

A semi-physiological model with circadian rhythm of nevirapine pharmacokinetics in African children.

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Background and Objectives

- Nevirapine (NVP) is a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) widely used for treatment of HIV-infected children in resource limited countries.[1]
- Studies report under-exposure in infants dosed according to WHO guidelines.[1,2]
- NVP has a long $t_{1/2}$ of 25-30h and is metabolised mainly by CYP3A4 and CYP2B6.[3] Large variability in NVP pharmacokinetics (PK) is attributed to *CYP2B6* polymorphisms 516G>T and 983T>C.[4]
- Despite reports of differences between A.M. and P.M. NVP exposures, circadian variation for this drug hasn't been previously characterised.[5]
- The aim was to develop a NVP PK model in African children accounting for the effect of *CYP2B6* polymorphisms and diurnal variation on clearance (CL) and 1st-pass metabolism, and suggest optimal dosing.

Methods

- Subjects** - Combined data from 2 studies in African children:

Table 1 Patient demographic characteristics and dosage in the studies

Characteristics	CHAPAS-1 [6]	CHAPAS-3 [7]	Combined
No. of children	84	336	420
No. of samples included	539	2766	3305
Age [years] *	6.2 (0.4-15.0)	2.6 (0.3-12.2)	2.92 (0.3-15.0)
Weight [kg] *	15.75 (3.5-29.0)	11.5 (4.9-29.6)	12.2 (3.5-29.6)
Sampling scheme**	Week 6: 0h, 1h, 2h, 4h, 6h, 8h, 12h	Weeks 6, 36, 60, 84, 108, 136: 1-2 samples, 2-3h apart	*Median at baseline (range) **Not equal number per patient
Dosage	WHO 2006 [8]	WHO 2010 [3]	

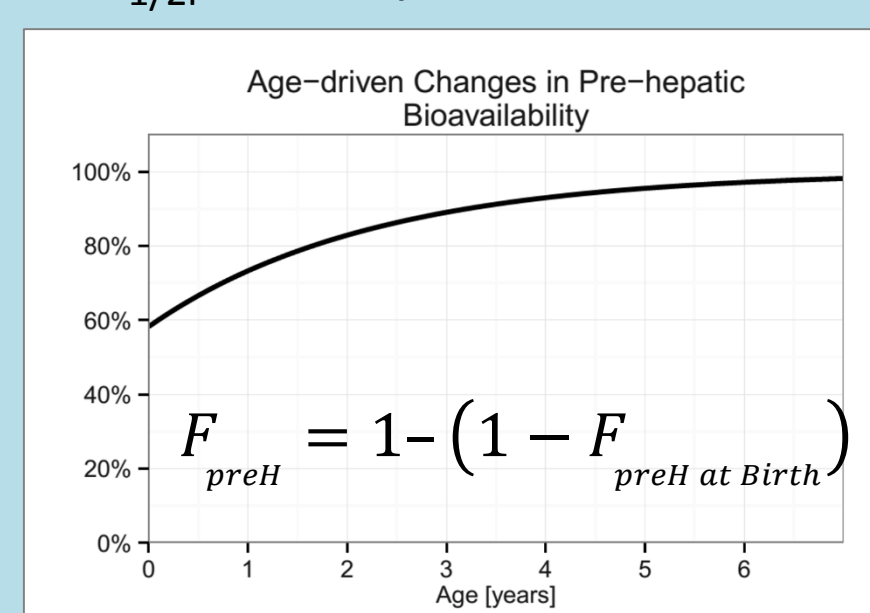
- Model building** in NONMEM 7.3 (FOCE-I).

- Allometric scaling** applied to all CL and volume parameters.[9] The effect of diurnal variation and maturation were tested on intrinsic CL (CL_{int}) and pre-hepatic bioavailability (F_{preH}).[9-10] **Mixture modelling** was used to impute missing genotypes (n=96).[11]
- Simulations** were used to evaluate **(1)** the effect of genotype, **(2)** intake time (6:00, 7:00, 8:00, 9:00 AM/PM), and **(3)** dose-splitting strategies (A.M./P.M. - D1:100/50 mg, D2:75/75 mg, D3:50/100 mg) on C_{min} and AUC.

