

Population pharmacokinetics of rifampicin in Vietnamese Children with tuberculous meningitis

Navarat Panjasawatwong¹, Nguyen Duc Bang^{2,3}, Maxine Caws^{2,4,5}, Thai Thanh Truc², Tran Ngoc Duong³, Nguyen Huy Dung³, Dang Thi Minh Ha^{2,3}, Guy E. Thwaites^{2,5}, Doortje Heemskerk^{2,5}, Laura Merson^{2,5}, Pham Van Toi^{2,5}, Thomas Pouplin^{5,6}, Marcel Wolbers^{2,5}, Jeremy J. Farrar^{2,5}, Jeremy N. Day^{2,5} and Joel Tarning^{5,6}

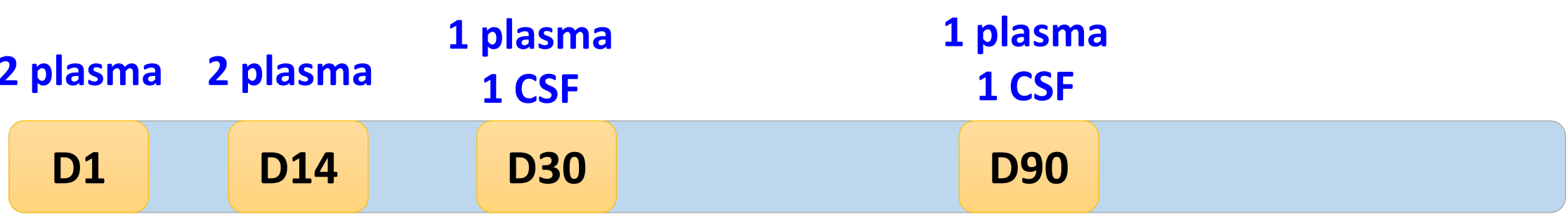
(1) Faculty of Pharmacy, Mahidol University, Bangkok, Thailand; (2) Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; (3) Pham Ngoc Thach Hospital, Ho Chi Minh City, Vietnam; (4) Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK; (5) Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK; (6) Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, Thailand

Background & Objective

Rifampicin is the backbone of the first-line anti-TB combination treatment (i.e. isoniazid, rifampicin, pyrazinamide and ethambutol). The anti-TB regimens used to treat tuberculous meningitis (TBM) in children have been extrapolated from the treatment of pulmonary TB in adults. Nevertheless, several studies suggested that drug exposures to the four first-line anti-TB drugs were lower in children than that in adults after standard treatment. In addition, population PK studies in adult TB patients have shown high inter-individual variability (IIV) in rifampicin plasma concentrations. The aim of this study was to investigate the population PK of rifampicin in Vietnamese children with TBM.

Methods

One-hundred Vietnamese children with TBM were treated with an 8-month pediatric anti-TB treatment regimen (2HRZES /1HRZE/5HRE). The treatment consisted of isoniazid (5 mg/kg), rifampicin (10 mg/kg) and ethambutol (15 mg/kg) for 8 months, with the addition of pyrazinamide (25 mg/kg) for the first 3 months and streptomycin (15 mg/kg) for the first 2 months. The drugs were given once daily. Samples were collected on 4 occasions as shown below.



Pharmacokinetic properties of rifampicin in plasma were evaluated using nonlinear mixed-effects modelling in NONMEM 7.4. FOCE-I was used throughout the model-building process. Different structural, variability and covariate models were evaluated. Enzyme maturation and enzyme turnover models were also evaluated.

Results

A total of 492 plasma concentrations from 100 participants were included in the model.

Demographic data

Fifty-six percent (56%) of the patients were male and the median age was 3 years (IQR: 1-7). The median weight and BMI were 11 kg (IQR: 8.5-16.38) and 14.30 kg/m² (IQR: 13.21-16.77), respectively. Most of children (92%) were HIV negative, 4% were HIV positive and the remaining 4% had unknown HIV status.

