

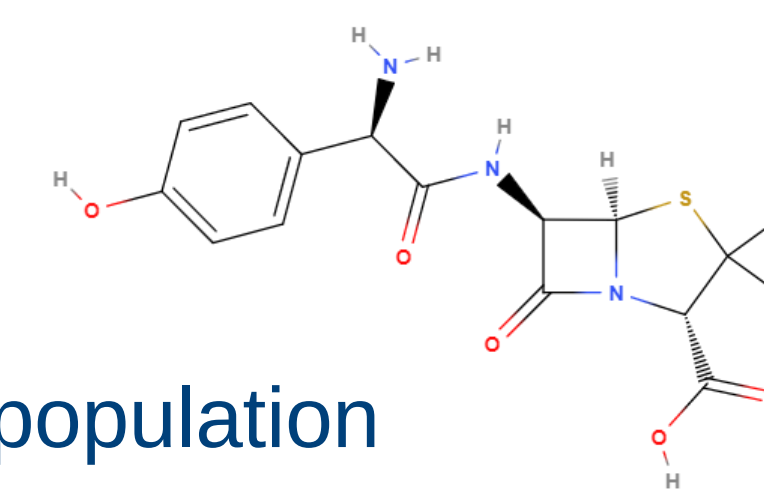
Population Pharmacokinetics of Amoxicillin in Postpartum Minipig Plasma

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Introduction

- Antibiotics are frequently prescribed to postpartum women and nursing mothers for prophylaxis and treatment of infections
- Infant exposure to maternal antibiotics is a safety issue commonly addressed
- The Göttingen Minipig can serve as a non-clinical species for in vivo lactation studies with good bio-relevance to humans¹
- As the first step to investigate the transfer of amoxicillin (AMX) from maternal plasma to milk, the present study aimed to develop a population pharmacokinetic (Pop PK) model to capture the PK characteristics of intramuscular (IM) AMX in postpartum minipig plasma



Methods

Dataset

- Postpartum Göttingen Minipigs
- AMX (Clamoxyl[®] RTU; 7 mg/kg, IM, Once daily) for 21 – 23 days
- 125 plasma concentration data from 3 minipigs
- 118 plasma concentrations were included in the analysis
 - 7 plasma concentrations collected on Day 1 from one of the minipigs were excluded because the animal had developed fever 4 hours post-dose

Model Development

- Pop PK analysis was performed using nonlinear mixed-effects modeling approach (Monolix[®] 2020R1125)
- The initial structural model was optimized to the plasma concentrations within 24 hours, and then modified to fit the multiple-dose data
- Covariate analysis
 - Forward selection
 - OFV ↓ >3.84 (p <0.05)
 - Backward elimination
 - OFV ↑ >6.63 (p <0.01)

Model Evaluation

- The predictive performance of the final model was evaluated by internal validation
 - Goodness-of-fit (GOF) plots
 - Visual predictive check (VPC)
- Model-based simulation (N = 1000)
 - The population and individual parameters derived from the final model were used
 - Individual weight from animals included in Pop PK analysis was used
 - Results were visualized using R version 4.0.3 and RStudio version 1.3.1093

Results

Table 1. Demographics

ID	Weight (kg)	Days postpartum on Day 1 (day)
I19	47	7
I20	48	6
I21	34	8
Mean ± SD	43.0 ± 7.81	7.00 ± 1.00

