



Semi-mechanistic pharmacodynamics modeling of aztreonam- avibactam combination to understand its antimicrobial activity against multidrug-resistant Gram(-) bacteria

Alexia Chauzy, Bruna Gaelzer Silva Torres, Julien Buyck, Boudewijn Jonge,
Christophe Adier, Sandrine Marchand, William Couet, Nicolas Grégoire

► To cite this version:

Alexia Chauzy, Bruna Gaelzer Silva Torres, Julien Buyck, Boudewijn Jonge, Christophe Adier, et al.. Semi-mechanistic pharmacodynamics modeling of aztreonam- avibactam combination to understand its antimicrobial activity against multidrug-resistant Gram(-) bacteria. PAGE meeting, Jun 2019, Stockholm, Sweden. hal-02528382

HAL Id: hal-02528382

<https://hal.science/hal-02528382>

Submitted on 1 Apr 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Semi-mechanistic pharmacodynamics modeling of aztreonam-avibactam combination to understand its antimicrobial activity against multidrug-resistant Gram(-) bacteria

Chauzy A.^{1,2}, Torres BGS.^{1,2}, Buyck J.^{1,2}, de Jonge BLM.⁴, Adier C.^{1,3}, Marchand S.^{1,2,3}, Couet W.^{1,2,3}, Grégoire N.^{1,2}

¹INSERM U-1070, Poitiers, France; ²University of Poitiers, France; ³Laboratoire de Toxicologie-Pharmacocinétique, CHU de Poitiers, France; ⁴Pfizer Essential Health, Cambridge, USA

INTRODUCTION

- Aztreonam-avibactam (ATM-AVI) is a combination, currently in development by Pfizer, intended to treat serious infections caused by multi-drug resistant (MDR) pathogens including those producing metallo- β -lactamases (MBLs).
- Sy et al.¹ developed a semi-mechanistic PD model for ATM-AVI combination in which 3 effects for AVI were characterized : inhibition of ATM degradation; intrinsic bactericidal effect and enhancement of ATM bactericidal activity.
- The aims of this study were to apply this PD model for 4 additional MDR strains with different β -lactamase profiles, including isolates of other species, and to investigate the individual contribution of each of the 3 AVI PD effects.

METHODS

- 4 MDR *Enterobacteriaceae* strains (1 *E. coli*, 1 *C. freundii* and 2 *E. cloacae*) expressing MBLs and other β -lactamases were evaluated in *in vitro* static time-kill studies using wide concentration ranges of ATM and AVI alone and in combination.
- A common structural model with 2 sub-populations, slightly different from the one developed by Sy et al., was applied for all strains using NONMEM 7.4² (Fig 1).
- ✓ The proportion of pre-existing resistant bacteria was determined by plating the initial inoculum onto agar plates supplemented with ATM-AVI and used to define the initial conditions of S and R.
- ✓ ATM degradation by β -lactamases was taken into account by measuring the actual concentrations of ATM by LC-MS/MS and was modeled depending on the bacteria density (S+R) according to an exponential function, and AVI concentration according to a fractional inhibitory Emax model (**inhibitory effect**).
- ✓ ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations, according to a sigmoidal Emax model with a higher EC₅₀ for the resistant state explaining regrowth. Whereas **AVI bactericidal effect**, characterized by a sigmoidal Emax model, was incorporated in the model only for the susceptible subpopulation.
- ✓ The **enhancement of ATM bactericidal activity by AVI** was modeled as a decrease of ATM EC₅₀ with increasing AVI concentrations using a bi-exponential function:

$$EC_{50,ATM} = A \exp^{-\alpha AVI} + B \exp^{-\beta AVI}$$

Where A and B (μ g/mL) are model constants that added together correspond to the ATM EC₅₀ value when AVI concentration is zero; α and β (mL/ μ g) are exponential constants that describe the relationship between AVI concentration and ATM potency.

- Final model was used to simulate the 3 AVI effects separately in order to evaluate the impact of each effect at clinical ATM and AVI concentrations (C_{avg} = 25 and 4.5 μ g/mL respectively, corresponding to a dosing regimen of 2g and 0.5g q8h in human^{3,4}).
- The maximum effect of the combination was defined as the difference between the AUBC⁵ of the control (AUBC_{control}) and the AUBC when all effects (ATM effect + the 3 AVI effects) were taken into account (AUBC_{full}). The percentage of the maximum effect induced by each AVI effect was then calculated, as follow:

$$\% \text{ maximum effect} = \frac{(AUBC_{\text{control}} - AUBC_i)}{(AUBC_{\text{control}} - AUBC_{\text{full}})} \times 100$$

Where i corresponded to the AVI effect considered.

