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Development and application of a pediatric mechanistic kidney model

Farzaneh Salem[1] | **Ben G. Small**[2] ⓘ | **Trevor N. Johnson**[2] ⓘ

[1]Drug Metabolism and
Pharmacokinetics, GlaxoSmithKline
R&D, Ware, UK

[2]Simcyp Division, Certara UK Limited,
Sheffield, UK

Correspondence
Trevor N. Johnson, Simcyp Division,
Certara UK Limited, Level 2-Acero,
1 Concourse Way, Sheffield S1 2BJ, UK.
Email: trevor.johnson@certara.com

Abstract

Pediatric physiologically-based pharmacokinetic (P-PBPK) models have been used to predict age related changes in the pharmacokinetics (PKs) of renally cleared drugs mainly in relation to changes in glomerular filtration rate. With emerging data on ontogeny of renal transporters, mechanistic models of renal clearance accounting for the role of active and passive secretion should be developed and evaluated. Data on age-related physiological changes and ontogeny of renal transporters were applied into a mechanistic kidney within a P-PBPK model. Plasma concentration–time profile and PK parameters of cimetidine, ciprofloxacin, metformin, tenofovir, and zidovudine were predicted in subjects aged 1 day to 18 years. The predicted and observed plasma concentration–time profiles and PK parameters were compared. The predicted concentration–time profile means and 5th and 95th percent intervals generally captured the observed data and variability in various studies. Overall, based on drugs and age bands, predicted to observed clearance were all within two-fold and in 11 of 16 cases within 1.5-fold. Predicted to observed area under the curve (AUC) and maximum plasma concentration (C_{max}) were within two-fold in 12 of 14 and 12 of 15 cases, respectively. Predictions in neonates and early infants (up to 14 weeks postnatal age) were reasonable with 15–20 predicted PK parameters within two-fold of the observed. ciprofloxacin but not zidovudine PK predictions were sensitive to basal kidney uptake transporter ontogeny. The results indicate that a mechanistic kidney model accounting for physiology and ontogeny of renal processes and transporters can predict the PK of renally excreted drugs in children. Further data especially in neonates are required to verify the model and ontogeny profiles.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
A number of glomerular filtration rate ontogeny models have been incorporated into pediatric physiologically-based pharmacokinetic (P-PBPK) models to predict the renal clearance of drugs. However, prediction of age changes in active tubular secretion has used a more empirical approach.

WHAT QUESTION DID THE STUDY ADDRESS?
A mechanistic kidney model as part of a PBPK simulator was extended to the pediatric population by incorporating kidney physiological development and ontogeny of renal transporters.
WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
Incorporating a mechanistic kidney model enabled the prediction of pharmacokinetics (PKs) for five drugs, from neonates onward, that are substrates of renal transporters. Further evaluation is needed with other renally cleared drugs.
HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, OR THERAPEUTICS?
Our findings demonstrate the potential for pediatric mechanistic kidney models to allow more accurate PK predictions for renally cleared drugs in children as well as application in assessing renal toxicity.

INTRODUCTION

Among the processes involved in renal clearance of drugs, glomerular filtration rate (GFR) is better understood than active processes. Many publications have modeled the pediatric age-related changes in GFR.[1–4] Using specific markers, Cristea et al.,[5] compared predictive values of various GFR models against inulin and mannitol clearance values. A recent publication has taken this a step further by accounting for both gestational age and postnatal age, thus defining GFR in terms of prematurity and time after birth.[6]

A number of GFR ontogeny models have been incorporated into pediatric physiologically-based pharmacokinetic (P-PBPK) models[3,7] to predict the renal clearance of drugs. The predictive performance of such models is high. In one study involving nine renally eliminated drugs, 10 out of 11 predicted clearance values were within 1.5-fold of the observed in children between 1 month and 2 years.[8] A few drugs in this study showed evidence of active tubular secretion which was assumed to have the same ontogeny as GFR. However, this may not be the case; P-PBPK models that incorporate age-related changes in other renal routes, such as active tubular secretion and re-absorption, are less explored and instead have tended to use a more empirical approach for scaling these processes.[7,9,10]

The development of a mechanistic kidney (Mech Kim) model, as part of a PBPK simulator, has been described previously.[11,12] In brief, the model links the physicochemical characteristics of a molecule and in vitro data with prior knowledge of renal physiology to predict the integrated effects of glomerular filtration, active and passive tubular secretion, intra-renal drug metabolism, active and passive tubular re-absorption, and the impact of covariates, such as age, sex, genetics, race, diet, concomitant drugs, and disease. The model not only predicts pharmacokinetics (PKs) but also accumulation of drugs within

kidney cells and associated risks of nephrotoxicity due to high dose or drug–drug interactions (DDIs). Extension of this model to the pediatric population requires additional information on developmental renal physiological and ontogeny of renal transporters.[13]

The aims of this study were first to incorporate age-related changes into the key parameters within the Mech Kim model. Second, to undertake performance verification using drugs with known active tubular secretion that are used clinically across the pediatric age range, and last to undertake a sensitivity analysis using available renal transporter ontogeny profiles. Drugs selected for this study were cimetidine, ciprofloxacin, metformin, tenofovir, and zidovudine.

METHODS

Development of pediatric Mech Kim model

The pediatric Mech Kim model is an extension of the Simcyp Adult Mech Kim model[12] where additional age-related changes in anatomy and physiology parameters are considered. In this model, the nephron is divided into eight segments, beginning with the glomerulus followed by three representing the proximal tubule, one the loop of Henle, one the distal tubule, and two the collecting ducts. Length and diameter of these tubules in pediatrics are scaled using Equations 1 and 2.

$$L_{\text{Pediatric}} = L_{\text{Adult}} \times \left(\frac{\text{Kidney Weight}_{\text{Pediatric}}}{\text{Kidney Weight}_{\text{Adult}}} \right)^{0.6} \quad (1)$$

$$D_{\text{Pediatric}} = D_{\text{Adult}} \times \left(\frac{\text{Kidney Weight}_{\text{Paediatric}}}{\text{Kidney Weight}_{\text{Adult}}} \right)^{0.6} \quad (2)$$

where $L_{pediatric}$ and L_{Adult} are length of tubules (mm) in pediatrics and adults, respectively, and $D_{Pediatric}$ and D_{Adult} are diameter of tubules (mm) in adults and pediatrics, respectively. The length of proximal tubule, Henle's loop, distal tubule and collecting duct in adults are 18, 7, 5.5, and 22 mm, respectively. The diameter of proximal tubule, Henle's loop, distal tubule, and collecting duct in adults are 0.06, 0.018, 0.05, and 0.2 mm.[11,12] Equation 1 is fitted to the proximal tubule length data from Darmady et al.[14] and the exponent of 0.6 is estimated. The same relationships are assumed for length and diameter of all tubules.