Results

- NVP PK was best described using a 1-compartmental disposition model with absorption through transit compartments [12] and elimination through a well-stirred hepatic model accounting for 1st-pass effect.[13]

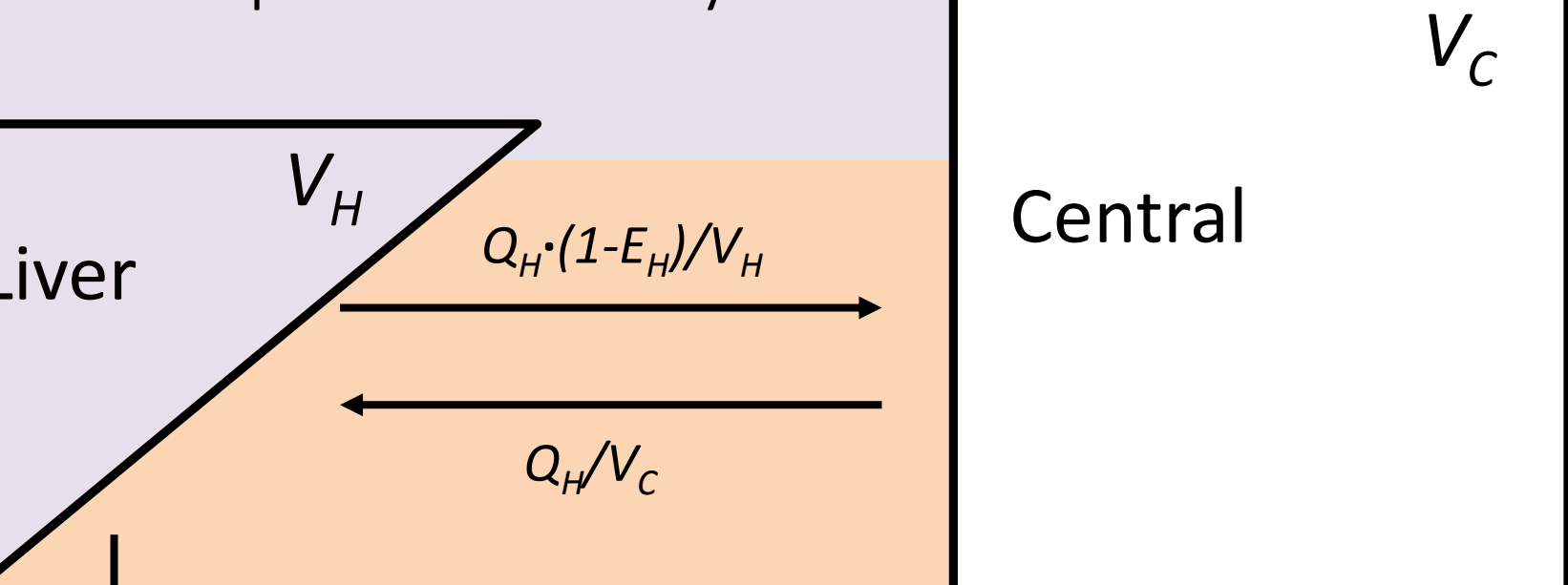
Age-driven differences in F_{preH} were described using an exponential model with F at birth = 58.3% and $t_{1/2F}$ = 0.64 year



