ORIGINAL ARTICLE

Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children

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Predictive performance of physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) models of drugs predominantly eliminated through kidney in the pediatric population was evaluated. After optimization using adult clinical data, the verified PBPK models can predict 33 of 34 drug clearance within twofold of the observed values in children 1 month and older. More specifically, 10 of 11 of predicted clearance values were within 1.5-fold of those observed in children between 1 month and 2 years old. The PopPK approach also predicted 19 of 21 drug clearance within twofold of the observed values in children. In summary, our analysis demonstrated both PBPK and PopPK adult models, after verification with additional adult pharmacokinetic (PK) studies and incorporation of known ontogeny of renal filtration, could be applied for dosing regimen recommendation in children 1 month and older for renally eliminated drugs in a first-in-pediatric study.
CPT Pharmacometrics Syst. Pharmacol. (2016) **5**, 475–483; doi:10.1002/psp4.12101; published online 27 August 2016.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Allometric scaling via PopPK can reasonably extrapolate drug clearance for children older than 6 years old from adult PK data. PBPK models can be used to predict the clearance of children in younger age groups.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ We developed PBPK models and conducted simulations using PopPK models to predict exposure of renally cleared drugs in children across all age groups and systematically characterized the predictive performance of two approaches.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ PBPK and PopPK modeling can reasonably predict PK of renally eliminated drugs in children 1 month and older.
HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS
☑ Our systematic characterization supports use of PBPK or PopPK models to guide pediatric clinical trial design for renally cleared drugs in children 1 month and older.

In 2007, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act under the US Food and Drug Administration (FDA) Amendments Act were implemented to encourage better understanding of drug safety and efficacy in children.[1] Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) are two modeling approaches often used to characterize pediatric pharmacokinetic (PK)[2] and to support clinical trial design in children.[3,4] Mechanistic PBPK models are parameterized with system-related and drug-specific information.[5] With appropriate calibration using clinical studies, PBPK models can provide a reasonable extrapolation to populations in which clinical data are not available.[6] Although PBPK modeling application in pediatrics has been actively investigated in both academia and industry[7,8] and has been increasingly used to support drug submission to regulatory agencies,[9,10] the systematic evaluation of the accuracy of prediction using the PBPK modeling approach in patients <2 years old is still lacking. Recently, researchers were able to predict the acetaminophen concentration-time

profile in neonates using a PBPK model developed and validated with adult and pediatric clinical PK results.[11]

A "learn-and-confirm" strategy is well accepted when developing a pediatric PBPK model.[9,11–13] General work flow starts with model development using drug-specific physicochemical properties, *in silico*, *in vitro*, and preclinical data to build a model in adults. The initial PBPK model will then be verified/refined using available clinical observations in adults. Finally, pediatric PBPK modeling is achieved by applying ontogeny of enzymes or renal function and other age-dependent physiological information, such as liver blood flow. The optimized models can then be used to guide dose selection, sampling time in a first-in-pediatric study design, and subsequently, the reliability of PBPK-based prediction of drug exposure may be further evaluated when pediatric clinical data become available.

Pediatric PopPK modeling has been a conventional approach to support clinical trial design and dosage selection in children.[2,14,15] The analysis was conducted using 39 drugs and suggested that drug clearance can be reasonably

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extrapolated to children older than 6 years from adult clearance through an allometric scaling approach.[16] With the consideration of allometric scaling and incorporation of the maturation profile of the glomerular filtration rate (GFR) and the pathophysiology of the disease in adult and pediatric patients, PopPK has also been used to guide the pediatric clinical trial design of teduglutide in neonates and infants.[17]

The main objective of this study was to systematically characterize the pediatric predictive performance of both PBPK and PopPK approaches for drugs predominantly eliminated via kidney. By considering physiologic changes (multiple for PBPK described by Johnson *et al.*[7] and body weight for PopPK) and renal function maturation (both approaches) in pediatrics, predictions of drug exposure by both approaches were compared with clinical observations conducted in infants, children, and adolescents. The work flow is illustrated in **Figure 1**. The PBPK model of each drug was built and optimized using published adult clinical PK data. The accuracy of pediatric exposure was evaluated by comparing simulated concentration-time profiles with observed clinical PK results in children at respective age groups for each drug. Simulations using structural models developed in adults with plausible combinations of covariates were performed to assess the predictive performance of PopPK modeling in children.

METHODS
Compound selection and clinical data collection
The FDA New Pediatric Labeling Information Database,[18] University of Washington Drug Interaction Database, and PubMed.gov website were searched for pediatric clinical studies. Drugs with at least 60% of the dose excreted unchanged through urine were considered. Additional criteria include: (1) at least two separate clinical studies in adults with intensive PK sampling; (2) PK studies in pediatric population in more than two age groups; and (3) PK studies in children younger than 2 years old. Clinical plasma concentration profiles and variability (if available) were digitized using PlotDigitizer version 2.6.3 (Huwaldt and Steinhorst). Five orally administered drugs: ceftibuten, cetirizine, levocetirizine, pregabalin, and sotalol and four i.v. administered drugs: avibactam, ceftazidime, meropenem, and vancomycin were evaluated for the PBPK approach. For evaluation of the PopPK approach, models generated using adult clinical data were obtained from literature for avibactam, ceftazidime, meropenem, pregabalin, and vancomycin. Detailed clinical trial information for each study of nine drugs is described in **Supplementary Table S1**.

