

# Pharmacodynamic modeling of checkerboard data obtained with $\beta$ -lactam- $\beta$ -lactamases inhibitor combination: aztreonam-avibactam

Alexia Chauzy

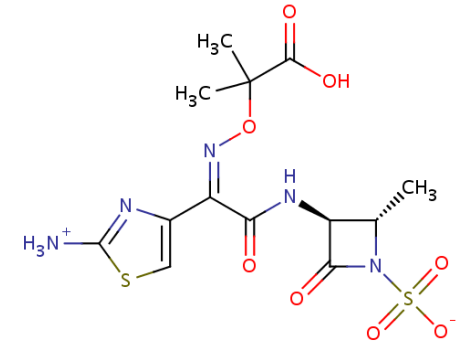
Inserm U1070, University of Poitiers

*Vienna, 21 April 2017*

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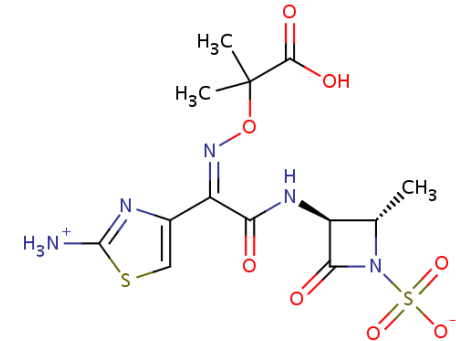
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Monocyclic  $\beta$ -lactam antibiotic  
Not hydrolyzed by MBLs



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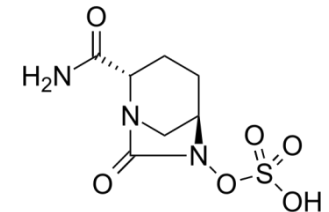
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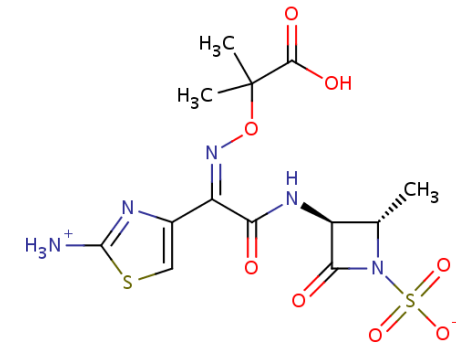
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Non- $\beta$ -lactam  $\beta$ -lactamase inhibitor of a broad spectrum of enzymes (Ambler Class A ESBLs, Class A KPC, Class C enzymes, and some Class D enzymes)



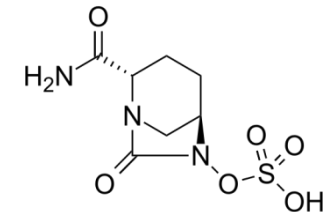
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**PK/PD target: 60% fT<sub>>MIC</sub>**

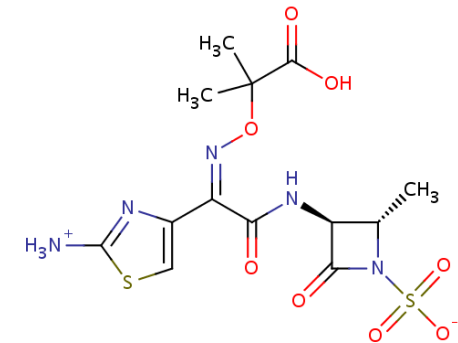
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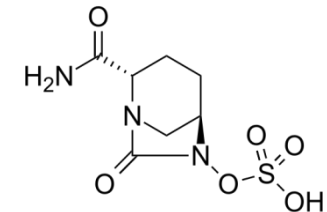
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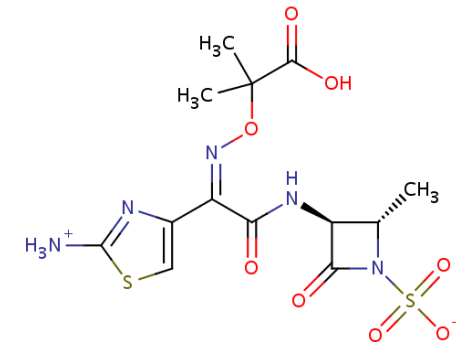
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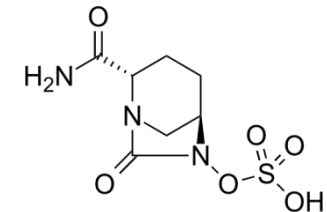
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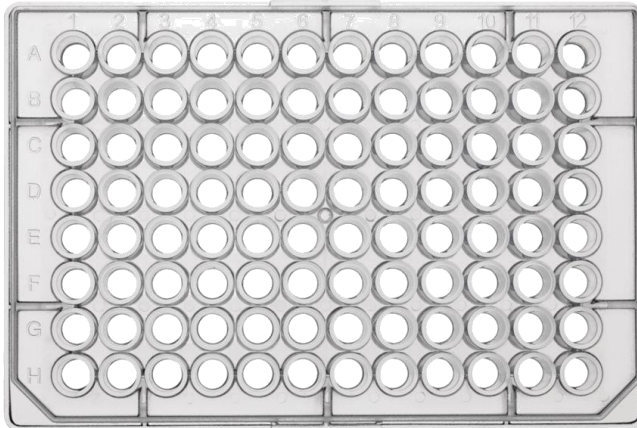
**PK/PD target: 50% fT<sub>>CT</sub> of 2.5mg/L**

