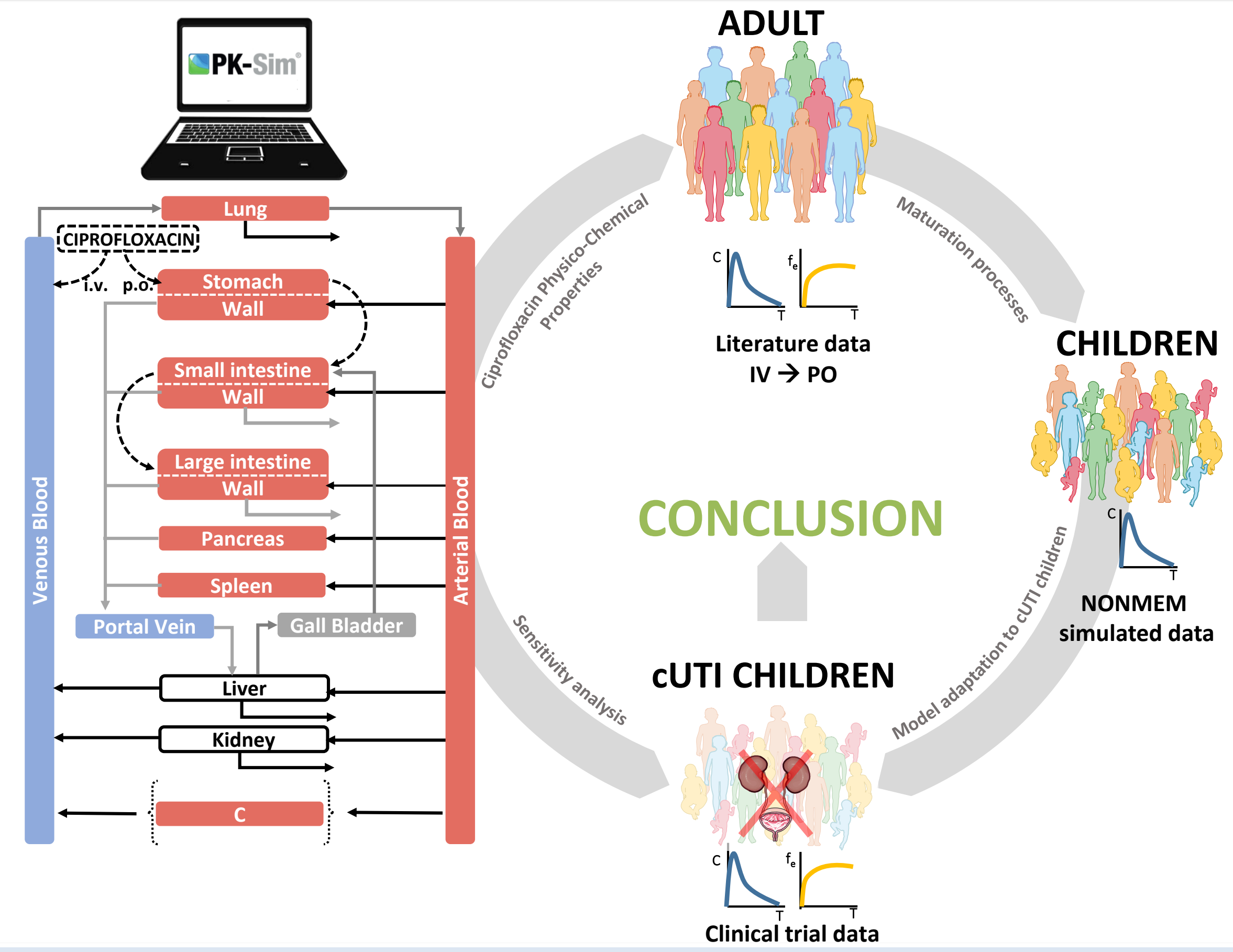


BACKGROUND AND OBJECTIVES

- Complicated Urinary Tract infection (cUTI)**
- It is an urinary tract infection in a patient with a structural or functional abnormality of the genitourinary tract (CAKUT).
- cUTI children**
- Children with CAKUT are at major risk for complications of UTI such as sepsis, renal scarring or reflux nephropathy, which could result in chronic kidney disease [1].
 - In a recent study, cUTI children showed a reduction of 83.6% and 41.5% in the ciprofloxacin volume of distribution (V_d) and total plasma clearance (CL) compared to healthy children [2,3].