PBPK modeling
Population component. The PBPK model was constructed using a population-based absorption, distribution, metabolism, and excretion simulator, Simcyp version 14.1 (Sheffield, UK). Default system parameter values of a virtual healthy volunteers population (physiological parameters, including liver volume and blood flows, and enzyme abundances) were reported by Howgate *et al.*[19] The pediatric module that includes the PBPK model together with extensive libraries on pediatric demography (age, height, weight,

and body surface area), developmental physiology (liver size, renal function, and liver blood flow), and biochemistry (albumin, CYP ontogeny) was used to predict PK in pediatrics[7] once a drug model was developed in adults. The advanced dissolution absorption metabolism model was applied to describe the drug absorption process.[20] This model contains information on the size of the gastrointestinal tract, fasted and fed gastric pH, fasted and fed bile concentration, fluid dynamics, feed type, stomach volume, and how these change with age from birth onward; other parameters, such as gastric emptying and intestinal transit times, have been shown to be at adult values from birth.[21] The PK simulations in adults and pediatrics were conducted using the same clinical study conditions as reported in the actual clinical trials (**Supplementary Table S1**). The 10 trials of 10 subjects per trial were applied for all drugs. Mean and distribution of demographic covariates and drug parameters were generated using a Monte-Carlo approach, under predefined study designs, within Simcyp.[22]

Development and optimization of PBPK models in adults. Detailed drug-specific parameters are listed in **Supplementary Table S2**. The effective permeability values of sotalol in man calculated from *in vitro* data do not correlate with the high permeability and bioavailability profile observed clinically,[23,24] therefore, permeability values for sotalol were optimized to describe adult PK profile, as reported by Feras *et al.*[12] Similar approaches were used for ceftibuten[25] and pregabalin[26,27] with effective permeability in man values optimized to 1.2 and $6.0*10^{-4}$ cm/s, respectively, to describe the absorption profile for both drugs. Preclinical studies suggested intestinal uptake transporters may contribute to cetirizine absorption.[28] Therefore, absorption of cetirizine and levocetirizine (*R*-enantiomer of cetirizine) was parameterized as the combination of an *in vitro* estimated apparent passive permeability $56.0*10^{-6}$ cm/s with an active intestinal uptake of 5.0 µL/min to capture absorption profiles observed clinically. Full PBPK models were used to describe tissue-plasma partition for all drugs and the volume of distribution of each drug was predicted using the Poulin and Theil or the Rodgers and Rowland method.[29,30] Multiple published adult clinical data were reviewed and the median reported clearance and dose excreted unchanged through urine values were used to estimate the renal clearance and additional systemic clearance with the retrograde method, a feature included in Simcyp (**Table 1**).

PBPK simulation in children. The PBPK models verified in adults were used to predict plasma concentration profiles in children using the virtual pediatric population incorporated within Simcyp for different age groups, which are defined as: neonates (0–1 month), infants (1 month to 2 years), young children (2–6 years), school aged children (6–12 years), and adolescents (12–18 years). The virtual trial design (age range, male/female ratio) was kept the same as reported in the actual clinical studies for each drug (**Supplementary Table S1**). Most of the drugs are excreted unchanged via the kidneys, but nonrenal clearance could still contribute a reasonable portion of the overall clearance for certain drugs (**Table 1, Supplementary Table S3**).
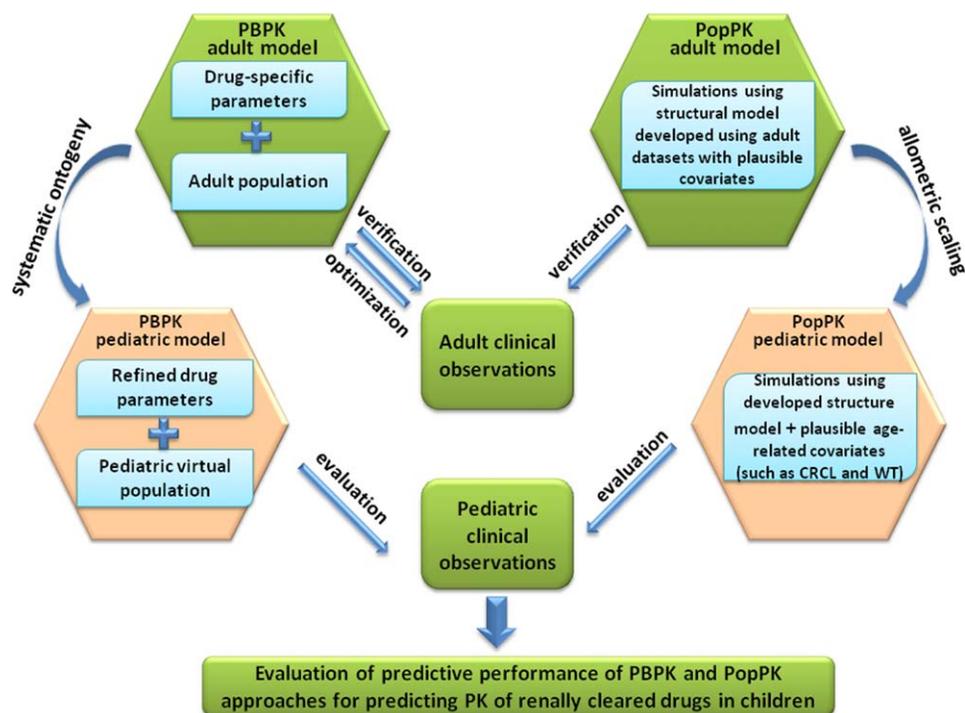
Figure 1 Workflow of the development of physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) models and prediction of pharmacokinetic (PK) in pediatrics for drugs primarily eliminated by the kidneys. CRCL, creatinine clearance; WT, body weight.

Ontogeny of renal function (GFR) captured in the Simcyp pediatric module, as described by Johnson *et al.*,[7] was used. No ontogeny was applied for nonrenal clearance for all drugs except for meropenem, which was assumed to have similar maturation profile as GFR. The assumption that ontogeny of active tubular secretion or reabsorption is the same as for GFR was applied in all simulations.

PopPK modeling
PopPK models in adults. PopPK models developed using only adult data were adapted from literature for avibactam,[31] ceftazidime,[31] meropenem,[32] and vancomycin[33] via i.v. administration and pregabalin[34] via oral administration.