## Objective:

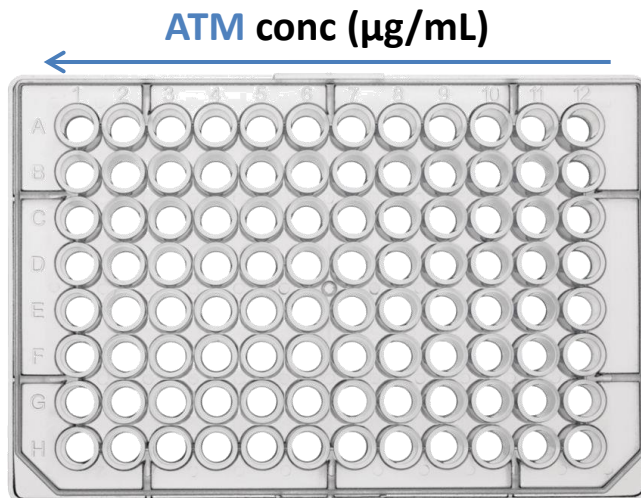
Develop a simple semi-mechanistic modelling approach to quantify the *in vitro* antimicrobial activity of ATM-AVI combination against  $\beta$ -lactamases producing *Enterobacteriaceae*



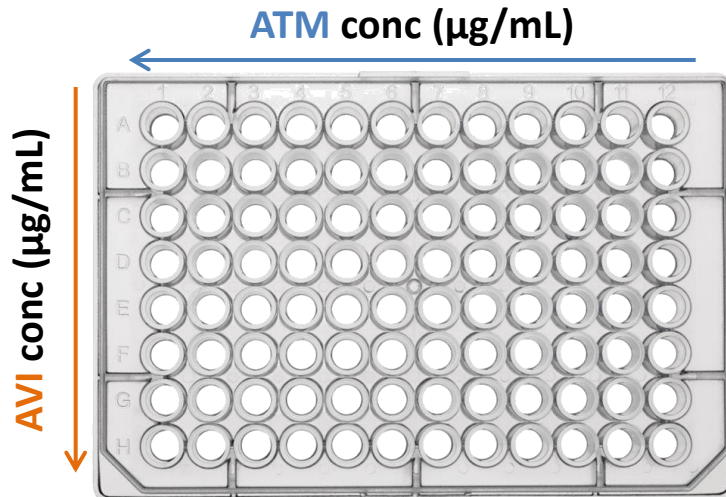
- **MIC checkerboard** assays performed with **11** *Enterobacteriaceae* isolates with diverse  $\beta$ -lactamases profiles
  - Checkerboards set up with 2-fold dilutions of ATM and AVI



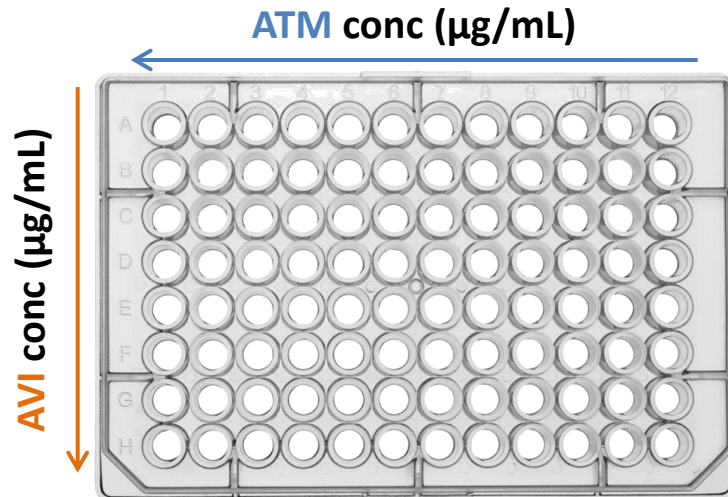
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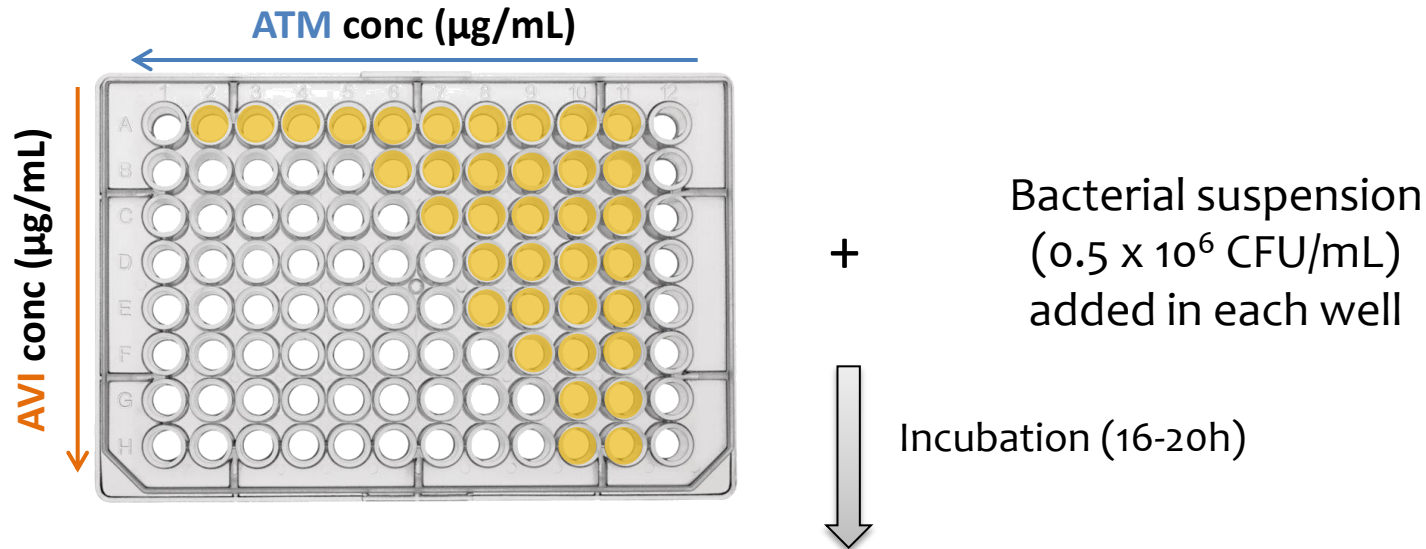
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+

