PK/PD modeling of amoxicillin/clavulanic acid *in vitro* effects on bacterial growth and killing and in vivo exposure evaluation in young pediatric patients

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INTRODUCTION

- ✓Amoxicillin/clavulanic acid is currently the most effective antimicrobial for the treatment of children with acute otitis media or recurrent acute otitis media.
- ✓Augmentin ES-600®, an amoxicillin/clavulanic acid (45/3.2 mg/kg) formulation approved by the FDA for pediatric use, is known to cause potentially troublesome diarrhea, which may delay the return of children to daycare and the return of parents to work.
- ✓A lower dose of clavulanic acid than currently used may be associated with fewer side effects without compromising clinical efficacy.

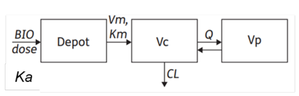
This study employed a model-informed approach to estimate amoxicillin/clavulanic acid exposure in middle ear fluid (MEF) to evaluate the validity of a reduced clavulanic acid dose based on *in vitro* exposure-response (E-R) data.

MATERIALS & METHODS

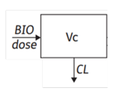
Final pediatric population PK model structure and parameters

- ✓ Previously developed and qualified pediatric population PK models[1] for oral amoxicillin/clavulanic acid were employed using NONMEM to simulate drug exposures in plasma and MEF for the reduced amoxicillin/clavulanic acid doses (45/1.425 mg/kg) administered every 12 hours.

Final amoxicillin PK model structure



Final clavulanic acid PK model structure



Volume of Distribution (V):

$$V_{pediatric} = V_{adult} \times \left(\frac{BW}{70}\right)$$

Clearance (CL):

$$CL_{pediatric} = CL_{adult} \times \left(\frac{BW}{70}\right)^{0.75} \times F_{mat}$$

Maturation effect (F_{mat})

$$F_{mat} = \left(\frac{PMA^{Hill}}{TM50^{Hill} + PMA^{Hill}}\right)$$

Amoxicillin

PK parameter	Population mean	IIV (%)
Vc (L/70 kg)	25.2	34.4
Vp (L/70 kg)	2.75	-
CL (L/h/70kg)	19.8	25.8
Q (L/h/70kg)	1.58	-
BIO	0.53	35.1
Vmax (mg/h)	1220	31.9
Km (mg)	287	98.7
Ka (h^{-1})	0.46	-
Hill	4.29	-
TM50 (weeks)	49.0	-

Vc, distribution volume of the central compartment
Vp, distribution volume of the peripheral compartment
CL, clearance
Q, inter-compartment clearance

Clavulanic acid

PK parameter	Population mean	IIV (%)
Vc (L/70 kg)	30.4	23.9
CL (L/h/70kg)	22.7	26.7
BIO	0.64	40.0
Ka (h^{-1})	0.75	52.8
Hill	3.4	-
TM50 (weeks)	47.7	-

BIO, bioavailability
Vmax, maximum absorption rate
Km, amount corresponding to 50% Vm
Ka, absorption rate constant
Hill, slop of the maturation profile
TM50, postmenstrual age at which 50% of the maturation effect is reached

[1] Fukushima K, et al. *Clin Pharmacol Ther*, 113(2), 762-7 (2023).

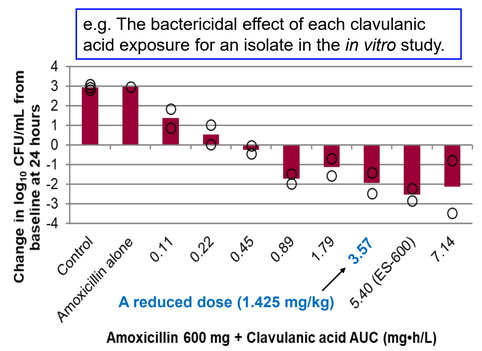
Generation of a virtual population

- ✓ A virtual pediatric population (age range of **3-24 months**) was generated for simulations using publicly available data from the National Health and Nutrition Examination Survey (NHANES) database.

In vitro infection model

- ✓ Bacterial killing data from *in vitro* infection experiments were available for exposure-response evaluation [2].
- ✓ Challenge organisms were exposed to amoxicillin and clavulanic acid with various exposure levels designed to simulate MEF concentration-time profiles in pediatric patients.
- ✓ Relationships between *in vitro* observed changes in log10 CFU/mL at 24 h from baseline and the exposure were evaluated.

[2] VanScoy BD, et al. *Antimicrob Agents Chemother*, 64(6), e02265-19 (2020).



PK model-informed simulation and E-R analysis

- ✓ Drug concentrations in MEF were determined based on plasma concentrations with the penetration ratio of amoxicillin from plasma to MEF (**36.9%** as listed in the ES-600® package insert).
- ✓ E-R analysis was performed using *in vitro* bacterial growth and killing data against five different isolates of ***Haemophilus influenzae*** to determine effective AUC/MIC metrics to be compared with the simulated amoxicillin/clavulanic acid exposures in MEF.

