POPULATION PHARMACOKINETICS OF TRIMETHOPRIM-SULFAMETHOXAZOLE IN INFANTS AND CHILDREN

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Pediatric Trials Network
Leading the Way

Eunice Kennedy Shriver National Institute of Child Health and Human Development

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Disclosures

- Nothing to disclose

TMP/SMX is recommended for CA-MRSA infections in children[1,2]

- Pharmacokinetics (PK)
  - Elimination pathways undergo maturation during childhood
  - TMP and SMX PK are poorly described in infants and children
- Pharmacodynamics (PD)
  - Dosing based on TMP[3]: activity is time dependent
  - 90% of CA-MRSA have minimum inhibitory concentration (MIC) ≤0.5 mg/L[4]
- TMP/SMX has no FDA-approval for CA-MRSA treatment
  - vs clindamycin indicated for CA-MRSA treatment

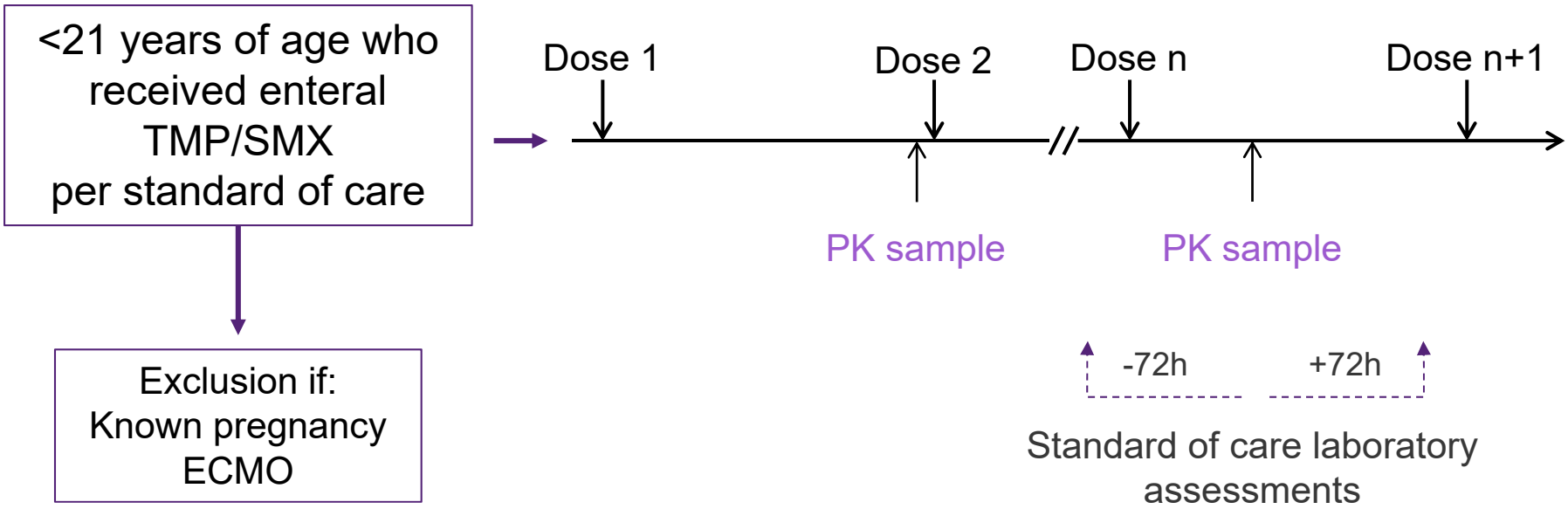
TMP/SMX: trimethoprim/sulfamethoxazole
CA-MRSA: community acquired methicillin-resistant *S. aureus*
[1]Liu CID 2011 ; [2]Miller NEJM 2015 ; [3]Joos AAC 1995; [4]Mendes AAC 2010

Objective

- Develop a population pharmacokinetic (PopPK) model for TMP and SMX in children <21 years of age

- Perform dose-exposure simulations to assess optimal TMP/SMX dosing for CA-MRSA in infants and children

Methods – POPS trial
Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care



[1]NCT01431326

Methods

- Development of separate TMP and SMX population PK models
  - Nonlinear mixed effect modeling (NONMEM v.7.2)
  - Population estimates and inter-individual variability
    - Absorption rate constant (KA)
    - Volume of distribution (V/F)
    - Clearance of elimination (CL/F)
  - Covariate selection: forward inclusion ($p<0.05$) and backward elimination ($p<0.01$) approach

- TMP dosing-exposure simulations
  - Surrogate PD target for efficacy: steady-state, free TMP concentration above the MIC (0.5 mg/L) at 50% of the dosing interval

