Physiologically-based Pharmacokinetic modelling to predict the systemic exposure of medicines in infants via breastmilk: a contribution from the ConcePTION Project.

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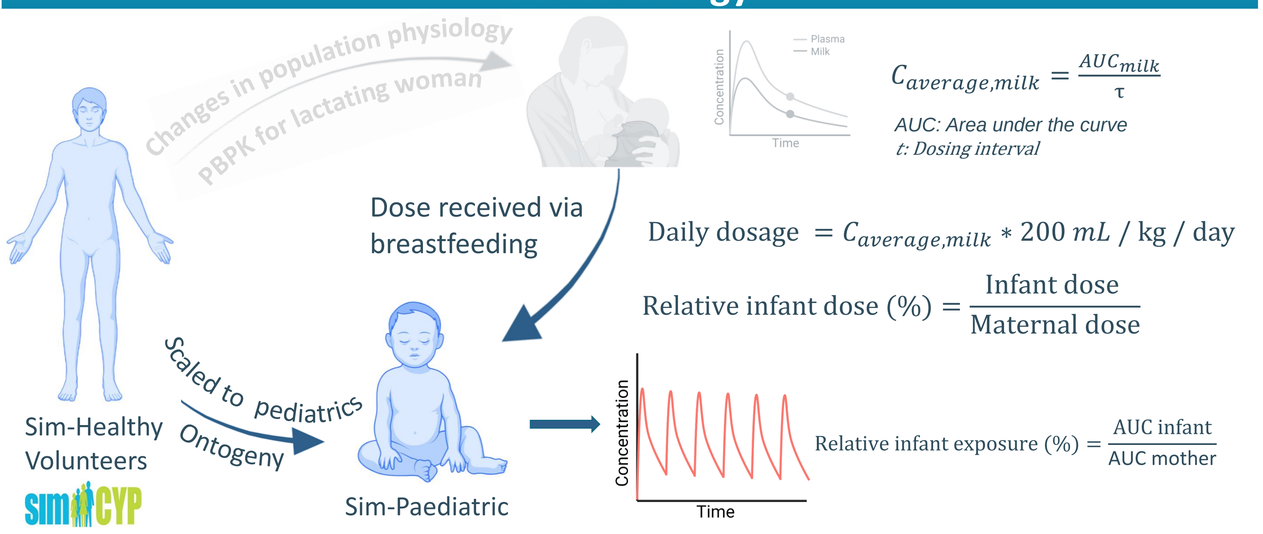
Background

Physiologically-based Pharmacokinetic (PBPK) is a very useful tool to predict the concentrations of medicines in human milk during the lactation phase and subsequently, the systemic exposure in infants[1]. This work is part of the Innovative Medicines Initiative (IMI) research consortium and project ConcePTION, with the main goal to reduce uncertainty about the use of medication during pregnancy and breastfeeding.

Objective

The aim of this study was to develop and evaluate the performance of lactation and infant PBPK model approaches to determine the infant (28 days to 3 months old) systemic exposure to maternally administered amoxicillin (AMX), cetirizine (CET), levetiracetam (LEV), valproic acid (VPA) and zidovudine (ZDV) via human milk.

Methodology



✓ A PBPK model was developed, reproduced [2], [3] or adapted [4] from literature for healthy volunteers (HV). The evaluated PBPK models for HV were extrapolated to infant population for each medicine.

Table 1 – Summary of the Physiologically-based Pharmacokinetic models developed using Simcyp.

