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PHARMACOLOGY

External Evaluation of Two Pediatric Population Pharmacokinetics Models of Oral Trimethoprim and Sulfamethoxazole

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ABSTRACT The antibiotic combination trimethoprim (TMP)-sulfamethoxazole (SMX) has a broad spectrum of activity and is used for the treatment of numerous infections, but pediatric pharmacokinetic (PK) data are limited. We previously published population PK (popPK) models of oral TMP-SMX in pediatric patients based on sparse opportunistically collected data (POPS study) (J. Autmizguine, C. Melloni, C. P. Hornik, S. Dallefeld, et al., Antimicrob Agents Chemother 62:e01813-17, 2017, https://doi.org/10.1128/AAC.01813-17). We performed a separate PK study of oral TMP-SMX in infants and children with more-traditional PK sample collection and independently developed new popPK models of TMP-SMX using this external data set. The POPS data set and the external data set were each used to evaluate both popPK models. The external TMP model had a model and error structure identical to those of the POPS TMP model, with typical values for PK parameters within 20%. The external SMX model did not identify the covariates in the POPS SMX model as significant. The external popPK models predicted higher exposures to TMP (median overprediction of 0.13 mg/liter for the POPS data set and 0.061 mg/liter for the external data set) and SMX (median overprediction of 1.7 mg/liter and 0.90 mg/liter) than the POPS TMP (median underprediction of 0.016 mg/liter and 0.39 mg/liter) and SMX (median underprediction of 1.2 mg/liter and 14 mg/liter) models. Nonetheless, both models supported TMP-SMX dose increases in infants and young children for resistant pathogens with a MIC of 1 mg/liter, although the required dose increase based on the external model was lower. (The POPS and external studies have been registered at ClinicalTrials.gov under registration no. NCT01431326 and NCT02475876, respectively.)

KEYWORDS pediatric, population pharmacokinetics, trimethoprim, and sulfamethoxazole, pediatric, sulfamethoxazole

Trimethoprim (TMP) and sulfamethoxazole (SMX) are two antifolate antibiotics with broad spectra of activity and wide tissue distribution. These characteristics allow the combination to be used for treating diverse bacterial and fungal infections in pediatric patients, including urinary tract infections, acute otitis media, shigellosis, *Pneumocystis jirovecii* pneumonia, and uncomplicated skin infections due to methicillin-resistant *Staphylococcus aureus* (1–4). For bacterial infections, the recommended dose is 160 to 320 mg (based on the TMP component) every 12 h for adults and 4 to 6 mg/kg of body weight every 12 h for pediatric patients older than 2 months (1, 2).

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Pharmacokinetic (PK) studies in adults have reported that the absorptions of both TMP and SMX are rapid and complete following oral administration (1, 5). Approximately 42 to 46% of TMP and 70% of SMX are bound to plasma proteins (6). TMP is largely (61 to 85%) eliminated unchanged by the kidneys, with a small fraction metabolized by liver cytochrome P450 (CYP) 2C9 and CYP3A4 to inactive metabolites; in contrast, SMX is mainly metabolized by CYP2C9 and *N*-acetyltransferase (NAT) 1 and NAT2 to various metabolites, with only 10 to 12% excreted unchanged in urine (7). In adults, the apparent volumes of distribution (*V*/*F*) are 1.0 to 1.8 liters/kg for TMP and 0.17 to 0.27 liter/kg for SMX, and the apparent clearances (CL/*F*) are 0.071 to 0.11 liters/h/kg for TMP and 0.013 to 0.024 liters/h/kg for SMX (8–17).

TMP-SMX PK data for infants and children are relatively sparse (18), but an understanding of the underlying mechanism for elimination may provide some insights. For renally eliminated drugs, such as TMP, non-weight-adjusted clearance is expected to increase less than proportionally to weight and to increase sigmoidally with age, with most of the age-related change occurring in the first year of life, following renal function maturation (19). Weight-adjusted TMP clearance was lowest in neonates, at 1.84 ml/min/kg (20), and higher in infants than in older children (9, 21). Weight-adjusted volume of distribution data were conflicting, with one study suggesting lower values for younger children (9) and another study reporting a decrease with age (22). For SMX, CYP2C9 activity is known to rapidly increase to adult values after birth (23), but the ontogeny of the NATs has not been clearly elucidated, although some evidence suggested maturation around the age of 4 years (24). Based on studies with different median ages, weight-adjusted clearance and volume of distribution showed opposite trends, with neonates having the lowest clearance and highest volume of distribution, younger children having the highest clearance and lowest volume of distribution, and older children having a clearance and volume of distribution in between (20, 21, 25). A direct comparison of SMX PK from the same study was not available. Overall, both age and weight appeared to contribute to differences between adult and pediatric TMP-SMX PK.

Our group previously conducted a population PK (popPK) study of TMP-SMX, referred to below as the POPS (Pediatric Opportunistic PK Study) study (ClinicalTrials registration no. NCT01431326), which leveraged sparse opportunistically collected samples from pediatric patients treated for bacterial infections per standard of care (21). The dispositions of TMP and SMX were characterized using one-compartment PK models with first-order kinetics. After accounting for actual body weight (WT) using an allometric relationship, postnatal age (PNA) and serum creatinine level (SCR) were identified as significant covariates for TMP CL/*F*, while PNA and albumin concentration were identified as significant covariates for SMX CL/*F*. The POPS study aimed to achieve a free concentration at 50% of the dosing interval at steady state greater than the MIC of 0.5 or 1 mg/liter in the majority of each age cohort. The results suggested that for pathogens with a MIC of 1 mg/liter, a dose increase to 7.5 mg/kg TMP every 12 h for children 2 months to $<$6 years of age, and to 6 mg/kg TMP every 12 h for children 6 years of age or older, may be warranted. However, the POPS popPK models have not yet been externally evaluated.

External evaluation is an important component of popPK model evaluation to ensure the robustness and generalizability of the model (26), in particular for pediatric populations, where PK sampling is often sparser, and where there is substantial heterogeneity in disease severity and drug dosing. We have collected an independent data set for infants and children using a traditional, dedicated PK sampling strategy (ClinicalTrials.gov registration no. NCT02475876). Our objectives were to develop a new popPK model for TMP and SMX based on the new data set alone and to cross-evaluate the newly developed external popPK model and the POPS popPK model using the available data. Finally, we sought to use a simulation approach to evaluate TMP-SMX dosing for populations from infants to adolescents based on each popPK model.