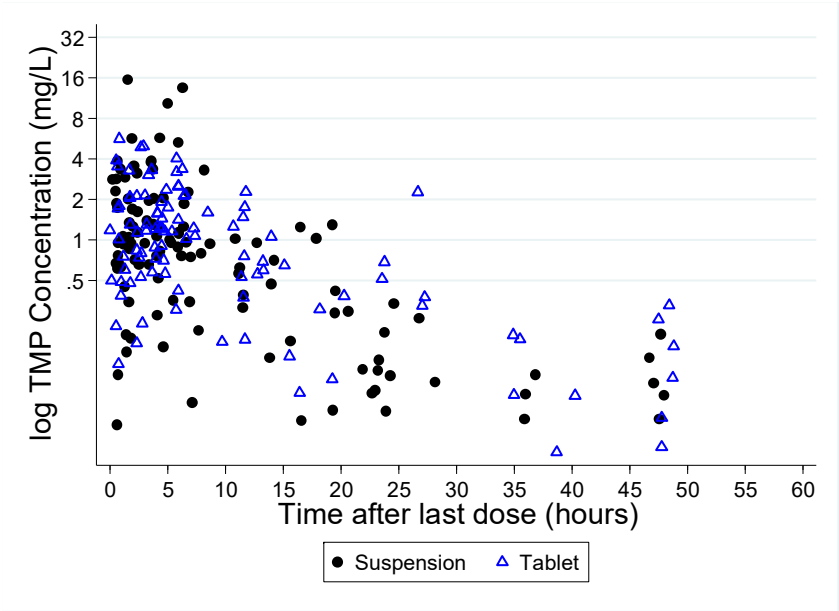
Results - 153 children contributed 240 PK samples

	Median (range)*
Age (years)	7.9 (0.1, 20.2)
Male, n (%)	82 (54%)
Weight (kg)	30.8 (2.4-147.9)
Serum creatinine (mg/dL)	0.5 (0.1-5.9)
Albumin (g/dL)	3.4 (1.7-4.8)
Obese, n (%)	53 (35%)
TMP/SMX formulation, n (%)	
Suspension	78 (51%)
Tablets	75 (49%)
Route of drug administration, n (%)	
Oral	125 (82%)
Gastrostomy	17 (11%)
Others	11 (7%)
Daily dose (mg/kg/day)	
TMP	4.6 (0.5-12.1)
SMX	23.0 (2.5-120.5)