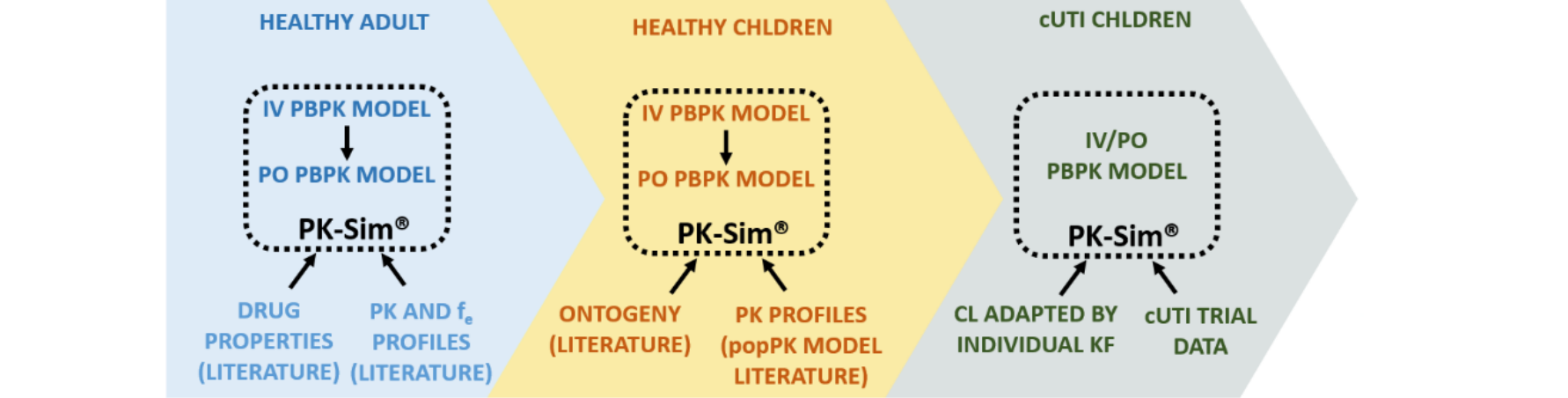
- Ciprofloxacin**
- Fluoroquinolone with linear pharmacokinetics which undergoes renal (it is filtrated and actively secreted) and non-renal elimination (CL_{CYP1A2} and CL_{biliar}) [4].
 - It is labelled for treatment of cUTI in children, excluding patients with moderate to severe renal insufficiency [4].

Objective

The goal of the present evaluation was to develop a PBPK model in the paediatric population with cUTI (from 3 months onwards), and identify physiological parameters that may be responsible for altered PK in those children compared to a healthy population.

METHODS

The FDA guidance-based workflow for PBPK model development in children was used:



1. ADULT PBPK MODEL

First, a PBPK model for ciprofloxacin in the adult population was developed with PK-Sim® v.7.2.1 [5].

Parameter	Value
MW (g/mol)	331
logP	1.63
pKa acidic	6.10
pKa basic	8.60
Solubility at pH7 (mg/ml)	6.18
f_u	0.67