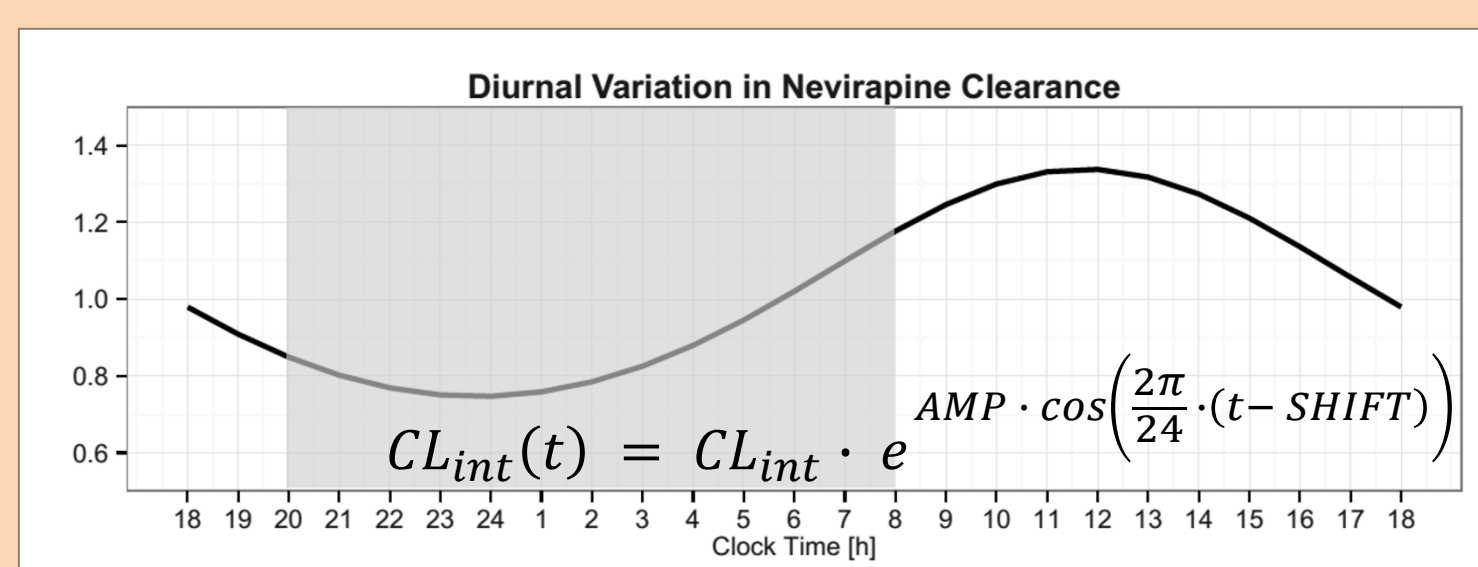
Hepatic well-stirred model implemented as per Gordi *et al* [13] had following assumptions:

- NVP fraction unbound (f_u) = 0.4 [3]
- hepatic plasma flow (Q_H) = 50 L/h in a 70 kg person [14]
- liver volume (V_H) = 1 L in a 70 kg person [13]

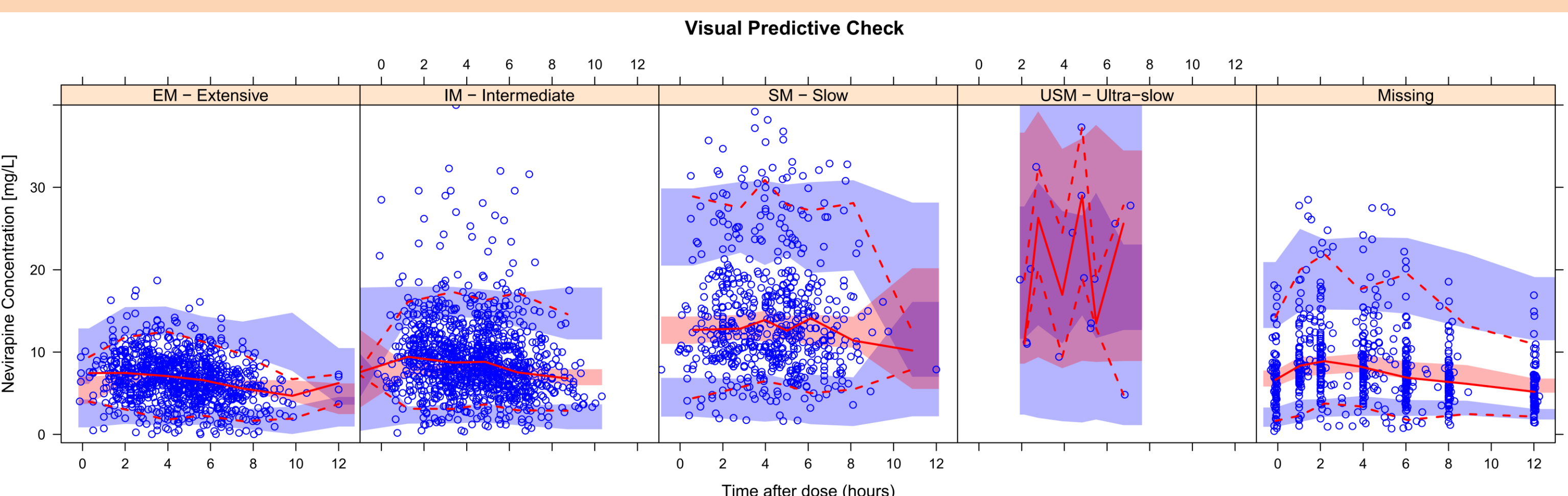
$F = F_{preH} \cdot F_H$ and $F_H = 1 - E_H$ allowing clearance covariates to affect hepatic bioavailability



Diurnal variation in CL_{int} was best described using a cosine function with peak amplitude of ~29% at 12 p.m.



