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Semi-mechanistic pharmacokinetic/pharmacodynamics modeling of aztreonam-avibactam combination against multidrug resistant Gram(-) organisms

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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. developed a semi-mechanistic PK/PD model for ATM-AVI combination in which 3 effects for AVI were characterized : inhibition of ATM degradation; enhancement of ATM bactericidal activity and bactericidal effect.
- The aims of this study were to apply this PK/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 *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 (Fig 1).
 - 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), remaining ATM in the system and AVI concentration (inhibitory effect).
 - ATM bactericidal effect was modeled as an increase in the killing rate for both subpopulations with a higher EC_{50} for the resistant state. Whereas AVI bactericidal effect was incorporated in the model only for the susceptible subpopulation.
 - The enhancing effect of AVI was characterized by a reduction of the ATM EC_{50} in a concentration-dependent manner.

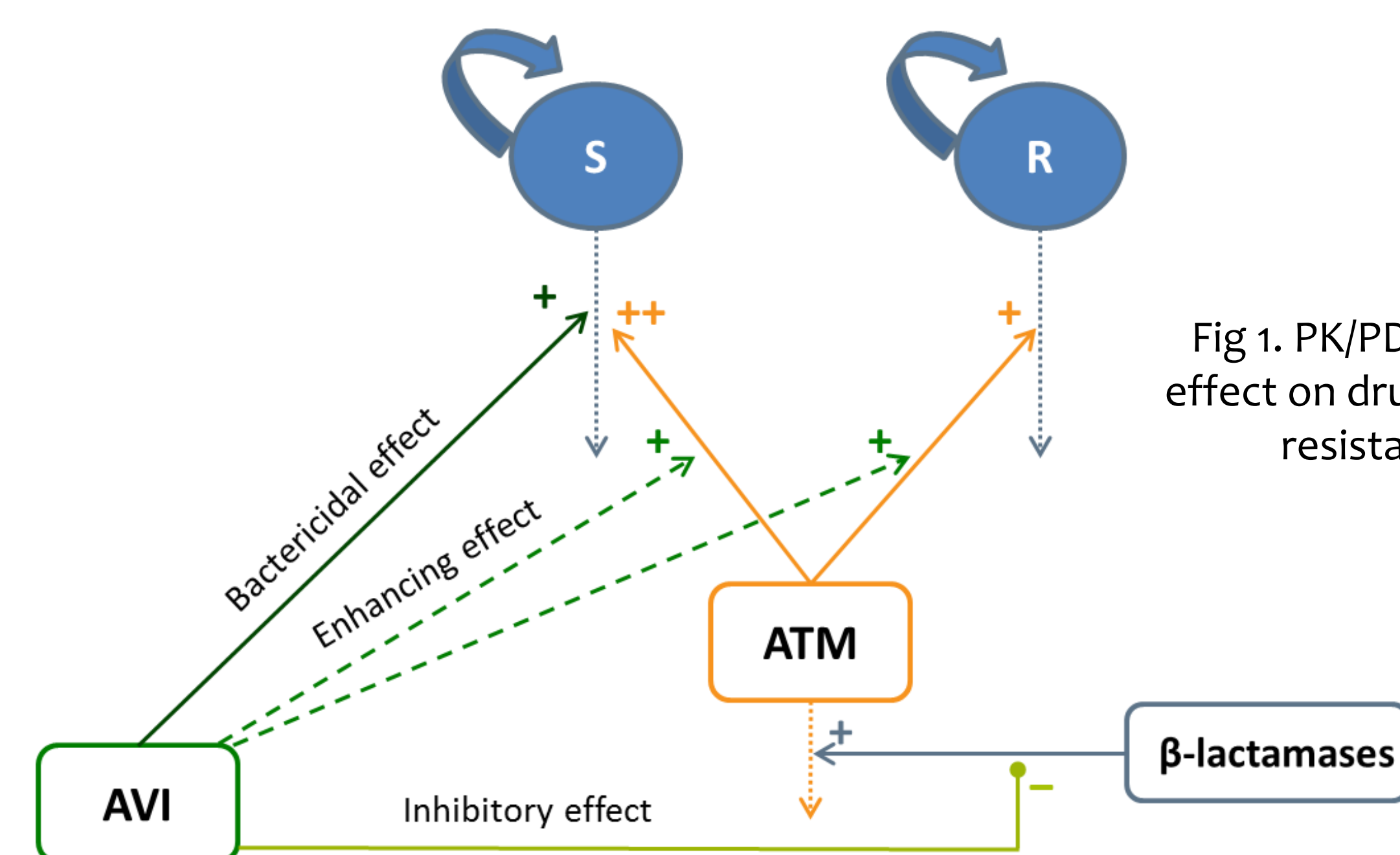


Fig 1. PK/PD model for ATM-AVI effect on drug-susceptible (S) and resistant (R) bacteria.

References:

- ¹Sy, SKB et al., CPT Pharmacometrics Syst. Pharmacol., 2016 ;
²Vinks, AA et al., AAC, 2007 ;
³Merdjan, H et al., Clin. Drug Investig., 2015

- 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 $4.5 \mu\text{g/mL}$ respectively, corresponding to a dosing regimen of 2g and 0.5g q8h in human^{2,3}).

RESULTS

- All strains were resistant to ATM alone although the susceptibility was restored in the presence of $4 \mu\text{g/mL}$ of AVI (Table 1)
- The PK/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 (Fig 3). Thus, for this strain, only the bactericidal and the enhancing effects of AVI could be characterized.

Table 1. Susceptibility and β -lactamase content of the MDR strains

Strain	β -lactamases	MIC (mg/L)	
		ATM	ATM-AVI ^a
<i>E. coli</i> 1266865	NDM-5, TEM-OSBL(b), CMY-42	32	4
<i>C. freundii</i> 974673	NDM-1, SHV-12(2be), TEM-OSBL(2b), CTX-M-3, CMY-34	512	0.125
<i>E. cloacae</i> 1285905	NDM-1, CTX-M-15	64	0.25
<i>E. cloacae</i> 1318536	NDM-1, CTX-M-15	512	0.125