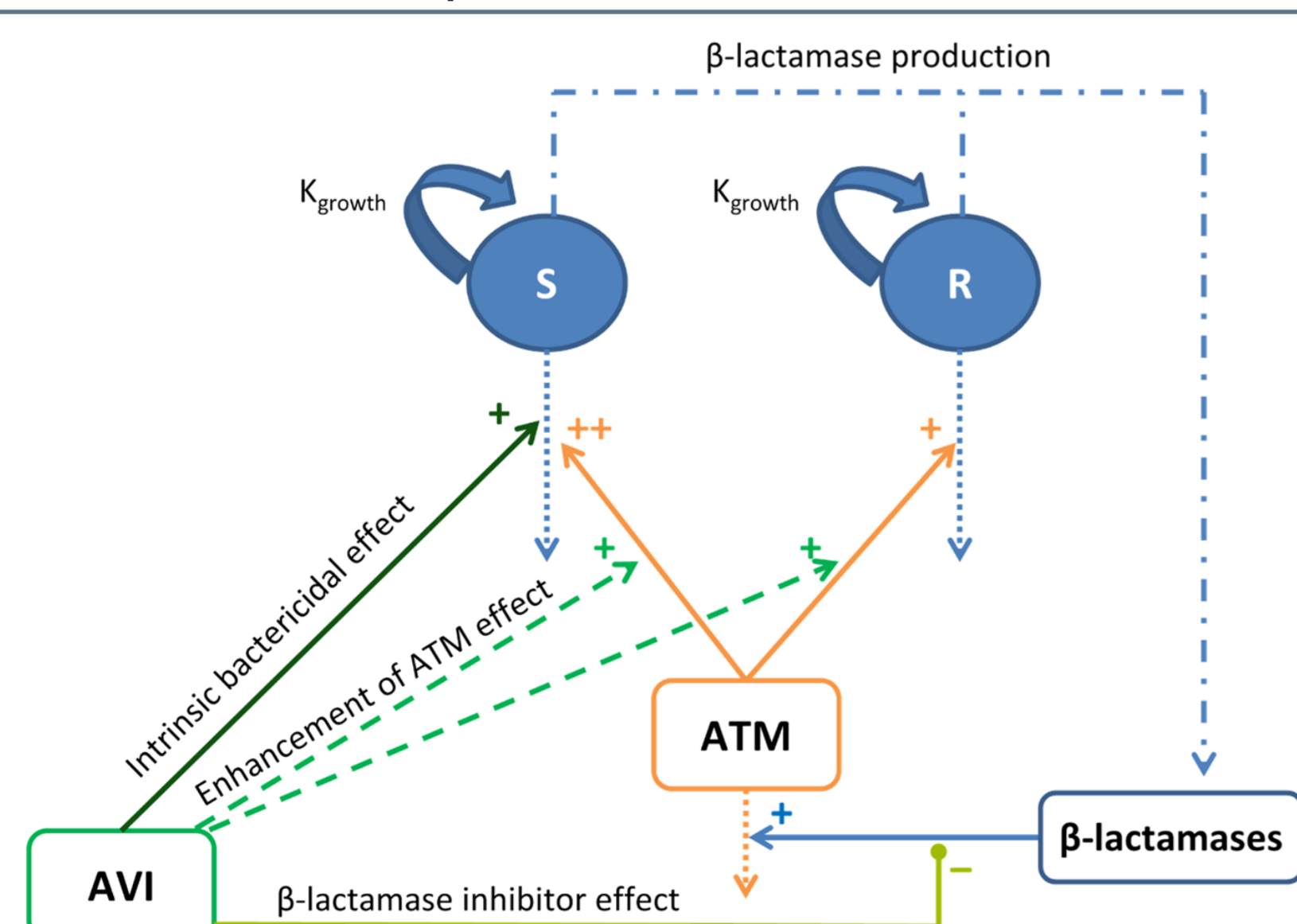


Fig 1. PD model for ATM-AVI effect on drug-susceptible (S) and resistant (R) bacteria.

RESULTS

- The PD model succeeded in capturing the bacterial growth, regrowth and killing kinetics and ATM degradation profiles for all strains as shown in Fig 2, using *E. cloacae* 1318536 as an example.
- No ATM degradation, even in the absence of AVI, was observed for *E. coli* 1266865. Thus, for this strain, only the bactericidal and the enhancing effects of AVI could be characterized.