CYP2B6 Metabolic Status		Drop in CL_{int}	E_H
EM	516GG 983TT	ref	7.9%
IM	516GT 983TT 516GG 983TC	- 17%	6.6%
SM	516TT 983TT 516GT 983TC	- 50%	4.1%
USM	516GG 983CC	- 68%	2.6%



From top left clockwise: **Figure 1** Age-driven differences in pre-hepatic bioavailability. **Figure 2** Diurnal variation in clearance intrinsic. **Figure 3** Visual predictive check of the final model split by CYP2B6 metabolic status. **Figure 4** (Middle) Schema of the final PK model.

We thank all patients and staff from the centres involved in CHAPAS-1 and CHAPAS-3 studies.
The studies were a joint collaboration of following institutions: JCRC, Kampala, Uganda; Baylor-Uganda, Paediatric Infectious Disease Centre, Mulago Hospital, Uganda; University Teaching Hospital, School of Medicine, Lusaka, Zambia*; JCRC, Gulu, Uganda; MRC CTU, London, UK*; Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands*; University of Cape Town, Cape Town, South Africa*
Funding: CHAPAS-1 and CHAPAS-3 were founded by EDCTP
*CHAPAS1, *CHAPAS-3
Drugs were provided by: CIPLA, India

Table 2 Final parameter estimates (5th and 95th percentile)*

Parameter	Typical values	Variability**
F_{preH}		
Older Children	1 (FIXED)	BSV: 18.72 (6.59 – 20.66)
At Birth [%]	58.3 (50.5 – 68.2)	BOV: 17.02 (16.12 – 20.87)
$t_{1/2} - F_{preH}$ [years]	1.54 (1.47 – 2.58)	
MTT [h]	0.56 (0.49 – 0.70)	BOV: 199.73 (177.23 – 217.70)
KA [1/h]	0.84 (0.67 – 1.12)	BOV: 44.91 (31.32 – 50.46)
N_{TRANS} [number]	3 (FIXED)	
Volume [L]	21.9 (20.2 – 26.2)	
CL_{int}		
EM [L/h]	3.27 (3.00 – 3.69)	BSV: 21.40 (20.08 – 32.46)
IM [L/h]	2.72 (2.27 – 2.94)	
SM [L/h]	1.65 (1.47 – 1.89)	Increased BOV F_{preH} for unobserved intake
USM [L/h]	1.04 (0.87 – 1.38)	Additive error [mg/L]
AMP [%]	29.2 (27.7 – 45.2)	Proportional error [%]
SHIFT [h]	-12.3 (-13.3 – -10.4)	Increased error for sparse data
		1.56 (1.49 – 1.81)

* Estimated from nonparametric bootstrap (n=50) of the final model, **Expressed as approximate %CV

Simulations

- Simulated average exposures were within the therapeutic target (3 - 8 mg/L)[16] for majority of children dosed following WHO 2010 guidelines.[2]
- C_{min_PM} <3mg/L was observed in 43% of EM <6kg and 26% of IM <6kg while 78% of SM and 94% USM in all weight bands had C_{min_PM} >8mg/L.

