New amoxicillin-clavulanate dispersible tablets in children: a population pharmacokinetic analysis

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Background and Objectives

Background **Amoxicillin** alone **or in combination with clavulanate (co-amoxiclav)** is the most widely prescribed antibiotic in paediatric infectious disease:

- The 2022 WHO AWaRe Book provides weight band dosing for co-amoxiclav for children currently using the syrup formulation.[1]
- In 2023, the co-amoxiclav dispersible tablet formulation was added to the WHO essential medicines list for children.[2]

Yet oral pharmacokinetic (PK) data of these drugs remains limited.

Study The PediCAP trial (ISRCTN63115131) is an open-label randomised controlled trial evaluating amoxicillin and different ratios of co-amoxiclav dispersible tablets in severe childhood community acquired pneumonia (CAP).

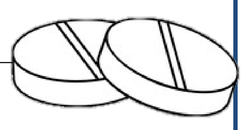
Objectives We developed a population PK model of a new dispersible tablet formulation of 4:1, 7:1, and 14:1 co-amoxiclav (provided by Sandoz) in African children enrolled in the PediCAP trial.

Methods

PediCAP recruited Mozambican, South African, Ugandan, Zambian, and Zimbabwean children between 2 months and 6 years old hospitalized with severe CAP. All children received at least 24 hours of intravenous antibiotic treatment prior to switching to twice-daily oral co-amoxiclav dispersible tablets (Table 1).

Table 1: PediCAP twice-daily co-amoxiclav dose regimens.

Dispersible tablet ratio	Weight band (kg)	Daily dose (mg)
Co-amoxiclav 7:1 200/28.5 mg	< 6	400/57
	6 - <10	800/114
	10 - <14	1000/142.5
	14 - <20	1600/228
	20 - <25	2000/285
Co-amoxiclav 4:1 250/62.5 mg	< 6	500/125
	6 - <10	750/188
	10 - <14	1000/250
	14 - <20	1500/375
	20 - <25	2000/500
Co-amoxiclav 14:1 150/10.725 mg	< 6	450/32.2
	6 - <10	850/53.6
	10 - <14	1000/75.1
	14 - <20	1600/139
	20 - <25	2000/172



Five blood samples were obtained over a six-hour period immediately prior to and following administration of dispersible co-amoxiclav. Amoxicillin and clavulanate were quantified by HPLC-MS/MS with a limit of detection (LOD) 0.05 ug/mL and 0.005 ug/mL, respectively. Data below the LOD were treated as censored data and incorporated in the likelihood function (M3 method).

Nonlinear mixed effects modelling was conducted in NONMEM (v.7.5.1) with FOCE-I parameter estimation. Statistical and graphical analysis was performed in R (v.4.3.1).

Conclusions

We adequately described the PK of oral amoxicillin and clavulanate with a two-compartment lagged absorption model. Implementation of D1 absorption removed flip-flop behavior and stabilized the model.

We included a maturation function on clearance and estimated a steep hill coefficient for amoxicillin and clavulanate compared to the 2.68 hill coefficent previously reported for amoxicillin[3], which requires further investigation.

The current study is ongoing, and we are awaiting further data from the PediCAP trial for confirmation of results which will enable testing of clavulanate dose linearity**. The final model of the PediCAP study can inform future WHO guidance on weight-based dosing for co-amoxiclav dispersible tablet formulations in children.**

References

1. The World Health Organization (WHO), *The WHO AWaRe (Access, Watch, Reserve) antibiotic book*. Geneva, 2022.
2. Barker, C. I. S. *et al*. The Neonatal and Paediatric Pharmacokinetics of Antimicrobials study (NAPPA): investigating amoxicillin, benzylpenicillin, flucloxacillin and piperacillin pharmacokinetics from birth to adolescence. *Journal of Antimicrobial* Chemotherapy, 2023.
3. 'Web Annex B. WHO EMLc - 9th List, 2023', in *The selection and use of essential medicines 2023: Executive summary of the report of the 24th WHO Expert Committee on the Selection and Use of Essential Medicines*, Geneva: World Health Organization, 2023.