Bacterial suspension  
( $0.5 \times 10^6$  CFU/mL)  
added in each well

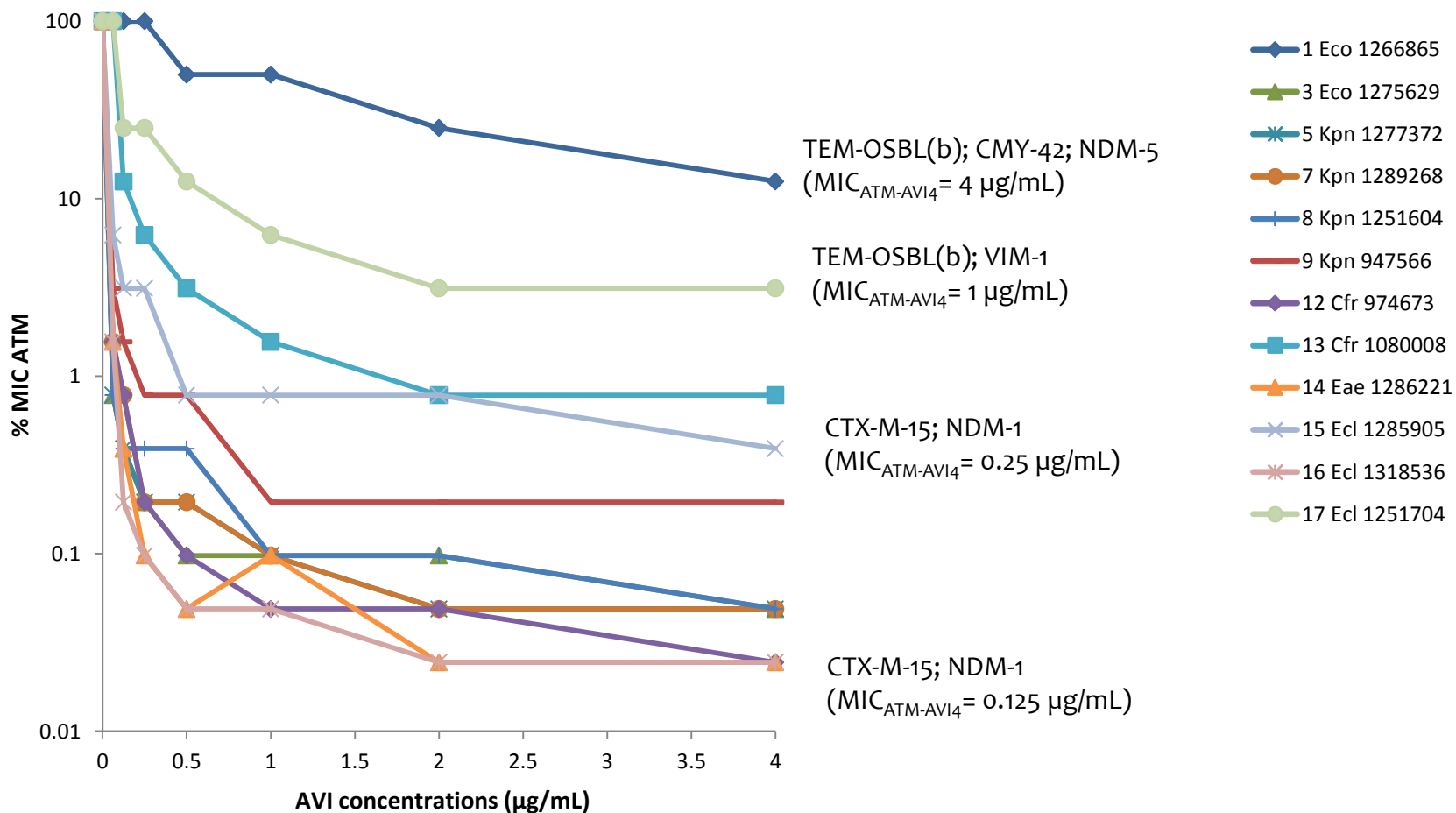
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- **Susceptibility determination:** spectrophotometrically assessment of growth

Determination of ATM MICs ( $\text{MIC}_{\text{ATM}}$ ) in the absence and in the presence of AVI at different concentrations (ranging from 0.0625 to 4  $\mu\text{g/mL}$ )

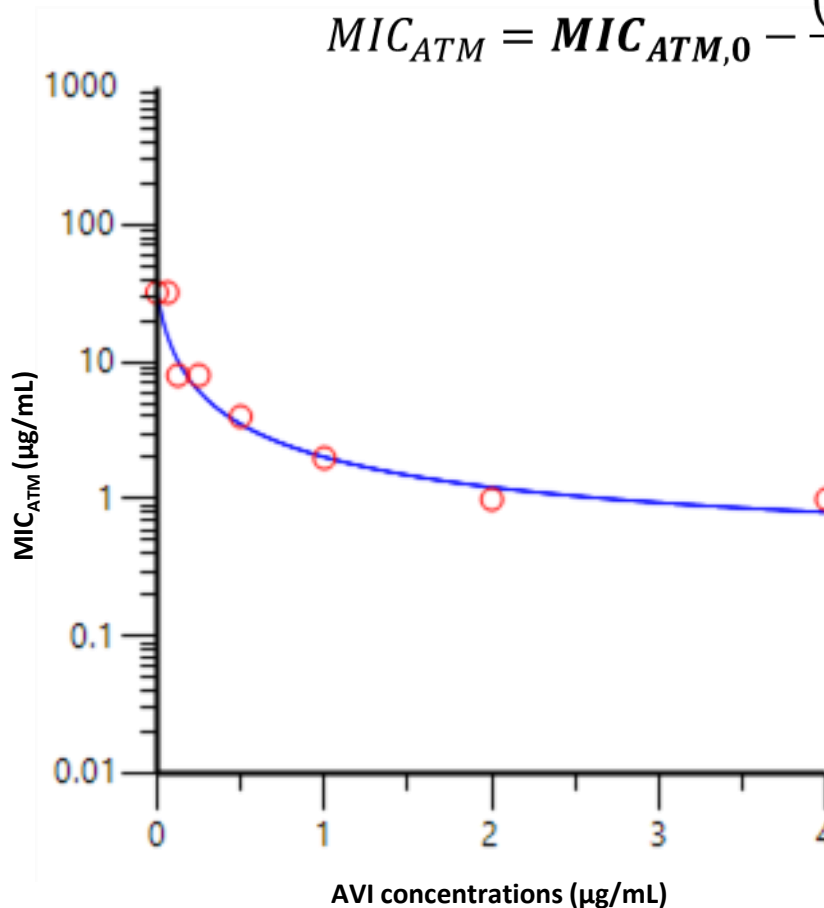
## Normalized ATM MICs as a function of AVI concentrations