Final rifampicin pharmacokinetic model

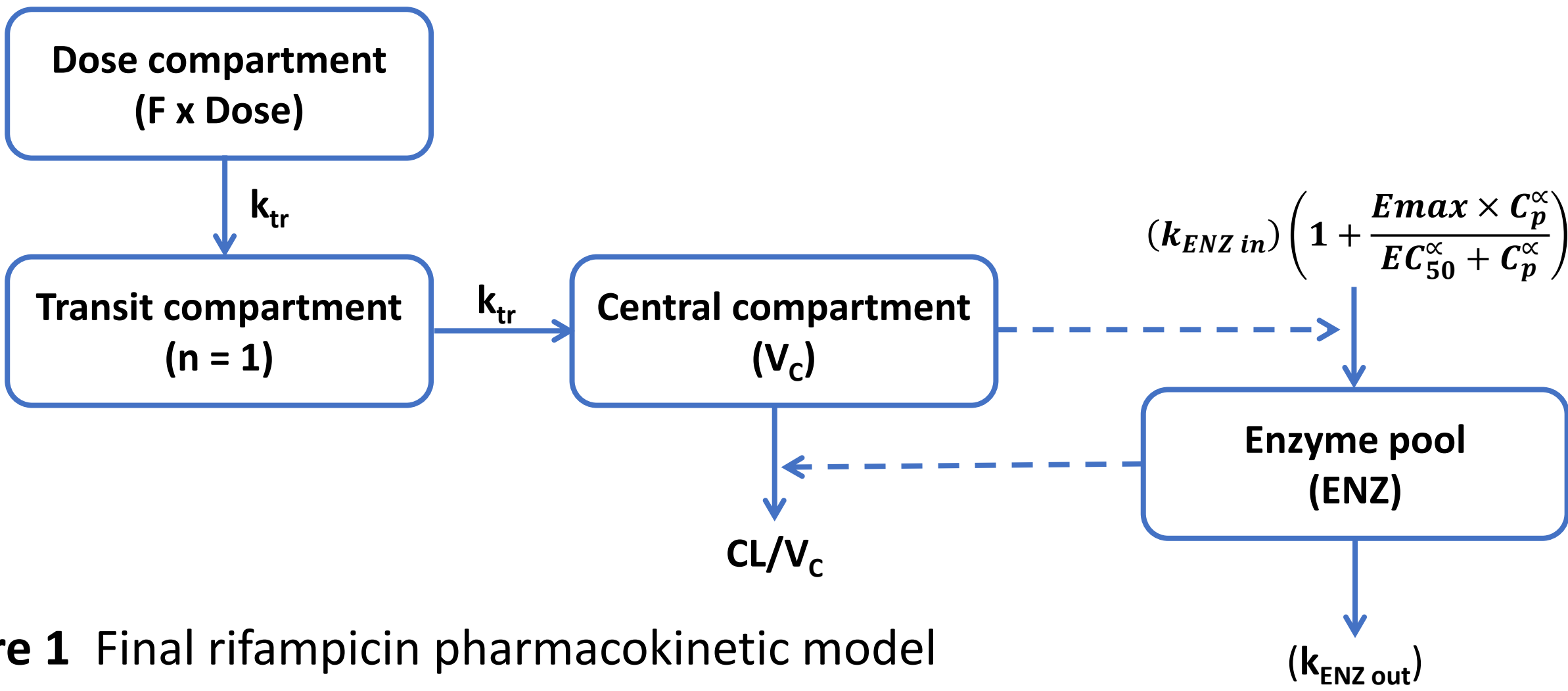


Figure 1 Final rifampicin pharmacokinetic model

Final rifampicin parameter estimates

Table 1 Parameter estimates of the final population pharmacokinetic model of rifampicin

Parameters	Population estimates ^a (%RSE ^b)	95%CI ^b	%CV for IIV ^a (%RSE ^b)	95%CI for IIV ^b
CL/F ^c (L/hr)	2.55 (9.18)	2.09 - 3.02	22.1 (45.1)	13.0 - 32.2
V _c /F ^c (L)	11.9 (6.31)	10.5 - 13.6	27.4 (37.0)	18.1 - 38.6
F (%)	1 FIX	-	0 FIX	-
MTT (hr)	1.53 (12.7)	1.15 - 1.91	79.9 (25.1)	57.4 - 109
AG ₅₀ ^d (months)	1.52 (41.3)	0.401 - 2.77	0 FIX	-
K _{enz} (hr ⁻¹)	0.00872 (27.6)	0.00449 - 0.0137	0 FIX	-
Emax	3.78 (23.8)	2.33 - 5.87	0 FIX	-
EC ₅₀ (mg/L)	0.556 (31.4)	0.342 - 0.987	0 FIX	-
Residual unexplained variability				
Plasma	-	-	79.7 (7.72)	72.6 - 88.2