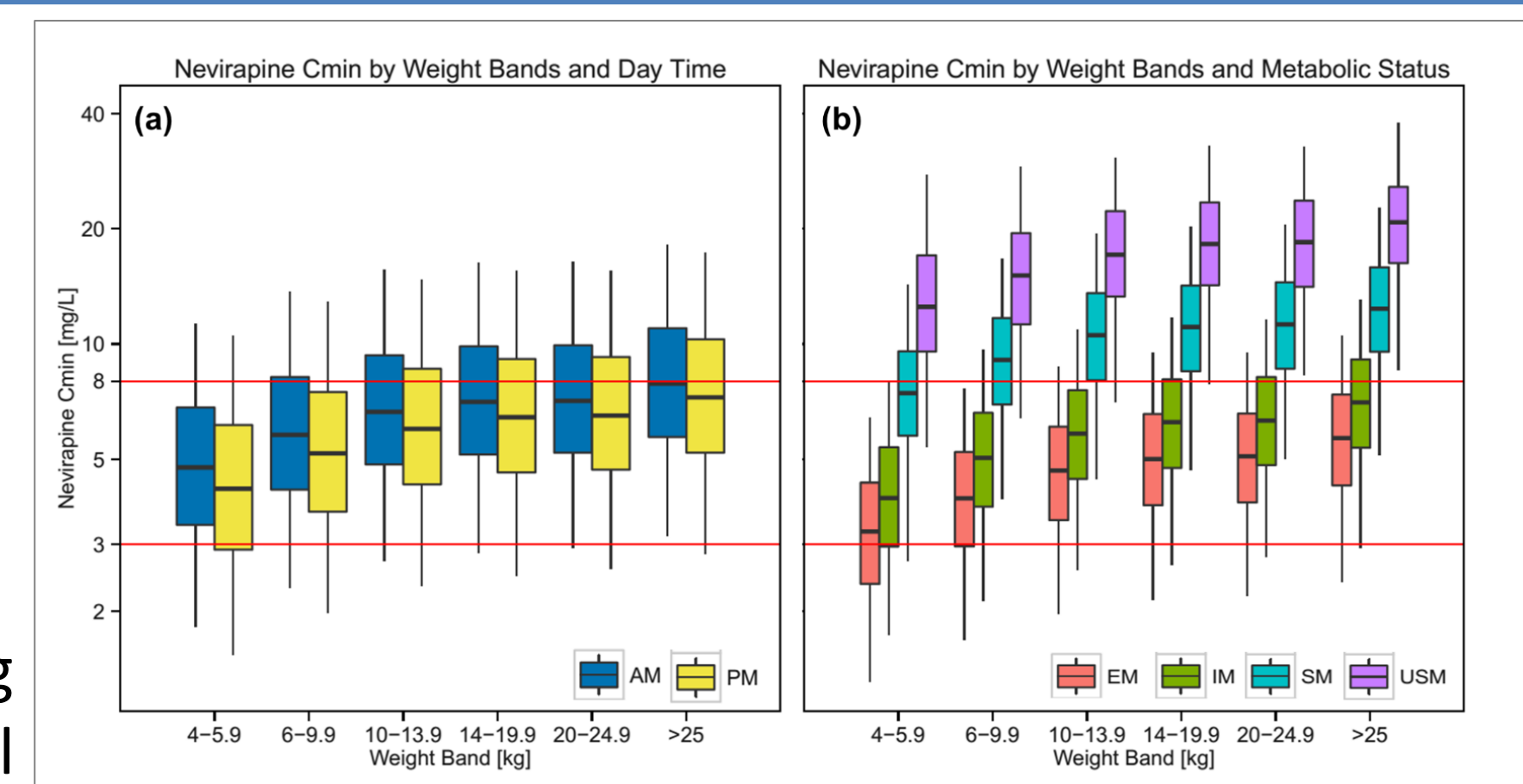


Figure 5 Simulated differences between average a.m./p.m. exposures by weight bands (a) and by metabolizer group (b) based on original data set (100 simulations)