Kidney weight$_{Adult}$ is the simulated adult kidney weight (g) of ~317 g. Kidney weight$_{pediatrics}$ is calculated based on the equations reported in Price et al.[15] and body weight (BW) using Equation 3.

$$\text{Kidney weight (g)} = \frac{4.214 \times BW^{0.823}}{4.456 + BW^{0.795}} \times 1.05 \quad (3)$$

Urine flow in (ml/min) in the proximal tubule is based on predicted GFR for boys and girls up to 15 years[3] and GFR calculated, using the Cockcroft and Gault equation, from representative population serum creatinine values (mean, coefficient of variation) for subjects older than 15 years, these are the default equations in the simulator.

Renal blood flow was calculated as an age-related change in percentage of cardiac output (RBF %) for boys and girls using Equations 4 and 5 based on data from references 16–18

$$\text{RBF\% of CO (males)} = 7.94 + \left(11 * Age^{3.34} / \left(0.97^{3.34} + Age^{3.34}\right)\right) \quad (4)$$

$$\text{RBF\% of CO (females)} = 6.35 + \left(10.89 * Age^{1.26} / \left(1.51^{1.26} + Age^{1.26}\right)\right) \quad (5)$$

Data on age-related changes in cortex: medulla volume ratio[19,20] was analyzed and accounted in the model using Equation 6.

$$\text{Ontogeny of cortex:Medulla ratio} = 0.7 + \frac{0.3 \times Age^{3.8}}{0.3 + Age^{3.8}} \quad (6)$$

Enzymes and transporters expression in the proximal tubule are considered in the model. Ontogeny of renal transporters for MATE1/2, MRP4, OAT1, OAT3, and OCT2 is currently based on the data from Cheung et al.,[13] the fraction with age is used as a direct multiplier of the adult expression. The ontogeny of renal enzymes (e.g., UGT2B7) are assumed to be the same as hepatic enzymes.

Drug selection and compound file development

The drugs selected were based on known active renal elimination and availability of clinical data on their PK in both adult and pediatric populations. Existing compound files for cimetidine, ciprofloxacin, metformin, and zidovudine were used in the simulations. These compound files were developed and verified in healthy volunteers in Simcyp version 20 as part of simulator quality assurance procedure, any modifications to the files are indicated below. The model inputs and references for all five compounds is shown in Table S1.

Tenofovir, developed as a new compound file, was modeled as a solution formulation, the adult tenofovir permeability value of 0.275728 (10^{-4} cm/s) was used as a starting point in the model, this value was fitted to capture the data of Blum et al.[21] For some of the neonatal studies, we optimized this value to better recover the oral absorption. The drug is dosed clinically as a pro-drug, tenofovir disoproxil, a correction was applied in the simulations as the drug model is for tenofovir base.

A modified compound file for ciprofloxacin incorporating the Mech Kim model has been described previously.[22] The drug undergoes renal elimination incorporating active tubular secretion by OAT3,[23] the input values for the Mech Kim model including the transporter mediated intrinsic clearance OAT3 was optimized to recapture the reported renal clearance of 21.5 L/h in the adult population (Simcyp value from unpublished meta-analysis, Certara UK Limited). This file was further modified to include information on its metabolism by CYP1A2, as reported in other PBPK models.[9,24] The compound has been shown to be eliminated by biliary excretion[25] and possibly direct transintestinal elimination,[26] both of these were subsumed into a biliary clearance pathway. The fraction eliminated by renal, CYP1A2, and biliary were 60%, 30%, and 10%, respectively. Specific ontogeny for CYP1A2,[27] OAT3,[13] and biliary excretion[28] were incorporated for ciprofloxacin predictions in the early pediatric populations. As part of the performance verification for this drug, the interaction with probenecid in adults was investigated as per the study design in Table S2.

PBPK modeling approach

The accepted learn and confirm approach was used in each case[29] with development and initial verification of each drug model in the adult population before moving on to pediatric application. The general approach is summarized in Figure 1. A literature search was performed using PubMed to identify clinical studies presenting PK data for the five selected drugs in the adult and pediatric populations, and these are shown in Table S2.

FIGURE 1 Workflow of drug model development and verification. PBPK, physiologically-based pharmacokinetic
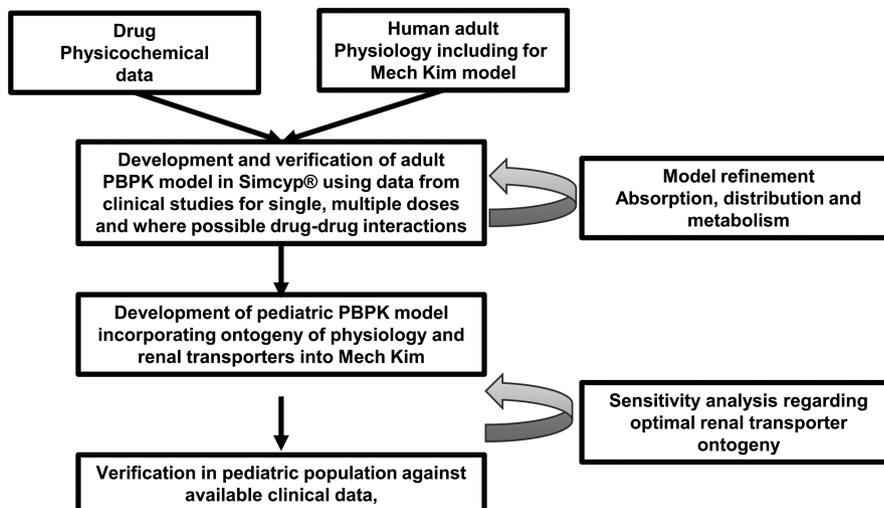
Simulation trial design

All simulations were undertaken using Simcyp version 20.1 (Certara UK Limited). Simulations were carried out using a trial design matched as closely as possible to the clinical study for age range and body weight (where indicated), number of individuals, proportion of male and female subjects, dose and dosing intervals, and duration of study (see Table S2). Simulations are carried out using 10 trials and the number of individuals. The observed mean and SD for plasma concentration–time profiles were digitalized from the references using GetData and overlaid in the simulation results.

For metformin, simulations were repeated in healthy[30] and obese children,[31,32] to match the simulated body weight in obese children from Gao et al. and Van Rongen et al.,[31,32] a scalar of 2.5 and 1.51, respectively, was applied to the BW in Lua code.