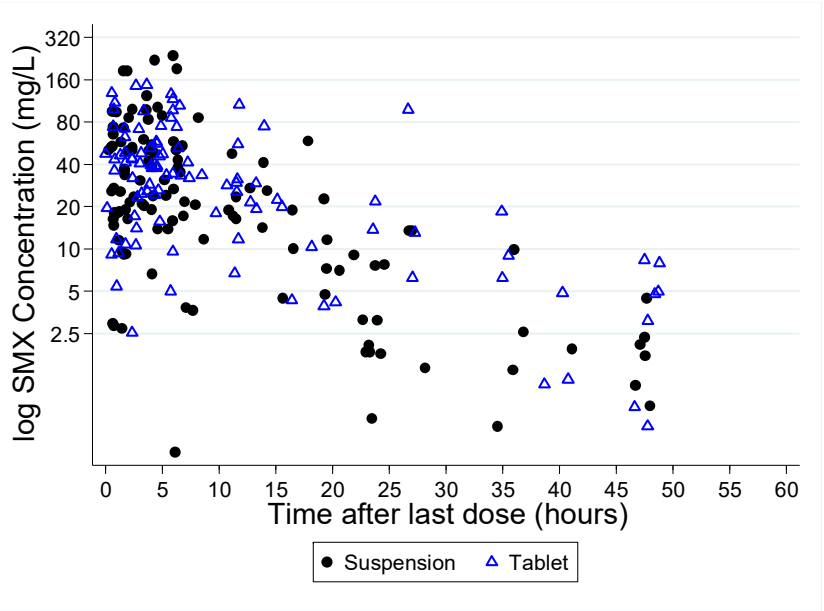
*otherwise specified

Observed concentrations vs. time after last dose

TMP



SMX



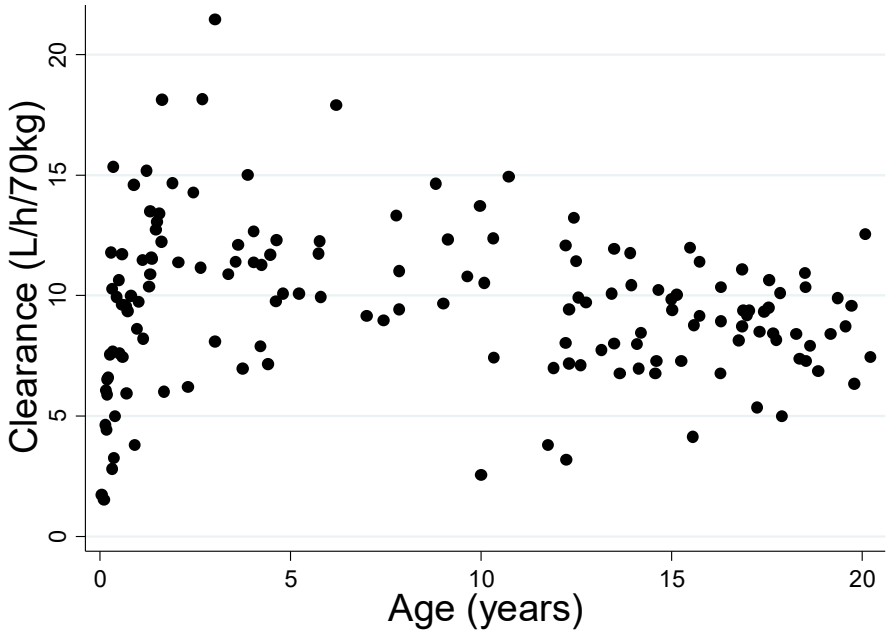
Population PK models

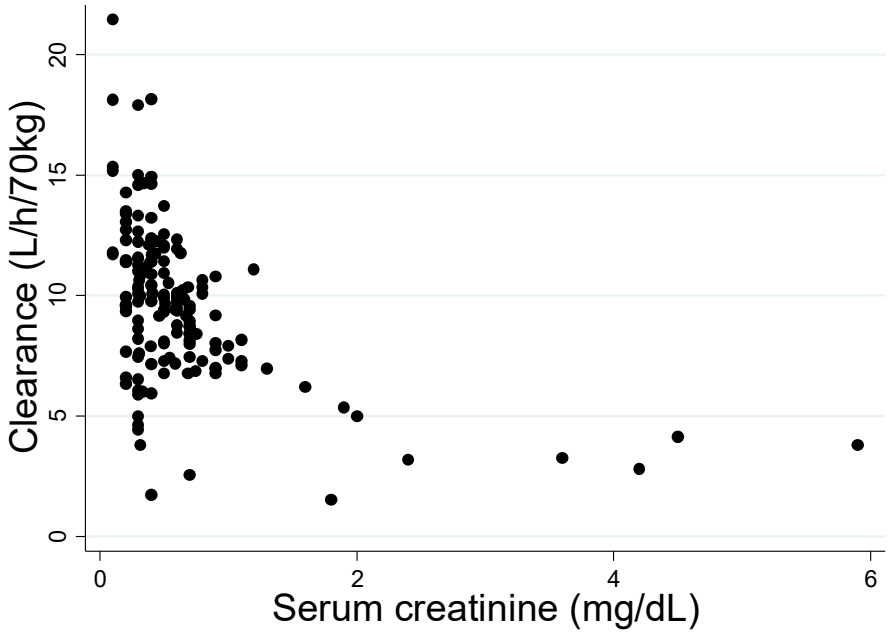
- One-compartment model with first-order absorption

	TMP		SMX	
Parameters	**Estimate (RSE)**	**Covariates**	**Estimate**	**Covariates (RSE)**
K_A (h^{-1})	1.27 (35.8)	-	0.58 (43.9)	-
CL/F_{70kg} (L/h)	10.0 (5.5)	Weight, Age Serum creatinine	1.46 (5.1)	Weight, Age Albumin
V/F_{70kg} (L)	148 (6.8)	Weight	24 (10.0)	Weight
IIV CL/F (%)	33.8 (36.8)	-	35.9 (46.2)	-
IIV V/F (%)	20.6 (89.2)	-	40.6 (41.1)	-
Residual error Proportional (%) Additive (mg/L)	 51.1 (14.4) -	 - -	 46.9 (16.7) 5.1 (38.0)	 - -

RSE: relative standard error (%); IIV: inter-individual variability

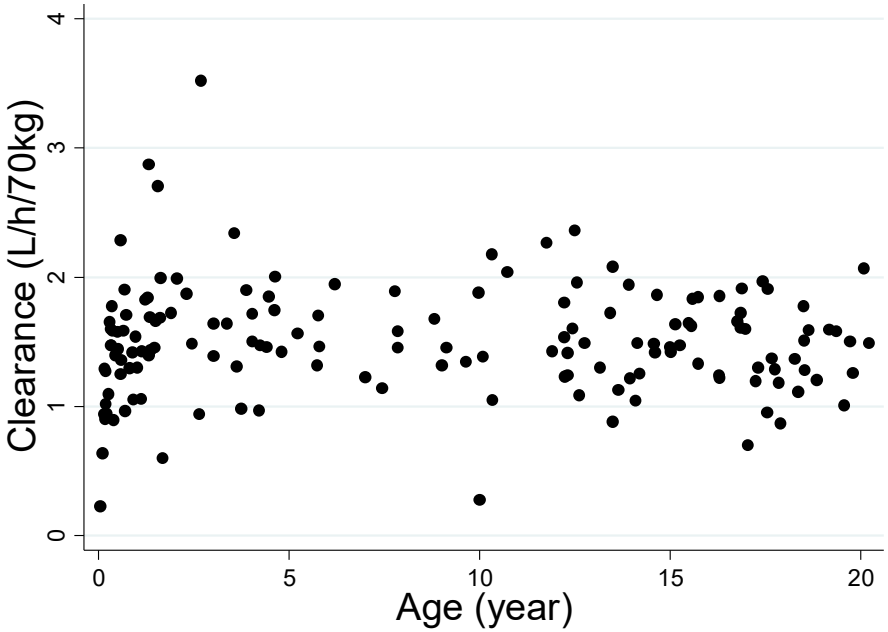
TMP clearance is correlated with age and serum creatinine