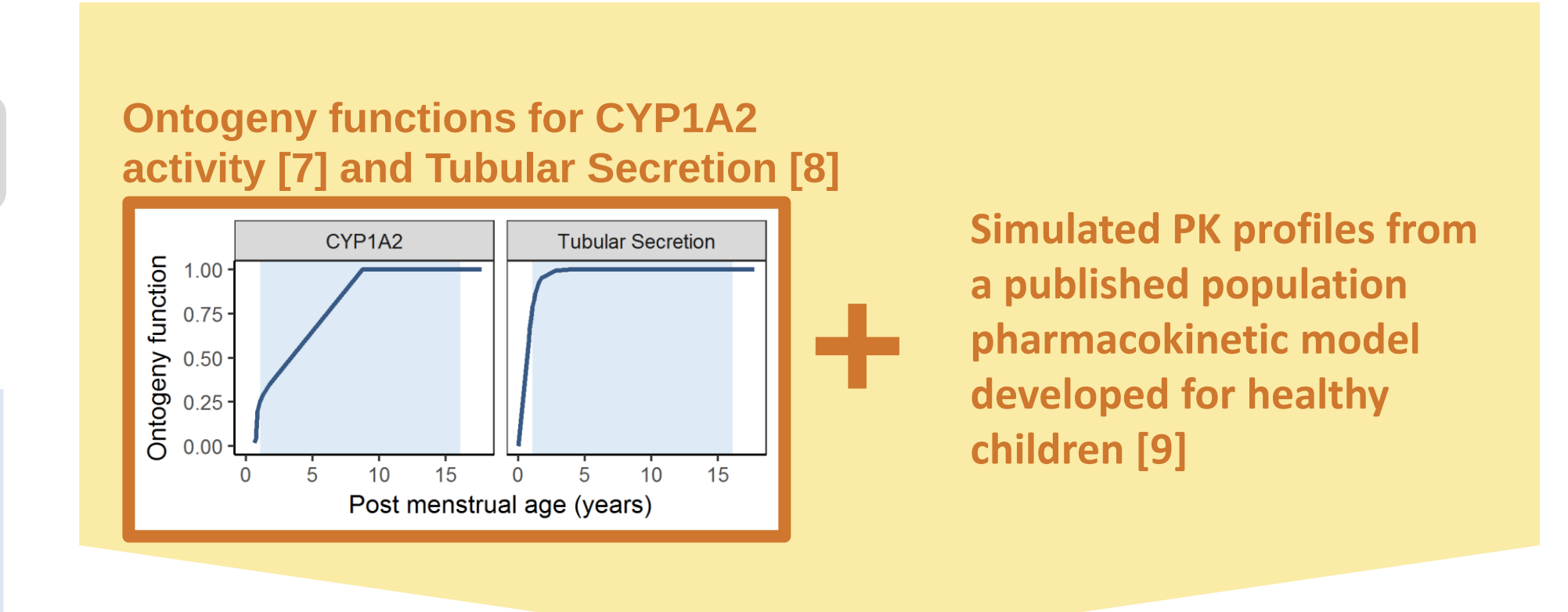
+

- Ciprofloxacin PK profiles and fraction excreted unchanged in urine (f_e) obtained from the literature
- Rodgers et al. [6] distribution method
- Monte Carlo estimation method → CL_{CYP1A2} and $TS_{CL_{int}}$

Then, it was challenged to predict systemic concentrations after intravenous (IV) and afterwards, oral (PO) administration.

2. PAEDIATRIC PBPK MODEL

The established PBPK model in adults was modified incorporating age-dependent physiological and anatomical changes to generate plasma ciprofloxacin concentrations for IV and PO administration in children.



PBPK paediatric model challenged against the typical predictions obtained from a population PK model reported by Rajagopalan and Gastonguay [9] for children without cystic fibrosis.

4. Sensitivity Analysis (SA)

Finally, a SA was performed to assess the impact of model parameters on the CL and V_d in healthy (KF = 1) and cUTI (KF = 0.5) children. An increase of 10% of every model parameter was evaluated. Parameters with sensitivity values < -0.25 or > 0.25 were reported for V_d and CL.

3. cUTI PAEDIATRIC PBPK MODEL

Afterwards, the PBPK model developed in healthy children was adapted to the paediatric population suffering from cUTI according to the patient's individually determined kidney function (KF). It was assumed that:

- Renal clearance decreases proportionally with KF.
- CYP1A2 activity was reduced to 63.46 and 46.15% for patients with KF values between 0.33-0.65 or lower than 0.33 of the normal (KF = 1) [10].

1 cUTI clinical trial data [2]:

- PK profiles
- f_e
- Serum cystatin C
- Serum creatinine
- Age, weight, sex, gender

2 Calculate individual KF:

$$KF_i = \frac{GFR_i [11]}{Theoretical\ GFR_i [12]}$$

3 Normalize by KF_i

- Renal CL
- GFR and $TS_{CL_{int}}$
- CL_{CYP1A2}

PBPK simulation of cUTI children and comparison with data from the clinical trial.