RESULTS

Data set characteristics. Demographic and clinical characteristics and dosing information for each data set are summarized in Table 1. Compared to subjects in the POPS data

TABLE 1 Population demographics, laboratory values, and drug dosing information for the POPS[a] and external data sets

Characteristic[b]	POPS data	External data
No. of participants	153	20
No. of PK samples [no. missing][c]	240 [4]	121 [0]
No. (%) of BLQ TMP samples	22 (9.3)	0 (0)
No. (%) of BLQ SMX samples	15 (6.4)	0 (0)
Median (range) value [no. of missing values] for:		
No. of PK samples per subject	1 (1–4)	7 (2–7)
Gestational age (wks)[d]	37 (30–39) [141]	32 (25–41) [14]
Postnatal age (yrs)	7.9 (0.055–20) [0]	4.4 (0.23–15) [0]
Weight (kg)	30 (2.3–150) [0]	15 (1.9–65) [0]
Height (cm)	130 (44–190) [3]	98 (44–160) [0]
Albumin (g/dl)	3.4 (1.7–4.8) [75]	3.9 (3.1–4.2) [13]
Serum creatinine concn (mg/dl)	0.50 (0.10–5.9) [33]	0.32 (0.13–0.60) [0]
Creatinine clearance (ml/min/1.73m^2)[e]	100 (5–420) [0]	120 (73–210) [0]
TMP dose (mg/kg)[f]	2.5 (0.49–12)	4.5 (2.1–6.6)
Dosing interval[f]	22 (6.3–84)	12 (7.8–24)
Corrected dosing interval[f,g]	13 (6.3–49)	12 (7.8–24)
No. (%) of subjects		
Male	82 (54)	12 (60)
Caucasian	109 (71)	18 (90)
Obese[h]	53 (35)	4 (20)

[a]POPS, Pediatric Opportunistic Pharmacokinetic Study.
[b]Descriptive statistics for demographics and laboratory values are calculated on the basis of the value at the time of the first recorded dose. BLQ, below the limit of quantification; PK, pharmacokinetic; TMP, trimethoprim; SMX, sulfamethoxazole.
[c]PK samples below the lower limit of quantification before the first dose were set as missing.
[d]Gestational age information was collected for infants with a postnatal age of <120 days for the POPS data set and for infants with a PNA of <1 year for the external data set.
[e]Calculated using the Bedside Schwartz formula.
[f]Median dose information was first summarized for each individual patient before descriptive statistics were calculated. Three participants in the external data set received doses lower than the protocol-specified doses throughout their PK data.
[g]Computed after excluding dose intervals of >60 h. A total of 99 dose intervals from the POPS study and 2 dose intervals from the external study were excluded. Extended dose intervals were likely to be due to separate dosing occasions for the same subject.
[h]Defined as a body mass index in the 95th percentile or higher; not assessed for subjects <2 years old.

set, subjects in the external data set had more samples per person, had a narrower PNA, and received higher and more-frequent doses. Albumin concentrations were missing from a significant proportion of subjects in both data sets. SCR was lower in the external data set, but creatine clearance was comparable for the two data sets. Although the external study had a prospective design with protocol-specified doses, subjects who started TMP-SMX at a lower dose were eligible for enrollment in the external study, which led to variability in the dosing regimens. The concentrations from both data sets were dose-normalized to 4 mg/kg TMP and 20 mg/kg SMX and are plotted against time after the last dose in Fig. S1 in the supplemental material.

External TMP-SMX popPK model development. Both TMP and SMX concentrations were adequately characterized using a one-compartment PK model with first-order absorption and elimination. For each drug, allometric scaling of total body WT using an exponent of 0.75 for CL/*F* and 1 for *V*/*F* was selected for inclusion in the base model, balancing practicality and improvement in objective function value.

For the TMP model, the interindividual variability (IIV) in the absorption rate constant (K_a) was fixed to zero because the shrinkage was large (99.6%), and the covariance between CL/*F* and *V*/*F* was fixed to zero because the estimated covariance was negligible with a very large relative standard error (RSE). PNA using a maximum-effect (E_{max}) maturation function and SCR using a power relationship were significant covariate relationships for CL/*F*. Therefore, the final external TMP model is as follows: $K_a = 1.40$, $CL/F = 8.79 \times (WT/70)^{0.75} \times$

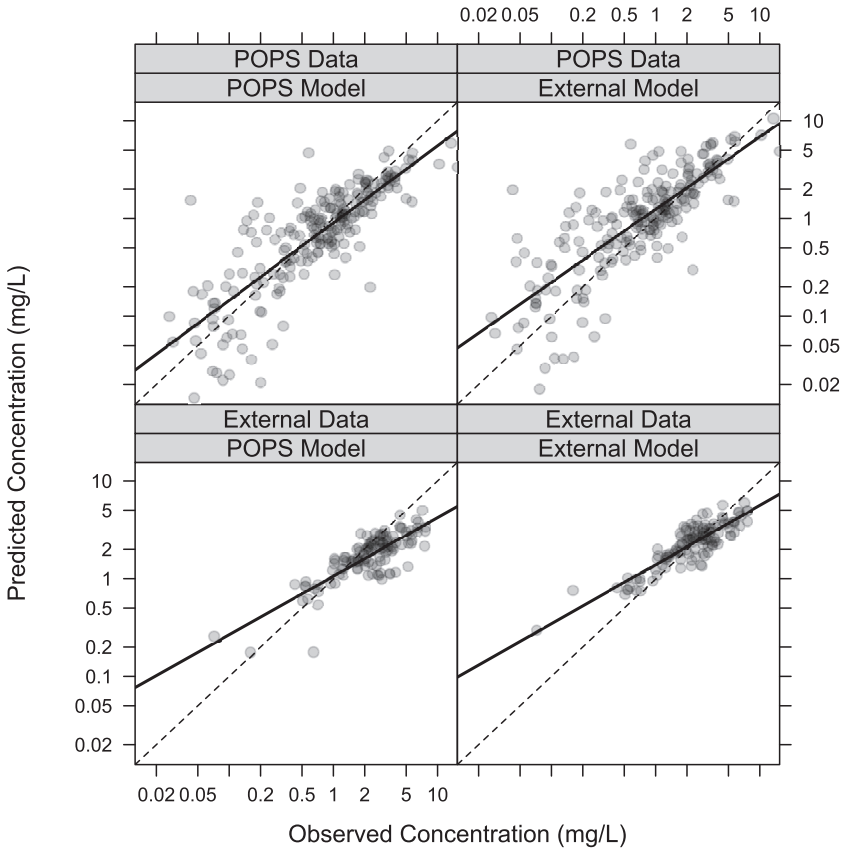

FIG 1 Goodness-of-fit plots comparing TMP PREDs with observations. PREDs were obtained by fixing the parameters in the published POPS model or the external model developed from the current study. The dashed line represents the line of unity; the solid line represents the best-fit line. We excluded 22 (9.3%) TMP samples and 15 (6.4%) SMX samples from the POPS data that were BLQ.

[PNA/(PNA + 0.91)] × (0.5/SCR)$^{0.71}$, and $V/F = 124 \times$ (WT/70), where K_a is in unit 1/hour, CL/F is in unit of liters per hour, WT is in kilograms, PNA is in years, SCR is in milligrams per deciliter, and V/F is in unit of liters.