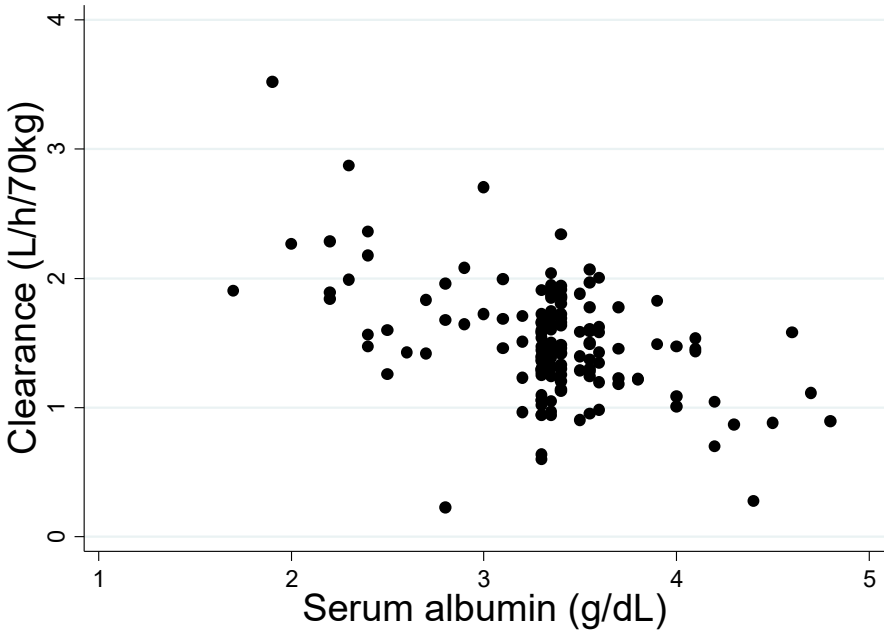




Maturation half-life (TM_{50})
13 weeks of age

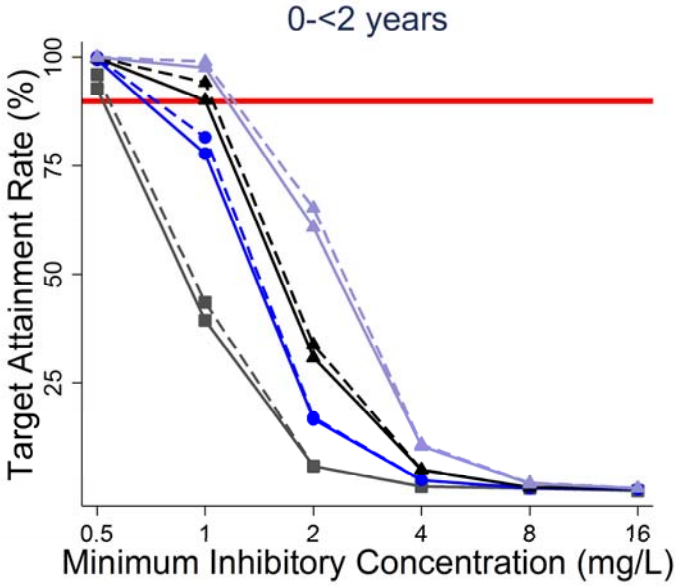
SMX clearance is correlated with age and albumin