## ■ Efficacy and potency modelling

- $MIC_{ATM}$  versus AVI concentrations were fitted according to:  
an inhibitory  $E_{max}$  effect model with baseline effect (WinNonlin, version 6.2):

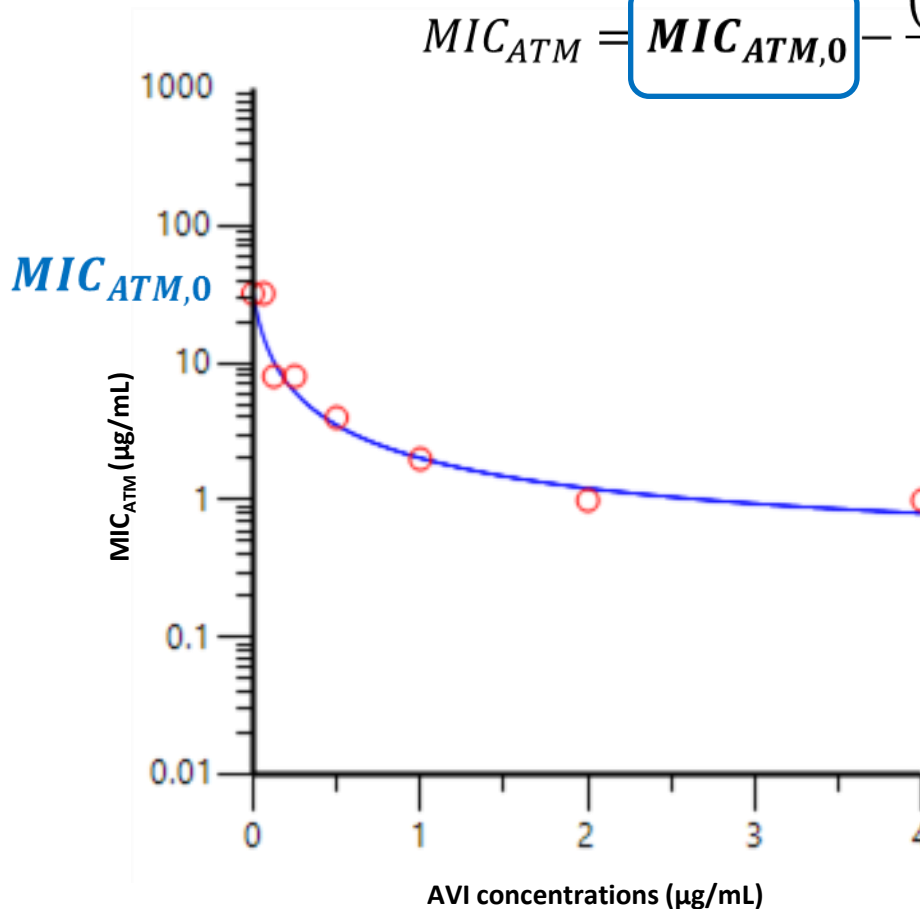
$$MIC_{ATM} = MIC_{ATM,0} - \frac{(MIC_{ATM,0} - MIC_{ATM,base}) \times C_{AVI}}{(C_{AVI} + IC_{50})}$$



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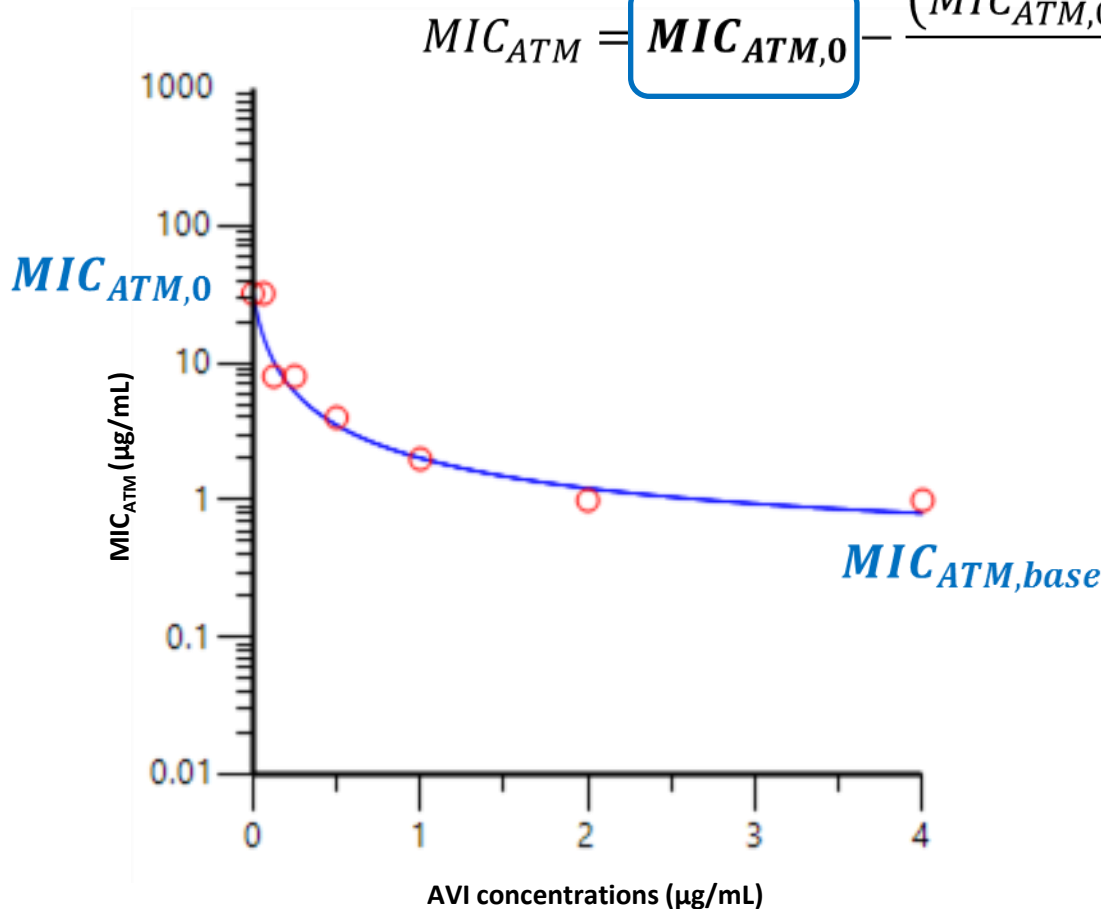