For the SMX model, the IIV for V/F was fixed to zero because it could not be precisely estimated (RSE, 170%) with high shrinkage (71.6%). The covariance between K_a and CL/F was fixed to zero because the estimated covariance was negligible, with an extremely large RSE, and the rationale for including covariance between CL/F and K_a was weak. No additional covariate effect was identified. The final SMX model is as follows: $K_a = 1.10$, CL/$F = 1.17 \times$ (WT/70)$^{0.75}$, and $V/F = 24 \times$ (WT/70), where K_a is measured per hour, CL/F is measured in liters per hour, WT in kilograms, and V/F in liters.

Bias and precision for each popPK model with either data set. The POPS study model was associated with a negative median prediction error (PE) for both TMP and SMX for both data sets, while the external study model was associated with a positive median PE for both drugs for both data sets (Table S1). With both drugs, the POPS model better characterized the lower concentrations while the external model better characterized the higher concentrations, which were more prevalent in the external data set (Fig. 1 [TMP] and Fig. 2 [SMX]). The conditional weighted residuals (CWRES) plots demonstrated a roughly even distribution of the residuals around zero, with most CWRES falling between −2 and 2 (Fig. S2 to S5). External evaluations were associated with more positive residuals for the POPS model and more negative residuals for the external model.

Reestimation and bootstrap analysis. Each model was reestimated using either data set, and bootstrap analysis was performed to assess model stability and the precision of estimates for each model. The results for the estimation and bootstrap analysis of

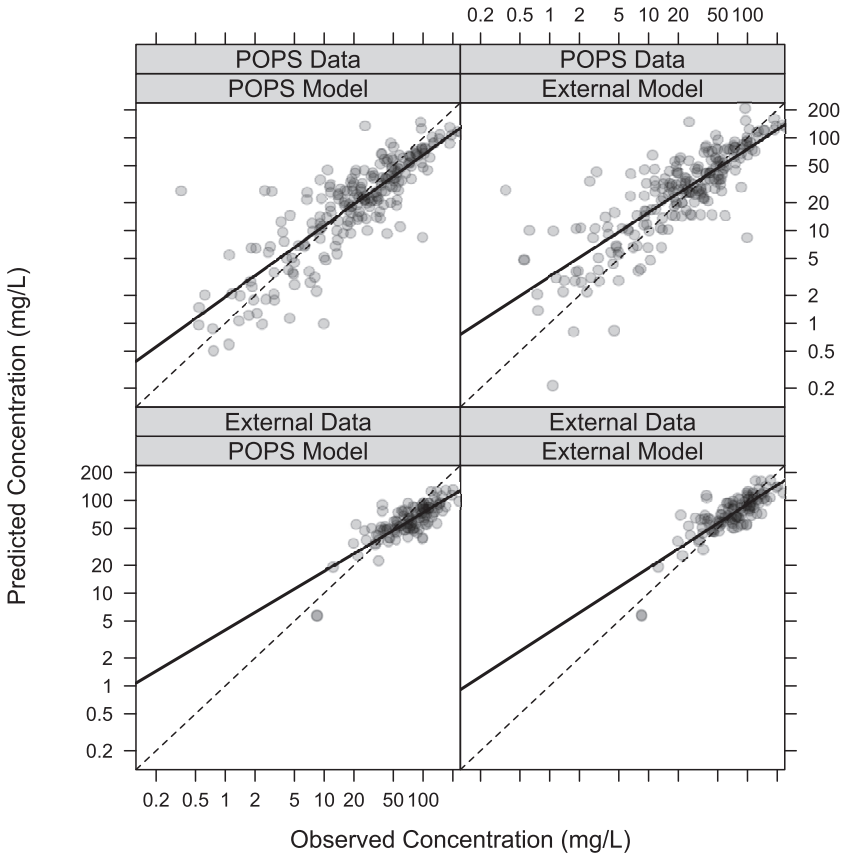

FIG 2 Goodness-of-fit plots comparing SMX PREDs with observations. PREDs were obtained by fixing the model parameters for the published POPS model or the external model developed from the current study. The dashed line represents the line of unity; the solid line represents the best-fit line. We excluded 22 (9.3%) TMP samples and 15 (6.4%) SMX samples from the POPS data that were BLQ.

the POPS and external TMP models are combined in Table 2, given that the TMP models have identical structures. The estimation step and nearly all 1,000 bootstrap runs minimized successfully using either data set. The final estimates for the PK parameters were within 20% of each other. The 95% confidence intervals (CIs) for the covariate relationships overlapped significantly and did not include the no-effect threshold. The residual variability estimated for the POPS data set was greater than that in the external data set.

The results of the reestimation and bootstrap analysis using the POPS SMX model with either data set are summarized in Table 3. When the POPS SMX model was reestimated and bootstrapped employing the data set used for its development, the results were similar to the results in the previous publication (21). However, the CIs for the K_a, V/F, the Hill coefficient on the maturation function with age, and the exponent on the albumin effect on clearance were wide, suggesting that these parameters could not be precisely identified. The reestimation and nearly half of the bootstrap analysis for the POPS SMX model did not minimize using the external data set, suggesting a lack of model stability. The bootstrap analysis yielded wide 95% CIs on the maturation half-life and on the albumin exponent, both of which included the no-effect threshold.

The results of the reestimation and bootstrap analysis using the external SMX model with either data set are summarized in Table 4. The reestimated K_a using the POPS data set was smaller than the K_a based on the external data set, but the CL/F and V/F were within 20% of each other. More than 90% of the bootstrap minimized successfully using either data set, indicating reasonable model stability. The 95% CIs for CL/F were narrow in both bootstraps and narrower than that estimated for each respective data set using the POPS SMX model. The 97.5th percentile for the IIV on K_a

TABLE 2 Parameter estimates and bootstrap analysis of the published POPS TMP model and the external TMP model developed from the current study using the POPS and external data sets[a]

	POPS data		External data	
Parameter[b]	Parameter value (% RSE)[c]	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles	Parameter value (% RSE)	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles
Minimization successful	Yes	998/1,000	Yes	999/1,000
Fixed effects				
K_a (h^{-1})	1.3 (36)	0.57–2.5	1.4 (21)	0.97–2.4
CL/*F* (liters/h)	11 (5.7)	9.3–12.0	9.8 (10)	7.9–13
V/*F* (liters)	150 (6.8)	130–170	125 (7.4)	110–150
PNA_{50} (yr)	0.24 (25)	0.13–0.41	0.91 (41)	0.35–2.7
SCR exponent	0.40 (20)	0.22–0.56	0.71 (25)	0.31–1.4
Random effects				
IIV, CL/*F* (%)	34 (18)	12–48	31 (9.9)	22–36
IIV, *V*/*F* (%)	21 (45)	0.21–46	16 (45)	0.16–29
Proportional error (%)	51 (7.2)	43–58	19 (13)	14–24

[a]The Pediatric Opportunistic Pharmacokinetic Study (POPS) trimethoprim (TMP) model and the external TMP model have the same structural relationship: $K_a\ (h^{-1}) = \theta_1$; $CL/F(\text{liters/h}) = \theta_2 \times (WT/70)^{0.75} \times [PNA/(PNA+\theta_3)] \times (0.5/SCR)^{-\theta_4}$; $V/F\ (\text{liters}) = \theta_5 \times (WT/70)$, where θ is an estimated fixed effect, WT is the actual body weight in kilograms, and PNA is the postnatal age in years.