	Absorption	Distribution	Metabolism/ Elimination
Amoxicillin	First order model	Full PBPK Rodgers and Rowland method	Renal (OAT3)
Cetirizine	ADAM		Renal
Levetiracetam	First order model		Renal
Valproic Acid	First order model		Hepatic (UGTs)
Zidovudine	First order model		Hepatic (UGT) (OAT1)

Results

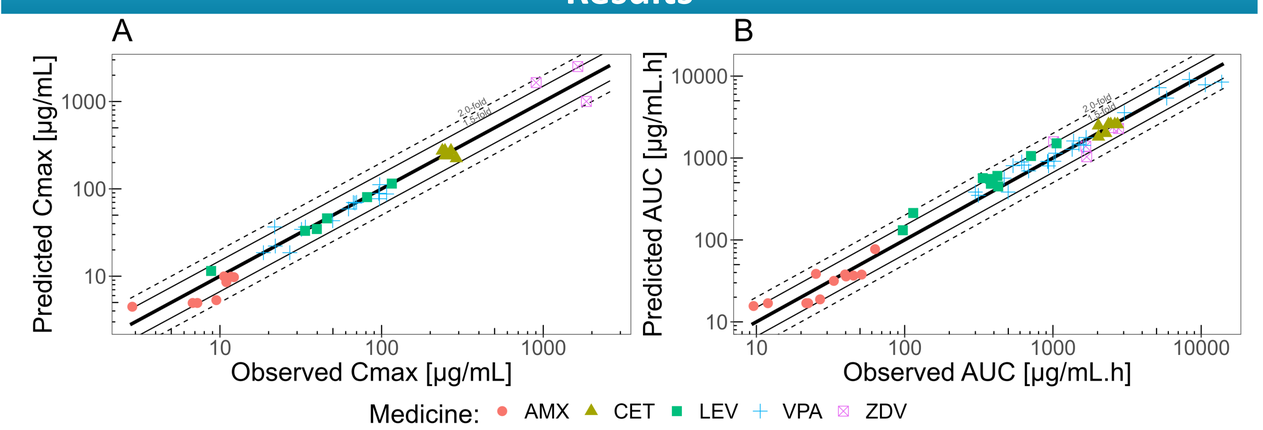


Figure 1. Predictive performance graphs for Cmax (A) and AUC (B) in plasma of AMX, CET, LEV, VPA, ZDV in healthy volunteers. Geometric mean of Cmax and AUC were predicted within 2-fold of the actual observed values.

✓ The models qualified as a base models to build the PBPK model for infants.

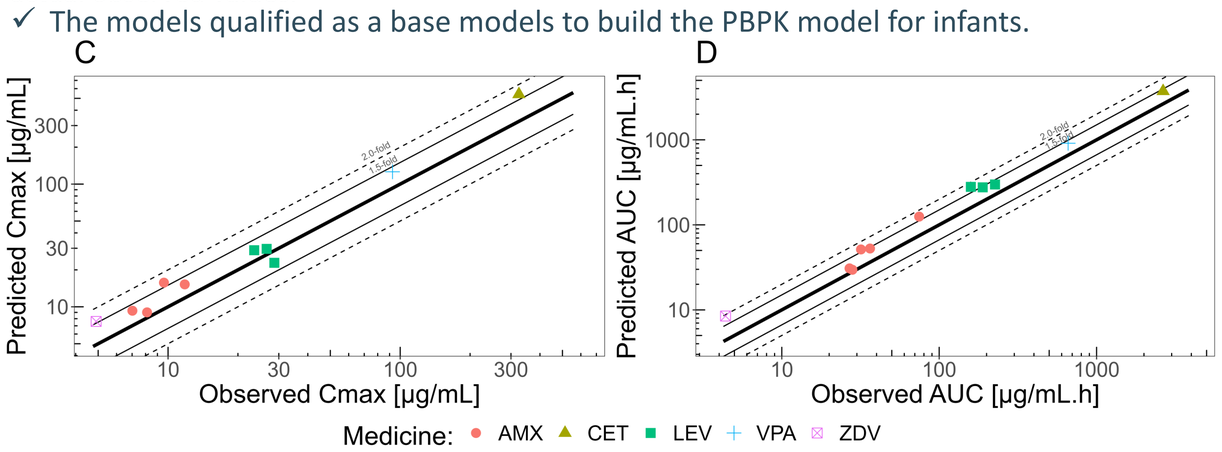


Figure 2. Predictive performance graphs for Cmax (C) and AUC (D) in plasma of AMX, CET, LEV, VPA, ZDV in infants. Geometric mean of Cmax and AUC were predicted within 2-fold of the actual observed values.

