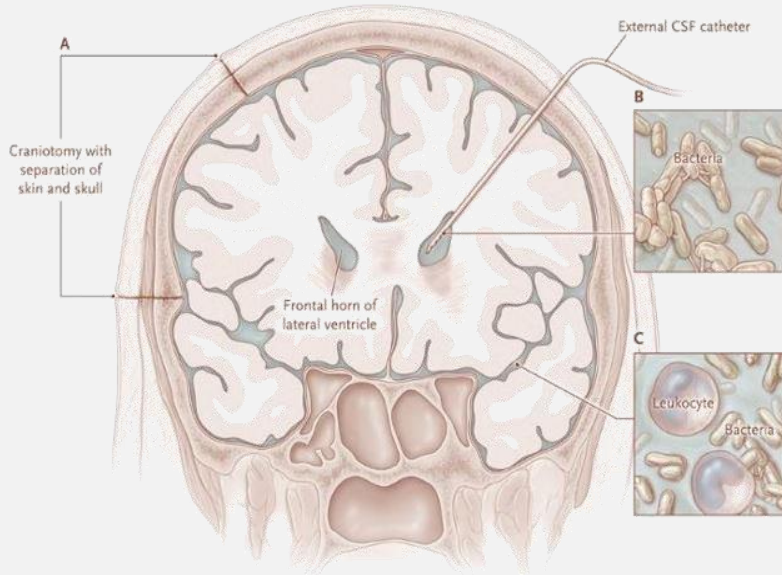


Pkpop-LCR study: Pharmacokinetic and Pharmacodynamic of linezolid in neurointensive care patients with external ventricular drainage

*Alexia Chauzy, Fanny Bernard, Nicolas Grégoire, Hélène Mirfendereski, Nadia Imzi,
Sandrine Marchand, Claire Dahyot-Fizelier*