^aNONMEM estimates ^bassessed by sampling importance resampling (SIR) ^cbased on median body weight ^dthe age at which 50% maturation of CL occurred

Conclusions

- ❑ Rifampicin data were best described by a one-compartment disposition model with transit absorption (one fixed transit compartment).
- ❑ High inter-individual variability was observed in the absorption of rifampicin.
- ❑ Body weight (allometric function on CL and V) and age (enzyme maturation on CL) were significant covariates.
- ❑ The elimination of rifampicin was dependent on drug concentrations (autoinduction), resulting in approximately 50% reduced exposure after one month of treatment (fully induced state).

Model diagnostics

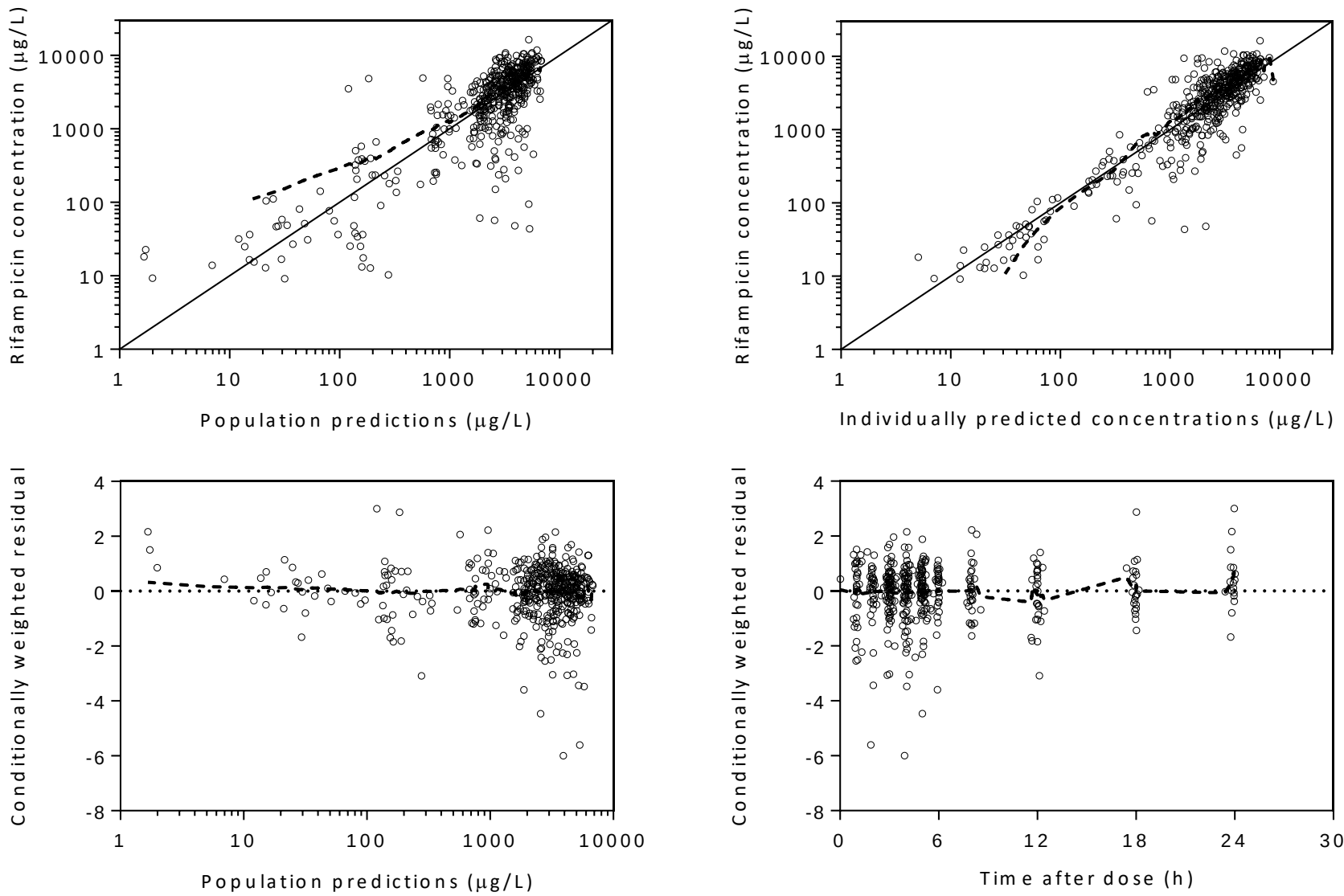


Figure 2 Goodness-of-fit (GOF) plots of the final rifampicin pharmacokinetic model

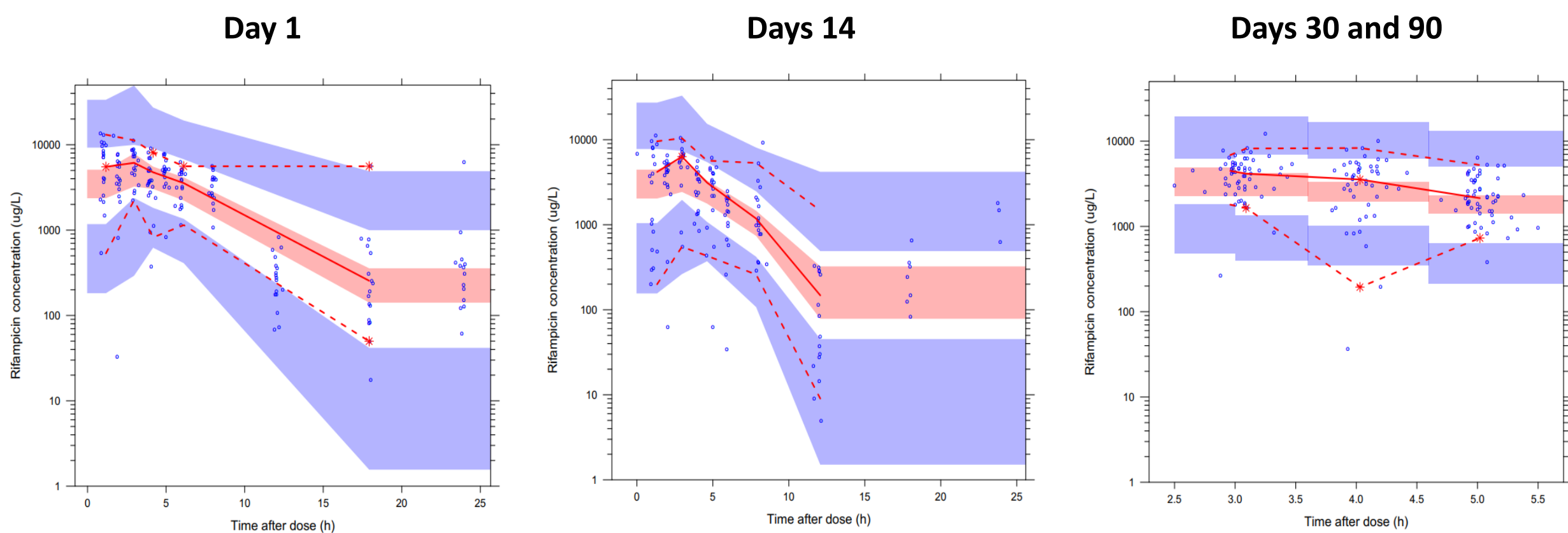


Figure 3 Visual predictive checks (VPC) of the final rifampicin pharmacokinetic model