^aAVI at 4 mg/L

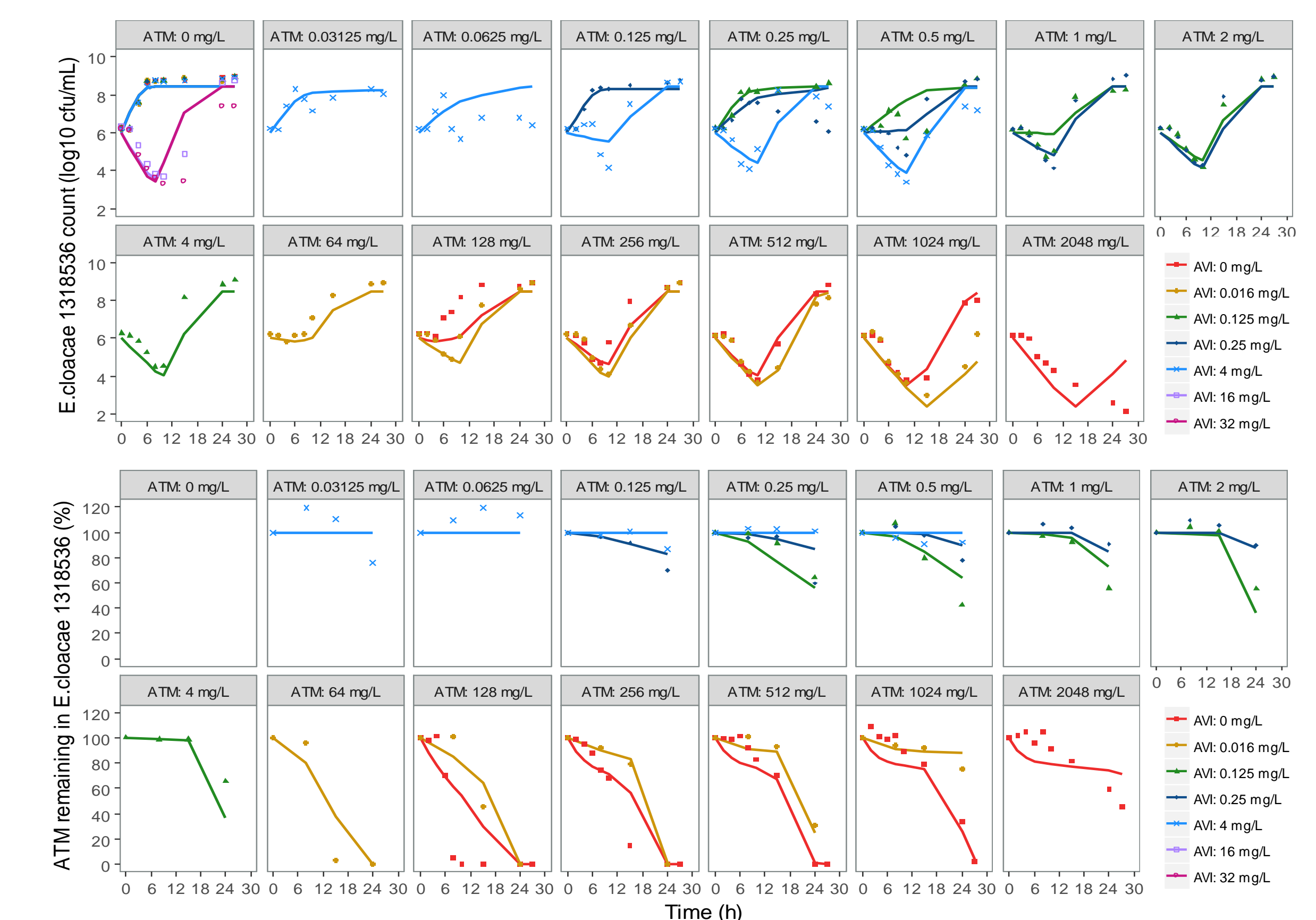


Fig 2. Model-prediction and observed static time-kill curves of ATM and AVI against *E. cloacae* 1318536 (top) and ATM concentration remaining in the system (bottom). The points show the experimental data and the lines the predictions from the model.

- AVI can prevent ATM degradation although this effect alone is not able to explain the bacterial killing due to the drug combination (Fig 3, light green triangles).
- When killing is observed, the lower number of bacteria, and consequently the lower quantity of β -lactamases produced, leads to a slower ATM degradation (Fig 3, green squares).
- According to the simulation results, among the 3 AVI effects, the enhancing effect is the most important.
- The way that the AVI effects are affected by different ATM-AVI concentrations within a clinical range was investigated (Fig 4). The inhibitory and bactericidal effects of AVI contribute to a faster killing rate only at high concentration ($5 \times C_{avg}$).