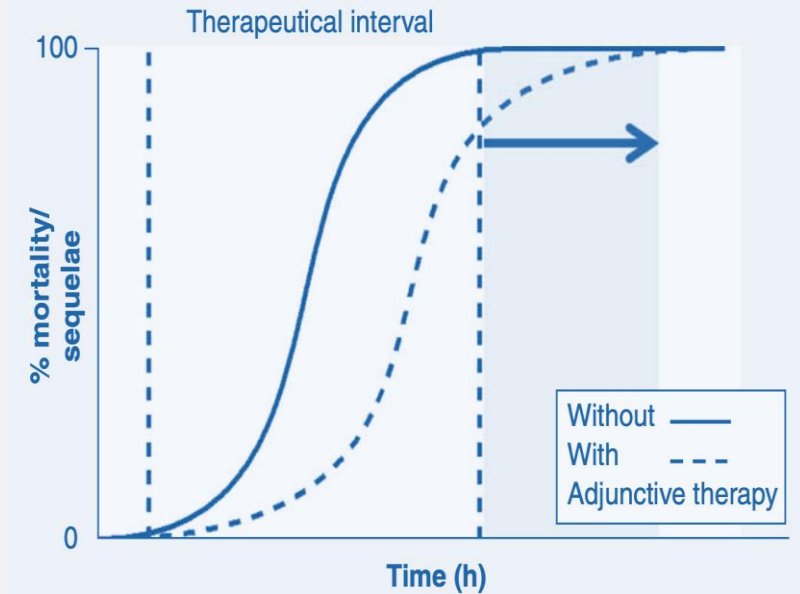
Inserm U1070 – University of Poitiers

Nosocomial CNS infection



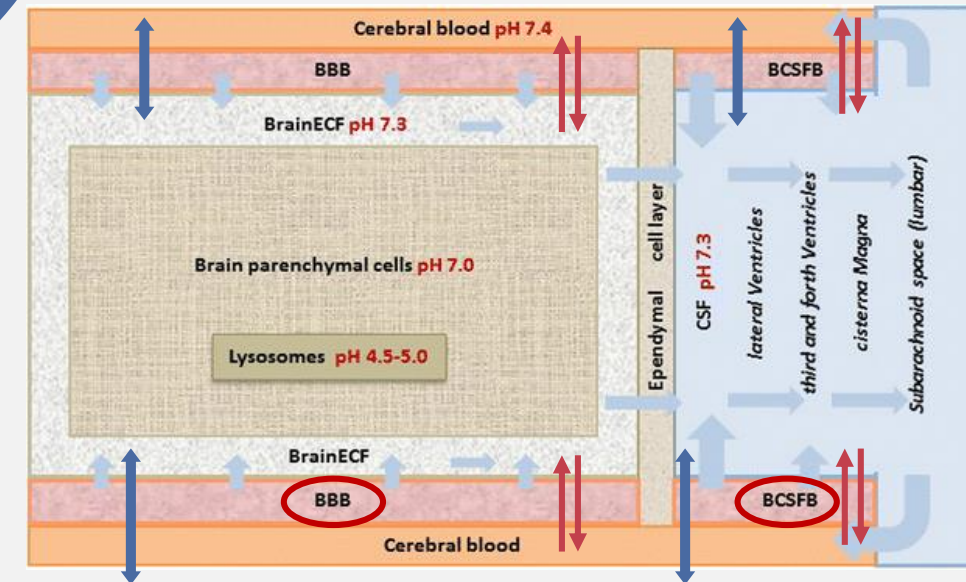
Need to optimize the treatment of CNS infection

Early-targeted antibiotherapy



- Incidence of nosocomial cerebro-meningeal infections:
 - **Post-neurosurgery:** 0.3-8.6%
 - **Post EVD:** 0-22%
- High morbidity/mortality: **15 - 23%**

Limited CSF distribution of antibiotics