[b]CL/*F*, apparent clearance; IIV, interindividual variability; K_a, absorption rate constant; PNA_{50}, maturation half-life calculated as a function of postnatal age (in years); SCR, serum creatinine; *V*/*F*, apparent volume of distribution.

[c]RSE, relative standard error.

using either data set exceeded 100%, so this parameter may not have been precisely estimated. K_a was larger in the external data set (1.1 h^{-1} versus 0.34 h^{-1}), and IIV for K_a was large (55% and 110%) for both data sets. This is likely due to the paucity of samples during the absorption phase in both data sets.

Pooled data analysis. Data from both studies were combined, and the results for the pooled data popPK model development are presented in the supplemental material only (Table S2).

TABLE 3 Parameter estimates and bootstrap analysis of the published POPS SMX model using the POPS and external data sets[a]

	POPS data			External data
Parameter[b]	Parameter value (% RSE)	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles	Parameter value (% RSE)[c]	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles
Minimization successful	Yes	959/1,000	No	502/1,000
Fixed effects				
K_a (h^{-1})	0.58 (44)	0.099 to 1.4		0.66 to 1.8
CL/*F* (liters/h)	1.5 (5.1)	1.3 to 1.8		1.0 to 6.0
V/*F* (liters)	24 (10)	6.4 to 28		20 to 28
PNA_{50} (yr)	0.12 (17)	0.051 to 0.19		3.8e−07 to 6.9e+5
PNA Hill	2.1 (57)	0.33 to 14		0.063 to 4.1
Albumin exponent	0.77 (34)	0.21 to 1.5		−3.9 to 0.26
Random effects				
IIV, CL (%)	36 (23)	8.9 to 53		16 to 37
ρ (CL − *V*)	0.68 (20)	−0.36 to 1.0		−1.0 to 1.0
IIV, *V* (%)	41 (21)	13 to 140		0.44 to 30
Proportional error (%)	47 (8.3)	36 to 54		15 to 21
Additive error (mg/liter)	0.071 (19)[d]	0.00071 to 0.50		3.2e−5 to 6.2

[a]The structural relationship is given by the following equations: $K_a\ (h^{-1}) = \theta_1$, $CL/F\,(\text{liters/h}) = \theta_2 \times (WT/70)^{0.75} \times \left[(PNA^{\theta_3})/(PNA^{\theta_3}+\theta_4{}^{\theta_3})\right] \times (3.4/\text{Albumin})^{-\theta_5}$, and $V/F\ (\text{liters}) = \theta_6 \times (WT/70)$, where θ is an estimated fixed effect, WT is actual body weight in kilograms, and PNA is postnatal age in years. POPS, Pediatric Opportunistic Pharmacokinetic Study; SMX, sulfamethoxazole.

[b]CL/*F*, apparent clearance; IIV, interindividual variability; K_a, absorption rate constant; PNA_{50}, maturation half-life calculated as a function of postnatal age (in years); PNA Hill, Hill coefficient in the maturation function; RSE, relative standard error; *V*/*F*, apparent volume of distribution.

[c]Minimization terminated with the full external data set.

[d]Different from the value for the publication by Autmizguine et al. (21), in which the authors neglected to calculate the square root of this variance estimate in order to transform it into concentration units.

TABLE 4 Parameter estimates and bootstrap analysis of the external SMX model developed from the current study using the POPS and external data sets[a]

Parameter	POPS data		External data	
	Parameter value (% RSE)	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles	Parameter value (% RSE)	Bootstrap analysis (n = 1,000), 2.5th–97.5th percentiles
Minimization successful	Yes	923/1,000	Yes	999/1,000
Fixed effects				
K_a (h^{-1})	0.34 (25)	0.16–0.60	1.1 (29)	0.66–3.2
CL/*F* (liters/h)	1.4 (5.0)	1.3–1.5	1.2 (6.9)	1.0–1.3
V/*F* (liters)	20 (8.5)	14–23	24 (7.7)	20–28
Random effects (%)				
IIV, K_a	110 (18)	41–260	55 (26)	0.55–160
IIV, CL	35 (20)	20–56	29 (17)	18–39
Proportional error	43 (10)	33–52	18 (7.8)	15–21

[a]The structural relationship is given as follows: K_a (h^{-1}) = θ_1, CL/*F* (liters/h) = $\theta_2 \times (WT/70)^{0.75}$, and *V*/*F* (liters) = $\theta_3 \times (WT/70)$, where θ is an estimated fixed effect and WT is actual body weight in kilograms. CL/*F*, apparent clearance; IIV, interindividual variability; K_a, absorption rate constant; POPS, Pediatric Opportunistic Pharmacokinetic Study; RSE, relative standard error; SMX, sulfamethoxazole; *V*/*F*, apparent volume.

Simulation-based evaluation of each model's predictive performance. The prediction-corrected visual predictive checks (pcVPCs) of each model–data set combination are presented in Fig. 3 for TMP and Fig. 4 for SMX. For both TMP and SMX, the median percentile of the concentrations over time was well captured within the 95% CI in three of the four model–data set combinations, while underprediction was more apparent when the POPS model was applied to the external data. The prediction interval based on the validation data set was larger than the prediction interval based on the model development data set for both the POPS and external models. For each drug, the observed 2.5th and 97.5th percentiles were captured within the 95% confidence interval of the corresponding prediction interval for each model and its corresponding model development data set pairs, but the POPS model underpredicted the 2.5th percentile in the external data set while the external model had a larger confidence interval for the 97.5th percentile in the POPS data set. The external data set was tightly clustered and had only 20 subjects, so that underprediction of the lower bound may reflect the lack of heterogeneity in the external data set rather than overprediction of the variability in the POPS model. For SMX, the POPS model had an observed 97.5th percentile higher than the 95% confidence interval of the corresponding prediction. The high observation was much higher than the rest of the data and appeared to be a singular observation, so overall, the SMX POPS model still appeared to be adequate for predicting variability in the majority of the subjects. Overall, both models appeared to be acceptable for use in predicting exposure.