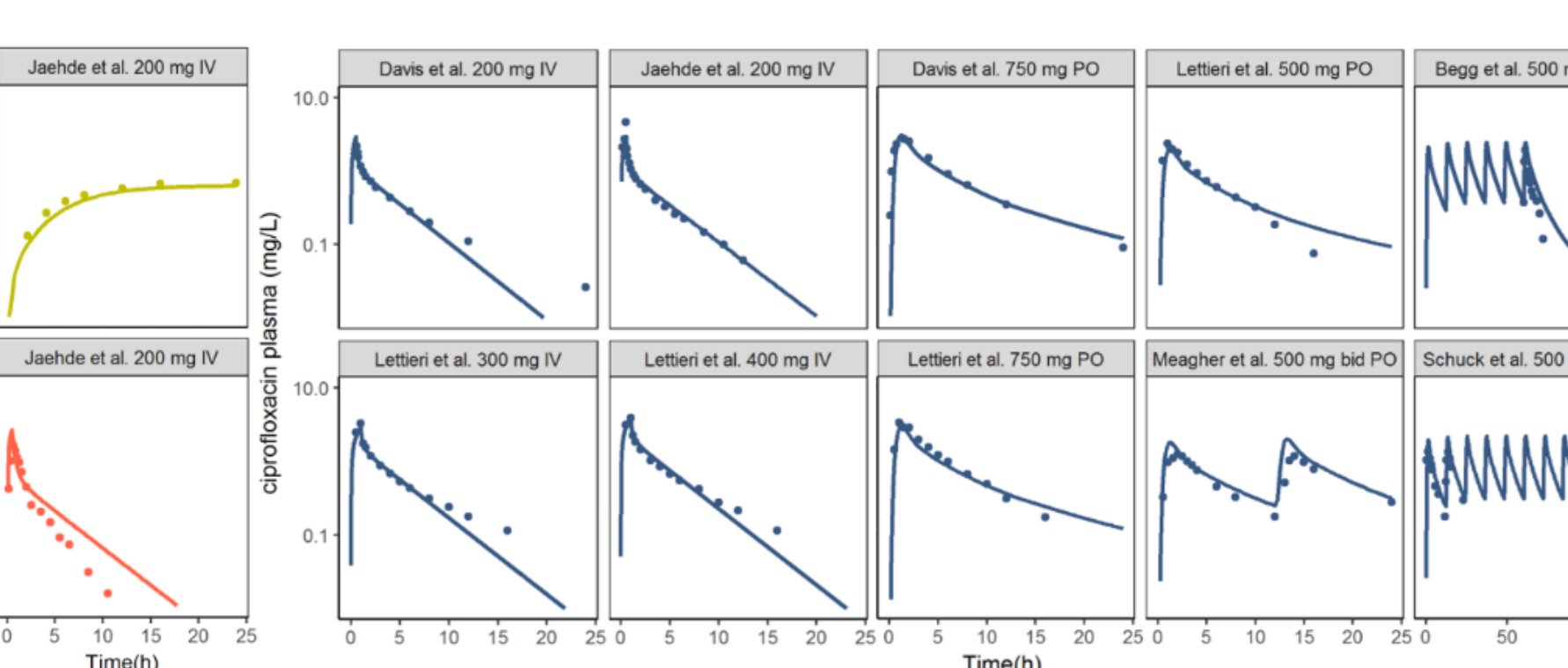
RESULTS

1. ADULT PBPK MODEL

The final parameter estimates are listed in the following table:

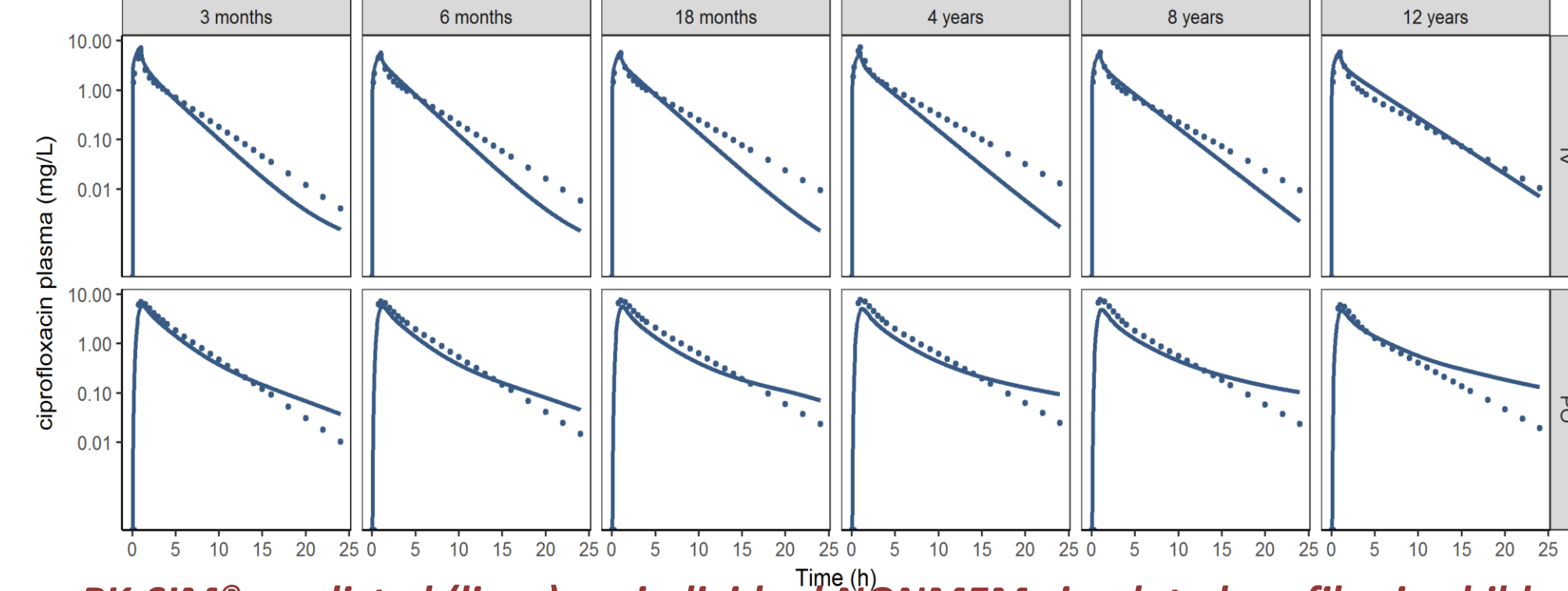
Parameter	Value
Specific Intestinal permeability, transcellular (cm/min)	3×10^{-6}
CL_{CYP1A2} (ml/min)	20.61
GFR (ml/min/g of organ)	0.266
$TS_{CL_{int}}$ (L/min/kg tissue)	1.32
CL_{bil} (ml/min/kg)	1.25

Simulations agreed in general very well with the typical observed profiles reported in the literature:



2. PAEDIATRIC PBPK MODEL

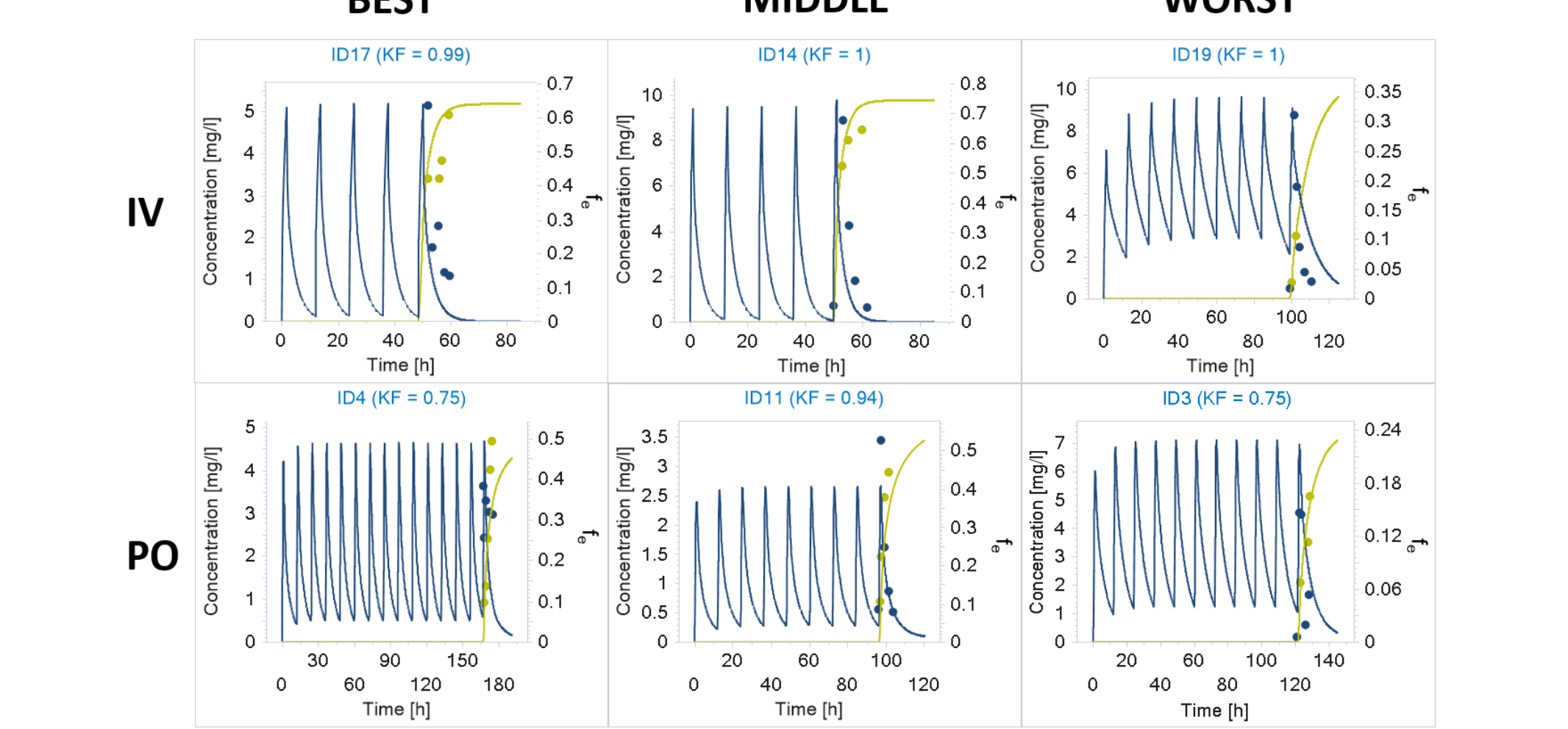
The total plasma ciprofloxacin concentrations predicted by the PBPK model are in close agreement with the simulations obtained from the published population PK model [9].



PK-SIM® predicted (lines) vs. individual NONMEM simulated profiles in children (symbols) for a single administration of 9 mg/kg as a 60 min IV infusion or 15 mg/kg tablet PO.

3. cUTI PAEDIATRIC PBPK MODEL

The renal function showed a mean reduction of 15.8 % with respect to normal, ranging from 0.07 to 1.



Individual simulations of the best, the middle and the worst predicted ciprofloxacin profiles or f_e after IV or PO administration.

4. SENSITIVITY ANALYSIS

V_d

Intracellular, plasma, blood and interstitial pH, f_u , dose, kidney and muscle volume.

CL

f_u , dose, kidney and liver volume, tubular and biliary secretion.

Renal function patterns

- V_d : pH (intracellular and blood) and kidney volume
- CL: liver and kidney volumes

CONCLUSIONS

The presented PBPK model for ciprofloxacin has demonstrated to be adequate to simulate different dosing scenarios and to obtain accurate PK predictions in a healthy population from 3 months old. Model adaptation of GFR, $TS_{CL_{int}}$ and CL_{CYP1A2} according to KF partially explained the differences seen in the plasma drug concentrations and f_e vs. time profiles between healthy and cUTI children. Through the SA, it was observed that the impact of pH and f_u greatly affected V_d . As metabolic acidosis is a common complication of chronic kidney disease, it would be very interesting to further study the internal pH state in cUTI children and the extent of pH-induced changes in the f_u of ciprofloxacin. Surprisingly, dose has shown an impact on both, V_d and CL in the SA, even if ciprofloxacin pharmacokinetics is known to be dose linear over therapeutically relevant doses. This study provides essential parameters suggesting hypotheses for future fine-tuning of the PBPK model in a cUTI population.