- ↔ Passive diffusion
- ↔ Active transport
- Fluid flows

Hussein et al., CMI, 2017

Nau et al., Expert Rev Anti Infect Ther, 2015

Yamamoto et al., AAPS J, 2017

PKpop-LCR

- Multicenter clinical trial
- Prospective
- Randomized



9 broad-spectrum antibiotics

Linezolid, Meropenem, Ceftazidime, Cefepime, Ceftaroline, Vancomycin, Piperacillin-Tazobactam, Daptomycin, Colistin.



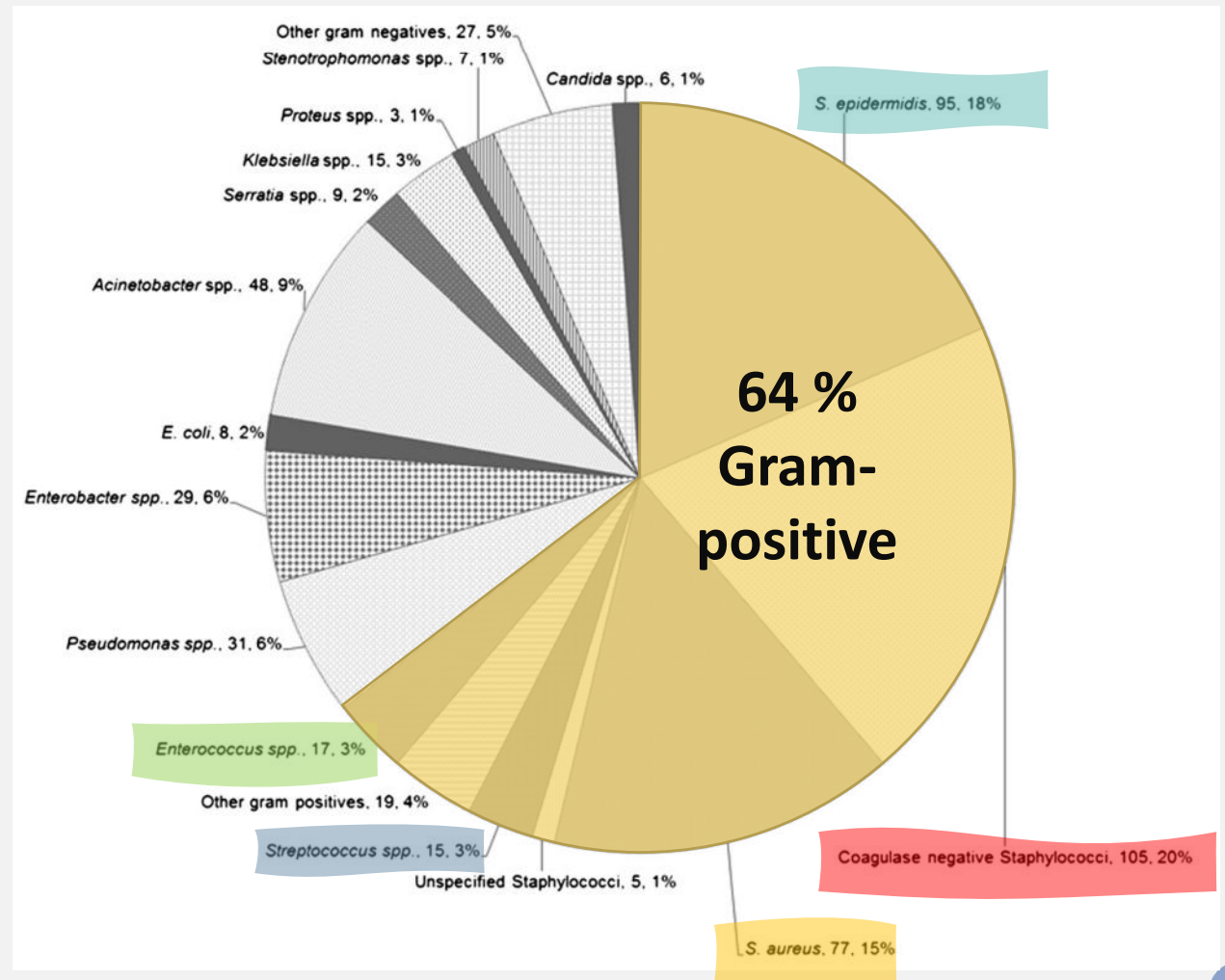
Objective :