Simulations using the POPS and external TMP popPK models. Dosing simulations showed that the external TMP model predicted higher exposure across all age groups (Fig. 5). For children below the age of 12 years, the dose that matched the area under the plasma concentration-versus-time curve in one dosing interval at steady state (AUC_{ss}) of adults taking the labeled dose of 160 mg every 12 h was 6 mg/kg every 12 h according to the POPS model and 4 mg/kg every 12 h according to the external model. In the cohort of individuals 12 to 18 years of age, most (88%) virtual subjects weighed 40 kg or more and received the standard adult dose of 160 mg every 12 h, so no difference between the dose levels was apparent. The POPS TMP model predicted slightly lower adult exposure than the literature adult AUC_{ss} range.

The proportion of subjects with concentrations above the MIC for more than half of the dosing interval at steady state is presented in Fig. S6. At each dose and MIC value, the external TMP model predicted a larger proportion than the POPS TMP model. At a MIC of 0.5 mg/liter, both models predicted that >90% of the virtual subjects in each age group achieved adequate time above the MIC at the labeled dose of 4 mg/kg every 12 h. However, when the MIC was increased to 1 mg/liter, only ≥41% based on the POPS model and ≥76% based on the external model had adequate exposure at 4 mg/kg every

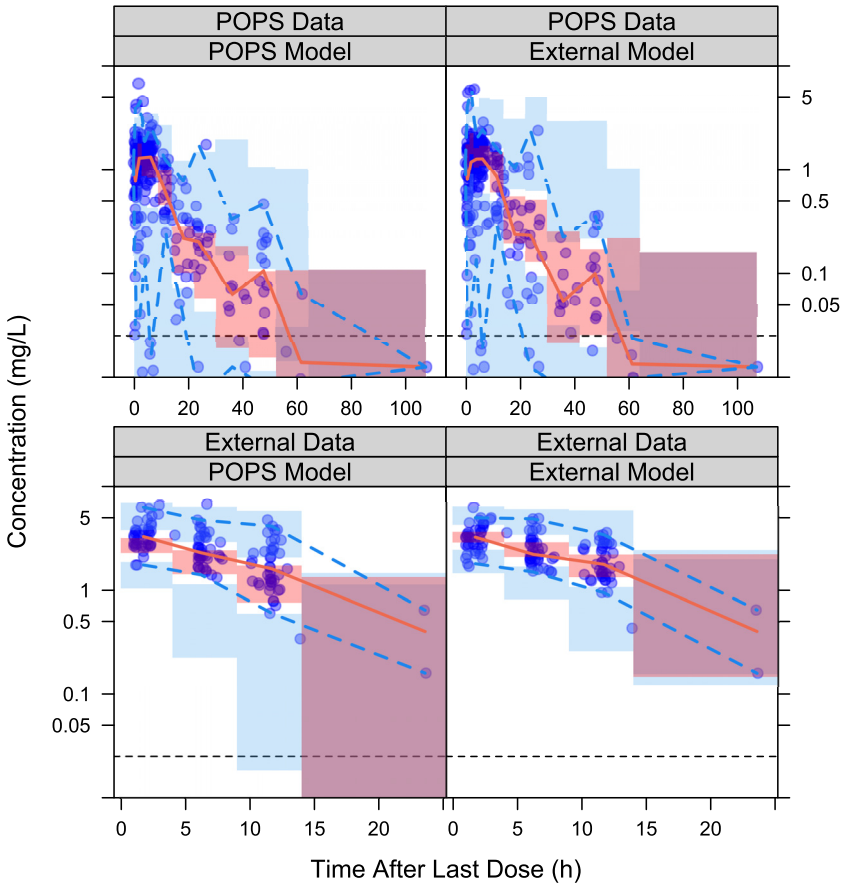

FIG 3 pcVPCs for each TMP model–data set combination. The red shaded region represents the simulated 95% prediction interval for the median; the solid red line represents the observed median; the blue region represents the simulated 95% prediction interval for the 2.5th and 97.5th percentiles; the dashed blue lines represent the observed 2.5th and 97.5th percentiles; and the horizontal dashed black line represents the lower limit of quantification.

12 h. In order for at least 90% of the subjects to achieve concentrations above 1 mg/liter for more than half of the dosing interval, the POPS model simulations suggested that a dose increase to 7.5 mg/kg every 12 h for infants and young children might be necessary. In the two cohorts above the age of 6 years, many subjects had doses capped at the adult dose of 160 mg every 12 h, which appeared to be subtherapeutic. In comparison, the external model suggested that a dose of 6 mg/kg every 12 h was likely adequate for all subjects, although only 88.6% of the virtual subjects in the adolescent cohort who predominantly received the adult dose of 160 mg every 12 h attained the specified target.

With WT-based dosing, the risk of supratherapeutic exposure is highest in the youngest cohort. The POPS TMP model predicts a minimal number of virtual subjects with an average simulated concentration at steady state ($C_{avg,ss}$) above 8 mg/liter at the tested doses of 4, 6, and 7.5 mg/kg every 12 h. The highest-risk cohort, 2-month-olds to <2-year-olds receiving a regimen of 7.5 mg/kg every 12 h, has 1.8% of subjects with $C_{avg,ss}$ of >8 mg/liter. In contrast, the external TMP model predicts that a substantial proportion of the youngest cohort has supratherapeutic exposures, with 4%, 16%, and 26% of virtual subjects in the 2-month-old to <2-year-old cohort receiving 4, 6, and 7.5 mg/kg every 12 h, respectively, having $C_{avg,ss}$ of >8 mg/liter.

DISCUSSION

This study is the first external evaluation of the initial popPK analysis of TMP-SMX administered by the oral route to infants and children (18). External evaluation