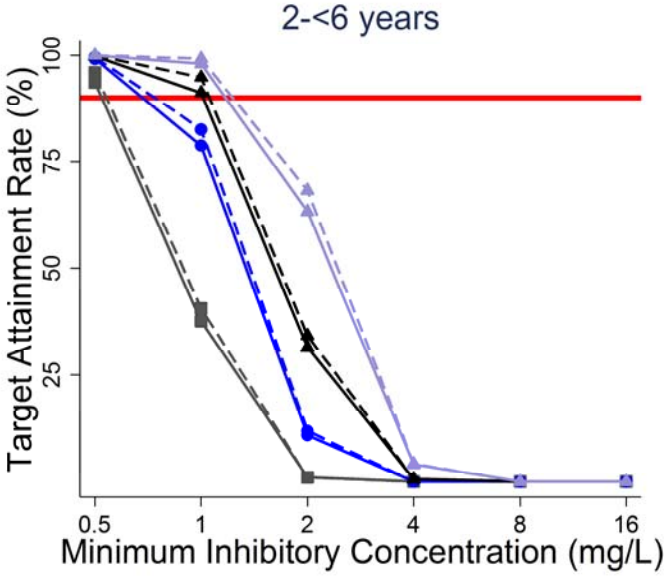


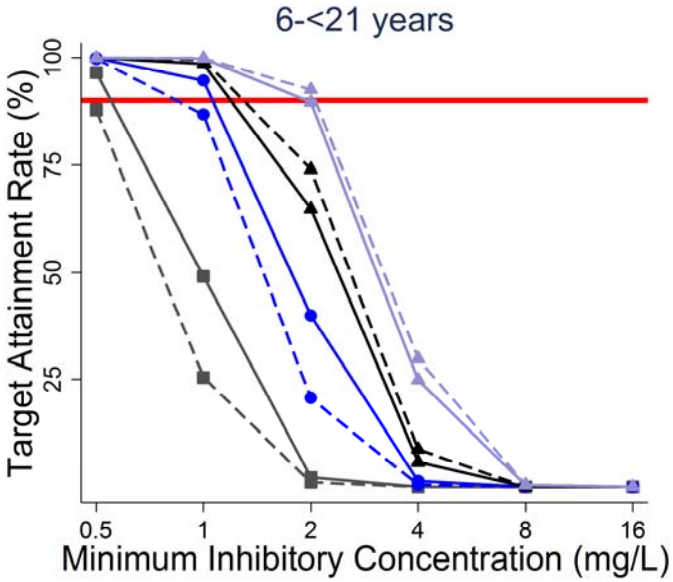


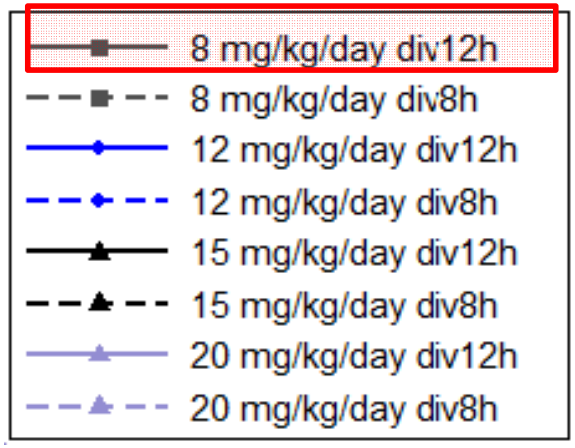
Maturation half-life (TM_{50})
6 weeks of age

TMP dose-exposure simulations









Discussion

- Limitations
  - Opportunistic design, sparse sampling
  - No safety assessment

- Efficacy and safety of oral TMP/SMX 8/40 mg/kg/day divided every 12h was similar to oral clindamycin for uncomplicated skin infections in children[1]

[1]Miller NEJM 2015

Conclusions

- TMP and SMX apparent enteral CL increased with weight and age
- TMP and SMX apparent enteral CL were inversely related with serum creatinine and albumin, respectively
- In line with Infectious Diseases Society of America (IDSA) recommendations, a TMP/SMX weight-based dosing of 8/40 mg/kg/day divided every 12h would be optimal for term infants and children with CA-MRSA

[1]Liu CID 2011

Acknowledgement

- We thank the principal investigators, research teams, and patients in their support of the POPS study.

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James, Laura	Little Rock	AR
Laughon, Matthew	Chapel Hill	NC
Bizzarro, Matthew	New Haven	CT

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Additional slides

	Median (range)
Age (years)	7.9 (0.1, 20.2)
Weight (kg)	30.8 (2.4-147.9)
Serum creatinine (mg/dL)	0.5 (0.1-5.9)
Albumin (g/dL)	3.4 (1.7-4.8)
Male	82 (54%)
Race	
White	109 (71%)
Black	29 (19%)
Unknown	3 (2%)
Others	12 (8%)
Ethnicity	
Hispanic	26 (17%)
Not Hispanic	123 (80%)
Unknown	4 (3%)
Obese	53 (35%)
Drug formulation	
Oral suspension	78 (51%)
Tablets	75 (49%)
Route of drug administration	
Oral	125 (82%)
Gastrostomy	17 (11%)
Others	11 (7%)

46 (30%) <=2y

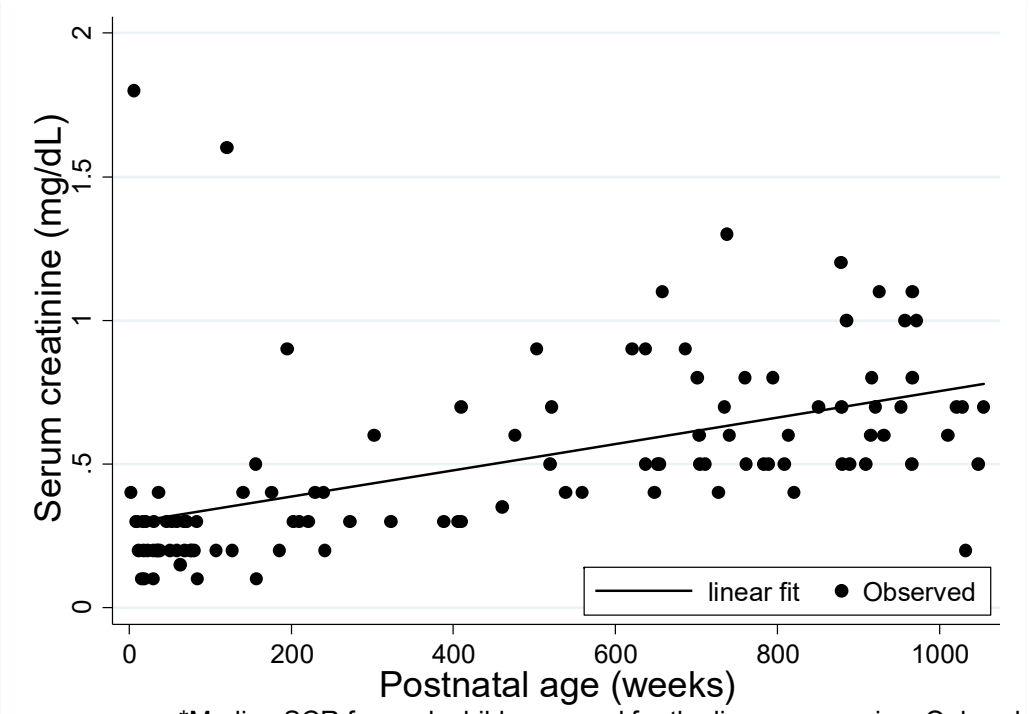
10 (7%) were ≤120 days of age
GA: 38 (32-39)