A PopPK model was not available for the other four drugs; hence, no evaluation was conducted. PopPK models developed with pediatric clinical studies were not used as the purpose of the current analysis was to extrapolate from adults to pediatrics. When multiple PopPK models are available, models with relevant covariates (creatinine clearance [CRCL], body weight) and those developed in the same ethnic group between adults and children were selected. The age effect was fixed to one if the age was a significant covariate in the adult PopPK model. If the disease state was a significant covariate in adult models, the disease effect in children was reevaluated based on the nature of the disease and the detailed clinical trial information. The

Table 1 Pooled clinical observed PK parameters of drugs in adults

Drug, administration	CL[a,b] (L/h)	Vss[c,d] (L/kg)	fe %[b,e]	Reference
Avibactam, i.v.	**12.5** (9.4 ∼ 13.9)	0.22 ∼ 0.35	100[f]	31
Ceftazidime, i.v.	**6.9** (6.6 ∼ 6.9)	0.24 ∼ 0.26	**98** (96 ∼ 100)	31
Ceftibuten, oral	**4.8** (4.3 ∼ 5.5)	0.21 ∼ 0.26	**62** (58 ∼ 74)	47, S1–S5
Cetirizine, oral	**2.9** (1.8 ∼ 3.3)	0.24 ∼ 0.58	**66** (58 ∼ 73)	S6–S11
Levocetirizine, oral	**2.6** (2.5 ∼ 2.6)	0.33 ∼ 0.4	**85** (68 ∼ 95)	S8, S12,S13
Meropenem, i.v.	**12** (8.3 ∼ 15.2)	0.17 ∼ 0.29	**70** (67 ∼ 75)	S14–S17
Pregabalin, oral	**4.8** (4.0 ∼ 5.5)	0.5 ∼ 0.7	**95** (90 ∼ 99)	S18–S20
Sotalol, oral	**10.4** (7.7 ∼ 11.3)	1.3 ∼ 2.4	**95** (90 ∼ 100)	S21–S26
Vancomycin, i.v.	**4.4** (3.8 ∼ 5.8)	0.52 ∼ 0.72	**81** (77 ∼ 83)	S27–S31

CL, clearance; fe, dose excreted unchanged through urine; Vss, volume of distribution at steady state.
[a]Clearance values for i.v. drugs and apparent clearance values for oral drugs. [b]Median (bold) and range of reported values. [c]Volume of distribution for i.v. drugs and apparent volume of distribution values for oral drugs. [d]Range of the reported values. [e]Percentage of drug excreted unchanged *via* renal clearance. [f]Reported value.

PopPK models were refined by keeping only relevant covariates before extrapolation. Detailed information of the PopPK models can be found in **Supplementary Table S4**.

Predictions in pediatrics. Simulations were performed with refined PopPK models in both adults and children. The simulation datasets for each drug were generated via a Monte-Carlo approach, as described by Li *et al.*[31] For each simulation in children and adults, 1,000 subjects (500 in each gender) were created using randomly assigned percentile of body weight and height in each age group based on the growth charts from the Center for Disease Control and Prevention.[35] Specific dosing information was applied as reported in respective clinical trials. The CRCL values in children were estimated using the equations described by Schwartz *et al.*[36] for neonates and infants or by Rhodin *et al.*[37] for 2 years and older. Therefore, a maturation of renal filtration was also applied in the PopPK modeling approach.[15,37] NONMEM version 7.3 (Hanover, MD); Perl-speaks-NONMEM version 4.4[38] were used for all PopPK simulations.

Model evaluation
The predictive performance was evaluated for each drug at each age group by overlaying the observed concentration-time profile with the model predicted profile and 90% predictive interval. The prediction accuracy for area under the curve (AUC), maximum plasma concentration (C_{max}), and clearance values were calculated as a ratio of mean predicted values over mean observed values with a ratio SD ($Ratio_{sd}$):[13,39]

$$Ratio_{sd} = \sqrt{\left[\frac{sd\ (observed)}{Mean\ (observed)}\right]^2 + \left[\frac{sd\ (predicted)}{Mean\ (predicted)}\right]^2} \times \frac{Mean\ (predicted)}{Mean\ (observed)} \quad (1)$$

Where *sd(observed)* and *sd(predicted)* are the SD of observed and predicted values; mean*(observed)* and mean*(predicted)* are the arithmetic mean of observed and predicted values, respectively. Model performance was qualified by comparing the mean ratios $\pm Ratio_{sd}$ with the lines of identity (prediction/observation ratio of one) and the twofold window, which has been applied for determination of successful prediction of pediatric PK modeling.[3,11]

RESULTS
Data collection
A total of 36 clinical studies were available across all pediatric age ranges, 2 studies in neonates (<1 month old), 11 studies in infants (1 month to <2 years), 10 studies in young children (2 to <6 years), 9 studies in school-aged children (6 to <12 years), and 4 studies in adolescents (12 to <18 years). Detailed data specification and clinical trial information for these nine drugs is presented in **Supplementary Table S1**.
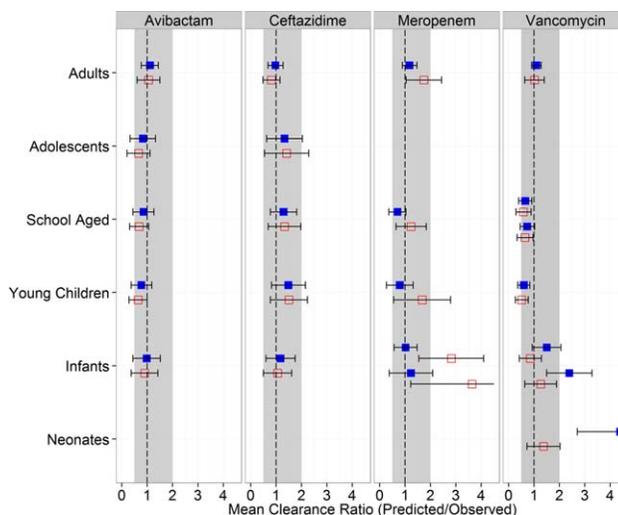
Figure 2 Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) prediction of i.v. drugs in adults and children. Predictions are expressed as ratios of predicted over observed of clearance values: mean of PBPK (blue filled squares) and PopPK (red open squares) with SD (bars). The dashed line represents the identity (predicted/observed ratio = 1); the gray shade represents the 0.5–2.0 ratio window. Literature sources are presented in Supplementary Material online. Observed data sources for avibactam, ceftazidime,[28,S32] meropenem,[S33] and vancomycin.[42,S30] The bottom two labels in the meropenem infant groups indicate a study in children 3 months to 1 year old and the top two labels indicate a study in children 1–2 years old. The bottom two labels in the vancomycin infant groups indicate a study in children 2–4 months, and the top two labels indicate a study in children 2–7 months old.