RESULTS & DISCUSSIONS

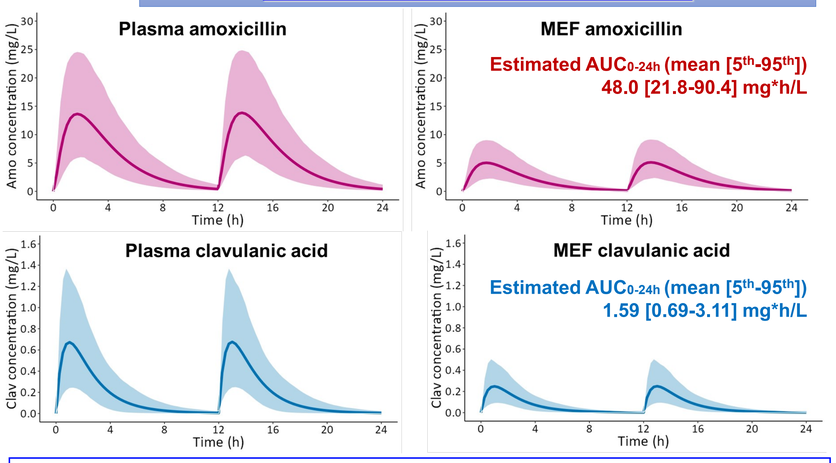


Figure 1 PK model-informed simulation of plasma and MEF concentration-time profiles.
Line: mean predicted concentration; Shaped area: 5-95th prediction intervals of predicted concentrations.

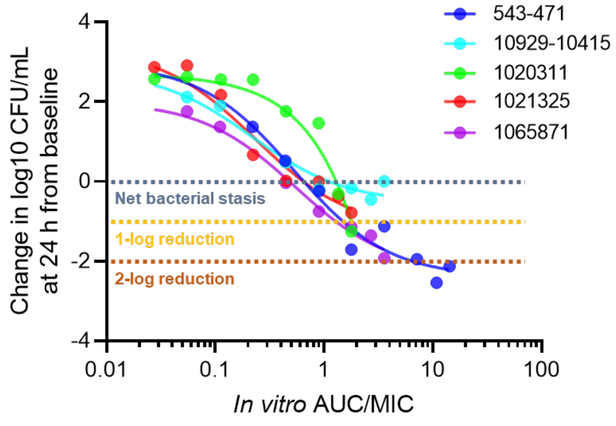
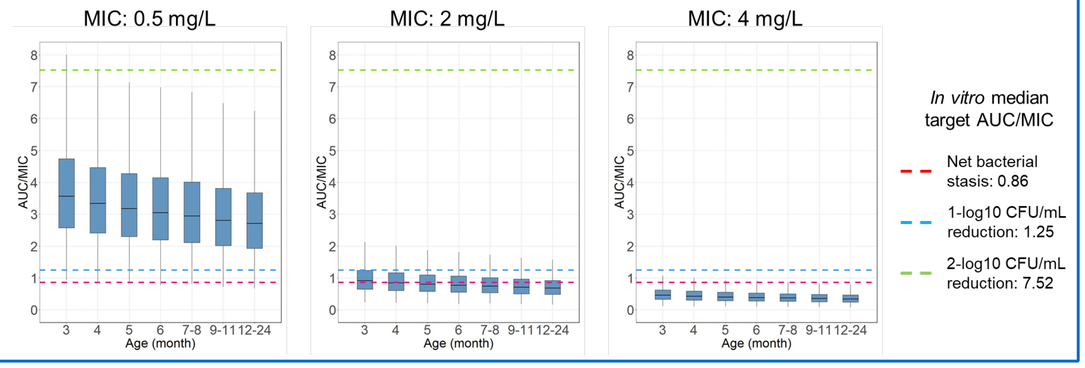


Figure 2 E-R analysis for five *Haemophilus influenzae* isolates.
The nonlinear regression line was obtained by exposure-response analysis using GraphPad Prism 8.

Table 1 Summary of the results of E-R analysis.
Amoxicillin MIC when treated at amoxicillin: clavulanic acid ratio of 2:1.

No.	*H. influenzae*		AUC/MIC			
		MIC* (mg/L)	Net bacterial stasis	1-log10 CFU/mL reduction	2-log10 CFU/mL reduction	PK model simulated mean
1	543-471	0.5	0.90	1.78	10.8	3.18
2	10929-10415	2	0.90	-	-	0.80
3	1065871	2	1.35	1.79	-	0.80
4	1021325	4	0.89	-	-	0.40
5	1020311	4	0.45	1.79	-	0.40

Figure 3 Age-dependent MEF clavulanic acid exposure predicted by model-informed simulation (3-24 months).



- ✓The model-informed simulations provided both plasma and MEF concentration-time profiles for amoxicillin /clavulanic acid **(Figure 1)**.
- ✓With *in vitro* E-R analyses, the mean $AUC_{0\text{-}24h}$/MIC ratios for achieving net bacterial stasis and 1- and 2-log 10 CFU/mL reduction were determined as 0.90, 1.79, and 10.8, respectively **(Figure 2)**.
- ✓The simulated mean $AUC_{0\text{-}24}$ exceeds the *in vitro* $AUC_{0\text{-}24}$/MIC to achieve net bacterial stasis and 1-log 10 CFU/mL reduction against *Haemophilus influenzae* 543-471 (MIC: 0.5 mg/L) **(Table 1)**.
- ✓The median $AUC_{0\text{-}24h}$ for reduced clavulanic acid (1.425 mg/kg) still exceeds the $AUC_{0\text{-}24}$/MIC needed to achieve net bacterial stasis and 1-log 10 CFU/mL reduction against *Haemophilus influenzae* 543-471 in the age range of 3-24 months **(Figure 3)**.

Conclusion

The combination of model-informed simulations and E-R analyses indicates that the reduced clavulanic acid dose could provide effective drug exposure in MEF while mitigating the risk of adverse events.

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Conflict of Interest/Disclosure
Presenter ： Ryota Tanaka

K.D. is an employee of Kaizen Bioscience.
T.M., C.P.,, and A.A.V are consultants with NDA Partners LLC.
Other authors declare no conflicts of interest.