Figure 1. AMX Concentration-Time Profile within 24 hr after the 1st Dose

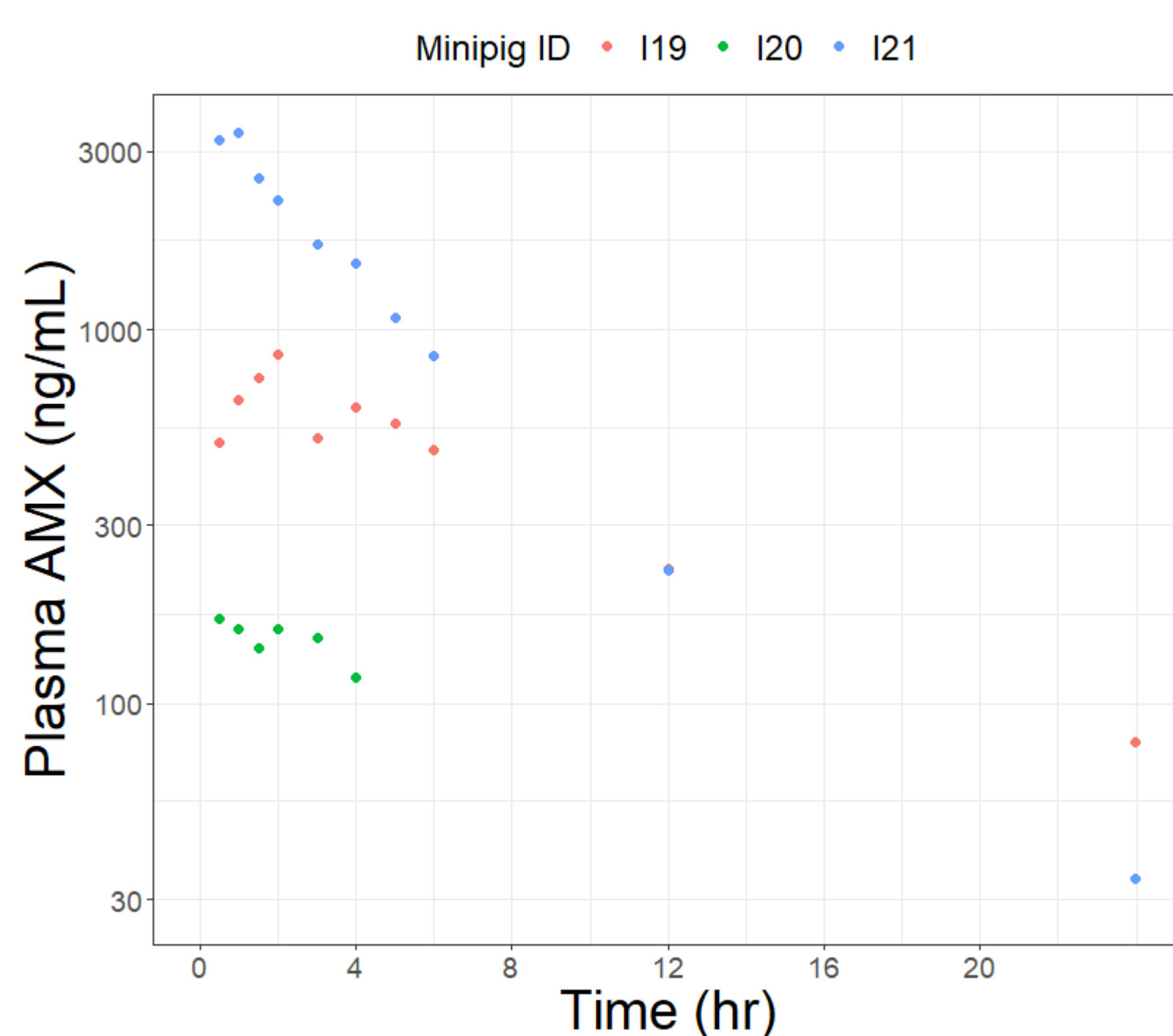


Figure 2. AMX PK Model



- Basic structural model comprised a one-compartment model with zero-order absorption and linear elimination

- Trough concentrations were observed to increase over time following repeated doses until the end of study
- CL was considered to change over time using days postpartum (DPP) as the regressor

$$CL_{TV} = CL \times \left(\frac{1}{DPP}\right)^{\beta}$$

where CL is the clearance (L/hr) at baseline; CL_{TV} is the time-varying clearance (L/hr)

- Body weight (log-transformed) was identified as a significant covariate on V, and correlation between V and CL was included in the final model

Table 2. Parameter Estimates

Parameter	Description	Value	RSE (%)
Fixed effects			
Tk0 (hr)	Duration of zero-order absorption	0.800	-
V (L)	Volume of distribution	253	12.1
β _{BW,V}	Effect of body weight on V	3.67	11.7
CL (L/hr)	Clearance	86.6	27.9
β	Effect of DPP on CL	0.628	12.5
Random effects			
ω _V	IIV of V	0.16	65.0
ω _{CL}	IIV of CL	0.30	43.4
Correlation			
ρ _{V-CL}	Correlation coefficient between V and CL	0.963	18.3
Residual variability			
σ	Proportional error	0.441	6.77

RSE: relative standard error; BW: body weight; IIV: Inter-individual variability

- Most of the observations fell within the 90% prediction intervals in VPC and the simulation range