PBPK modeling in adults and children
The developed PBPK models were first verified with clinical studies in adults to demonstrate that the models could reasonably predict drug exposure in adult populations before predictions in pediatrics. Using the same drug models validated in adults, pediatric PK was predicted with the same age range, male/female ratio, and dosing information, as in the actual clinical trials, which provided reasonable prediction for each drug in children across all age groups. For avibactam, ceftazidime, and meropenem via i.v. administration (**Figure 2**), the predicted clearance values across all pediatric age groups were within 50% error. A larger prediction error was observed for vancomycin, in which the clearance ratios of all prediction were within a generally accepted twofold error range, except neonates at 0 to 1 week and infants 2–4 months (ratios were 4.39 and 2.39, respectively).

The predicted AUC and C_{max} for five orally administrated drugs compared with those observed clinically are shown in **Figure 3**. The exposure values of these drugs were reasonably predicted for all age groups, and the ratios of predicted over observed AUC or C_{max} values mostly fall in the range of 0.67 and 1.5 (50% error). There were slightly larger errors in C_{max} for cetirizine in infants 0.5–2 years (ratio of 1.56) and C_{max} for sotalol in those younger than 1 month (ratio of 1.51). The predicted concentration-time profiles of pregabalin overlaid with observed exposure in adults and all pediatric age groups are presented in **Figure 4a**. Clinical
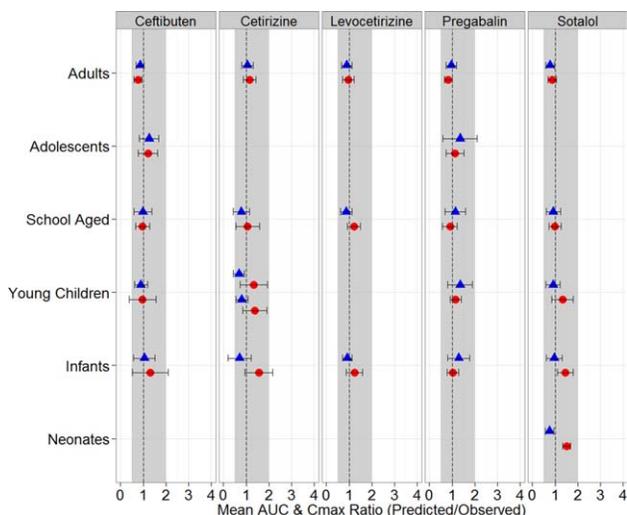
Figure 3 Physiologically based pharmacokinetic (PBPK) modeling performance of oral drugs in adults and children. Predictions are expressed as ratios of predicted over observed of area under the curve (AUC) and peak plasma concentration (C_{max}) values: mean AUC (blue triangles) and C_{max} (red circles) with SD (bars). The dashed line represents the identity (predicted/observed ratio = 1), and the gray shade represents the 0.5–2.0 ratio window. Some literature sources are presented in the Supplementary Material online. Observed data sources for ceftibuten,[S4,S34,S35] cetirizine,[S11,S36,S38] levocetirizine,[S8,S39,S40] pregabalin,[S18,S41] and sotalol.[S23,S42] The bottom two labels in the cetirizine young children groups indicate a study in children 2–4 years old and the bottom two labels indicate a study in children 2–6 years old.

observed plasma concentrations evenly distributed along with the model predicted profile and most observations were within the 5th percentile and 95th percentile of the prediction. The predicted concentration-time profiles overlaid with observed exposure for other drugs can be found in **Supplementary Figures S1–S8**. The plots indicated that the developed PBPK models can reasonably predict the exposure for these renal eliminated drugs in children down to the age of 1 month (**Supplementary Table S5**). About 70% of administered meropenem is eliminated unchanged through the kidneys and 30% of meropenem is metabolized by renal dehydropeptidase-1 (DHP-1). Two PBPK models were constructed to assess the ontogeny of DHP-I for 3-month to 2-year-old infants. Model 1 (final model presented in **Figure 1**) assumes DHP-1 had a similar maturation profile as GFR, whereas model 2 assumes full maturation at birth for this nonrenal elimination pathway. The median prediction trends of clearance values by two models were compared with those observed in infants 3 months to 2 years old (**Figure 5**). Without consideration of the maturation of DHP-1, model 2 overpredicted meropenem clearance in infants. The mean ratios of predicted over observed clearance of meropenem in infants from 3 months to 1 year and 1 to 2 years were 1.23 and 1.02, respectively, by using the model 1 approach.

The ratios of predicted over observed mean clearance values from all nine drugs were also plotted across all age groups (except neonates) in **Figure 6**. Collectively, 33 of 34

predictions were within the 0.5–2.0 range (twofold error); and 31 of 34 predictions were within the 0.67–1.5 range (50% error). Eleven clinical studies were available in infants between 1 month and 2 years old and 10 of 11 of the predicted clearance were within 50% error of observed values. The ratios of predicted over observed mean clearance for all these studies in adults (verification datasets) and children across all age groups can be found in **Supplementary Table S5**.

Prediction of drug PK in adults and children using PopPK modeling

PopPK models obtained from literature were first evaluated by simulating adult PK using datasets with covariates (CRCL, body weight) to predict adult PK data not used for model construction. The ratios of predicted to observed clearance were 1.05, 0.81, 1.02, and 1.07 for avibactam, ceftazidime, vancomycin, and pregabalin, respectively, in adults (**Figures 2 and 3, Supplementary Table S5**), indicating the PopPK models can reasonably capture other clinical studies in adults. Then, the PopPK models were applied to predict PK in pediatrics. Predicted clearance values were all within twofold error of observed values in children across all age groups, except for meropenem in infants (19 of 21). In addition, 14 of 21 predictions were within 50% error of observed values. In children younger than 2 years old, the ratios of clearance were 0.90, 1.06, and 1.08 for avibactam, ceftazidime, and pregabalin, respectively, and 1.37, 1.26, and 0.85 for vancomycin in 0–1 week, 2–4 month, and 2–7 month infants, respectively. The predicted concentration-time profiles of pregabalin were also in good agreement with the clinical observed drug exposure in all pediatric age groups, indicating reasonable extrapolation of the PopPK modeling approach (**Figure 4b**). The predicted concentration-time profiles overlaid with observed exposure in different age groups for other drugs can be found in **Supplementary Figures S1–S8**. For meropenem, more than 50% prediction error was observed in adults (ratio of 1.74). Significant over prediction of clearance was also observed in infants 3 months to 1 year (ratio of 3.63) and 1 to 2 years (ratio of 2.82).