Acknowledgements

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A list of all members of the PediCAP consortium can be found on https://projectpedicap.org/

EDCTP

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Results

Table 2: Participant characteristics

Characteristic	Overall	Formulation		
		7:1	4:1	14:1
	N = 82	n = 43	n = 17	n = 22
Median (range):				
Postnatal age (months)	12 (2 – 61)	13 (2 – 61)	10 (4 – 49)	8 (2 – 42)
Total body weight (kg)	9.8 (4.1 - 22)	9.8 (4.1 – 22.0)	8.0 (4.0 – 11.7)	7.2 (4.3 – 13.0)
Weight-for-age z-score	-1.12 (-5.1 – 1.97)	-0.60 (-5.08 – 1.07)	-1.82 (-5.61 – 0.94)	-1.41 (-3.80 – 0.27)
No. (%)				
Males	47 (57)	24 (56)	13 (76)	10 (45)

Table 3: Model parameters

	Amoxicillin				Clavulanate			
Parameter	Typical value	95%CI	Variability (%CV)	95%CI	Typical value	95%CI	Variability (%CV)	95%CI
CL/F (L/h) †	10.2	9.73-10.7	BSV: 14.4	12.6-16.0	5.03	4.02-7.68	BSV: 18.8	12.5-23.1
Vc/F (L) †	12.5	11.9-13.5			5.72	4.90-8.98		
ka (h^{-1})	1.04	0.952-1.14	BOV: 61.0	53.1-61.5	1.42	1.08-1.80	BOV: 37.3	22.2-43.0
D1 (h)	1.04	0.995-1.10	BOV: 51.7	40.3-51.9	0.321	0.0943-0.379	BOV: 97.8	72.6-182
Lag (h)	-				0.210	0.160-0.335	BOV: 69.2	47.8-93.4
F (.)	1 FIX		BOV: 37.6	36.3-42.3	1 FIX		BOV: 74.0	36.4-84.4
Vp/F (L) †	2.07	1.92-2.27			0.131	0.0657-0.211		
Q/F (L/h) †	0.342	0.320-0.393			0.313	0.232-0.716		
Hill coefficient (.)	9.05	9.05-9.70			10.5	4.95-11.5		
PMA_{50} (weeks)	47.8	46.4-48.3			44.4	44.3-48.7		
Prop error (%)	16.1	14.4-17.8			13.4	10.4-20.8		
Add error (mg/L)	0.103	0.084-0.103			0.0087	0.0049-0.0145		