Results

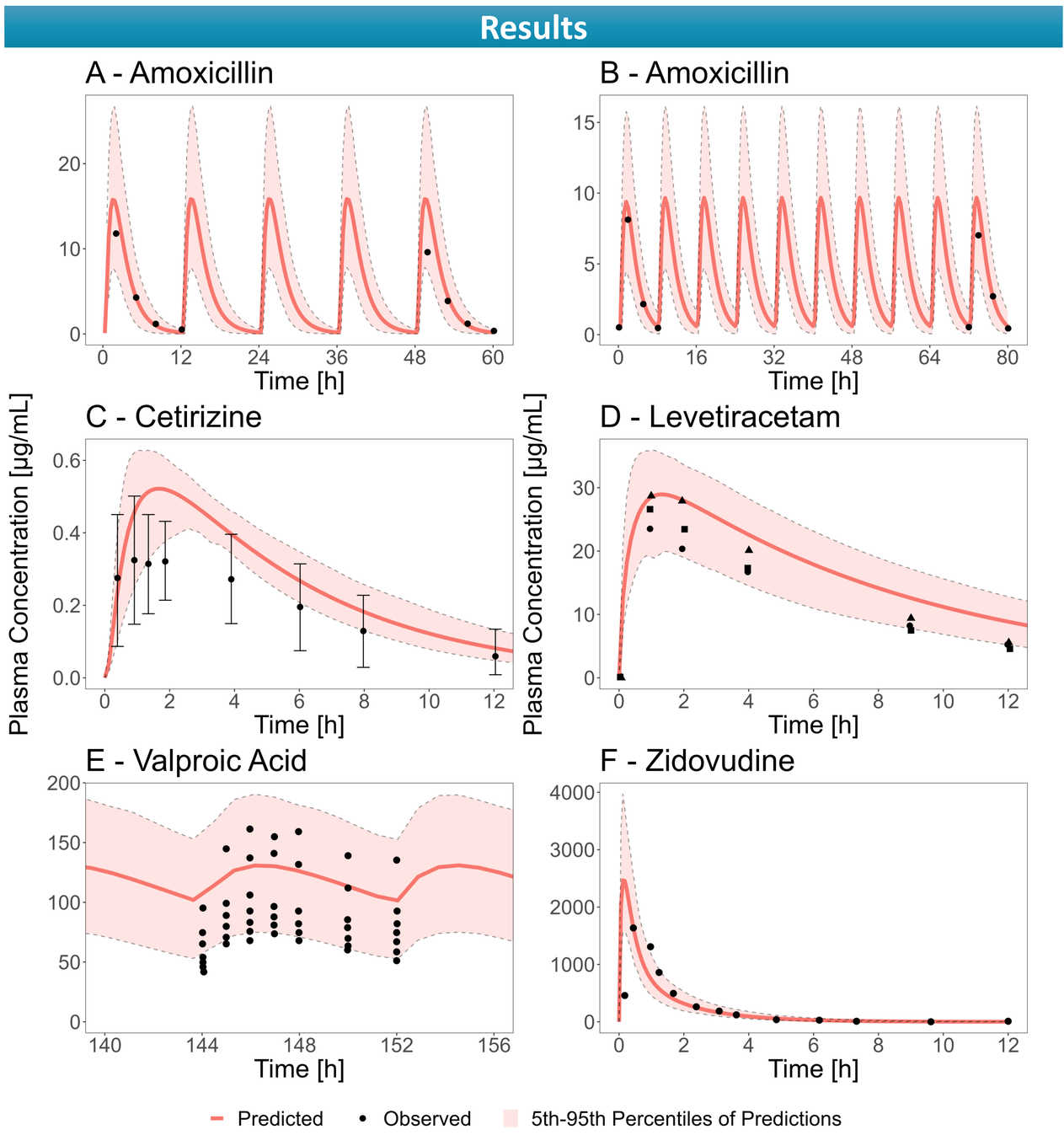


Figure 3. Predicted plasma concentration time profile for infants after oral administration. Points represent clinical observed data obtained from: **A -** Fonseca et al. (2002) [5] **B -** Fonseca et al. (2002) [5] **C -** Spicak 1997 [6] **D -** Glauser et al., (2006) [7] **E -** Herngren 1990 [8] **F -** Balis et al., (1989) [9].

Table 2 – Daily infant dosage (DID) predicted using Simcyp and PK-SIM [1] and the relative infant exposure (RIE).

	Simcyp			PK-SIM		
	DID (mg/kg/day) RID (%)	Dose per feed (mg/kg)	RIE (%)	DID (mg/kg/day) RID (%)	Dose per feed (mg/kg)	RIE (%)
Amoxicillin	0.24 (0.52)	0.04	2.57	0.16 (0.32)	0.03	3.86
Cetirizine	*In development*		--	0.003 (1.66)	0.0005	0.38
Levetiracetam	7.27 (15.94)	1.21	6.15	8.21 (16.50)	1.36	8.29
Valproic Acid	0.88 (2.75)	0.15	0.35	0.7 (2.00)	0.12	0.28
Zidovudine	0.21 (1.15)	0.035	1.48	0.05 (0.27)	0.008	0.30

Conclusion

✓ The PBPK models were developed to successfully predict plasma concentrations in adult HVs, as well as milk concentration in lactating women.

✓ The developed PBPK models in infants showed a good prediction (within 2-fold prediction) of the PK parameters (i.e., Cmax and AUC).

✓ **Infant systemic plasma exposure simulations revealed a low (<10%) exposure compared to the maternal exposure.**