DISCUSSION

The FDA requires pediatric study plans before the end of phase II clinical trials and an approved pediatric investigation plan is required before a marketing authorization application can be submitted to the European Medicines Agency (EMA).[40] Pediatric PBPK and PopPK modeling approaches using only adult clinical trial results become exceptionally valuable if accurate extrapolation can be achieved to guide selection of doses in first-in-pediatric studies. In this study, the predictive performance of the PBPK modeling approach was systematically evaluated using nine renally cleared drugs. In comparison, the performance of the PopPK modeling approach was also characterized using five of the nine drugs.

The PBPK modeling approach could predict clearance for all nine drugs in the studies from infants to adolescents

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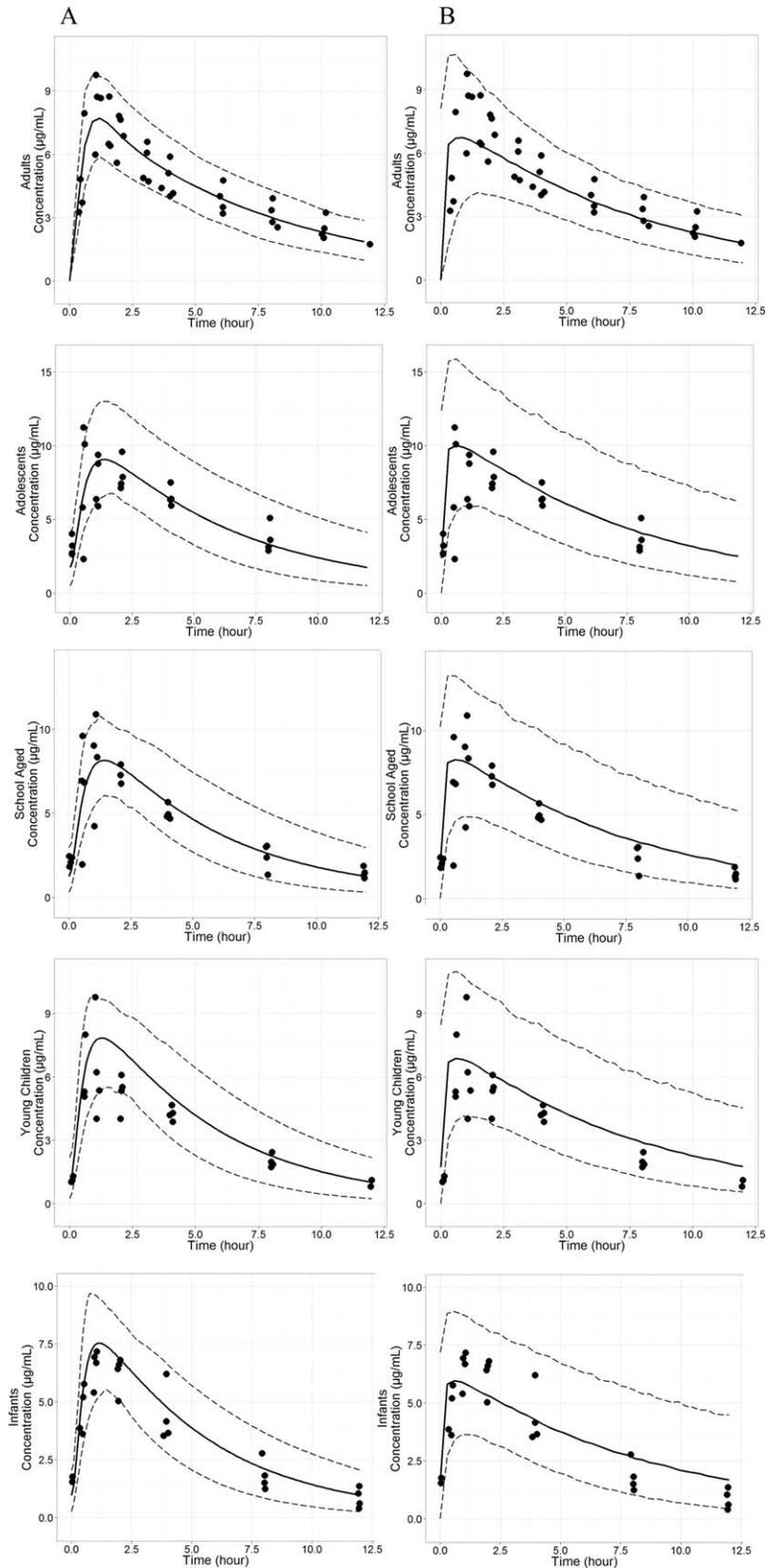
Figure 4 Physiologically based pharmacokinetic (PBPK) and population pharmacokinetic (PopPK) predicted and clinical observed concentration-time profile of pregabalin adults and children across all age groups. (**a**) PBPK and (**b**) PopPK predicted mean (solid lines) with 5% and 95% confidence interval (dashed lines). Filled circles represent clinical observed values.[S18,S41]
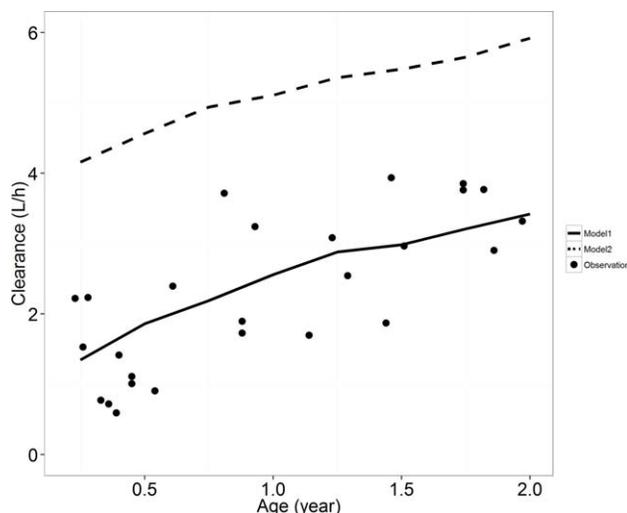
Figure 5 Comparison of two physiologically based pharmacokinetic (PBPK) meropenem models in children 3 months to 2 years old. Model 1 (solid line) and model 2 (dashed line) represents predicted clearance values in infants with or without consideration of maturation effect on nonrenal clearance. Observation (filled circles) represents clinical observed clearance values from literature.[S33]