† Allometrically scaled for an 8 kg individual

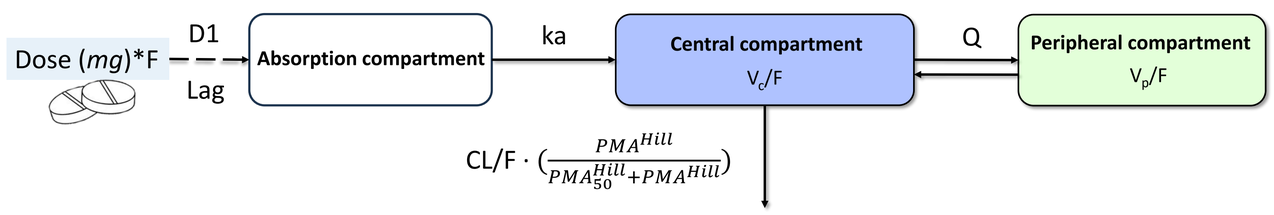

Figure 1: Structural diagram

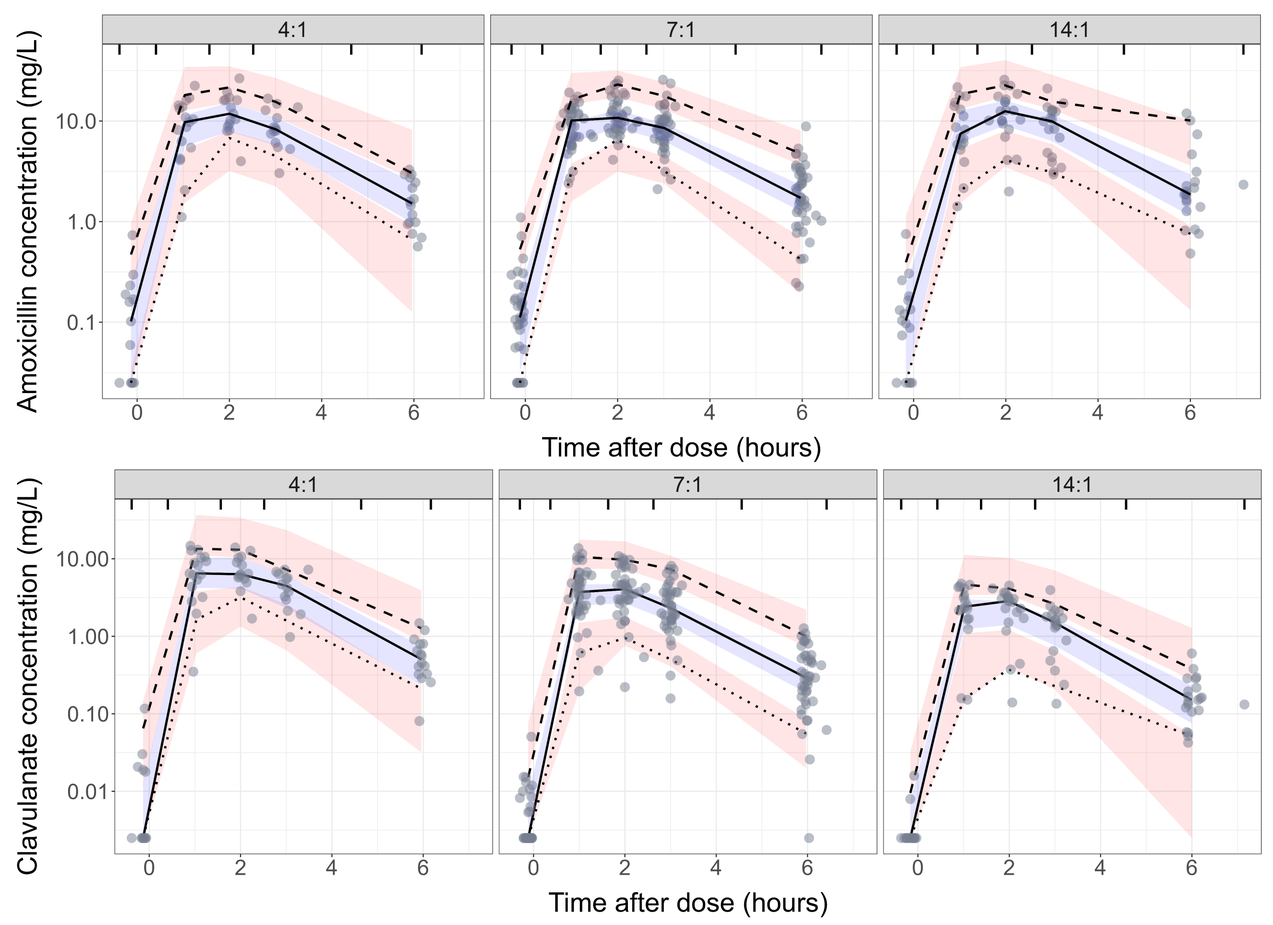

Figure 2: Visual predictive check

The visual predictive check for amoxicillin (top) and clavulanate (bottom) are displayed. Solid circles represent observed data. The solid, dotted, and dashed lines represent the 50th, 5th, and 95th percentiles of observed data. The shaded areas represent the model-predicted 95% confidence intervals for the same percentiles.

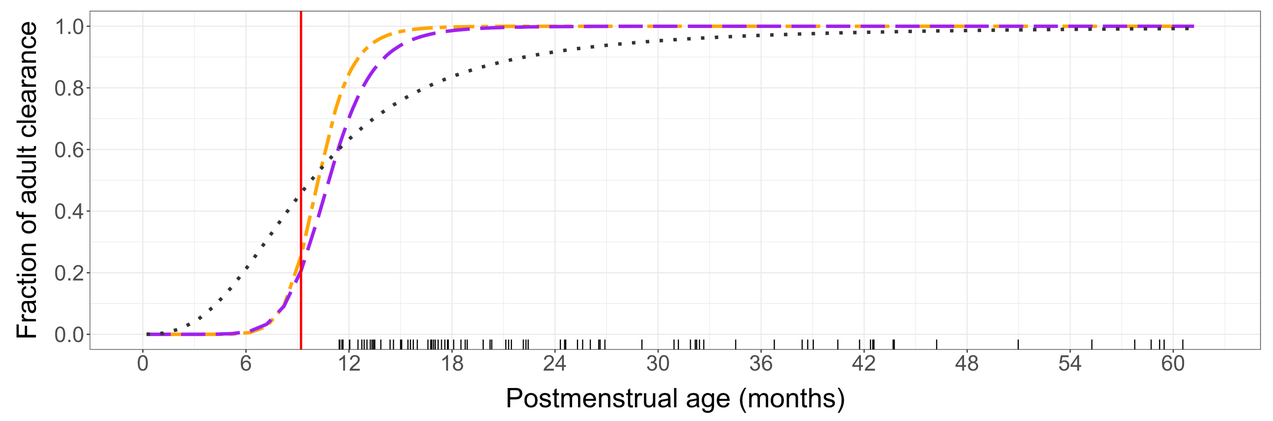

Figure 3: Maturation function on clearance

The estimated maturation function of amoxicillin (purple, dashed) and clavulanate (orange, two-dash) clearance from our model is plotted alongside the estimated maturation function of amoxicillin clearance from the Barker *et al.* model[2] (black, dotted). Grass on the x axis represents observed ages from our dataset.