The custom trial design functionality within Simcyp was used for two tenofovir studies[33,34] to simulate the individuals as closely as possible. In Aurpibul et al.,[33] dose was given based on the BW of subjects. In order to simulate this study, a large number of subjects, age range of 3.1–17.7 years, were generated and those within the desired weight range selected out and used in in custom trial design to mimic the population of the clinical study.

Sensitivity analysis

For the ciprofloxacin and zidovudine simulations, a manual sensitivity analysis was undertaken regarding the ontogeny of OAT3 and OAT1, first, assuming the published ontogeny of Cheung et al.,[13] and then assuming no ontogeny, as indicated by Li et al.[35] The different ontogeny profiles are shown in Figure S1. In addition, a further sensitivity analysis was undertaken regarding the ontogeny pattern for CYP1A2 in the hepatic elimination of ciprofloxacin, the ontogeny from Salem et al., was compared to no ontogeny.[27]

Statistical methods

Simulated mean, 5th and 95th percentiles of plasma concentration–time profiles were compared with observed data and their variability. Predicted and observed area under the curve from zero to infinity (AUC_{0-inf}) or AUC_{0-t}, maximum plasma concentration (C_{max}), and clearance (CL) values were plotted with two-fold (starting point for acceptable predictions) and 1.5-fold intervals and compared.

For the predicted to observed ratios for these PK parameters, the SD was calculated using Equation 7.

$$\text{Ratio}_{SD} = \sqrt{\left[\frac{\text{sd (observed)}}{\text{Mean (observed)}}\right]^2 + \left[\frac{\text{sd (predicted)}}{\text{Mean (predicted)}}\right]^2}$$
$$\times \frac{\text{Mean (predicted)}}{\text{Mean (observed)}} \quad (7)$$

For the sensitivity analysis regarding optimal ontogeny, the mean squared error and mean error were used as measures of precision and bias according to Equations 8 and 9.

$$\text{MSE} = \frac{1}{N} \times \sum_{n=1}^{N} \text{PE}^2 \quad (8)$$

$$\text{ME} = \frac{1}{N} \times \sum_{n=1}^{N} \text{PE} \quad (9)$$

where $\text{PE} = \frac{\text{Predicted PK parameter}}{\text{Observed PK parameter}} - 1$, n is the individual value and N is the overall number of values.

RESULTS

Adult compound verification

Representative adult predicted and observed concentration time data for all the existing Simcyp standard compounds (cimetidine, metformin, and zidovudine) is shown in Figure S2. Because of the changes to the ciprofloxacin file, activating the MechKim model and included OAT3 transporter kinetics, further verification was done. The results for ciprofloxacin in the adult population are shown in Figure S3 and Table S3. There was close agreement between simulated and observed mean concentration–time data following both intravenous and oral administration. For the individual studies, the predicted versus observed AUC were within two-fold in all cases, within 1.5-fold in seven of eight cases and within 0.8–1.25-fold in seven of eight cases, for C_{max}, the predicted versus observed values were within two-fold in all cases, within 1.5-fold in seven of nine cases and within 0.8–1.25-fold in five of nine cases. The DDI between intravenous ciprofloxacin and probenecid was predicted to be 1.74-fold compared to the observed value of 1.53-fold. Because the tenofovir file was newly developed more verification data is also shown for this compound. Adult verification data for tenofovir is shown in Figure S4 and Table S3. Predicted to observed AUC ratio was between 0.69 and 1.25 and C_{max} ratio between 0.66 and 1.04. The DDI between oral tenofovir and probenecid was predicted to be 1.4-fold compared to the observed value of 1.6-fold.

Pediatric simulations

The results for prediction of the concentration-time profiles for cimetidine are shown in Figure 2. The figure shows observed systemic concentrations in plasma (Figure 2a) and blood (Figure 2b,c) are predicted well with most data

points within the 5th and 95th percentiles. The predicted and observed renal clearance after iv administration are 11.23 and 9.3 ± 1.5 (ml/min/kg), respectively, and after oral administration are 12.7 and 8.9 ± 2.3 and (ml/min/kg).[36] Comparison of the predicted to observed PK parameters is shown in Figure 3 (2 studies, minimum age 3 maximum 15 years). Predicted to observed CL_{iv} from two studies gave ratios of 1.25 and 1.14 and CL_{po} from a single study a ratio of 1.42 with a corresponding AUC ratio of 1.26.

The results for prediction of the concentration–time profiles for oral ciprofloxacin assuming either the published OAT3 ontogeny or no ontogeny against observed data are shown in Figure 4. The "no ontogeny" simulations visually show better prediction of the clinical data, the corresponding predicted to observed PK parameter data is shown in Figure 3. Predicted versus observed AUC ratios for the three age groups studied (0.3–7.1 years, 1–5 years and 5–14 weeks), were 1.11, 1.98, and 1.08 assuming no OAT3 ontogeny and 1.31, 2.19, and 1.44, assuming OAT3 ontogeny, respectively. Prediction of C_{max} was similar regardless of OAT3 ontogeny, predicted versus observed C_{max} ratios were 0.89, 1.25, and 0.96 assuming no ontogeny and 0.92, 1.25, and 1.03 assuming OAT3 ontogeny, respectively. The mean squared predictive error around AUC were 0.328 assuming no OAT3 ontogeny and 0.537 assuming ontogeny, predictive errors were 0.394 and 0.531, respectively, corresponding values for C_{max} were 0.020 and 0.023 and 0.016 and 0.07, respectively. Overall, the no ontogeny scenario showed higher precision and less bias.

A further sensitivity analysis on influence of CYP1A2 ontogeny on predicted pediatric ciprofloxacin concentration-time profiles is shown in Figure S5. Overall, not including CYP1A2, ontogeny made the PK predictions worse particularly for the 1–5 years age group.