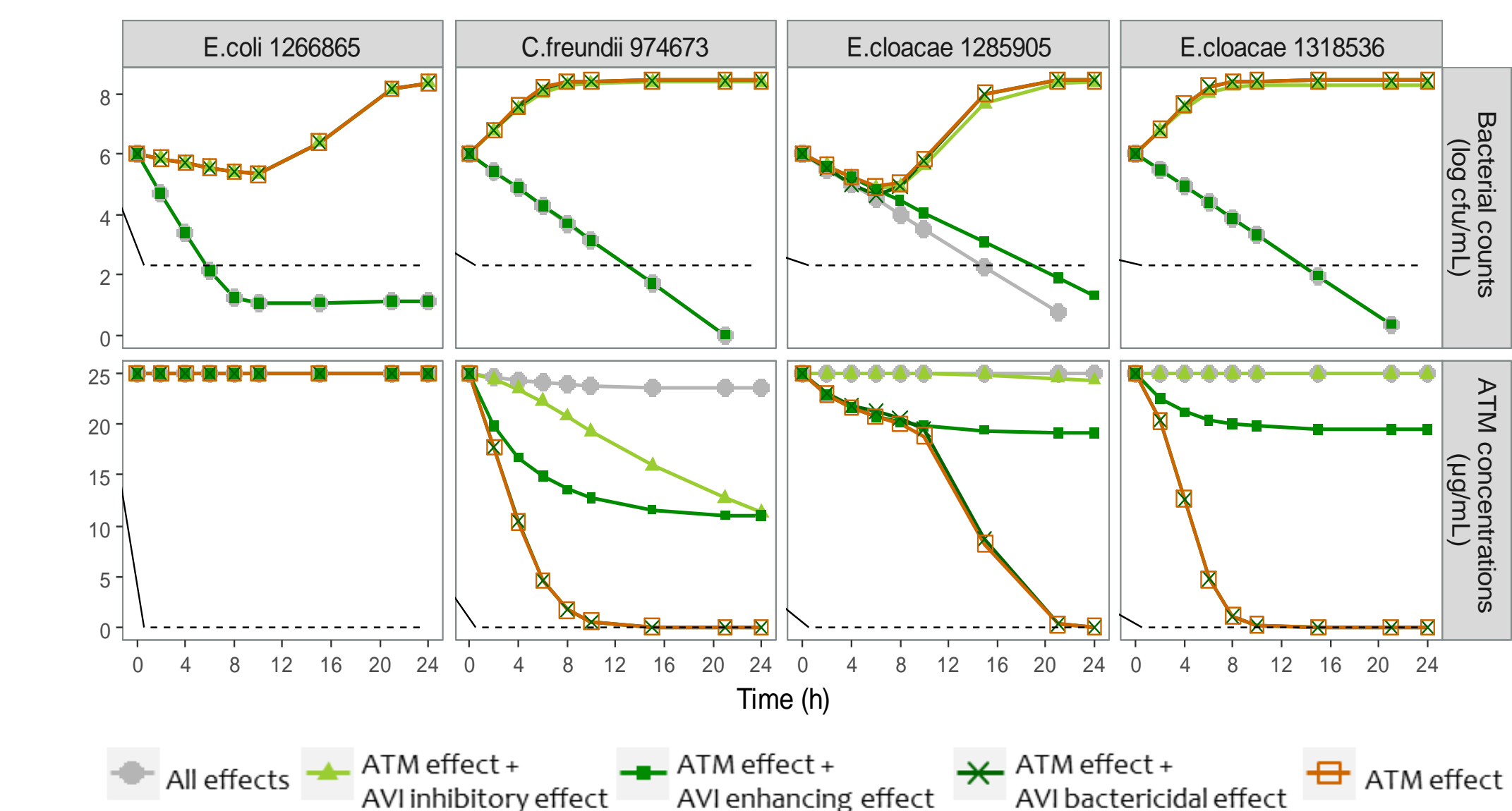


Fig 3. Model simulations of static time-kill curves and ATM concentrations for ATM-AVI combination of 25 - $4.5 \mu\text{g/mL}$. Each color represents the simulated profile for the different effects of AVI and ATM against the 4 investigated strains. Dashed lines correspond to the limit of quantification.