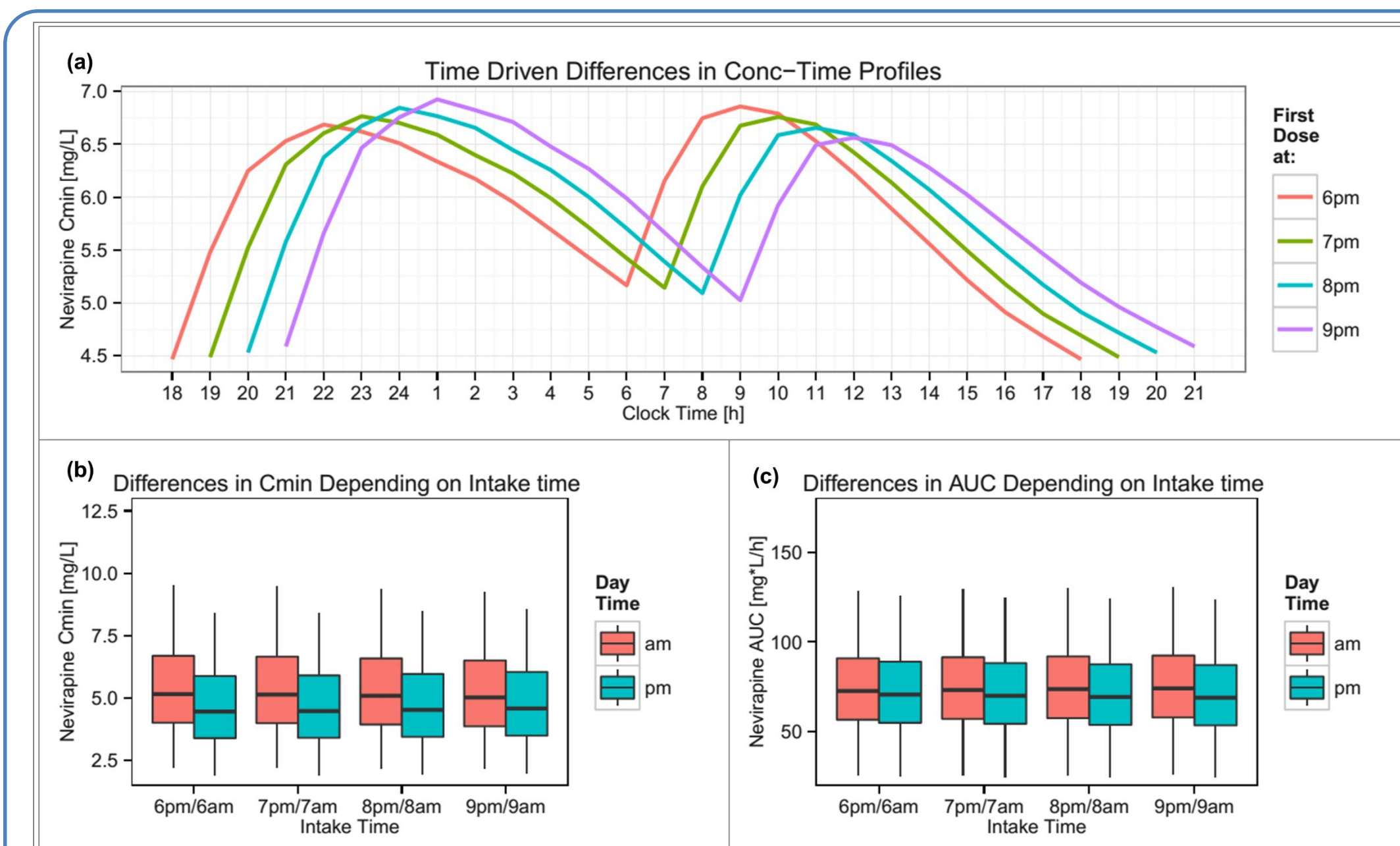


Figure 6 Simulated median concentration time curve depending on administration time (a) and histograms comparing a.m./p.m. C_{min} (b) and AUC (c) -single child (0.44 years, 7.2 kg, IM) simulated 1000 times, dose 75 mg BD

- Intake time had negligible effect on average exposures.
- Depending on administration time the ratio between median A.M./P.M. exposures was:
 - C_{min} : 1.09–1.15
 - AUC: 1.03–1.07

- Differences in ratios between median A.M./P.M. for tested dose-splitting strategies were:
- C_{min} : D1 - 0.93, D2 - 1.13, D3 - 1.41
- AUC: D1 - 0.90, D2 - 1.04, D3 - 1.22