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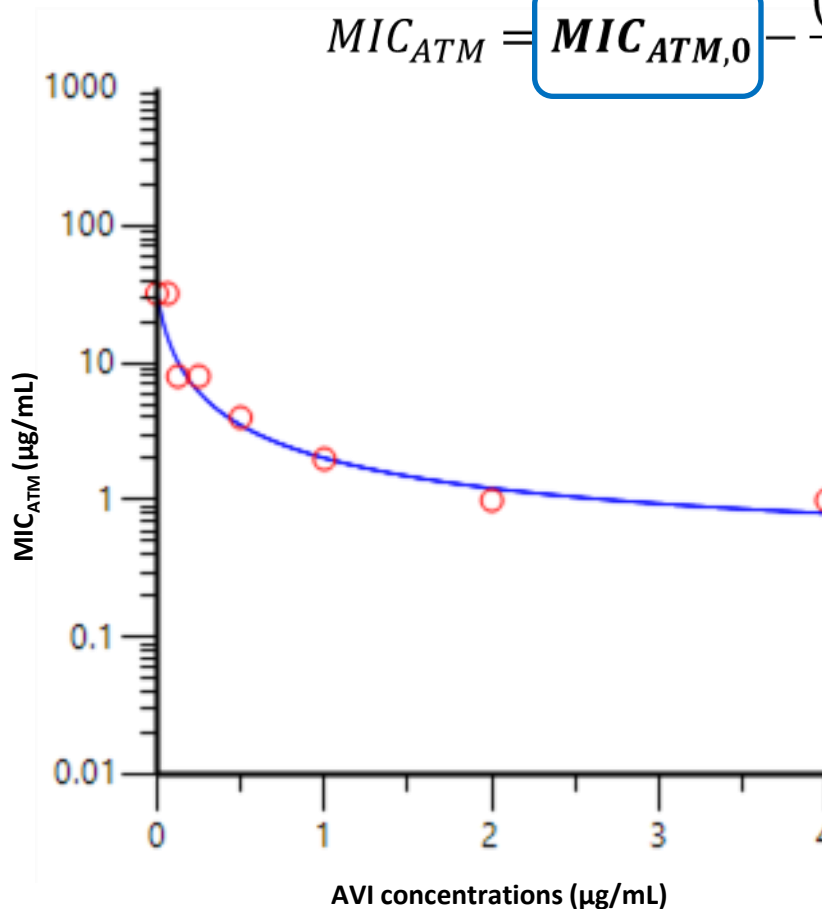
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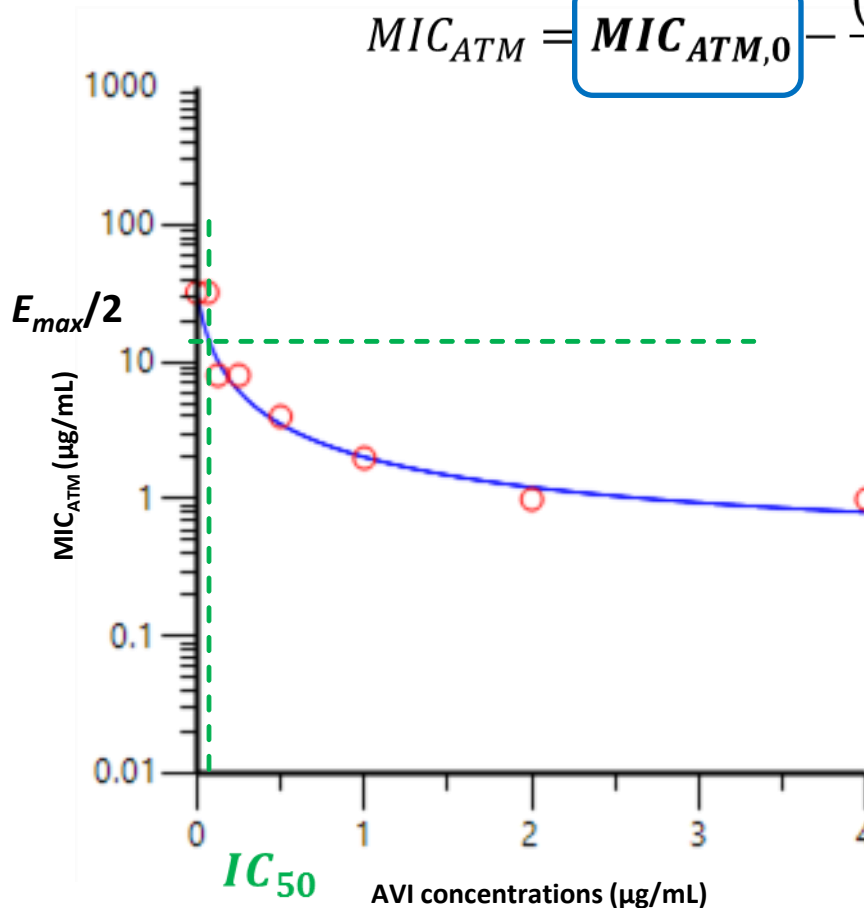