Population PK models

- TMP
  - K_A (h^{-1}) =1.27
  - CL/F (L/h) = $10.0*(Weight/70)^{0.75}*(PNA^{1}/(0.24^{1}+PNA^{1}))*((0.5/SCR)^{0.40})$
  - V/F (L) = 148*(Weight/70)
- SMX
  - K_A (h^{-1}) = 0.58
  - CL/F (L/h) = $1.46*(Weight/70)^{0.75}*(PNA^{2.13}/(0.12^{2.13}+PNA^{2.13}))*(ALB/3.4)^{-0.77}$
  - V/F (L) = 24*(Weight/70)

Serum creatinine and Age relationship

Supplementary Fig S1. SCR level* vs. PNA in weeks



*Median SCR for each child was used for the linear regression. Only subjects with SCR <1.8 mg/dL were included in the regression.

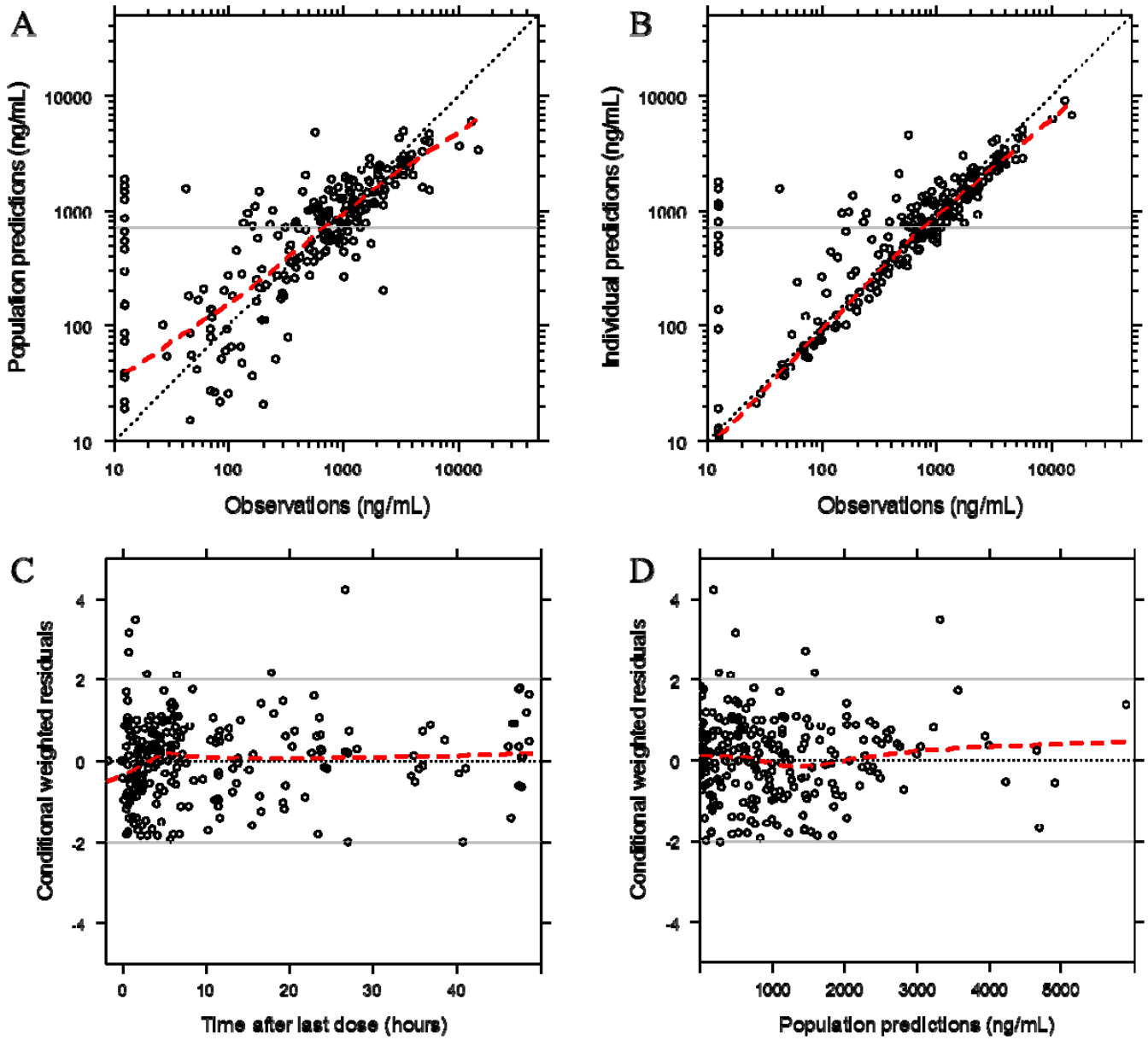
Population TMP PK parameter estimates for the final model