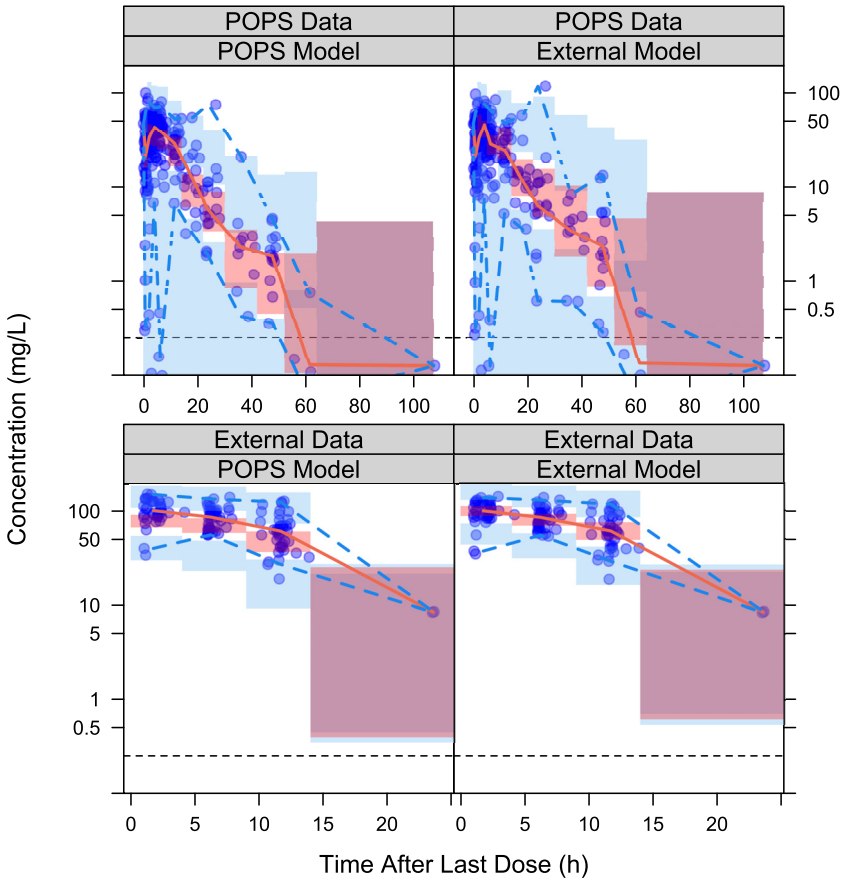

FIG 4 pcVPCs for each SMX model–data set combination. The red shaded region represents the simulated 95% prediction interval for the median; the solid red line represents the observed median; the blue region represents the simulated 95% prediction interval for the 2.5th and 97.5th percentiles; the dashed blue lines represent the observed 2.5th and 97.5th percentiles; and the horizontal dashed black line represents the lower limit of quantification.

elucidates the generalizability of the proposed model, which is important when the popPK model is used to assess exposure targets and make dosing recommendations, as with the POPS model. The newly collected external study data had much fewer subjects, though more samples per subject. In an exploratory analysis (results not shown), subjects with differing numbers of samples appeared to weigh equally in the parameter estimation, at least for a one-compartmental model. The decision was to emphasize the separate popPK model development and evaluation instead of the pooled data analysis, given that the more populous but sparse POPS study data strongly determine the outcome of the pooled model.

The independently developed external TMP model had a structure identical to that of the POPS TMP model. Therefore, the original model was reproducible with similar population estimates for the PK parameters. The external TMP model's maturation half-life, calculated as a function of postnatal age in years (PNA_{50}), was at nearly 1 year after birth (0.91 year), while the POPS TMP model had PNA_{50} at the age of ~3 months (0.24 year). The external model's PNA_{50} was likely overestimated, due to the lack of subjects below the age of 2.8 months in the external data set. Considering that TMP is mostly renally eliminated, the PNA E_{max} relationship likely described the effect of renal maturation on CL/*F*. Based on the work of Rhodin et al., 50% of the adult glomerular filtration rate is attained at a postmenstrual age (PMA) of 47.7 weeks, suggesting that the 3-month PNA_{50} estimate in the POPS TMP model has a stronger physiologic rationale (19). The inclusion of SCR as a covariate on CL/*F* further described the renal effect on TMP elimination. The exponent on the SCR was larger for the external TMP model

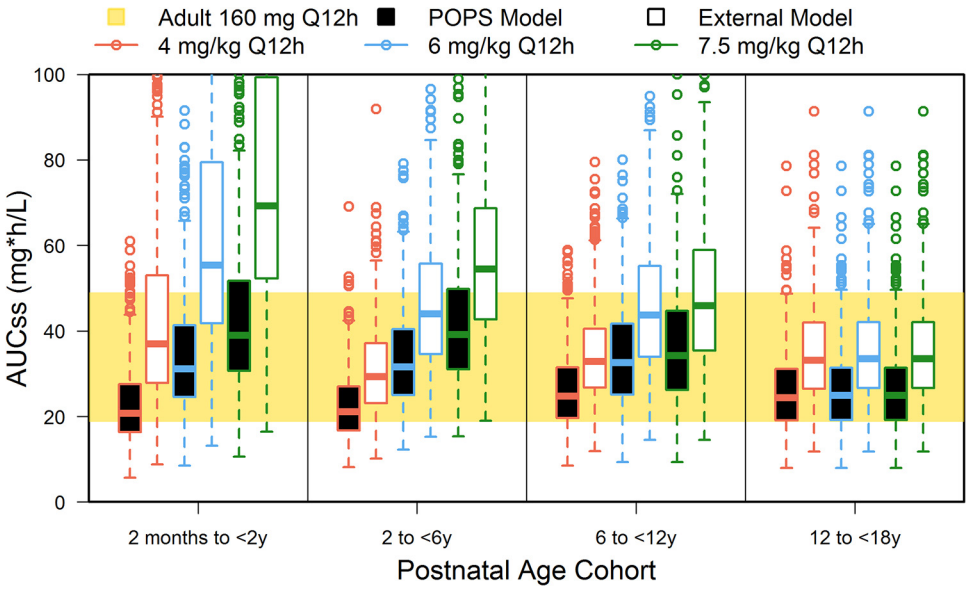

FIG 5 Box plots of the AUC_{ss} (area under the plasma concentration-versus-time curve in one dosing interval at steady state) for TMP in virtual children (2 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years of age) compared to the exposure of adults taking 160 mg every 12 h. The mean ± twice the standard deviation for AUC_{ss} in one 12-h dosing interval at steady state based on seven studies of adults aged 18 to 60 years without significant renal or hepatic impairment taking 160 mg of TMP every 12 h (Q12h) is plotted in yellow (8–10, 12–15).

(0.71) than for the POPS TMP model (0.40). For evaluating the exponent on the SCR, the external data set is limited by having renal impairment as an exclusion criterion, while the POPS data set included subjects with SCRs as high as 5.9 mg/dl. For subjects with normal SCR values, the two models predict similar effects of renal function on CL/*F*; for subjects with impaired renal function, the external TMP model predicts a more precipitous drop in CL/*F* than the POPS TMP model, and extrapolation of the external TMP model in these subjects may result in underprediction of TMP CL/*F*. Therefore, the covariate assessment based on the POPS TMP model may be more reliable.

In contrast, the external and POPS SMX models, though both one-compartment PK models, detected different covariate relationships and applied different residual error model structures. The POPS SMX model estimated a PNA_{50} of 0.12 year, which was less than the age of the youngest subject in the external data set. Assuming that the maturation effect in the POPS SMX model was accurate, the effect of age was expected to be negligible in the external data set, with the youngest two subjects most expected to be impacted, having only 20% and 3% decreases in CL/*F*. Given that TMP-SMX is usually contraindicated in pediatric patients below the age of 2 months due to the risk of kernicterus, the effect of age on clearance is unlikely to be relevant. The covariate effect of albumin was not assessed in external SMX model development, given that albumin data were not available from most subjects. The albumin level was also missing from nearly half of the subjects in the POPS study, and the imputation of missing albumin values based on age range could potentially confound the effects of age and albumin. For practical purposes, as well, it may be reasonable to exclude a covariate that is not routinely collected from patients. Although albumin may have an effect on protein binding and thus may affect the volume of distribution, SMX is only 70% protein bound, so alterations in albumin are expected to have limited clinical significance (27). While the independent external SMX model could not confirm the covariate relationships in the POPS SMX model, the difference likely reflected insufficient data in the external data set to evaluate the effects or overparameterization of the POPS model.