(1 month to 18 years old). The twofold range of the prediction accuracy is a commonly used standard in pediatric PK modeling,[14] and *in vitro-in vivo* extrapolation prediction.[41] Although twofold boundaries are wide for drugs with PK parameters that have low variability and have been accurately characterized with large sample size, such boundaries are considered reasonable when the observed data are obtained from studies with small sample size.[41] Considering many clinical studies were conducted in less than 10 subjects for a specific age group (**Supplementary Table S1**), a twofold boundary is considered to be reasonable in the current analysis. The only clearance prediction in 1 month to 18 years studies that exceeded the twofold
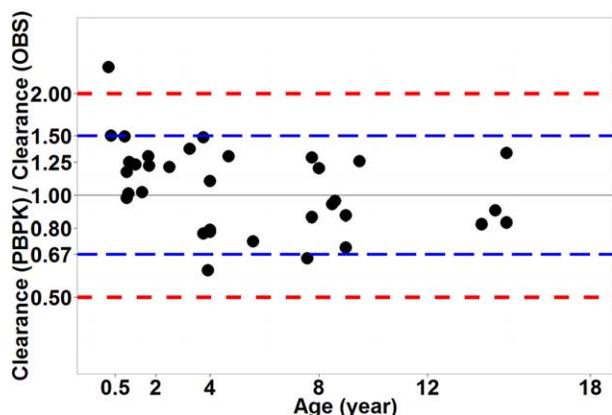
Figure 6 Overall predictivity of physiologically based pharmacokinetic (PBPK) models. Filled circles represent mean ratios of PBPK predicted clearance over observed clearance of all drugs in children 1 month to 18 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and twofold error.

range was for vancomycin in 2–4 month infants (mean ratio of 2.39). However, the PBPK could reasonably predict clearance of another vancomycin study[42] in 2–7 month infants (mean ratio of 1.50), suggesting that larger interstudy variability and relative small sample size may contribute to the prediction error. Two studies conducted in neonates were also evaluated. The clearance value of vancomycin was significantly overestimated in neonates at 0–1 week old, whereas the sotalol PBPK model was able to predict the drug exposure in neonates at 0–1 month old. The impact of infection on vancomycin PK in neonates cannot be fully characterized, which could be part of the reason for overestimation of vancomycin clearance. However, cases in neonate extrapolation are still limited, and more validations are necessary to determine if PBPK modeling could predict renally eliminated drugs in neonates.

Active tubular secretion has been suggested to contribute to the renal excretion of avibactam,[43] cetirizine,[44] levocetirizine,[44] meropenem,[45] and sotalol[S21] and active tubular reabsorption was reported for pregabalin.[S20] However, there currently is not enough information on the ontogeny of renal transporters to be considered within a pediatric PBPK model. The assumption that ontogeny of active tubular secretion or reabsorption is the same as for GFR was applied in our current simulations and the results indicated ontogeny of GFR could be a reasonable surrogate for these drugs with active tubular secretion or reabsorption.

The drugs selected in this study were predominantly eliminated via the kidneys, but the impact of age on nonrenal clearance should also be appropriately considered. With the exception of meropenem, the nonrenal clearance in PBPK models was parameterized as additional systemic clearance, in which the same nonrenal clearance values were applied for both adults and children. The metabolism of meropenem is primarily catalyzed by renal DHP-1[46] and accounts for about 30% of total elimination. By assuming that maturation of renal DHP-1 enzyme was similar to renal function, reasonable agreement between prediction and observation was achieved in 3 month to 2-year-old infants. Nonrenal clearance accounts for 38% and 34% of total drug elimination for ceftibuten and cetirizine, respectively. Ceftibuten is metabolized through an unknown pathway generating a trans-isomer metabolite, which accounts for about 10% of the total dose.[47] The metabolism of cetirizine was not well-characterized and two minor metabolites were identified accounting for <7% of the total dose.[48] Neither of these two drugs had clinical data on children younger than 6 months; therefore, no ontogeny was applied on nonrenal clearance for either drug. The ceftibuten model reasonably predicted the AUC ratio (1.05) in children 0.5–3 years old, which suggested potential fast maturation of nonrenal elimination. A larger, but still acceptable, prediction error was observed for cetirizine in infants 0.5–2 years old (AUC ratio of 0.71). PBPK model performance may be improved by including the ontogeny characterization of the nonrenal clearance pathway in this age group for cetirizine. However, arbitrary inclusion of the maturation factor could potentially improve the prediction performance for some drugs or for certain age groups but may introduce bias for other drugs or other age groups.

In comparison to PBPK, PopPK modeling is a conventional approach to predict pediatric drug exposure from adult PK information with or without consideration of ontogeny.[15,49,50] Only five of nine renally eliminated drugs with the adult PopPK model were available for analysis and 19 of 21 predicted clearance values (20 of 21 for the PBPK approach) were within twofold of those observed in children 1 month and older. In addition, 14 of 21 (18 of 21 for the PBPK approach) predictions fall within the boundaries of 0.67–1.5 of the observed values. For meropenem, a large prediction error (clearance mean ratio of 1.74) was observed in healthy volunteers using the reported PopPK model developed in adult infection patients, indicating that the disease state may significantly contribute to PK differences. In the meropenem PopPK model, CRCL was a covariate on clearance, and body weight was a covariate on volume of distribution. Even when these scalable covariates were included, the model was not able to accurately extrapolate the clearance in infants under 2 years old (**Figure 2**). The poor performance may result from missing maturation characterization of nonrenal elimination pathway, which contributes ~30% to total clearance in adults. Due to the limited number of available PopPK models, additional investigations are still warranted to fully characterize the modeling performance when extrapolating pediatric drug exposure using this approach.