Simulations

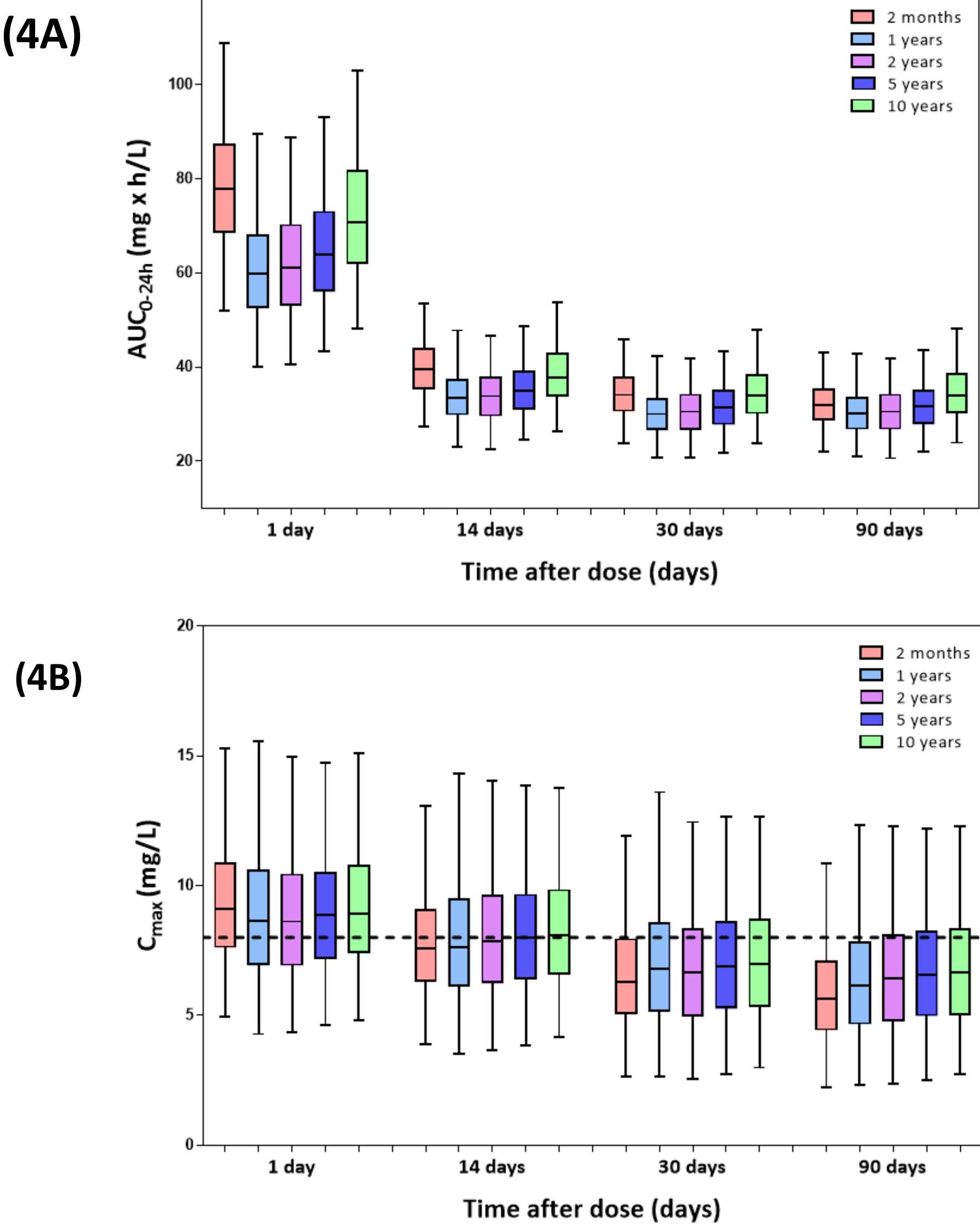


Figure 4 Box plots of simulated rifampicin (4A) area under the concentration-time curve from 0 to 24 h (AUC_{0-24 h}) and (4B) maximum concentration (C_{max}) at pre-induced and induced states (n=1,000) after receiving rifampicin 15 mg/kg/day. Sub-therapeutic threshold is set to 8 mg/L.

[1] Wynand S, Khandelwal A, Merle C, Rustomjee R, Gninafon M, Lo MB, et al. A semimechanistic pharmacokinetic-enzyme turnover model for rifampicin autoinduction in adult tuberculosis patients. Antimicrob Agents Chemother 2012;56(4):2091-8.

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