The results for predicted and observed plasma concentration time profile for metformin are shown in Figure 5
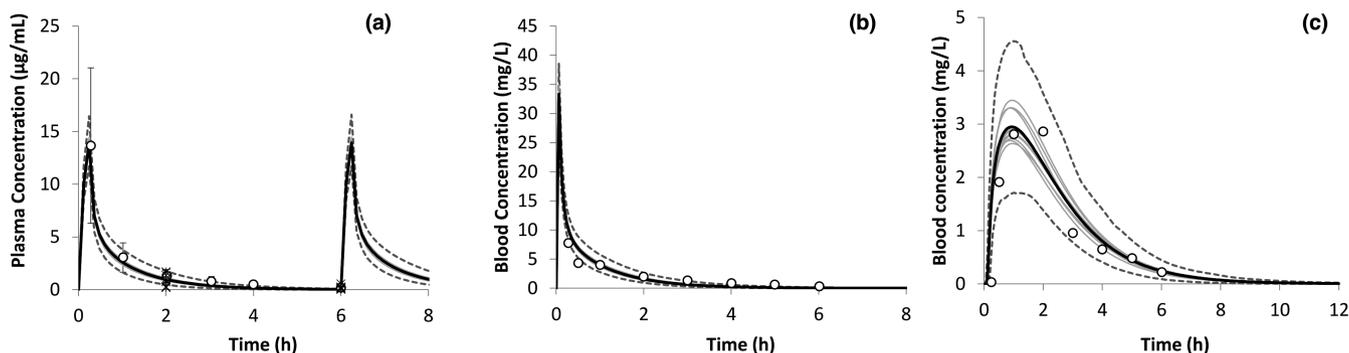

FIGURE 2 Plasma (a) concentration–time profiles of cimetidine in children following iv administration[53] and iv (b) and oral (c) blood concentration–time profiles.[36] Black solid line is the mean simulated profile, gray broken lines are the 5th and 95th percentile of predictions, and solid gray lines are individual trials. Open circles are observed data, error bars are ±SD, crosses are individual data at 2 and 6 h
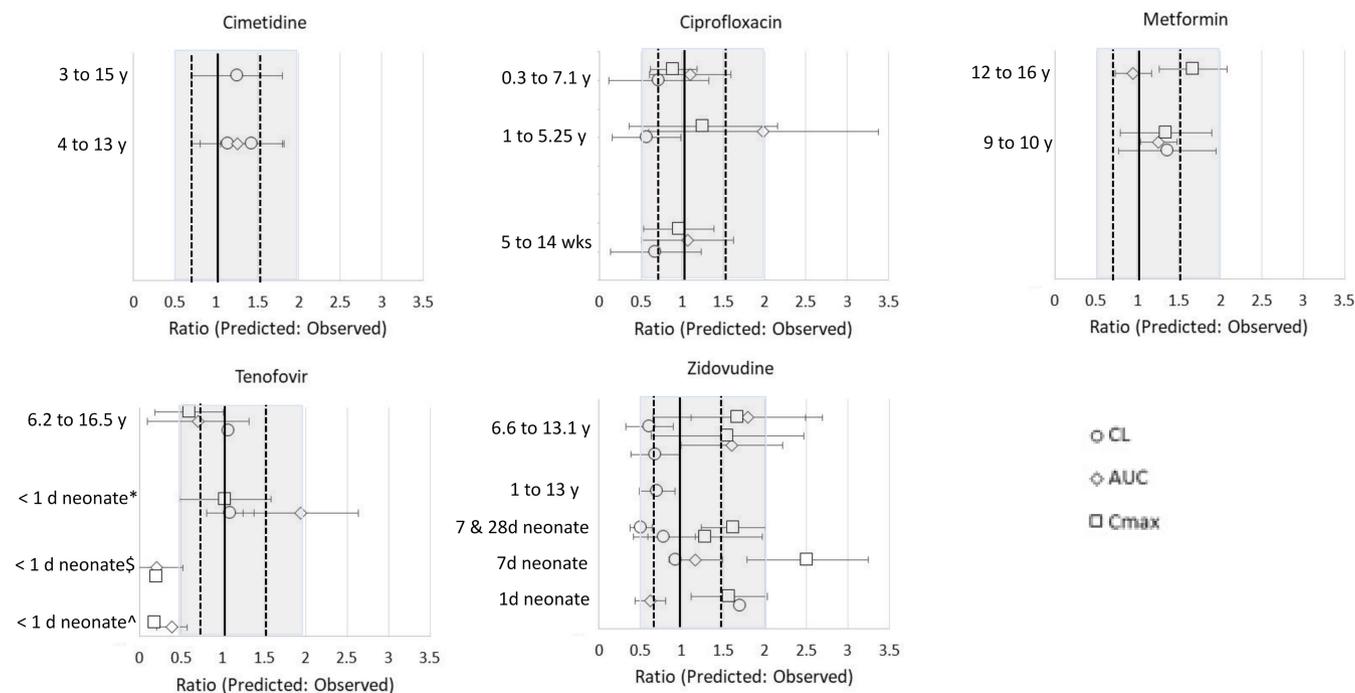
FIGURE 3 Predicted versus observed PK parameters for cimetidine, ciprofloxacin, metformin, tenofovir, and zidovudine. Solid black line is the line of unity, broken lines are the 1.5-fold, and the shaded gray area the two-fold intervals around the line of unity. The error bars are the calculated Predicted: observed SD (see Methods). In order top to bottom for data in each graph. Cimetidine - Lloyd et al.[53]; Somogyi et al.[36]: Ciprofloxacin - Peltola et al.[54]; Pelota et al.[44] (1–5.25 years and 5–14 weeks): Metformin - Goa et al.[31]; Sanchez-Infantes et al.[30]: Tenofovir - Hazra et al.[34]; Hirt et al.[55]*; Mirochnick et al.[37] $Cohort 4, ^Cohort 2: Zidovudine - Barry et al.[56]; Balis et al.[57]; Boucher et al.[58]; Peltola et al.[44]; Moodley et al.[50]. AUC, area under the curve; CL, clearance; C_{max}, maximum plasma clearance; PK, pharmacokinetic

indicated some overprediction of C_{max} but the observed data are still within the 5th and 95th centile of predictions. Overall, four of five of the predicted to observed PK parameters were within 1.5-fold (Figure 3) for the two studies in the age range 9–16 years. In a study of obese children, PK parameters were predicted reasonably well (Figure 5d). In an additional study, the predicted versus observed AUC_{inf} of metformin were 5985 and 6311 ng h/ml and C_{max} values were 859.2 and 898 ng/ml, respectively.[32]

Predicted and observed plasma concentration–time profiles for tenofovir are shown in Figure 6. The results show most of the observed data fall within the 5th and 95th percentile of the predictions. The plasma concentration in neonates after the first dose in Figure 6f from the study by Mirochnick et al.[37] is underpredicted, the subsequent dose concentrations and their variability are predicted reasonably well. The observed data in Figure 6 show large variability in concentrations, especially in neonates. Six out of 10 predicted to observed PK parameters (3 studies, 4 age bands, age birth to 16.5 years) are within two-fold (Figure 3) with the exception of the AUC and C_{max} from the neonatal study by Mirochnick, as indicated above.

