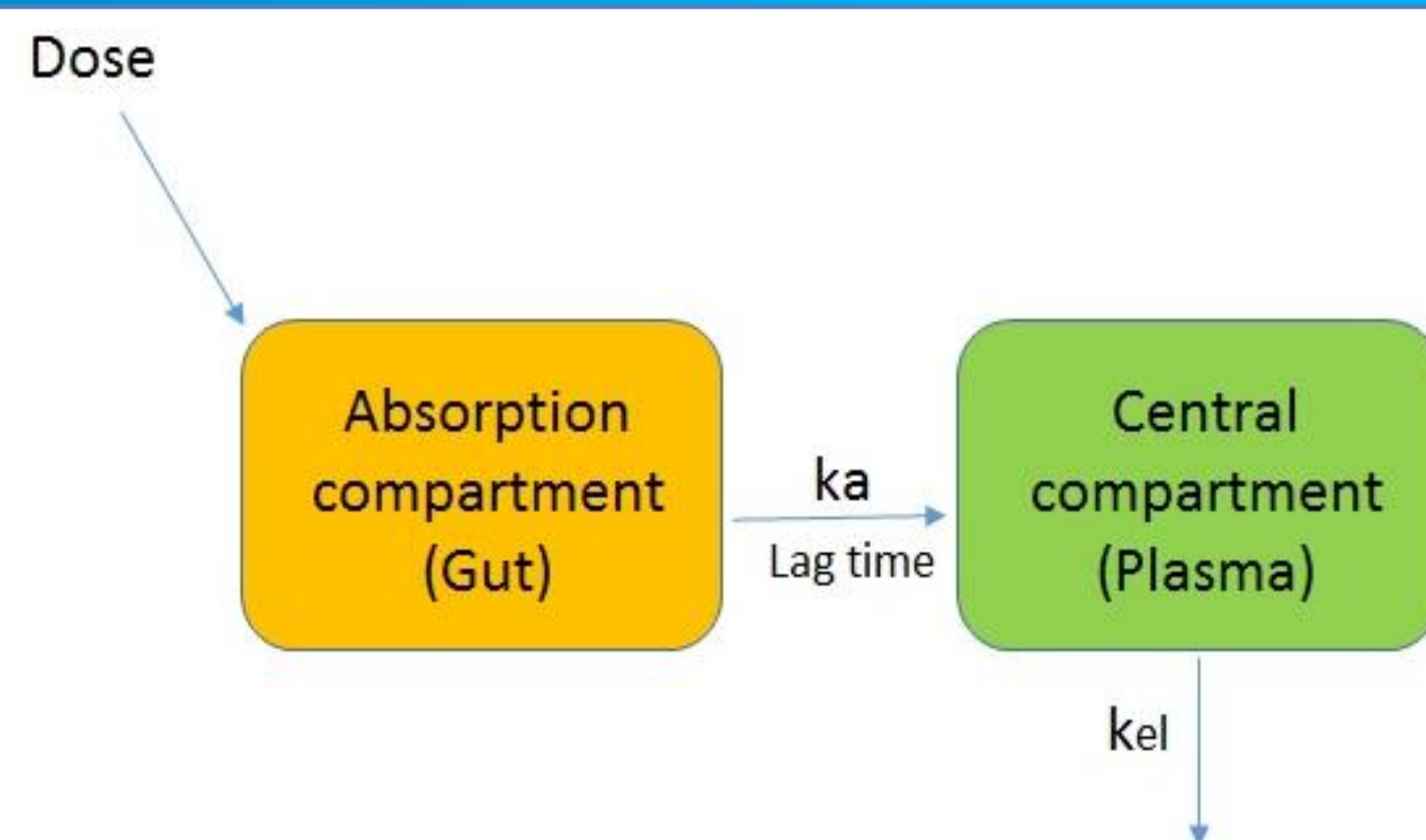


Figure 2 Structural model

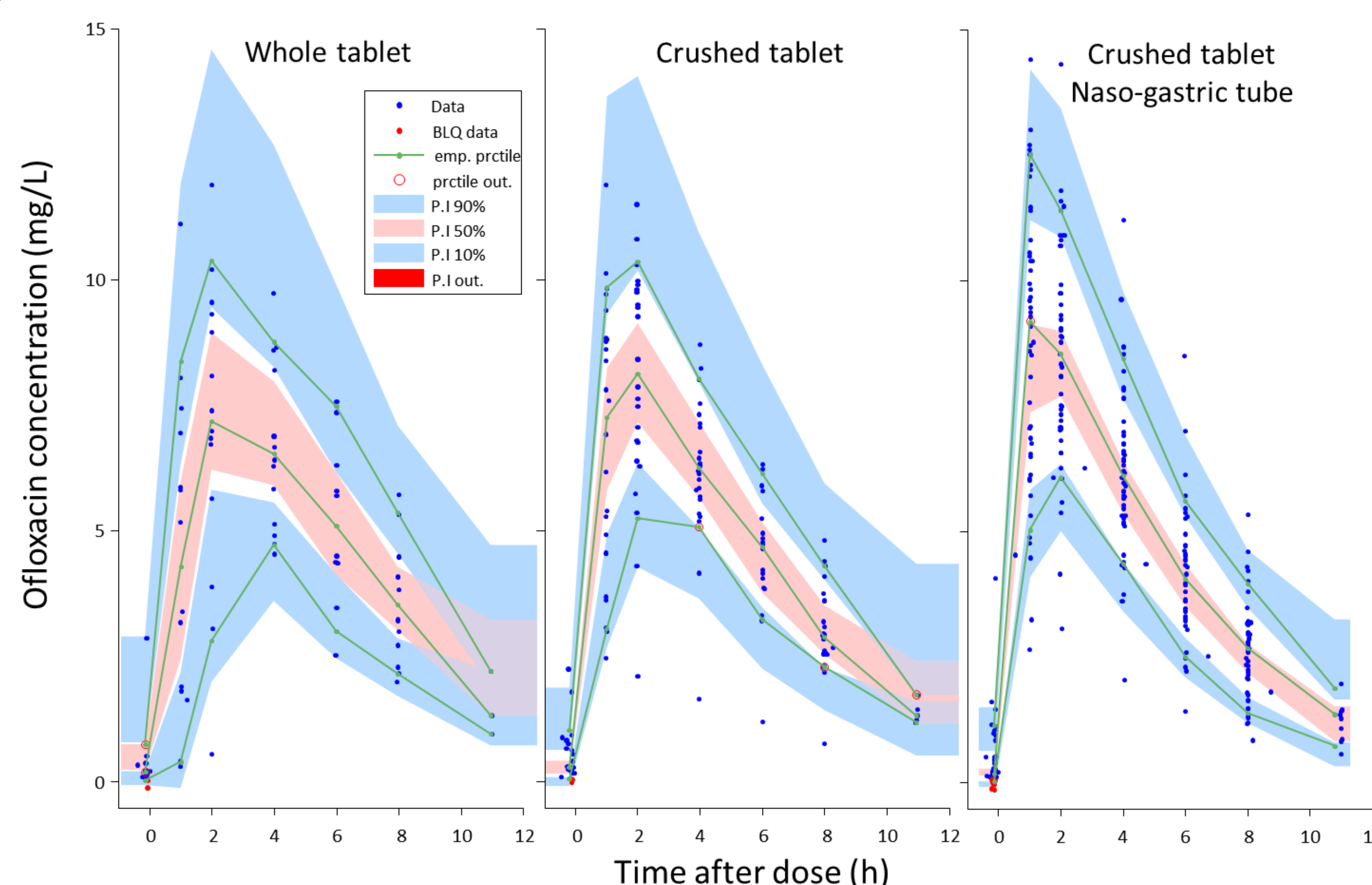


Figure 3 Visual predictive check, stratified by dosing procedure

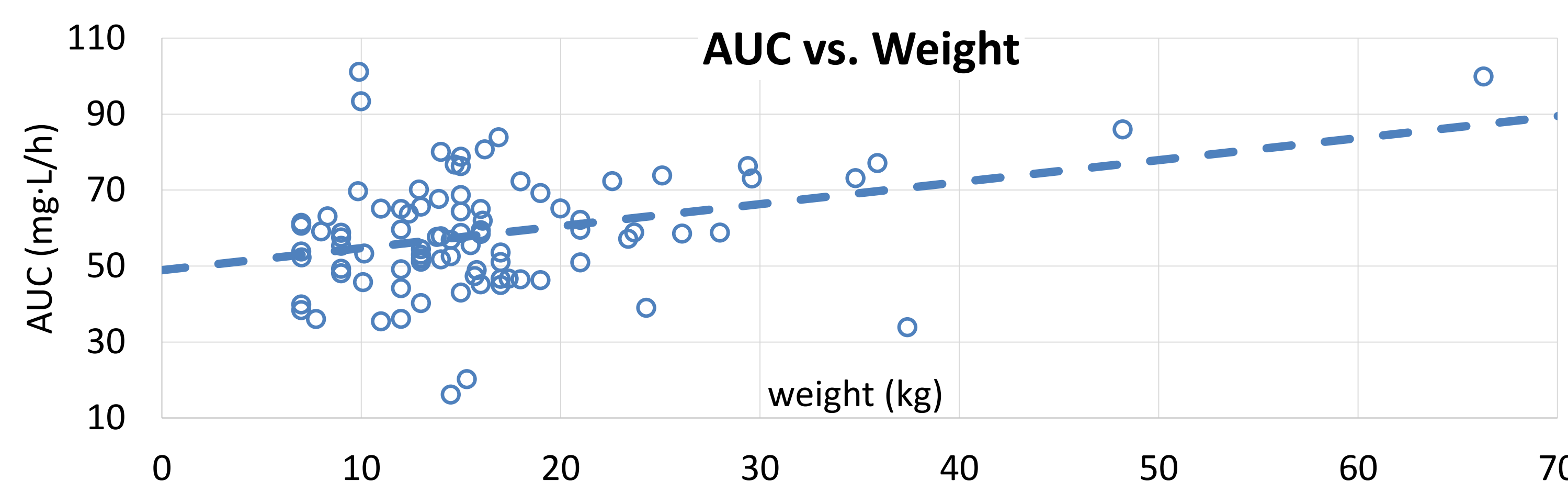


Figure 4. AUC (based on post-hoc estimates) vs. weight. <10% shrinkage for CL & F

Using constant mg/kg dosing, lower weight children achieved lower concentrations, consistently with allometric scaling (Figure 4).