✓ This workflow will be applied to additional medicines selected in the context of the IMI ConcePTION project.

Acknowledgements

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References

[1] N. Nauwelaerts et al., Pharmaceutics, vol. 15, no. 5, p. 1469, May 2023, doi: 10.3390/pharmaceutics15051469;**[2]** K. Abduljalil et al., Drug Metabolism and Disposition, vol. 50, no. 4, pp. 386–400, Apr. 2022, doi: 10.1124/dmd.121.000711; **[3]** F. Salem et al., CPT Pharmacometrics Syst Pharmacol, vol. 11, no. 7, pp. 854–866, Jul. 2022, doi: 10.1002/psp4.12798; **[4]** T. M. Conner et al., European Journal of Pharmaceutical Sciences, vol. 111, pp. 465–481, Jan. 2018, doi: 10.1016/j.ejps.2017.10.009; **[5]** W. Fonseca et al., Antimicrob Agents Chemother, vol. 47, no. 3, pp. 997–1001, Mar. 2003, doi: 10.1128/AAC.47.3.997-1001.2003; **[6]** V. Špičák et al., Clin Pharmacol Ther, vol. 61, no. 3, pp. 325–330, Mar. 1997, doi: 10.1016/S0009-9236(97)90165-X; **[7]** T. A. Glauser et al., Epilepsia, vol. 48, no. 6, pp. 1117–1122, 2007, doi: 10.1111/j.1528-1167.2007.01090.x; **[8]** L. Herngren et al., J Neurol, vol. 238, no. 6, pp. 315–319, Sep. 1991, doi: 10.1007/BF00315328; **[9]** F. M. Balis et al., J Pediatr, vol. 114, no. 5, pp. 880–884, May 1989, doi: 10.1016/S0022-3476(89)80158-1.