The results for zidovudine are shown in Figure 7, overall, there was reasonable prediction of the concentration time

data across all five studies and seven age ranges (birth to 13.1 years). The predicted to observed ratios are shown in Figure 3, 16 of 17 predictions were within two-fold and six of 17 were within 1.5-fold. A sensitivity analysis was undertaken comparing predictions incorporating OAT1 ontogeny with no ontogeny, visually there appeared to be little difference between the two sets of simulations (data not shown). The mean squared predictive error around predicted clearance were 0.142 assuming no OAT3 ontogeny and 0.161 assuming ontogeny, predictive errors were −0.173 and −0.132, respectively. The results are marginal with no OAT1 ontogeny having slightly higher precision but more bias.

DISCUSSION

Recent data on the ontogeny of renal transporters[13,35] has facilitated the expansion of the previously published mechanistic kidney model[12] for application in pediatrics. This development allows not only the prediction of renal elimination of drugs via GFR but also active tubular secretion and re-absorption within a P-PBPK framework. Such models open the possibility to understand the ontogeny of active renal elimination mechanisms and improve prediction of renal clearance in pediatric populations. In
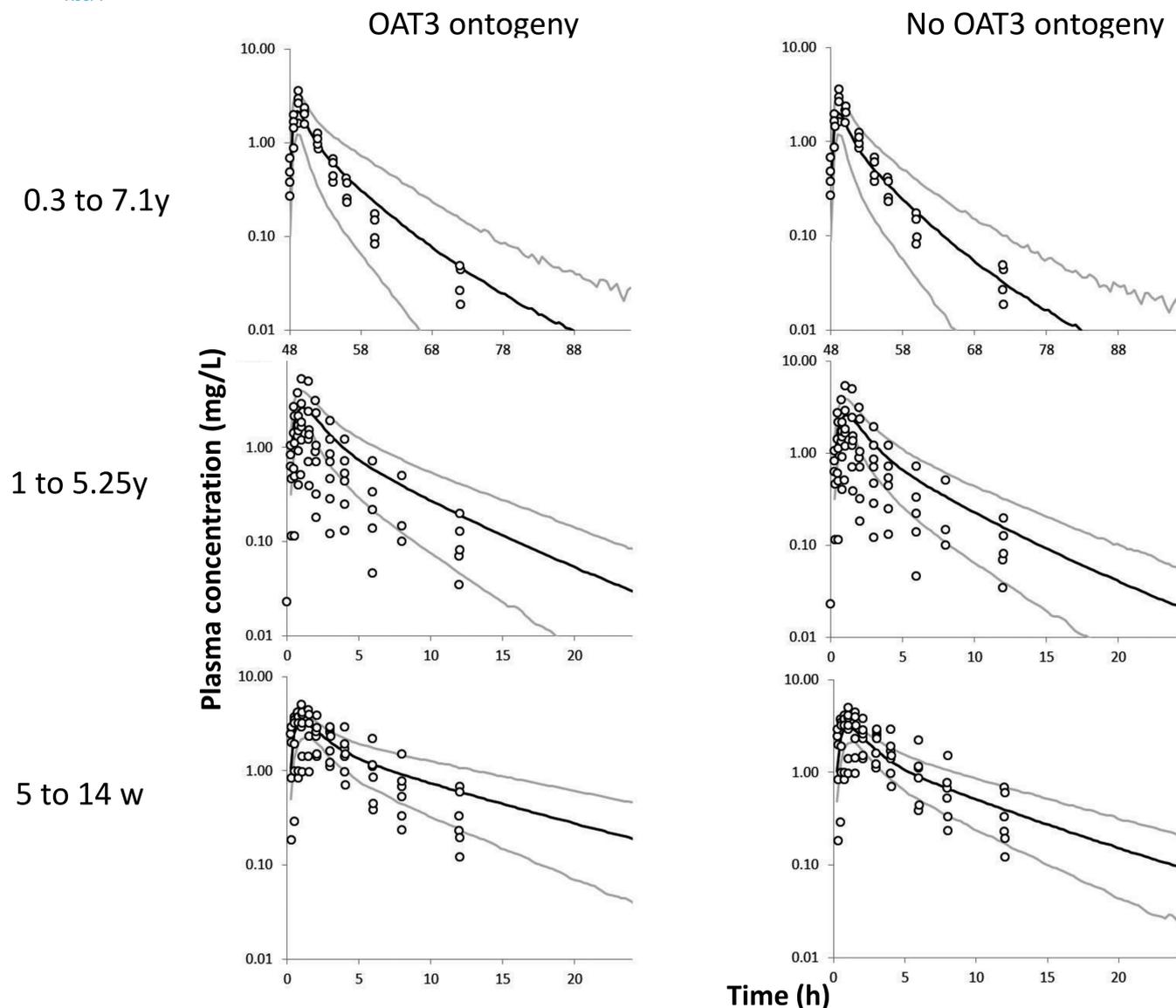
OAT3 ontogeny

No OAT3 ontogeny

FIGURE 4 Plasma concentration time profiles of oral ciprofloxacin in pediatrics assuming the OAT3 ontogeny of Cheung et al.,[13] or the no ontogeny profile of Li et al.[35] Black solid line is the mean simulated profile, gray lines are the 5th and 95th percentile of predictions. Open circles are observed data. Peltola et al.,[54] 0.3–7.1 years; Peltola et al.,[44] 5–14 week and 1–5.25 years

addition, these models will allow a detailed prediction of renally based DDIs and tissue concentrations, the latter is especially relevant to predicting possible renal toxicity in children.

Parametrizing a mechanistic model requires a large database of physiological parameters which are not always available. In this model, age-related changes in most of the physiological parameters are considered. The length and diameter of renal tubules are scaled allometrically with an estimated exponent to capture the in vivo data with the assumption that the same relationships are applicable to all tubules, availability of additional measured data across the nephron in pediatrics would verify this assumption. Blood, urine, and fluid flows in and out of each nephron segment are considered using pediatric data.