	Final Model		Bootstrap (n=1,000)*		
Parameter	Estimate	RSE (%)	2.5th percentile	Median	97.5th percentile
K_A	1.27	35.8	0.6	1.3	2.4
CL/F_{70KG} (L/H)	10.0	5.5	8.8	9.9	11.0
V/F_{70KG} (L)	148	6.8	129	148	173
TM_{50} (years)	0.24	24.8	0.14	0.24	0.40
HILL	1 FIXED	-	-	-	-
Exponent for SCR effect on CL/F	0.40	20.4	0.26	0.41	0.57
IIV (CL/F, %)	33.8	36.8	10.0	31.6	44.7
IIV (V/F, %)	20.6	89.2	4.7	22.3	50.1
Proportional Error (%)	51.1	14.4	42.3	50.0	57.6

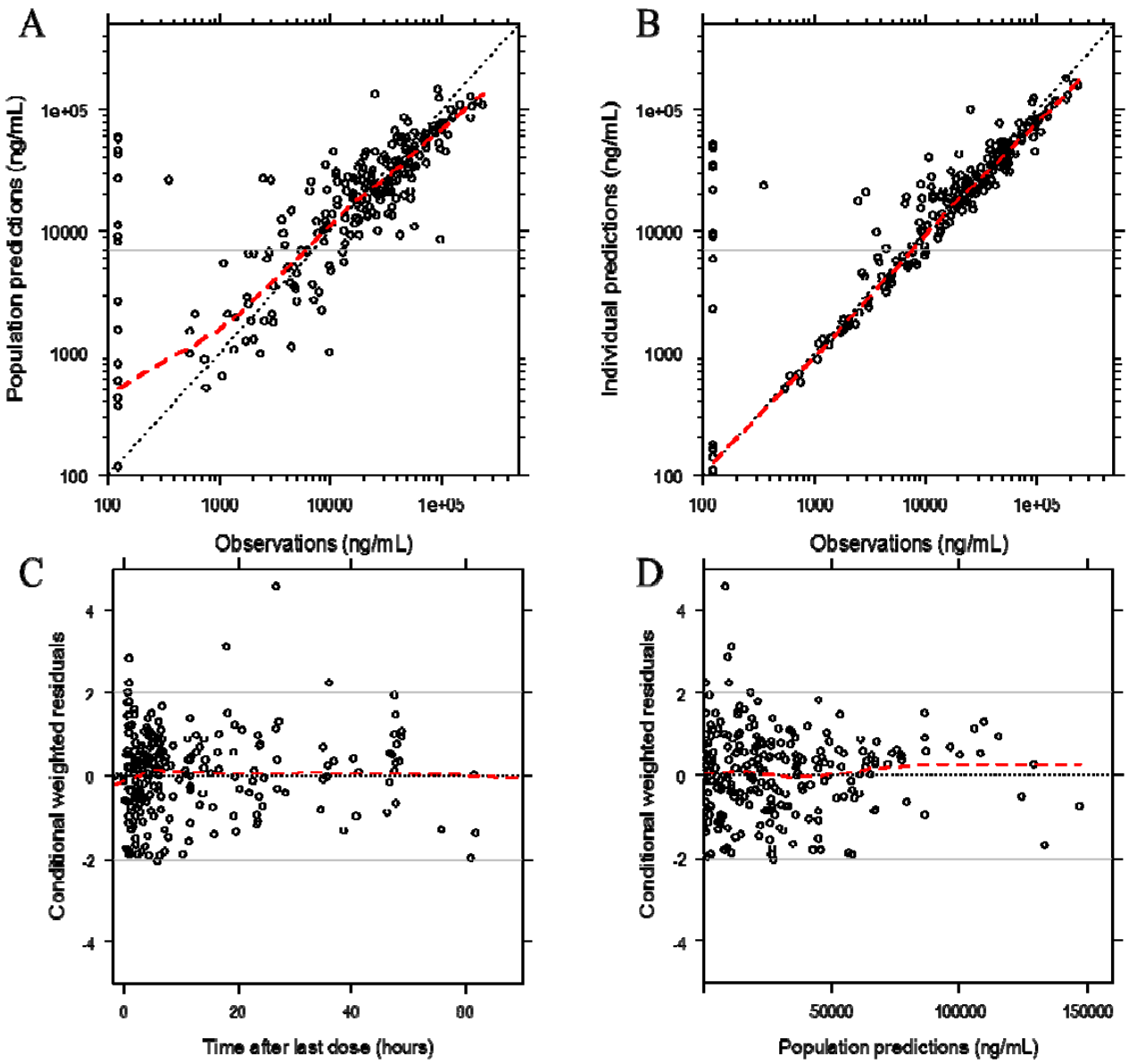
Population SMX PK parameter estimates for the final model