$$\text{Efficacy ratio} = \frac{MIC_{ATM,0}}{MIC_{ATM,base}}$$

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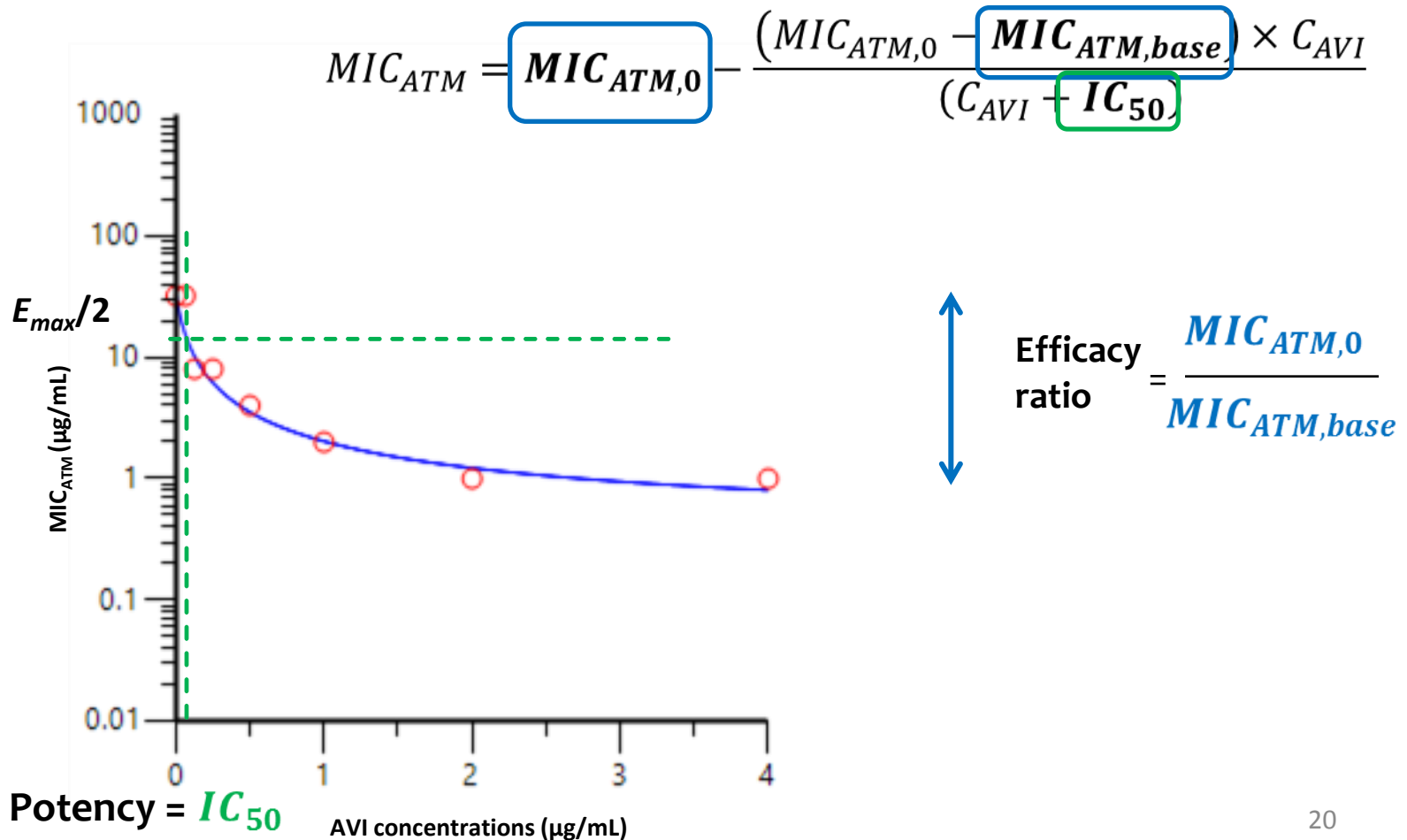
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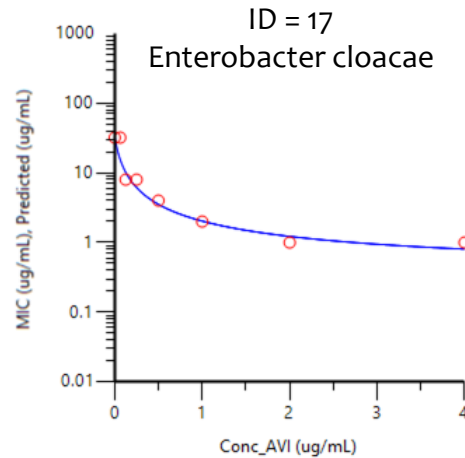
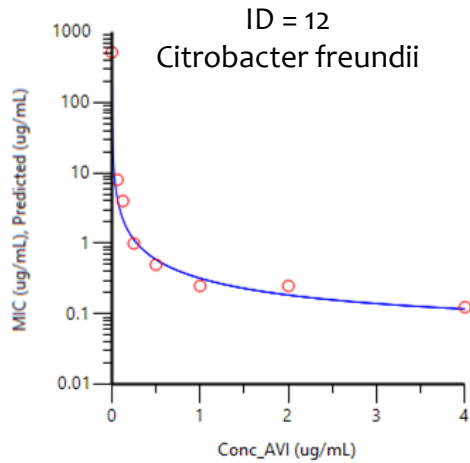
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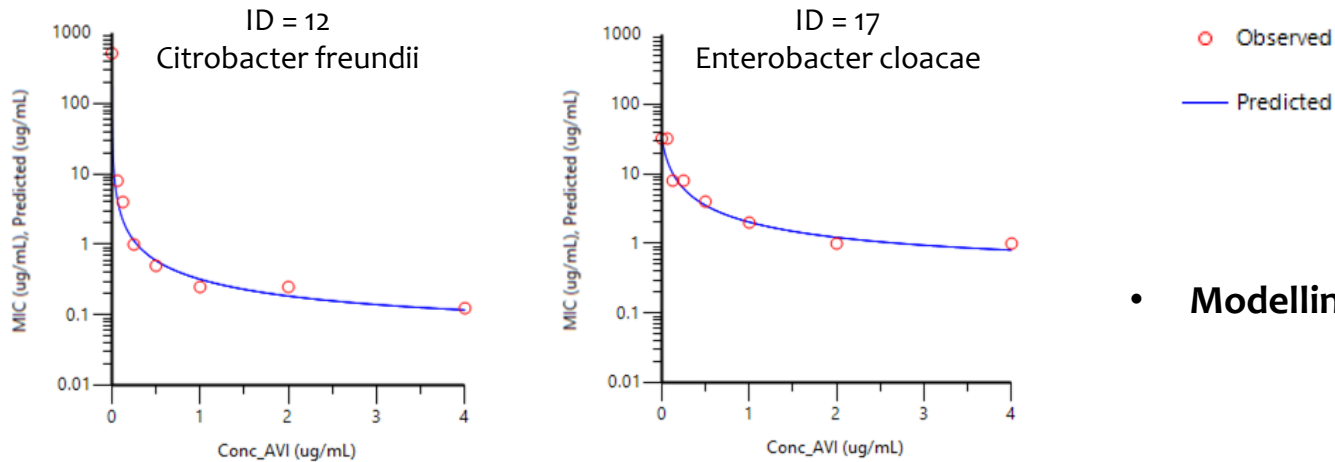
## Estimated values of parameters and individual plots (2 representative strains)