The ontogeny of renal transporters was incorporated into the model. Previous studies have shown maturation of renal transporters in preclinical species,[38–40] however, such data may not be applicable to humans. Recently, the ontogeny of renal transporters was studied in a wide age range of pediatric subjects using mRNA and protein abundance, the results indicate renal drug transporters exhibit different rates and patterns of maturation.[13] The results from a later study,[41] based on in vivo data using a combined population PK and PBPK approach, on the hybrid OAT1/OAT3 ontogeny agrees for these transporters. However, in another study, the authors reported little significant age-related abundance changes (age >1 year) for many renal transporters.[35] Although the latter study only included samples from 1 year of age there are still inconsistent results between this
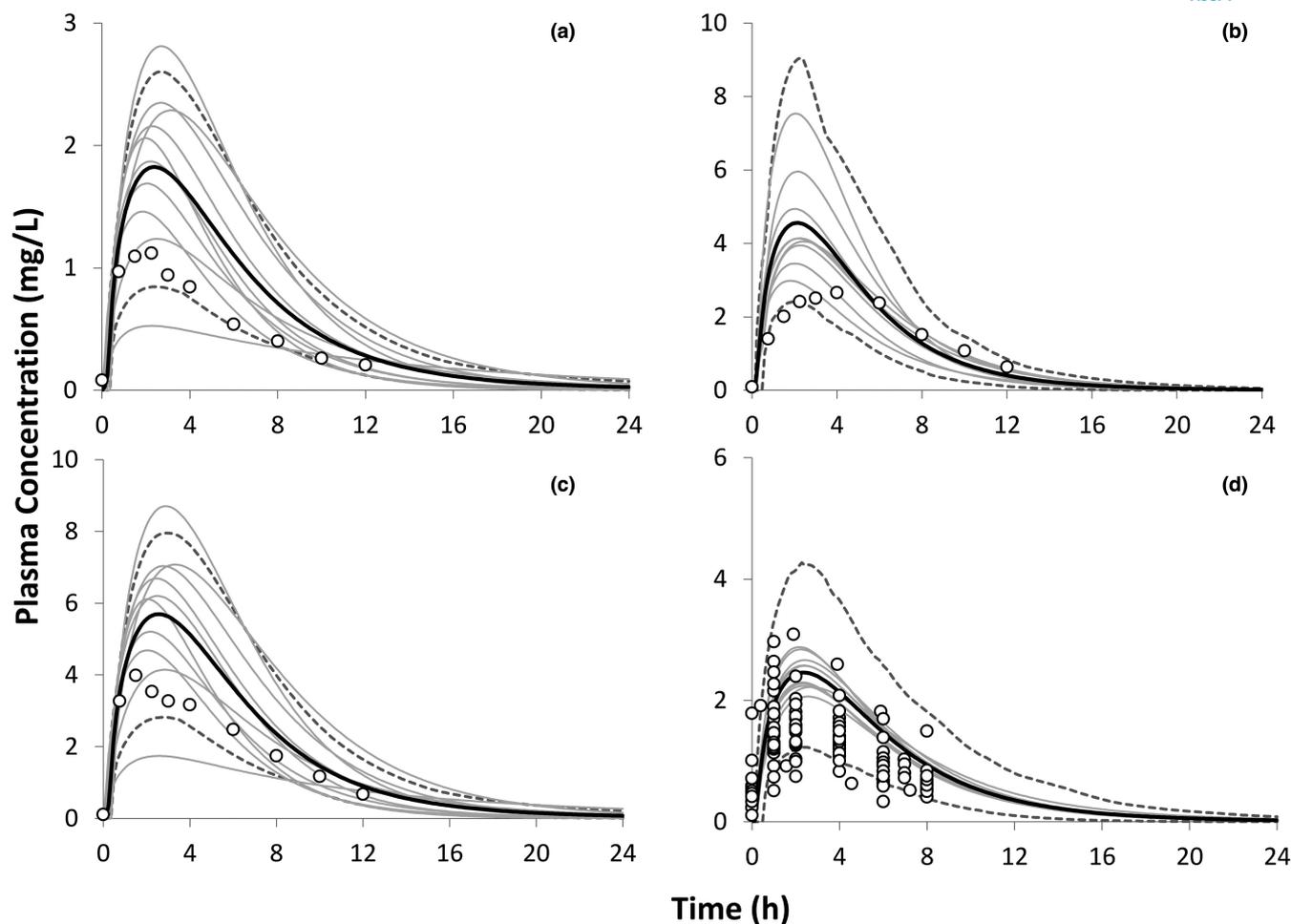
FIGURE 5 Plasma concentration time profiles of oral metformin in children. Black solid line is the mean simulated profile, gray lines are simulated trials, and gray broken lines are the 5th and 95th percentile of predictions. Open circles are observed data. (a–c) are low ($n = 1$), intermediate ($n = 4$) and high ($n = 4$) dose, respectively from study of Sanchez-Infantes et al.,[30] and (d) is metformin in overweight and obese adolescents from van Rongen et al.[32]

and the previous studies after 1 year. In this study, most of the case examples focused on young and school age children when maturation of transporter ontogeny profiles is completed. A few examples from ciprofloxacin, tenofovir, and zidovudine were in neonates (Figure 3) where the impact of ontogeny is greater and incorporating the correct ontogeny is important. Thus, the reason for undertaking sensitivity analysis (Figure 4 and Figure S5) incorporating ontogeny or no ontogeny for ciprofloxacin and zidovudine in this study. A summary of the knowledge gained and gaps in the current research regarding the pediatric Mech Kim model are shown in Table S4.

The ciprofloxacin compound file incorporating OAT3 transporter activity as a renal basal transporter was verified in the adult population by replicating both intravenous and oral studies and more informatively by simulating the interaction with probenecid following its iv administration (Figure S3). The simulated $AUC_{0-\infty}$ ratio was 1.54 compared to the observed value of 1.74; this was using a Ki value for OAT3 inhibition by probenecid of

3.53 μM obtained from an unpublished meta-analysis of studies. The lowest reported value is 1.3 μM[42] (DDI with fexofenadine) and when this value is used in the simulation, the predicted $AUC_{0-\infty}$ ratio was 1.65.

Performing sensitivity analysis on OAT3 suggests the ontogeny pattern proposed by Cheung et al.[13] based on transporter expression from proteomic data analysis does not translate into actual activity of the transporter in vivo. The no ontogeny scenario in line with another liquid chromatography-accelerator mass spectrometry proteomics study[35] may be more representative of the activity but further research into this is needed (Figure 4).