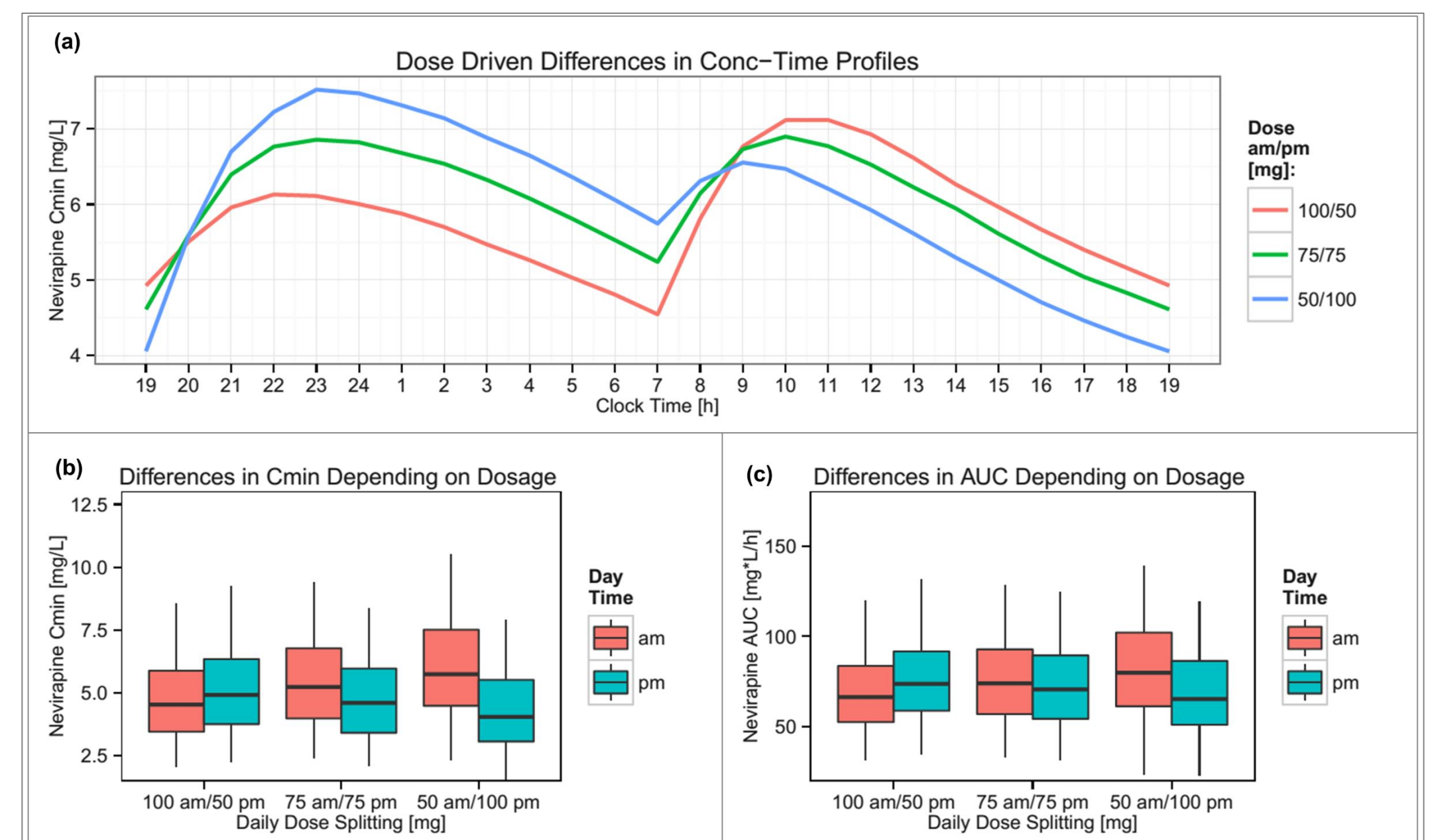


Figure 7 Simulated median concentration time curve depending on dose splitting strategy (A.M./P.M.: 100mg/50mg, 75mg/75mg, 50mg/100mg) (a) and histograms comparing A.M./P.M. C_{min} (b) and AUC (c) -single child (0.44 years, 7.2 kg, IM) simulated 1000 times

Conclusions

- Simulations suggest that despite diurnal variation in NVP CL_{int} the average C_{min} and AUC are not greatly affected by intake time, possibly due to long $t_{1/2}$.
- When dose cannot be split equally, larger doses should be given A.M.
- Results confirm that majority of children dosed according to WHO 2010 guidelines have NVP exposures above efficacy target of 3 mg/L.
- To prevent sub-therapeutic exposures children <6kg EM and IM should receive same the dose as those in the 6-10 kg weight band.
- To achieve homogenous exposures, the NVP dose for SM and USM should be reduced by 50%.

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