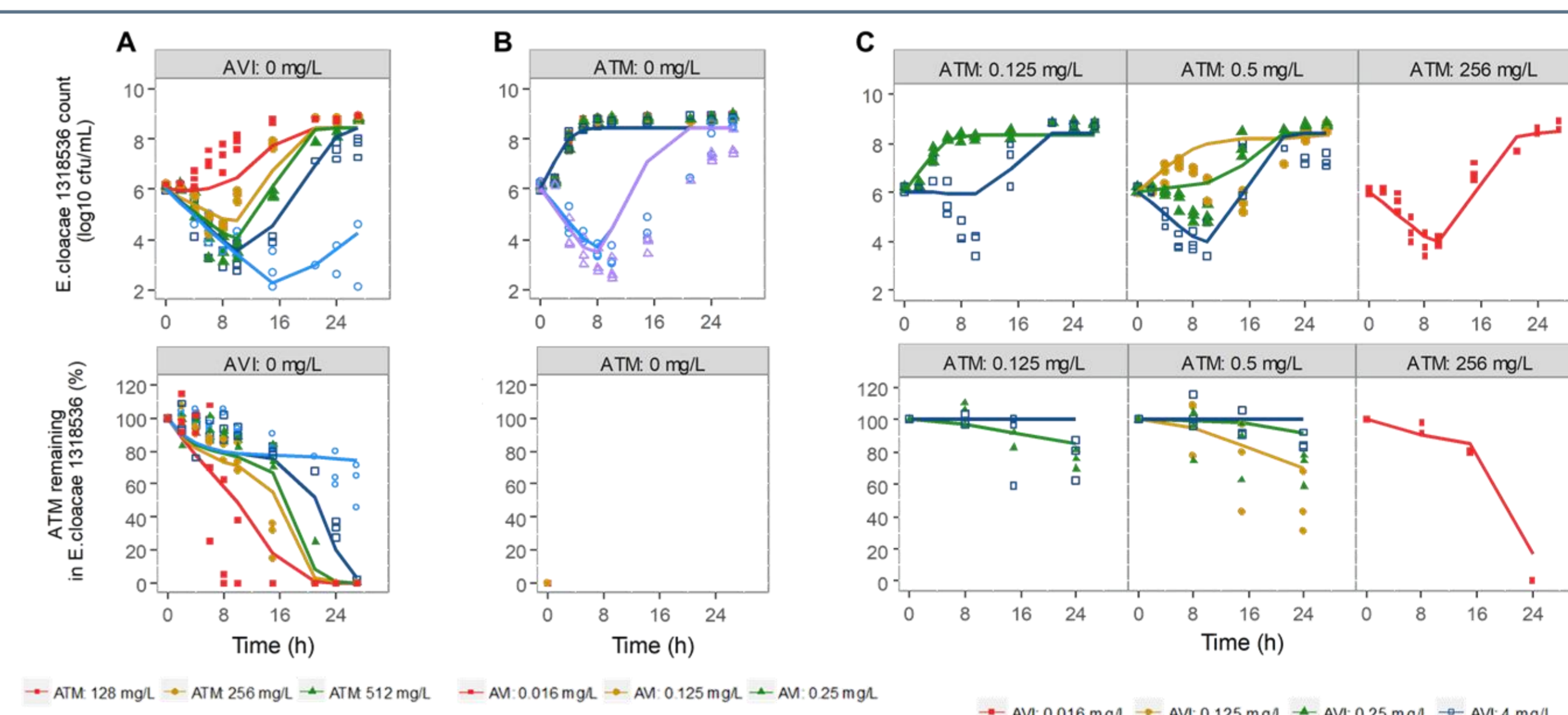


Fig 2. Model-prediction and observed static time-kill curves of A) ATM alone, B) AVI alone and C) ATM-AVI in combination against *E. cloacae* 1318536 over 27 h (top panels) and the percentage of the initial ATM concentration remaining in the system during the time-kill experiments (bottom panels). The symbols represent the experimental data (n=3) and the color-matched lines the predictions from the PD model.

- AVI can prevent ATM degradation (Fig 2, panel C) although this effect alone is not able to explain the bacterial killing due to the drug combination (Fig 3).
- According to the simulation results (Fig 3), among the 3 AVI effects, the enhancing effect is the most important, which by itself yielded a similar bacterial killing to the one obtained with the full model whatever the concentration level (between 71.3 and 100% of the maximum effect).
- The inhibitory and bactericidal effects of AVI poorly contributed to total effect and resulted in a percentage of maximum effect close to that obtained with ATM alone.