For the ciprofloxacin simulations, 30% of the metabolism as assigned to CYP1A2 based on other PBPK models, however, direct evidence for this is not available in the literature and previous studies have not provided relevant references for this.[9,24] The sensitivity analysis carried out in this study regarding ontogeny of the elimination of ciprofloxacin does provide evidence that the currently accepted CYP1A2 ontogeny pattern[27,43] improves the predictions
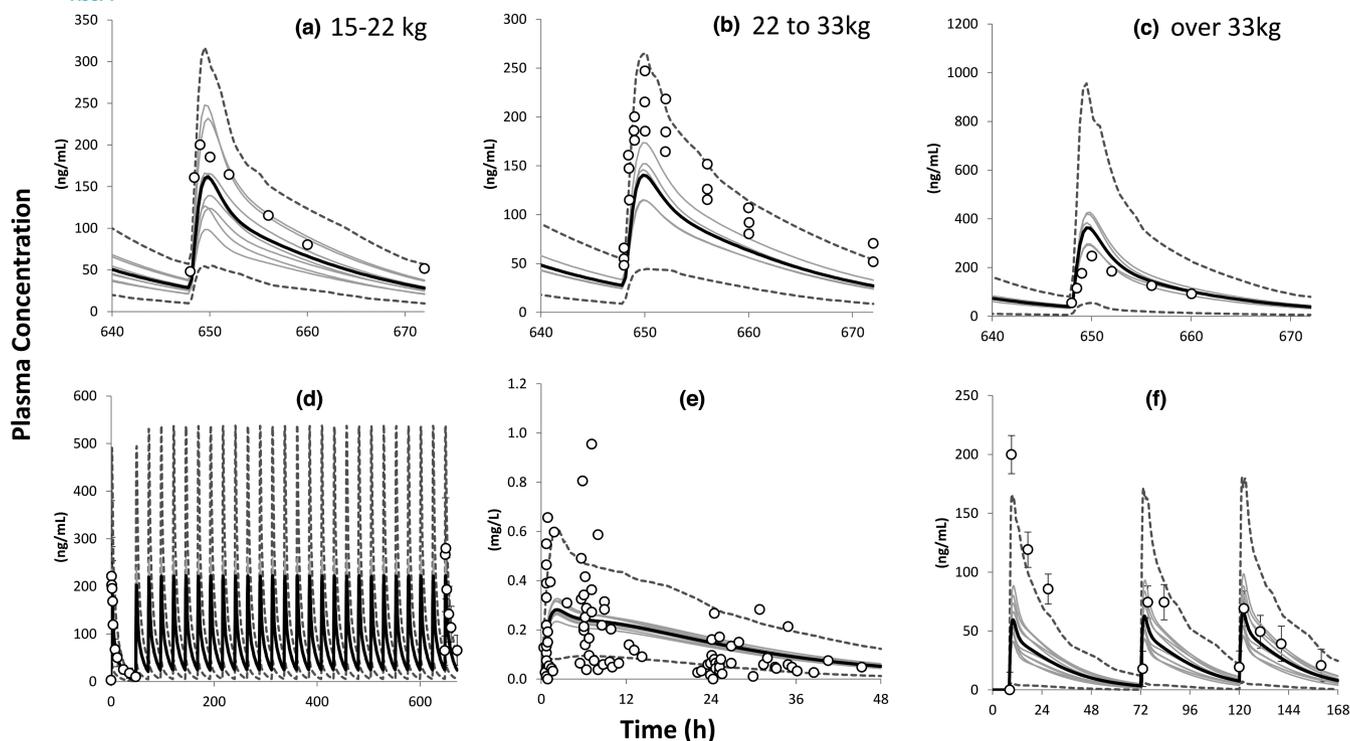
FIGURE 6 Plasma concentration time profiles of oral tenofovir in children. Black solid line is the mean simulated profile, gray lines are simulated trials, and gray broken lines are the 5th and 95th percentile of predictions. Open circles are observed data (a–c) are subjects from Aurpibul et al.,[33] for body weights of 15–22, 22–33 and over 33 kg, respectively, and (d–f) are from Hazra et al.,[34] Hirt et al.,[55] and Mirochnick et al.,[37] – cohort 2

in pediatric age ranges and suggests that this enzyme is indeed involved in the drug's metabolism. This helps explain some of the clinical data where the elimination was reported to be particularly rapid in young children.[44]

For metformin simulations in adults, the built-in morbidly obese population was used[45] as the BWs of patients in the clinical study were 114.6 ± 26.1 and 116.8 ± 10.8 kg. A slight overprediction was identified in adult obese simulations but still the observed plasma concentrations and their variability were within the 5th and 95th percentiles (Figure S2D). One potential reason for this observation could be the limited number of individuals in the Padwal et al. study.[46]

The obese pediatric population was created by increasing the BW, which in turn affects other physiological parameters such as most tissue volumes in the simulator. Although this increase is expected for adipose tissue, it might not affect other organs to the same extent. However, the profiles are still well-predicted and in good agreement with observed data, likewise, PK parameters were within two-folds of the reported observed data. The metformin model also overpredicts in the pediatric population, this again may be due to low numbers in the clinical studies. However, lack of inclusion of saturable intestinal transporters, limiting bioavailability, may partly explain the adult and pediatric results.[47]

Prediction of tenofovir plasma concentration–time profiles in neonates was reasonable (Figure 6e,f). However, further complexities that may influence the PKs of this drug particularly in young children need to be explored further. The current pediatric model assumes rapid hydrolytic conversion of the tenofovir disoproxil to active tenofovir and no ontogeny on any sinusoidal uptake into the hepatocytes and on the small undefined contribution of hepatic metabolism. In regard to active hepatic uptake, there may be an ontogeny involved as recent studies have shown this for a number of such transporters (e.g., OCT1 and OATP1B3).[48] However, using sensitivity analysis, changing the magnitude of the sinusoidal liver uptake resulted in a modest change in tenofovir exposure in neonates (data not shown) but further research is needed here.