○ Observed  
— Predicted

- **Modelling was quite successful**

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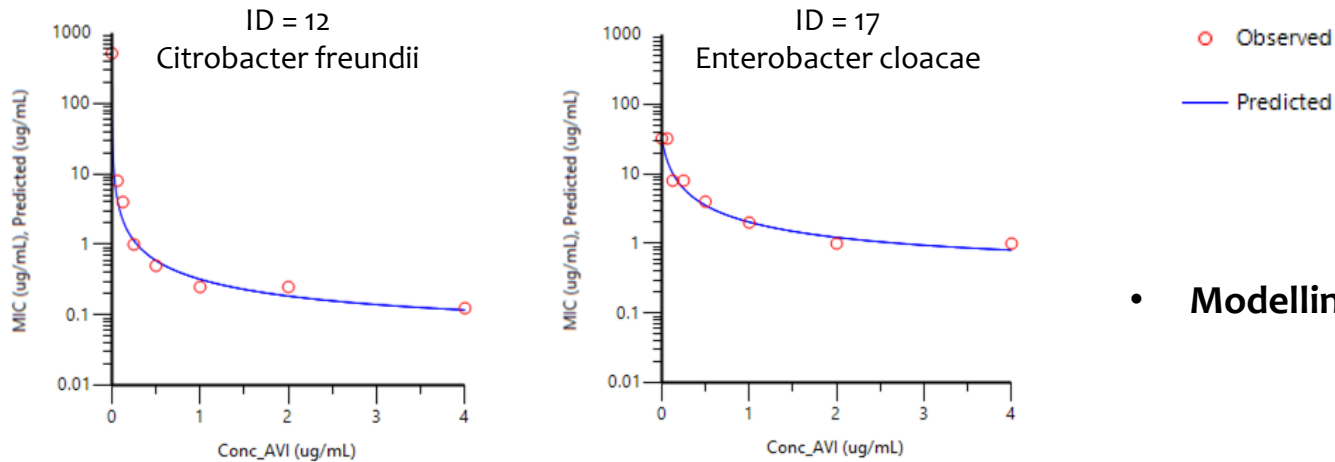
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### Parameter estimate ± CV%

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ID	Organism
12	Citrobacter freundii
17	Enterobacter cloacae

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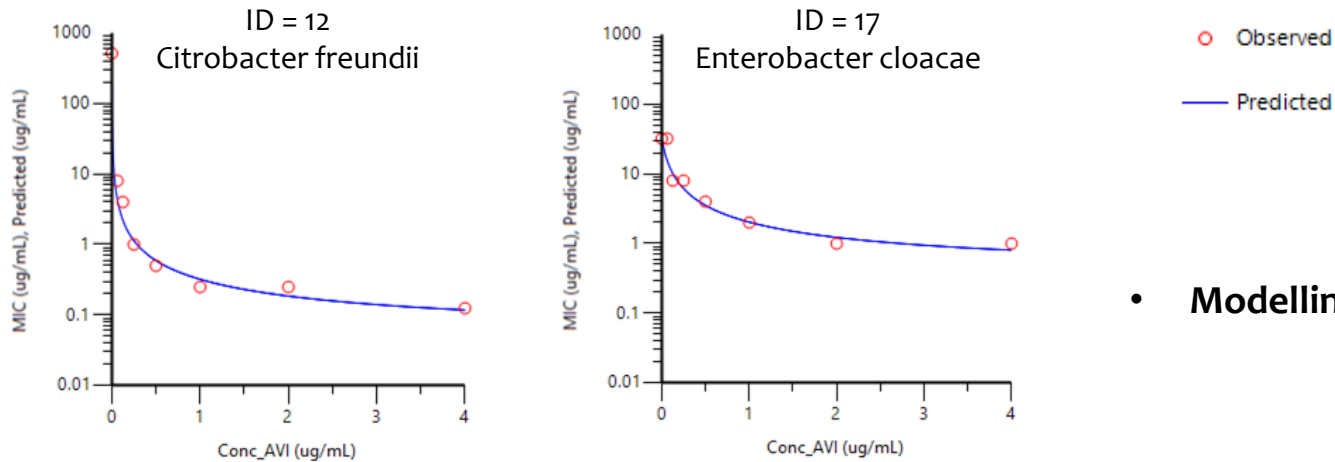


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### Parameter estimate $\pm$ CV%