	Final Model		Bootstrap (n=1,000)		
Parameter	Estimate	RSE (%)	2.5th percentile	Median	97.5th percentile
K_A	0.58	43.9	0.1	0.6	1.3
CL/F_{70KG} (L/H)	1.46	5.1	1.30	1.45	1.76
V/F_{70KG} (L)	24	10.0	6	23	29
TM_{50} (years)	0.12	16.4	0.05	0.13	0.17
HILL	2.13	59.6	0.3	2.3	11.4
Exponent for ALB effect on CL/F	-0.77	34	-1.5	-0.76	-0.20
IIV (CL/F, %)	35.9	46.2	9.2	33.2	51.3
IIV (V/F, %)	40.6	41.1	18.3	39.6	114.1
ρ (CL/F-V/F)	0.1	56.7	-0.1	0.1	0.3
Proportional Error, (%)	46.9	16.7	34.7	45.8	53.4
Additive error (mg/L)	5.1	38.0	1.8	5.5	322

TMP

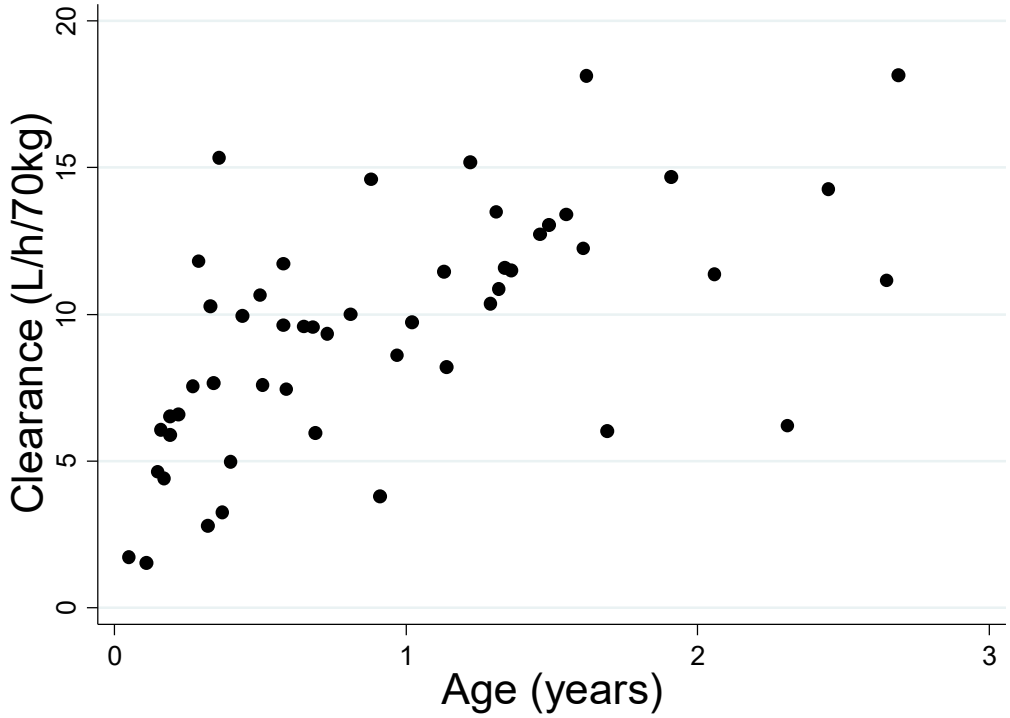

A
Population predictions (ng/mL)
10000
1000
100
10
10
100
1000
10000
Observations (ng/mL)
B
Individual predictions (ng/mL)
10000
1000
100
10
10
100
1000
10000
Observations (ng/mL)
C
Conditional weighted residuals
4
2
0
-2
-4
0
10
20
30
40
Time after last dose (hours)
D
Conditional weighted residuals
4
2
0
-2
-4
1000
2000
3000
4000
5000
Population predictions (ng/mL)

SMX


A
Population predictions (ng/mL)
Observations (ng/mL)
B
Individual predictions (ng/mL)
Observations (ng/mL)
C
Conditional weighted residuals
Time after last dose (hours)
D
Conditional weighted residuals
Population predictions (ng/mL)

	Parameters	Estimate	Covariates	Relative standard error (%)
TMP	K_A (h^{-1})	1.27	-	35.8
	CL/F_{70kg} (L/h)	10.0	Weight, Age, Serum creatinine	5.5
	V/F_{70kg} (L)	148	Weight	6.8
	IIV CL/F (%)	33.8	-	36.8
	IIV V/F (%)	20.6	-	89.2
	Residual error Proportional	51.1%	-	14.4
SMX	K_A (h^{-1})	0.58	-	43.9
	CL/F_{70kg} (L/h)	1.46	Weight, Age, Albumin	5.1
	V/F_{70kg} (L)	24	Weight	10.0
	IIV CL/F (%)	35.9	-	46.2
	IIV V/F (%)	40.6	-	41.1
	Residual error Proportional Additive	46.9% 5.1 mg/L	-	16.7 38.0

TMP



SMX