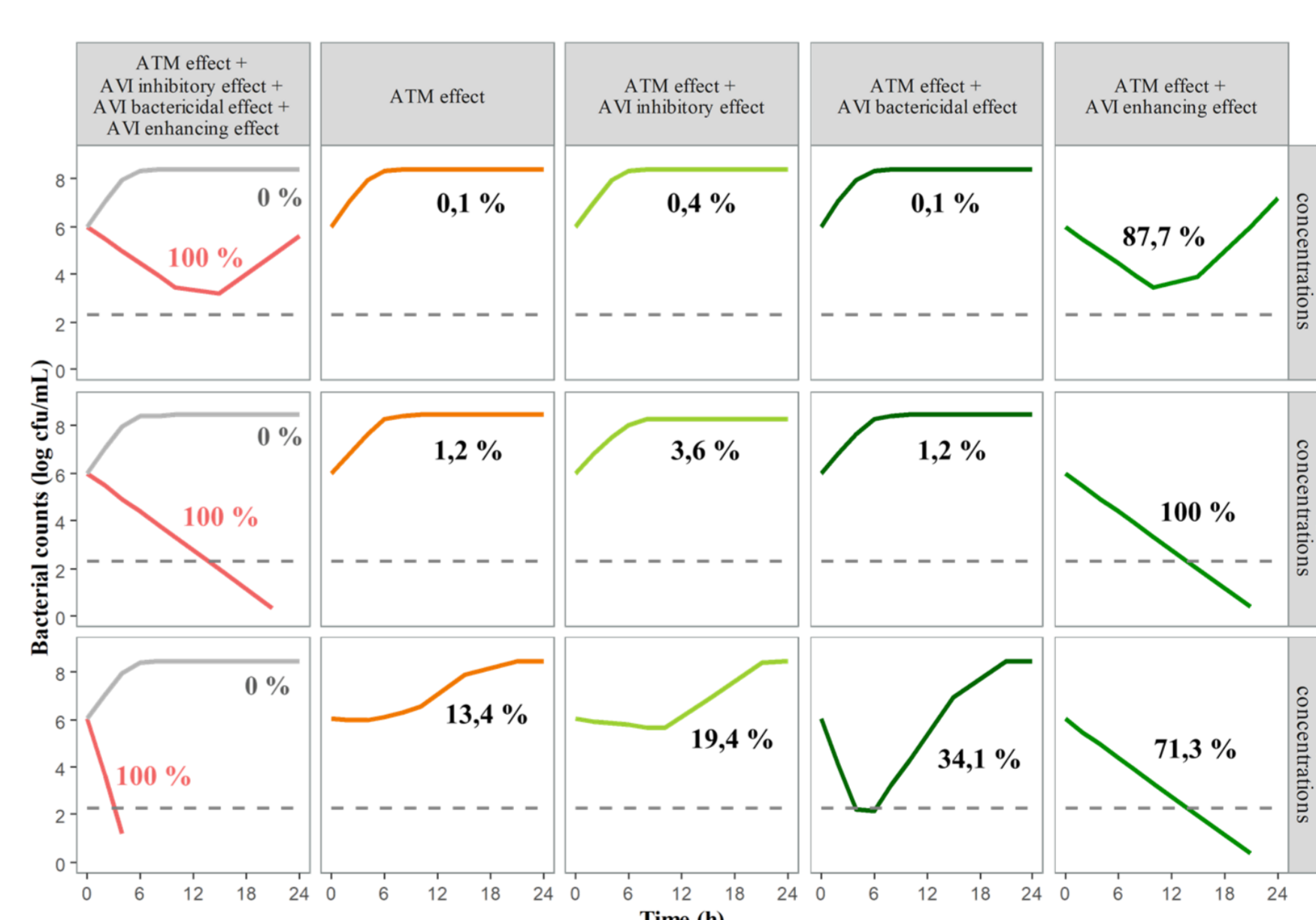


Fig 3. Simulations of the different effects of AVI on bacterial counts in *E. cloacae* 1318536 in response to different constant concentrations of ATM-AVI: low (5-0.9 mg/L), average (25-4.5 mg/L) and high (125-22.5 mg/L) concentrations. Dashed lines correspond to the limit of quantification. Grey curve represents the control (0% effect) and red curve the maximum effect in bacterial killing (100%) predicted when all effects (ATM effect + the 3 AVI effects) are taken into account. The percentage of the maximum effect induced by ATM and each AVI effect is indicated for each simulated profile.

CONCLUSIONS

- The 3 previously reported effects of AVI could be well characterized by the PD model for the additional MDR strains evaluated in this study.
- However, within the clinical range of ATM and AVI concentrations, even though AVI prevents ATM degradation, the combined bactericidal activity was mostly explained by AVI enhancing effect.
- These findings should be further investigated in hollow-fiber experiments where bacteria are exposed to dynamic antibiotic concentrations.

References:

- Sy SKB et al. CPT:Pharmacomet Syst Pharmacol (2017) 6, 197-207.
- Beal SL et al. 1989-2017. NONMEM 7.4 Users Guides. ICON plc, Gaithersburg, MD.
- Vinks AA et al. Antimicrob Agents Chemother (2007) 51, 3049-3055.
- Merdjan H et al. Clin Drug Investig (2015) 35, 307-317.
- Mouton JW et al. J Antimicrob Chemother (2005) 55(5), 601-607.

Conflict of interest: de Jonge BLM is a former employee of Pfizer