In conclusion, this analysis provides a systematic characterization for renally eliminated drugs demonstrating that both PBPK and PopPK approaches can reasonably predict exposure in children. PBPK models provided reasonable prediction of all drugs in children 1 month and older, 33 of 34 of the predicted mean clearances were within twofold of the observed values, and 31 of 34 predictions were within 50% error. Similar prediction accuracy was also achieved in infants between 1 month and 2 years old, 10 of 11 of the predicted mean clearance values were within 50% of the observed values. Prediction of pediatric exposure using PopPK also exhibited reasonable modeling performance in children, except the case of meropenem in infants younger than 2 years old. Both approaches share the same "learn-and-confirm" principles (**Figure 1**). First, the PBPK model in adult is built using drug-specific physiochemical, preclinical, and clinical information. Similarly, the PopPK model is developed using clinical studies in adults in which key covariates (CRCL and body weight) should be incorporated appropriately. Second, the developed PBPK or PopPK model should be verified with additional clinical studies in adults to demonstrate that the models could reasonably predict drug exposure in the adult population before predictions in pediatrics. Model refinement might be necessary at this step. Finally, using the validated drug model in adults, pediatric PK then can be predicted for different age groups by applying ontogeny of renal function and/or age-dependent physiological changes through a PBPK approach. For the PopPK approach, simulations using verified models with plausible age-related covariates (such as CRCL and body weight) would also provide reasonable extrapolation for renally cleared drugs in children.

Author Contributions. D.Z., W.Z., T.J., H.X., A.C., K.B., J.L., and N.A-H. wrote the manuscript. D.Z., W.Z., T.J., H.X., A.C., K.B., J.L., and N.A-H. designed the research. D.Z., W.Z., T.J., H.X., A.C., K.B., J.L., and N.A-H. performed the research. D.Z., W.Z., T.J., H.X., A.C., K.B., J.L., and N.A-H. analyzed the data.

1. U.S. Food and Drug Administration. <http://wwwgpogov/fdsys/pkg/PLAW–110publ85/html/PLAW–110publ85htm>. Assessed 28 October 2015.
2. Vinks, A.A., Emoto, C. & Fukuda, T. Modeling and simulation in pediatric drug therapy: application of pharmacometrics to define the right dose for children. *Clin. Pharmacol. Ther.* **98**, 298–308 (2015).
3. Johnson, T.N., Zhou, D. & Bui, K.H. Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents. *Biopharm. Drug Dispos.* **35**, 341–352 (2014).
4. Hong, Y. *et al.* Model-based approach for optimization of atazanavir dose recommendations for HIV-infected pediatric patients. *Antimicrob. Agents Chemother.* **55**, 5746–5752 (2011).
5. Jones, H. & Rowland-Yeo, K. Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development. *CPT Pharmacometrics Syst. Pharmacol.* **2**, e63 (2013).
6. Tsamandouras, N., Rostami-Hodjegan, A. & Aarons, L. Combining the "bottom up" and "top down" approaches in pharmacokinetic modelling: fitting PBPK models to observed clinical data. *Br. J. Clin. Pharmacol.* **79**, 48–55 (2015).
7. Johnson, T.N., Rostami-Hodjegan, A. & Tucker, G.T. Prediction of the clearance of eleven drugs and associated variability in neonates, infants and children. *Clin. Pharmacokinet.* **45**, 931–956 (2006).
8. Krekels, E.H. *et al.* From pediatric covariate model to semiphysiological function for maturation: part II-sensitivity to physiological and physicochemical properties. *CPT Pharmacometrics Syst. Pharmacol.* **1**, e10 (2012).
9. Leong, R. *et al.* Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clin. Pharmacol. Ther.* **91**, 926–931 (2012).
10. Wagner, C. *et al.* Application of physiologically based pharmacokinetic (PBPK) modeling to support dose selection: report of an FDA public workshop on PBPK. *CPT Pharmacometrics Syst. Pharmacol.* **4**, 226–230 (2015).
11. Jiang, X.L., Zhao, P., Barrett, J.S., Lesko, L.J. & Schmidt, S. Application of physiologically based pharmacokinetic modeling to predict acetaminophen metabolism and pharmacokinetics in children. *CPT Pharmacometrics Syst. Pharmacol.* **2**, e80 (2013).
12. Khalil, F. & Läer, S. Physiologically based pharmacokinetic models in the prediction of oral drug exposure over the entire pediatric age range-sotalol as a model drug. *AAPS J.* **16**, 226–239 (2014).
13. Maharaj, A.R. & Edginton, A.N. Physiologically based pharmacokinetic modeling and simulation in pediatric drug development. *CPT Pharmacometrics Syst. Pharmacol.* **3**, e150 (2014).
14. Anderson, B.J., Allegaert, K. & Holford, N.H. Population clinical pharmacology of children: general principles. *Eur. J. Pediatr.* **165**, 741–746 (2006).
15. Anderson, B.J., Allegaert, K. & Holford, N.H. Population clinical pharmacology of children: modelling covariate effects. *Eur. J. Pediatr.* **165**, 819–829 (2006).
16. Edginton, A.N., Shah, B., Sevestre, M. & Momper, J.D. The integration of allometry and virtual populations to predict clearance and clearance variability in pediatric populations over the age of 6 years. *Clin. Pharmacokinet.* **52**, 693–703 (2013).
17. Mouksassi, M.S., Marier, J.F., Cyran, J. & Vinks, A.A. Clinical trial simulations in pediatric patients using realistic covariates: application to teduglutide, a glucagon-like peptide-2 analog in neonates and infants with short-bowel syndrome. *Clin. Pharmacol. Ther.* **86**, 667–671 (2009).
18. Pediatric studies conducted under the US Food and Drug Administration. <http://wwwfdagov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>. Assessed 28 October 2015.

19. Howgate, E.M., Rowland Yeo, K., Proctor, N.J., Tucker, G.T. & Rostami-Hodjegan, A. Prediction of in vivo drug clearance from in vitro data. I: impact of inter-individual variability. *Xenobiotica* **36**, 473–497 (2006).

20. Jamei, M. *et al.* Population-based mechanistic prediction of oral drug absorption. *AAPS J.* **11**, 225–237 (2009).

21. Bonner, J.J. *et al.* Does age affect gastric emptying time? A model-based meta-analysis of data from premature neonates through to adults. *Biopharm. Drug Dispos.* **36**, 245–257 (2015).

22. Jamei, M., Marciniak, S., Feng, K., Barnett, A., Tucker, G. & Rostami-Hodjegan, A. The Simcyp population-based ADME simulator. *Expert Opin. Drug Metab. Toxicol.* **5**, 211–223 (2009).