Dose simulations from the model show that:

- to target similar AUC as adults [2,3] (~100 h·mg/L) 25-50 mg/kg are needed with smaller children receiving higher mg/kg doses.
- based on the low exposures in this cohort, even 800 mg (full adult dose) is not enough to achieve adult exposure in children >30kg.

Doses targeting the same AUC may cause larger Cmax in smaller children, raising toxicity concerns (Figure 5).

“Optimised” Exposure vs. weight

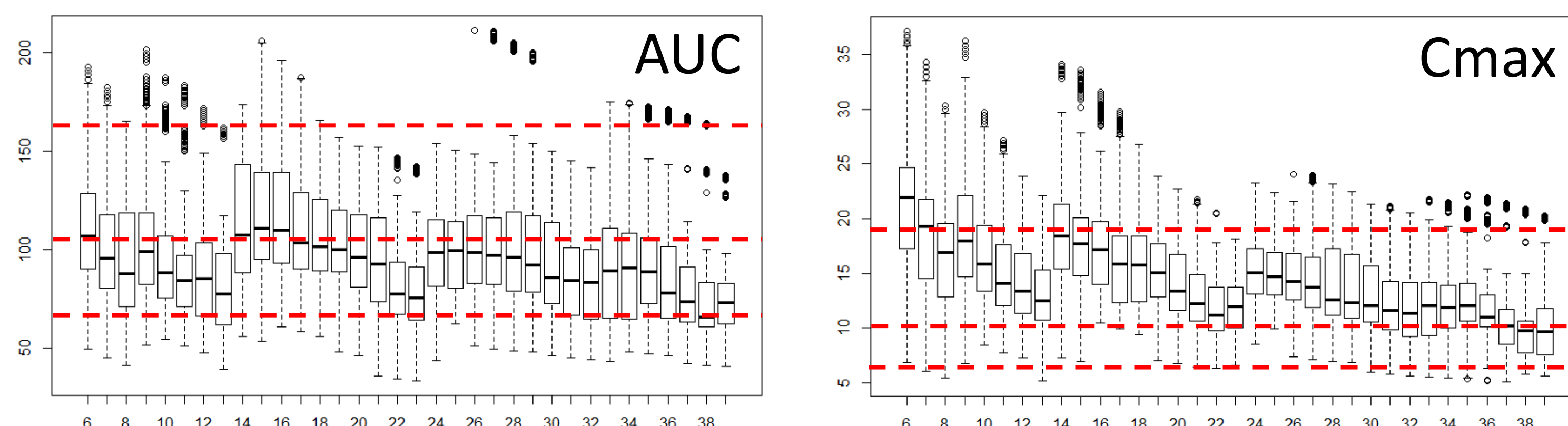


Figure 5. Optimized exposures (AUC and Cmax) for different weightbands.

Conclusions

With the current “constant mg/kg” dosing approach, smaller children are severely under-dosed and exposed.

Even accounting for allometric scaling, children in this cohort had larger clearance (and hence lower exposures) than previous reports in an ethnically similar adult population.

No maturation effect of age on CL was detected in this cohort, possibly due to the low number of children <1 yr.

The estimation of time of previous dose proved a useful tool to minimise the impact of unknown dosing history.

References

- [1] B. J. Anderson and N. H. G. Holford, “Mechanism-based concepts of size and maturity in pharmacokinetics,” Annu. Rev. Pharmacol. Toxicol., vol. 48, pp. 303–32, Jan. 2008.
- [2] E. Chigutsa, S. Meredith, L. Wiesner, N. Padayatchi, J. Harding, P. Moodley, W. R. Mac Kenzie, M. Weiner, H. McIlleron, and C. M. J. Kirkpatrick, “Population pharmacokinetics and pharmacodynamics of ofloxacin in South African patients with multidrug-resistant tuberculosis,” Antimicrob. Agents Chemother., vol. 56, no. 7, pp. 3857–63, Jul. 2012.
- [3] M. Zhu, J. J. Stambaugh, S. E. Berning, A. E. Bulpitt, E. S. Hollender, M. Narita, D. Ashkin, and C. a Peloquin, “Ofloxacin population pharmacokinetics in patients with tuberculosis,” Int. J. Tuberc. Lung Dis., vol. 6, no. 6, pp. 503–509, 2002.