The bootstrap analysis of the POPS SMX model using either data set affirmed that the model was overparameterized, and the parameters were not precisely

estimated. The other models of the POPS TMP model, external TMP model, and external SMX model had better model stability and narrower CIs. In the PE and pcVPC analyses for both drugs, the external model predicted higher exposure than the POPS model, and the POPS model predicted a larger prediction interval for the concentration ranges. Given that the external data set was composed of only 20 subjects, the possibility that it did not include enough data to represent the variabilities in the target population cannot be ruled out. Since the subjects in the POPS data set received lower doses and had a substantial fraction of concentrations below the limit of quantification (BLQ) (~10% versus none in the external data set), it was also possible that the BLQ management choice in the POPS study (calculating the BLQ ceiling as the value of the lower limit of quantification divided by 2) biased the POPS model. However, this possibility was ruled out, because reestimation of both the POPS TMP and SMX models using the M3 method (which estimates the likelihood of a BLQ result at each measurement time) produced similar concentration predictions (results not shown), showing that the choice of BLQ management strategy was not important.

As in the previous publication, we focused the dosing simulation on the TMP component because the combination was available only in 1:5 fixed ratios, and the SMX concentration has not been correlated with efficacy or toxicity previously, since SMX has an active metabolite (21, 28). Simulations of the POPS and external TMP models at various dose levels were compared to adult steady-state exposure at 160 mg every 12 h, an exposure derived from several studies of healthy adults without apparent renal or hepatic impairment (8–10, 12–15). The external TMP model consistently predicted higher exposures than the POPS TMP model for all age cohorts. The most likely reason is that the external data set, being composed of only 20 subjects, does not capture the entire range of IIV in PK parameters. Based on the external TMP model, the original label dose of 4 mg/kg every 12 h was equivalent to the adult dose of 160 mg every 12 h, while the POPS TMP model implied that adolescents taking the adult dose had exposures at the lower end of the adult range.

Whether TMP-SMX exhibits time- or concentration-dependent antimicrobial killing has not been conclusively elucidated (29–32). A high maximum concentration was associated with increased rates of hematologic abnormalities, and dosing frequency was usually every 12 h, so the proportion of subjects with plasma drug concentrations above the MIC for >50% of the dosing interval at steady state was evaluated (33). For pathogens with a MIC of ≤0.5 mg/liter, the original label-recommended dose of 4 mg/kg every 12 h was appropriate based on either the POPS or the external TMP model. For pathogens with a MIC of 1 mg/liter, the POPS TMP model simulations suggested that the TMP dose must be increased to 7.5 mg/kg every 12 h, while the external TMP model suggested that a dose of 6 mg/kg every 12 h was appropriate. Therefore, both models implied that a dose increase was needed to counter increased resistance. On the other hand, the external TMP model had simulated concentrations that may suggest a greater risk of hematologic abnormalities (based on the use of a $C_{avg,ss}$ value of >8 mg/liter as an upper exposure threshold) in the 2-month-old to <2-year-old cohort receiving a dose of ≥6 mg/kg every 12 h. For these subjects, a more conservative dosing approach or more-frequent laboratory monitoring may need to be considered.

While this is the first external evaluation analysis performed for pediatric TMP-SMX popPK models, several limitations must be considered. First, the external data set included only 20 subjects, which is unlikely to be a representative distribution of all children. Second, as discussed above, the external data set had a narrower age range, a narrower SCR range, and insufficient information on albumin levels, which limited its usefulness at evaluating all covariate effects in the POPS model. The covariate effects in the POPS TMP model were robust enough to be detected in the external data set, but the covariate effects in the POPS SMX model could not be evaluated, due to insufficient information in the external data set. With these limitations, a difference in conclusions based on either data set was unsurprising, and the conclusion based on the larger POPS study was considered to be more reliable.

MATERIALS AND METHODS

Study design. Oral TMP-SMX PK data from two studies were available for analysis. Each study protocol was approved by the institutional review boards of participating institutions. Informed consent was obtained from the parent or guardian, and assent was obtained from the subject when appropriate. The first study is the Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) trial (ClinicalTrials.gov registration no. NCT01431326), a multicenter ($n = 16$), open-label, prospective observational PK and safety study of understudied drugs administered to children (<21 years of age) per standard of care. Exclusion criteria included failure to obtain consent/assent or known pregnancy. Dosing differed between subjects, and PK samples were sparsely and opportunistically collected. The POPS study design has been described previously (21).

The external data study (ClinicalTrials.gov registration no. NCT02475876) was a multicenter ($n = 3$), open-label, interventional PK and safety study in which children between a postmenstrual age (PMA) of 36 weeks and the age of 16 years received either TMP-SMX or clindamycin at the discretion of the treating clinicians. Patients already receiving TMP-SMX were also allowed to be enrolled. Exclusion criteria included failure to obtain consent or assent, known pregnancy or breastfeeding, history of allergic reactions to study drugs, serum creatinine levels of >2 mg/dl, alanine aminotransferase concentrations of >250 U/liter or aspartate transaminase concentrations of >500 U/liter, or extracorporeal membrane oxygenation support. The protocol-specified doses were 6 mg/kg (based on the TMP component) every 12 h for subjects between the ages of 2 months and 12 years and 4 mg/kg every 12 h for subjects >12 to 16 years of age. PK samples were collected at protocol-specified times, which were 1 to 3 h and 6 to 8 h after the 1st and 6th dose and <30 min before the 2nd, 6th, and 7th dose.

Study data. The POPS data set included 240 plasma samples from 153 patients. Among these samples, 26 (10.8% of the data) TMP concentrations and 19 (7.9%) SMX concentrations were BLQ. BLQ results that occurred at any time after the first dose were assigned a value of half the lower limit of quantification (LLOQ); 4 (1.7%) BLQ samples were collected before the first dose and treated as missing. The external data set included 121 plasma samples from 20 patients. None of the TMP or SMX concentrations was BLQ. One sample (0.8%) was suspected to be erroneous and was excluded from analysis because the TMP component indicated a trough level higher than the peak concentration.

The demographic characteristics, laboratory values, and dose information for each data set are presented in Table 1. Gestational age (GA) was collected for infants up to the age of ~4 months for the POPS study and 1 year for the external data study; missing values were set to 40 weeks. The POPS study imputed missing height as the 50th percentile value of height for WT and sex, and it imputed missing SCR from PNA using linear regression as described previously (21). In the POPS data set, missing albumin measurements were set to the median albumin value for the age group (2.80 g/dl for ≤30 days, 3.30 g/dl for 31 days to <2 years, 3.35 g/dl for 2 to <13 years, 3.40 g/dl for 13 to <16 years, and 3.55 g/dl for 16 to <21 years). In the external data set, missing albumin measurements were set to a median albumin value of 3.35 g/dl from the overall POPS data set. A covariate correlation matrix plot is shown in Fig. S7 in the supplemental material.