Figure 3. GOF of the AMX PK Model

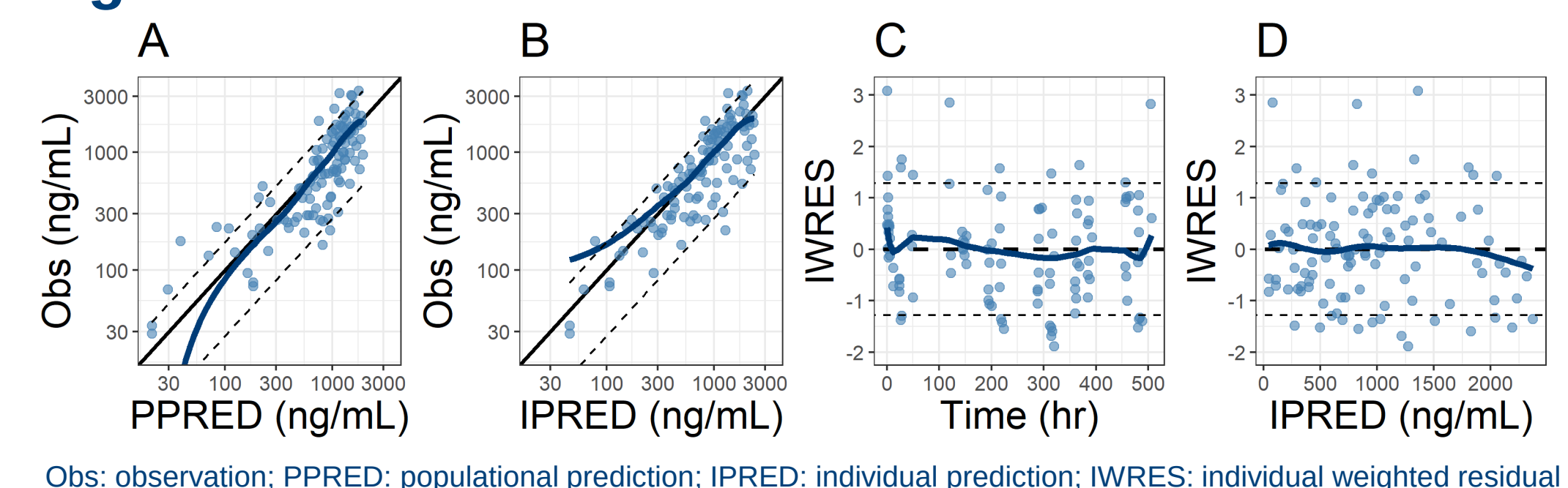


Figure 4. cVPC of the AMX PK Model

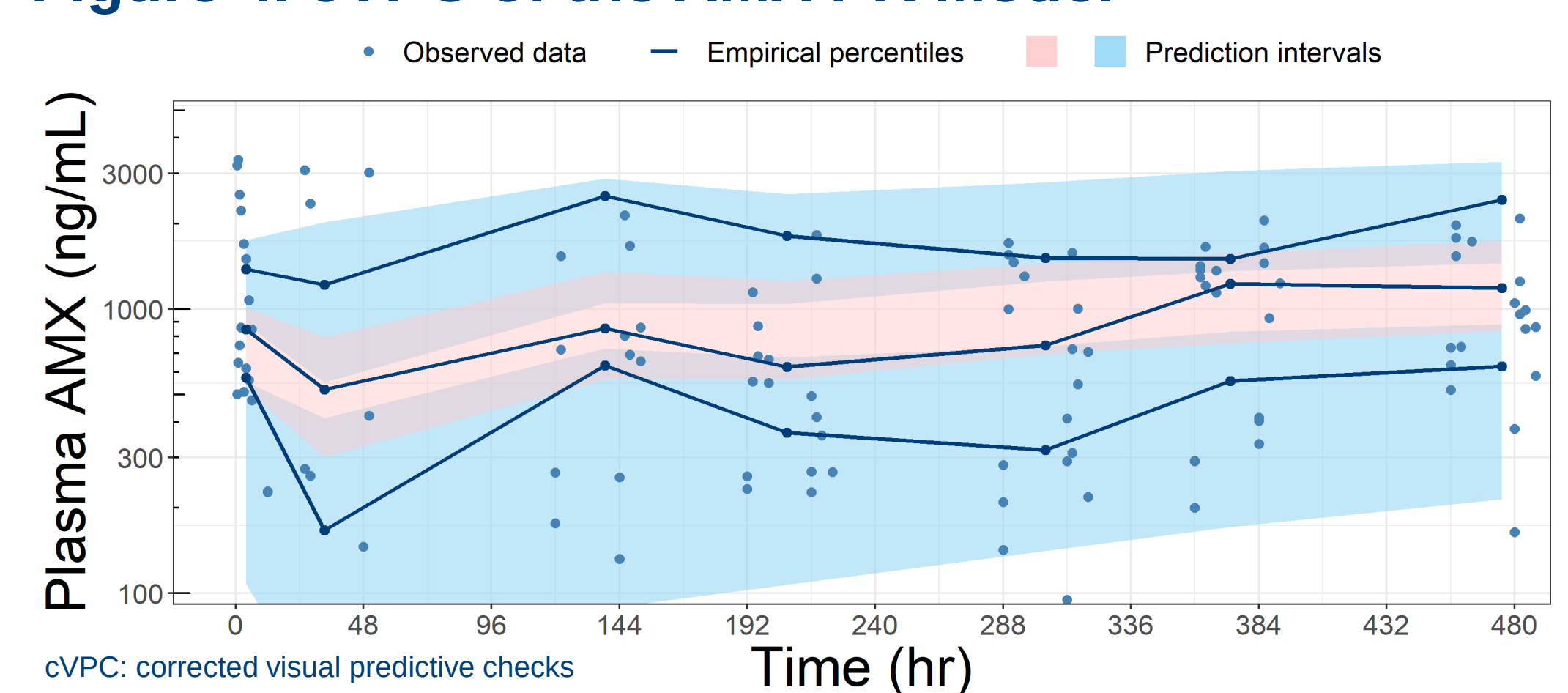
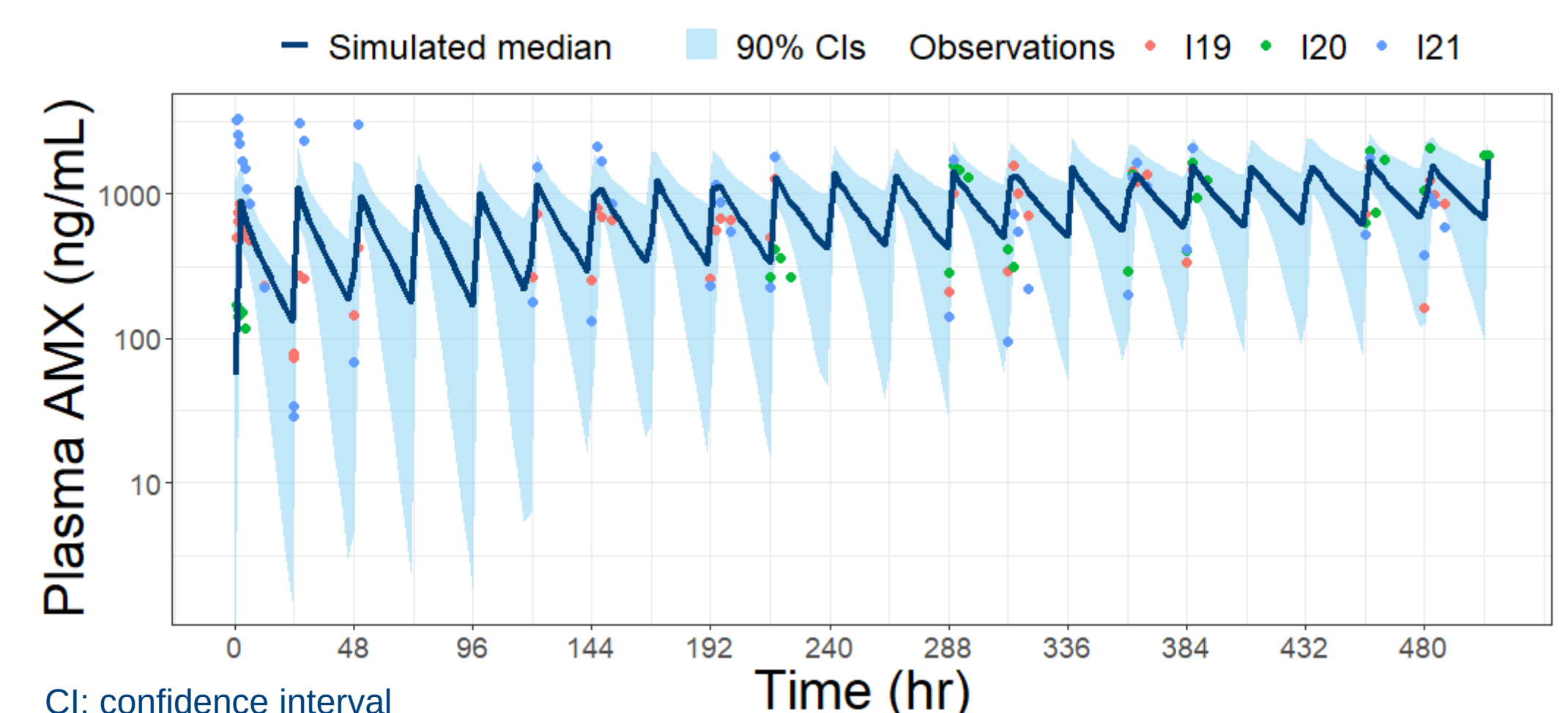


Figure 5. Simulated vs. Observed AMX Concentration-Time Profile



Conclusion

- The developed model demonstrated the ability to describe the PK profiles of AMX in postpartum minipig plasma with the interindividual-variability captured.
- The next step will be connecting this model to the milk data, and the simulation results will be compared with the published human model to obtain information for the inter-species extrapolation.

Reference

Ventrella D. et al. Animal Models for In Vivo Lactation Studies: Anatomy, Physiology and Milk Compositions in the Most Used Non-Clinical Species: A Contribution from the ConcePTION Project. Animals. 2021;11(3):714

Acknowledgement

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