23. Yang, Y., Faustino, P.J., Volpe, D.A., Ellison, C.D., Lyon, R.C. & Yu, L.X. Biopharmaceutics classification of selected beta-blockers: solubility and permeability class membership. *Mol. Pharm.* **4**, 608–614 (2007).

24. Alt, A., Potthast, H., Moessinger, J., Sickmüller, B. & Oeser, H. Biopharmaceutical characterization of sotalol-containing oral immediate release drug products. *Eur. J. Pharm. Biopharm.* **58**, 145–150 (2004).

25. Menon, R.M. & Barr, W.H. Comparison of ceftibuten transport across Caco-2 cells and rat jejunum mounted on modified Ussing chambers. *Biopharm. Drug Dispos.* **24**, 299–308 (2003).

26. Jezyk, N., Li, C., Stewart, B.H., Wu, X., Bockbrader, H.N. & Fleisher, D. Transport of pregabalin in rat intestine and Caco-2 monolayers. *Pharm. Res.* **16**, 519–526 (1999).

27. Su, T.Z., Feng, M.R. & Weber, M.L. Mediation of highly concentrative uptake of pregabalin by L-type amino acid transport in Chinese hamster ovary and Caco-2 cells. *J. Pharmacol. Exp. Ther.* **313**, 1406–1415 (2005).

28. Polli, J.W. *et al.* P-glycoprotein influences the brain concentrations of cetirizine (Zyrtec), a second-generation non-sedating antihistamine. *J. Pharm. Sci.* **92**, 2082–2089 (2003).

29. Rodgers, T., Leahy, D. & Rowland, M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J. Pharm. Sci.* **94**, 1259–1276 (2005).

30. Rodgers, T. & Rowland, M. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J. Pharm. Sci.* **95**, 1238–1257 (2006).

31. Li, J., Knebel, M., Riggs, M., Zhou, D., Nichols, W. & Das, S. Population pharmacokinetic modeling of ceftazidime and avibactam in healthy subjects and in patients with complicated intra-abdominal infection (cIAI). *ICAAC* (2012).

32. Li, C., Kuti, J.L., Nightingale, C.H. & Nicolau, D.P. Population pharmacokinetic analysis and dosing regimen optimization of meropenem in adult patients. *J. Clin. Pharmacol.* **46**, 1171–1178 (2006).

33. Dolton, M. *et al.* Vancomycin pharmacokinetics in patients with severe burn injuries. *Burns* **36**, 469–476 (2010).

34. Bockbrader, H.N., Burger, P., Knapp, L. & Corrigan, B.W. Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. *Epilepsia* **52**, 248–257 (2011).

35. Centers for Disease Control. Growthchart. <http://wwwcdcgov/growthcharts/>. Accessed 28 October 2015.

36. Schwartz, G.J., Feld, L.G. & Langford, D.J. A simple estimate of glomerular filtration rate in full-term infants during the first year of life. *J. Pediatr.* **104**, 849–854 (1984).

37. Rhodin, M.M. *et al.* Human renal function maturation: a quantitative description using weight and postmenstrual age. *Pediatr. Nephrol.* **24**, 67–76 (2009).

38. Lindbom, L., Ribbing, J. & Jonsson, E.N. Perl-speaks-NONMEM (PsN)–a Perl module for NONMEM related programming. *Comput. Methods Programs Biomed.* **75**, 85–94 (2004).

39. Einolf, H.J. Comparison of different approaches to predict metabolic drug-drug interactions. *Xenobiotica* **37**, 1257–1294 (2007).

40. US Food and Drug Administration Safety and Innovation Act. <http://wwwgpogov/fdsys/pkg/BILLS–112s3187enr/pdf/BILLS–112s3187enrpdf>. Assessed 10 September 2015.

41. Abduljalil, K., Cain, T., Humphries, H. & Rostami-Hodjegan, A. Deciding on success criteria for predictability of pharmacokinetic parameters from in vitro studies: an analysis based on in vivo observations. *Drug Metab. Dispos.* **42**, 1478–1484 (2014).

42. Schaad, U.B., McCracken, G.H. Jr & Nelson, J.D. Clinical pharmacology and efficacy of vancomycin in pediatric patients. *J Pediatr* **96**, 119–126 (1980).

43. Vishwanathan, K. *et al.* Assessment of the mass balance recovery and metabolite profile of avibactam in humans and in vitro drug-drug interaction potential. *Drug Metab. Dispos.* **42**, 932–942 (2014).

44. Strolin Benedetti, M., Whomsley, R., Mathy, F.X., Jacques, P., Espie, P. & Canning, M. Stereoselective renal tubular secretion of levocetirizine and dextrocetirizine, the two enantiomers of the H1-antihistamine cetirizine. *Fundam. Clin. Pharmacol.* **22**, 19–23 (2008).

45. Bax, R.P., Bastain, W., Featherstone, A., Wilkinson, D.M., Hutchison, M. & Haworth, S.J. The pharmacokinetics of meropenem in volunteers. *J. Antimicrob. Chemother.* **24**(suppl. A), 311–320 (1989).

46. Moon, Y.S., Chung, K.C. & Gill, M.A. Pharmacokinetics of meropenem in animals, healthy volunteers, and patients. *Clin. Infect. Dis.* **24**(suppl. 2), S249–S255 (1997).

47. Kelloway, J.S. *et al.* Pharmacokinetics of ceftibuten-cis and its trans metabolite in healthy volunteers and in patients with chronic renal insufficiency. *Antimicrob. Agents Chemother.* **35**, 2267–2274 (1991).

48. Campoli-Richards, D.M., Buckley, M.M. & Fitton, A. Cetirizine. A review of its pharmacological properties and clinical potential in allergic rhinitis, pollen-induced asthma, and chronic urticaria. *Drugs* **40**, 762–781 (1990).

49. Krekels, E.H. *et al.* From pediatric covariate model to semiphysiological function for maturation: part I-extrapolation of a covariate model from morphine to Zidovudine. *CPT Pharmacometrics Syst. Pharmacol.* **1**, e9 (2012).

50. De Cock, R.F. *et al.* A neonatal amikacin covariate model can be used to predict ontogeny of other drugs eliminated through glomerular filtration in neonates. *Pharm. Res.* **31**, 754–767 (2014).