ID	Organism	MIC <sub>ATM,0</sub> ( $\mu$ g/mL)
12	Citrobacter freundii	512 $\pm$ 32
17	Enterobacter cloacae	33 $\pm$ 29

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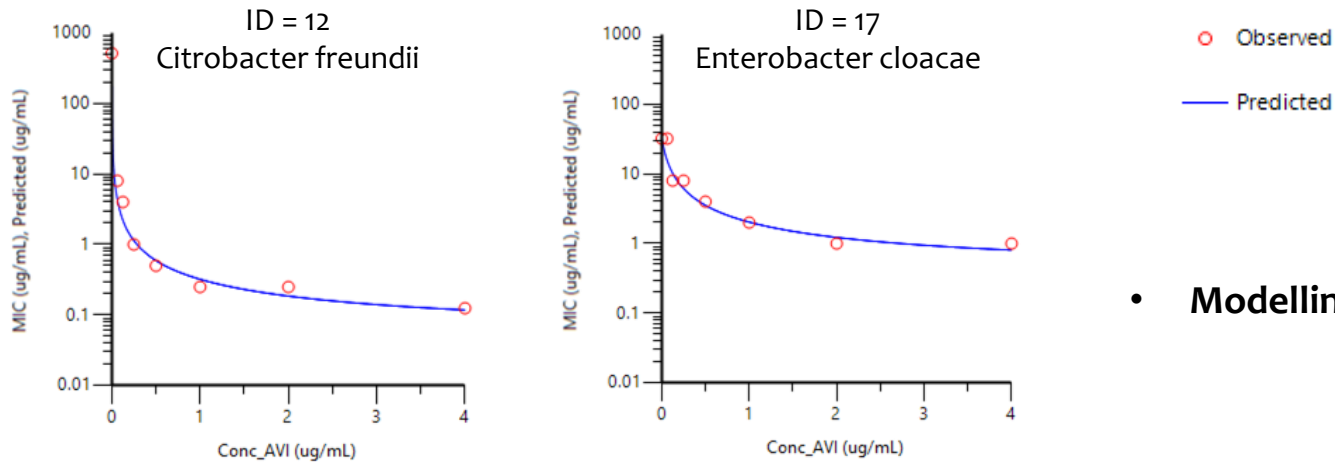


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		MIC <sub>ATM,0</sub> (µg/mL)	MIC <sub>ATM,base</sub> (µg/mL)
12	Citrobacter freundii	512 ± 32	0.05
17	Enterobacter cloacae	33 ± 29	0.37



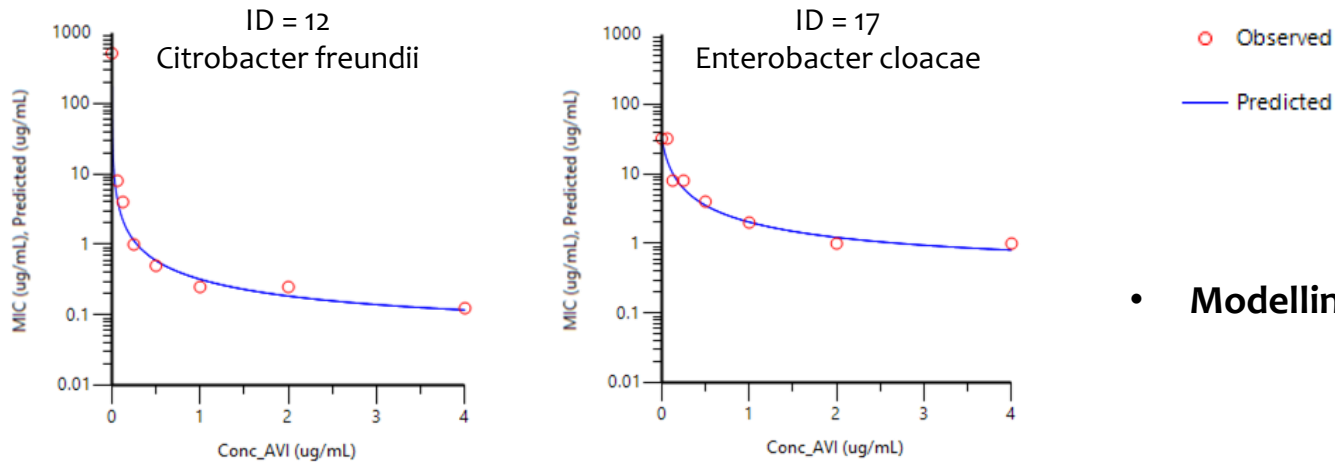
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ID	Organism	Parameter estimate ± CV%			
		MIC <sub>ATM,0</sub> (µg/mL)	MIC <sub>ATM,base</sub> (µg/mL)	Efficacy ratio	Potency (µg/mL)
12	Citrobacter freundii	512 ± 32	0.05	10207	0.00053 ± 38
17	Enterobacter cloacae	33 ± 29	0.37	89	0.053 ± 46

## ■ Conclusion

- An inhibitory Emax model with a baseline effect describes adequately these ATM-AVI checkerboard data
- Quantification of the wide differences between strains in terms of:
  - Efficacy** ( $MIC_{ATM,o}/MIC_{ATM,base}$  ranging between 89 and 10207)
  - Potency** ( $IC_{50}$  ranging between 0.00022 and 0.053  $\mu\text{g/mL}$ )

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## ■ Perspective

- Derive a strain dependent threshold AVI concentration from the model
- Complete these checkerboard experiments by:
  - *in vitro* static and dynamic time-kill kinetic studies
  - *in vivo* experiments using an animal infection model
- Find a link between this simple MIC related modelling approach with the more sophisticated mechanistic models (Sy S. & Derendorf H.)

## Acknowledgements

- **J. Buyck, E. Marquizeau, N.Grégoire, S.Marchand, W.Couet**  
**Inserm U1070, University of Poitiers, France**
- **B.L.M. de Jonge**  
**AstraZeneca Pharmaceuticals, Waltham, MA, USA**