Unsurprisingly, given their elimination route, cimetidine, ciprofloxacin, metformin, and tenofovir are all BCS/BDDCS class 3 or 4 compounds with low permeability.[49] In the current research, a first order oral absorption was used for all but tenofovir where we optimized permeability to recover neonatal data. The absorption of oral ciprofloxacin is also reported to be slower in the neonatal/infant population compared to older children absorption half-life was reported as 0.4 in the 5–14 week group and 0.29 in the 1–5 year group.[44] Bioavailability for ciprofloxacin has
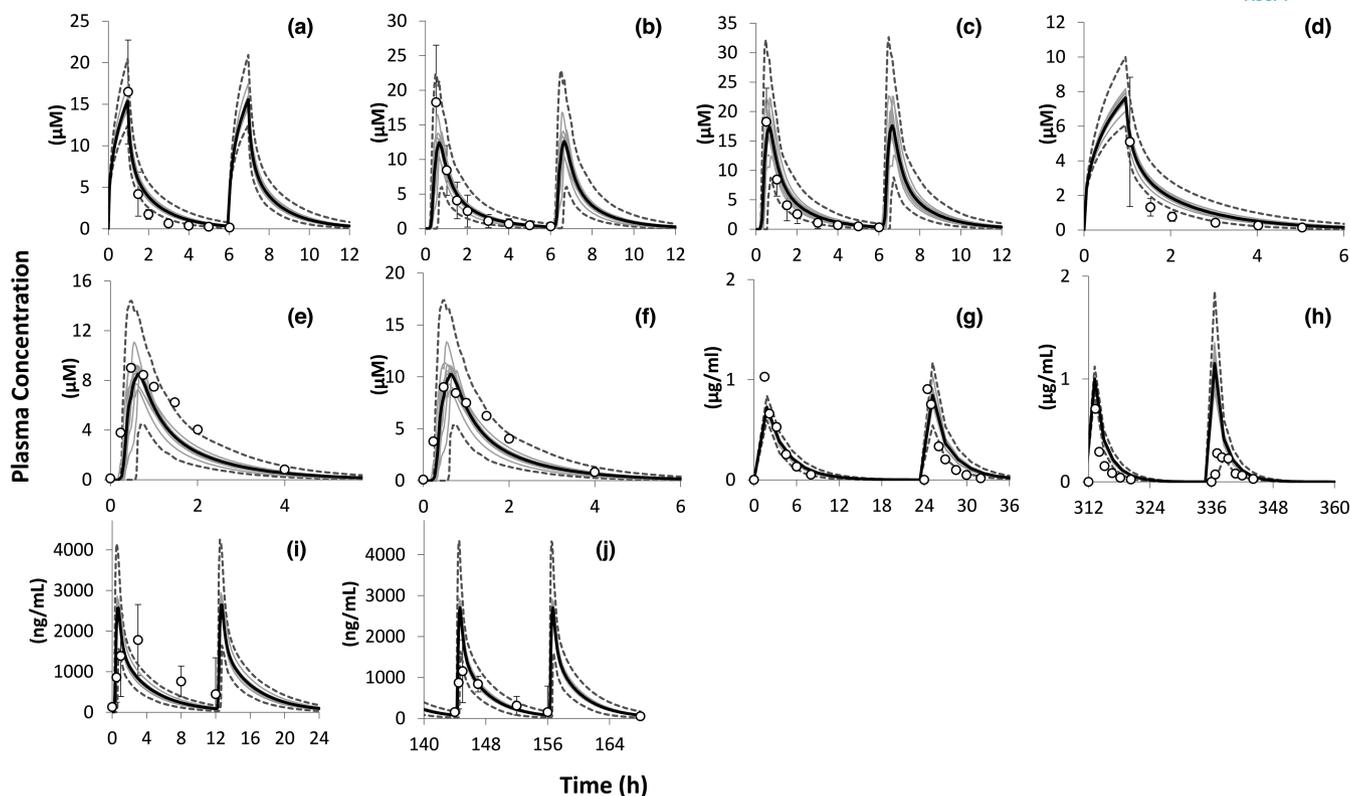
FIGURE 7 Plasma concentration time profiles of zidovudine in children. (a–c) are 160 mg/m² infusion over 1 h, 180 mg/m² p.o., and 240 mg/m² p.o., respectively,[57] (d) 80 mg/m² iv infusion,[59] (e, f) are 150 and 180 and mg/m² p.o. in hemophiliac and HIV children.[56] (g, h) are profiles from a single neonate on days 14 and 28 after birth following an iv and oral dose (2–4 mg/kg),[58] (i, j) are simulations in neonates on day 1 and day 7 after birth following 4 mg/kg p.o.[50] Black solid line is the mean simulated profile, gray lines are simulated trials, and gray dotted lines are the 5th and 95th percentile of predictions. Open circles are observed data

not been reported in pediatrics but reported adult values range from 0.6 to 0.9, an F of 0.67 was used in the pediatric simulations to capture the clinical data. Little is known about changes in drug permeability with age and how to mechanistically incorporate this into a PBPK models, this group of compounds could also be used to do further research on permeability limited oral drug absorption in children.

The zidovudine adult PBPK model shows little sensitivity to MATE activity but much more to OAT1 activity (data not shown). MATE is not reported to change with age, whereas OAT1 may have a specific ontogeny.[13] A sensitivity analysis of OAT1 ontogeny on zidovudine PK showed marginal difference between that suggested by Cheung et al., 2019 and no ontogeny with slightly better precision with the former and especially if only neonatal data considered. Zidovudine data from Moodley et al.[50] (Figure 7i,j) showed time to C_{max} (T_{max}) on day 1 is delayed compared to day 7. This might indicate an absorption profile in neonates hours after birth that will mature over the next hours or days. This could be due to gastric emptying, intestinal permeability, and remaining amniotic fluids in gastrointestinal (GI) tract or blood flow just after birth. The authors speculated this longer T_{max} on day

1 is because of irregularities both in neonates' GI function and in their feeding patterns.[50] The simulations for this study were repeated on day 1 (1-day-old subjects) and day 7 (7-day-old subjects). The observed and predicted data clearly showed the impact of maturation of UGT2B7 and other processes over the first week of life. In this study, mothers were administered zidovudine at the start of labor and the residual drug from maternal drug transfer to neonate in simulations was assumed negligible and not considered.

Other limitations in the current analysis include lack of comprehensive clinical pediatric data across the entire age range, although this is expected for drugs such as metformin where the use is more toward the adolescent age range. Some studies were performed in very wide age ranges which allows general comparisons to be made but not predictive performance in narrow age groups. Sometimes, studies were done in very specific populations such as asymptomatic HIV-positive individuals and it is not always possible to include true disease effects into the P-PBPK induced by things such as circulating cytokines. Rapid physiological changes during and hours after birth in cardiovascular, respiratory, hematologic, central nervous, endocrine, GI, and renal

systems are poorly understood and at the present time and unless specific data is available, cannot be considered in P-PBPK models.[51,52]

The results indicate that the reported ontogeny of renal OAT1, MRP4, and MATEs by Cheung et al.,[13] gives a reliable starting point, but more research is needed on OAT3 ontogeny, as indicated by the ciprofloxacin sensitivity analysis. More abundance data using proteomic techniques can only add to robustness of these ontogeny.

CONCLUSION

The comparison of predicted and observed plasma concertation-time profiles and PK parameters in this study showed that a pediatric Mech Kim model can predict PKs of drugs that are substrates of renal transporters. The ontogeny of several transporters is already included in the model. However, more PK data on compounds with different physicochemical properties especially in younger age groups and neonates are required to further verify the model and ontogeny profiles.

CONFLICT OF INTEREST
B.G.S. and T.N.J. are employees of Certara UK Limited, all other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
T.N.J., B.G.S., and F.S. wrote the manuscript. T.N.J. and FS. designed the research. F.S., T.N.J., and B.G.S. performed the research. F.S., T.N.J., and B.G.S. analyzed the data.

ORCID
Ben G. Small https://orcid.org/0000-0002-4387-5689
Trevor N. Johnson https://orcid.org/0000-0003-0778-0081

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