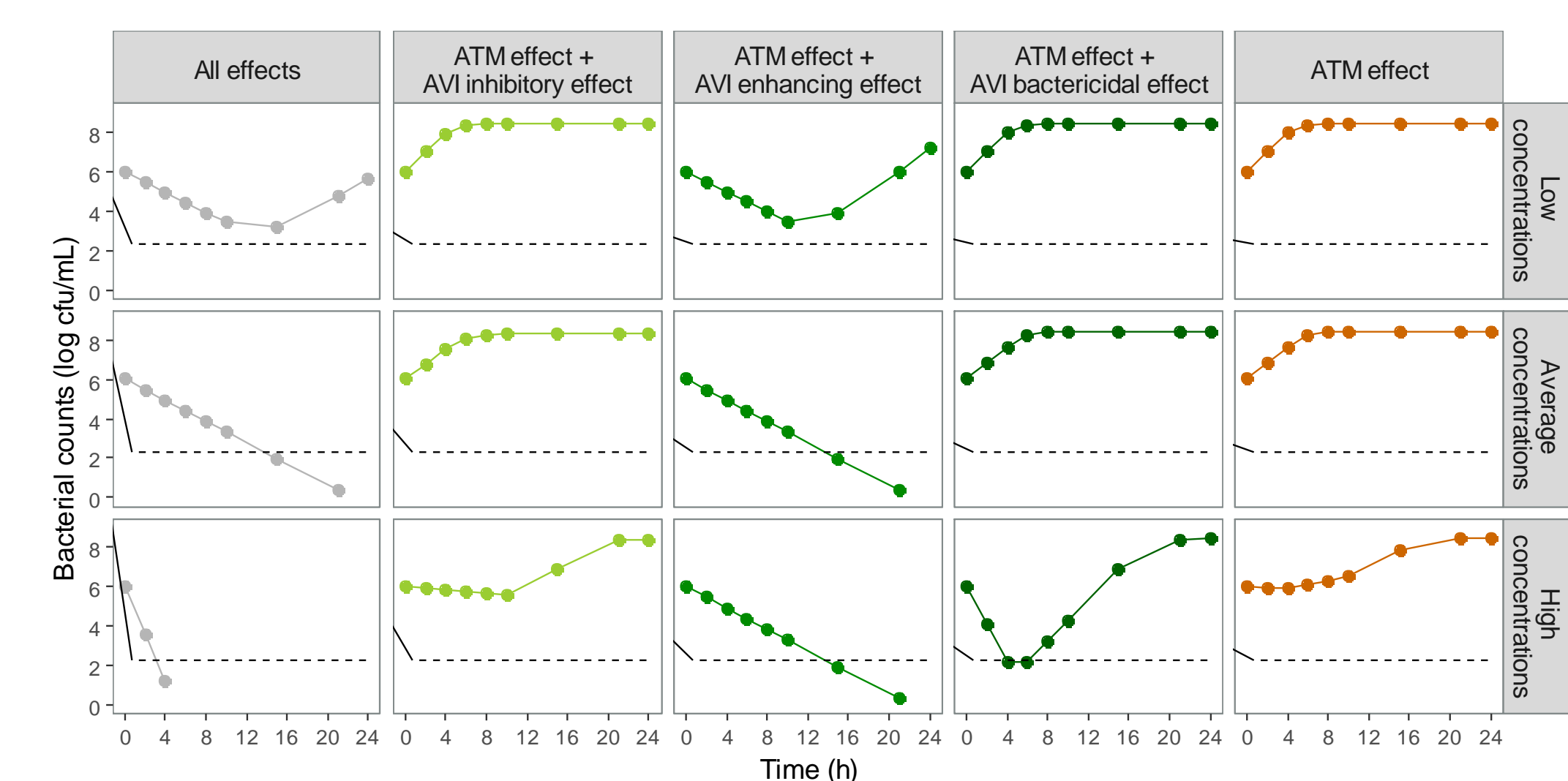


Fig 4. Simulations of the different effects of AVI and ATM against *E. cloacae* 1318536 in response to different constant concentrations of ATM-AVI: low concentrations (5 - $0.9 \mu\text{g/mL}$), average concentrations (25 - $4.5 \mu\text{g/mL}$) and high concentrations (125 - $22.5 \mu\text{g/mL}$). Dashed lines correspond to the limit of quantification.

CONCLUSIONS

- The 3 previously reported effects of AVI could be well characterized by the PK/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.

Conflict of interest: de Jonge BLM is currently an employee of Pfizer