The plasma samples of both studies were quantified at a single central laboratory (OpAns, LLC, Durham, NC, USA) using validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS-MS) assays. The LLOQs were 0.025 mg/liter for TMP and 0.25 mg/liter for SMX. The analytical method has been described previously (21).

Population PK model development. The POPS TMP and SMX popPK models were derived previously (21). In the current study, popPK modeling conducted using the merged data set is presented in the supplemental material, and independent popPK modeling using the external data set was performed to derive the external popPK models for TMP and SMX. The popPK modeling development followed a typical workflow of nonlinear mixed-effect modeling in NONMEM (version 7.4.3; Icon Development Solutions, Ellicott City, MD, USA) and a stepwise covariate modeling search. First-order conditional estimation with eta-epsilon interaction and log-normally distributed IIV in the PK parameters were assumed. One-, two-, and three-compartment PK models with linear kinetics were tested for both TMP and SMX. The correlations between random-effect parameters (ρ) were tested for each IIV pair in the model. The residual errors were explored using additive, proportional, or combined additive-plus-proportional error models. Total body WT scaled to a standard 70-kg adult with fixed allometric exponents of 0.75 for CL/*F* and 1 for *V*/*F* was assumed *a priori* (34, 35). Alternate size descriptors, including estimating the allometric WT, body mass index, body surface area, ideal body WT, adjusted body WT, lean body mass (3 different equations), fat-free mass, and normal fat mass, were also explored. The equations for the different size descriptors are summarized in Table S3.

Available covariates were tested for model inclusion using automated stepwise covariate modeling in the Perl-speaks-NONMEM (PsN) tool kit (version 4.7.0; Uppsala Pharmacometrics, Uppsala, Sweden) with a forward inclusion criterion of a *P* value of <0.05 (change in objective function value, >3.8 points) and backward elimination at a *P* value of <0.01 (change in objective function value, >6.6 points). The covariates of GA, PNA, PMA, SCR, and sex were tested in all parameter-covariate pairs. GA was not correlated to PMA, because there were only a few infants in our data set. PNA and PMA were highly correlated, but both were tested, because each had been used in ontogeny functions.

The effect of race was not explored because the data set consisted of predominantly Caucasian subjects. The effect of albumin was not explored because the data set did not have a sufficient number of albumin measurements. The effect of height was generally not explored in pediatric popPK studies that included infants, because height cannot be measured reliably in this population. The relationships tested included equation 1 for categorical covariates and equations 2 to 5 for continuous covariates, where COV denotes a covariate, COV_{med} indicates the median covariate value, PAR_{COV} denotes the covariate effect on the parameter, θ is estimated, and θ_j denotes the θ for the *j*th unique categorical value.

$$\mathrm{PAR}_{\mathrm{COV},j} = \theta_j \quad (1)$$

$$\mathrm{PAR}_{\mathrm{COV}} = 1 + [\theta \times (\mathrm{COV} - \mathrm{COV}_{\mathrm{med}})] \quad (2)$$

$$\mathrm{PAR}_{\mathrm{COV}} = e^{\theta \times (\mathrm{COV} - \mathrm{COVmed})} \quad (3)$$

$$\mathrm{PAR}_{\mathrm{COV}} = (\mathrm{COV}/\mathrm{COV}_{\mathrm{med}})^{\theta} \quad (4)$$

$$\mathrm{PAR}_{\mathrm{COV}} = \mathrm{COV}/(\mathrm{COV} - \theta) \quad (5)$$

Given that the covariate search was performed using an automated approach, failed individual model runs were manually repeated, and the final model was assessed for physiological plausibility.

External model evaluations. Patient-level data sets from both the POPS and external studies were used to evaluate the POPS and external models. The stability of the parameter estimates and the predictive performance of the models were evaluated in multiple ways. First, the parameters in each of the models were fixed to evaluate the goodness-of-fit plots, which included the population prediction (PRED) versus observation, CWRES versus time after last dose, and CWRES versus PRED. Then the improvement in prediction error (PE) and the relative root mean-square error (rRMSE) were computed using equations 6 and 7, respectively:

$$\mathrm{PE}_i = \mathrm{Predicted}_i - \mathrm{Observed}_i \quad (6)$$

$$\mathrm{rRMSE} = \sqrt{\frac{1}{N}\sum_{1}^{i}\frac{(\mathrm{Predicted}_i - \mathrm{Observed}_i)^2}{[(\mathrm{Predicted}_i + \mathrm{Observed}_i)/2]^2}} \times 100\% \quad (7)$$

where *i* represents the *i*th observation.

The parameter estimates of each model were reestimated using each data set and were bootstrapped 1,000 times using PsN to determine the 95% CI. The pcVPCs based on 1,000 simulations for each model and data set combination were generated using PsN.

Dosing simulations. Four virtual pediatric populations with 500 subjects each were created in the software R for the age groups of 2 months to <2 years, 2 to <6 years, 6 to <12 years, and 12 to <18 years. Equal probability of male and female gender, as well as a uniform distribution for PNA, was assumed. The distribution of GAs was based on the most recent U.S. birth data at the time of analysis (36). WT was based on age- and sex-appropriate growth charts, which included the Fenton preterm growth chart for infants up to a PMA of 51 weeks, the World Health Organization growth chart for infants up to the age of 2 years, and the Centers for Disease Control and Prevention growth chart for children 2 years old and older (37–39). Age- and sex-appropriate serum creatinine values were simulated for each virtual subject (40). The simulated distributions of covariates are shown in Fig. S8 to S13.

Exposure was simulated based on the TMP component for both the POPS and the external TMP model. Simulation was conducted for doses of 4, 6, and 7.5 mg/kg of TMP every 12 h, with the maximum dose capped at the adult dose of 160 mg TMP every 12 h (21). Simulation results were assessed by (i) the percentage of subjects with free TMP concentrations above the MICs of relevant bacteria (*Streptococcus pneumoniae*, *Escherichia coli*, and community-acquired methicillin-resistant *S. aureus* [CA-MRSA]) for >50% of the dosing interval at steady state, assuming an unbound fraction of 56% (6); and (ii) AUC_{ss} compared to the exposure of adults taking 160 mg of TMP every 12 h (6, 21). The adult exposure was assessed from seven studies of adults aged 18 to 60 years without significant renal or hepatic impairment taking 160 mg of TMP every 12 h (8–10, 12–15).

Pooled data set analysis. PopPK model development was also conducted with the pooled data set combining the POPS and external studies. The results are presented in the supplemental material (final model in Table S2; goodness of fit in Fig. S14).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.

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