Characterize CSF distribution and evaluate the efficacy of current dosing regimens of antibiotics indicated in nosocomial cerebro-meningeal infections using a PK/PD modelling approach

Linezolid

- Class: oxazolidinone
- Broad *in vitro* activity against Gram-positive isolates:
 - Coagulase negative Staphylococci and *Staphylococcus aureus*
 - *Streptococcus pneumoniae*
 - *Enterococcus faecium*

Bacterial pathogens responsible for EVD-associated CSF infections



PK/PD study of linezolid

Patients

Dosing regimens

Sampling

PK/PD analysis



Brain injured patients
with EVD

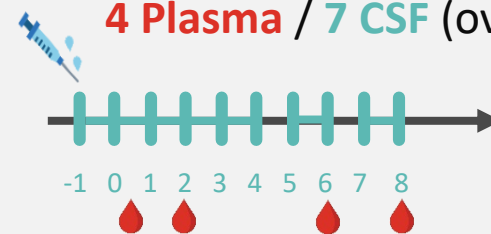


600 mg q12h
600 mg q8h

IV infusion over 30 min



4 Plasma / 7 CSF (over 1h)

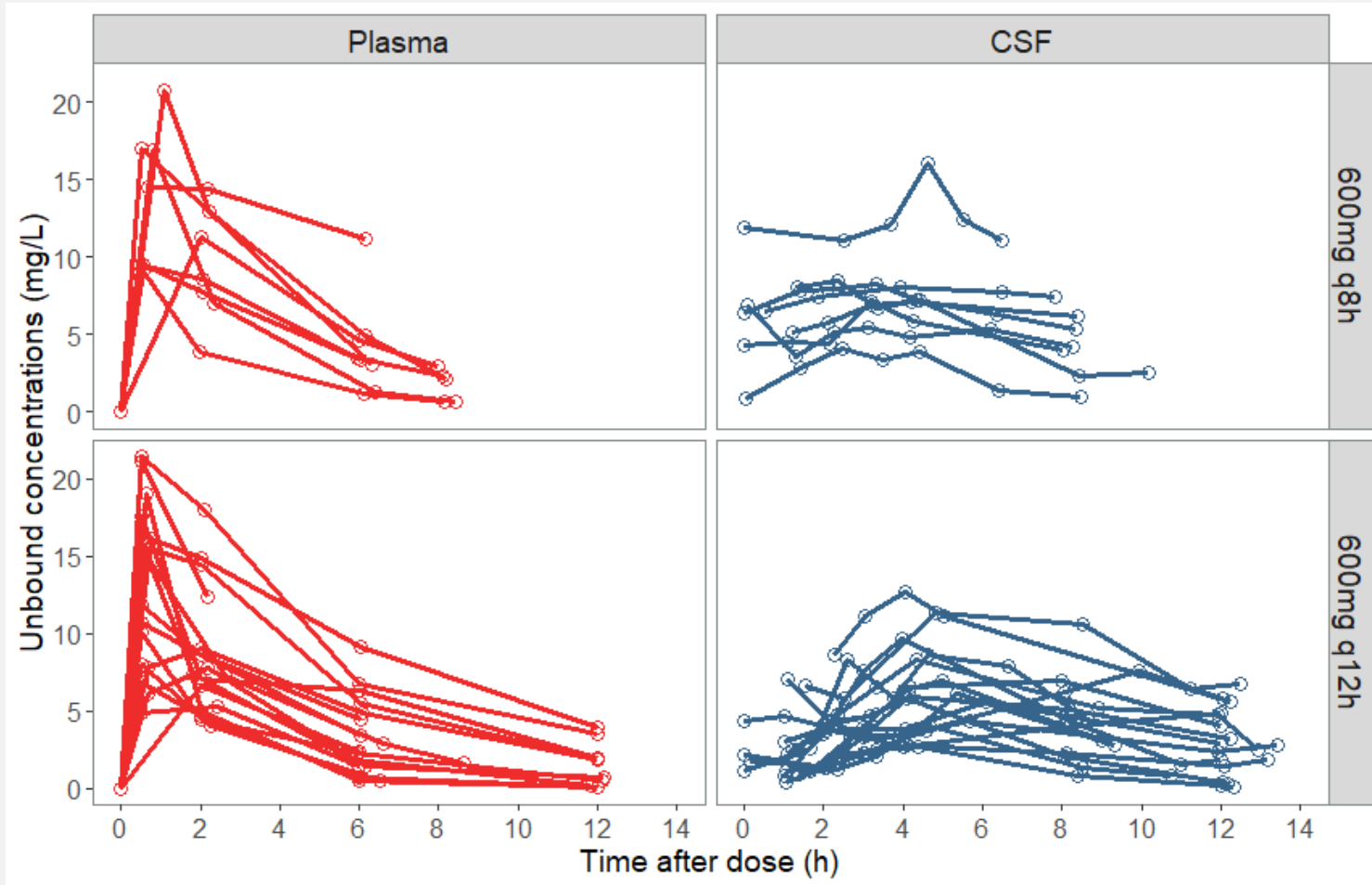


Population PK modeling
Dosing regimen
optimization

Inflammation markers:

*IL-6, IL-8, IL-10,
IL-17a, TNF α , albumin*

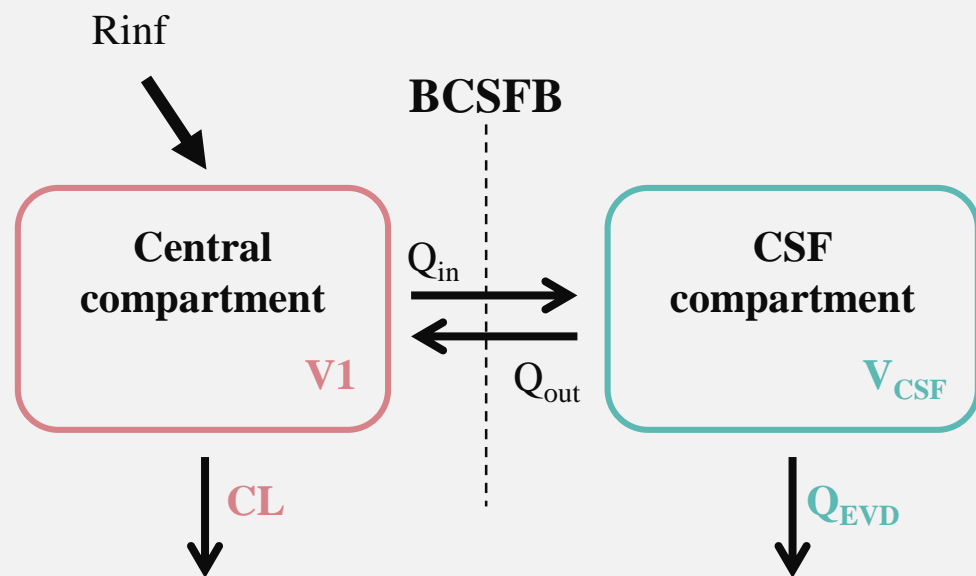
CSF distribution of linezolid



Unbound AUC ratio

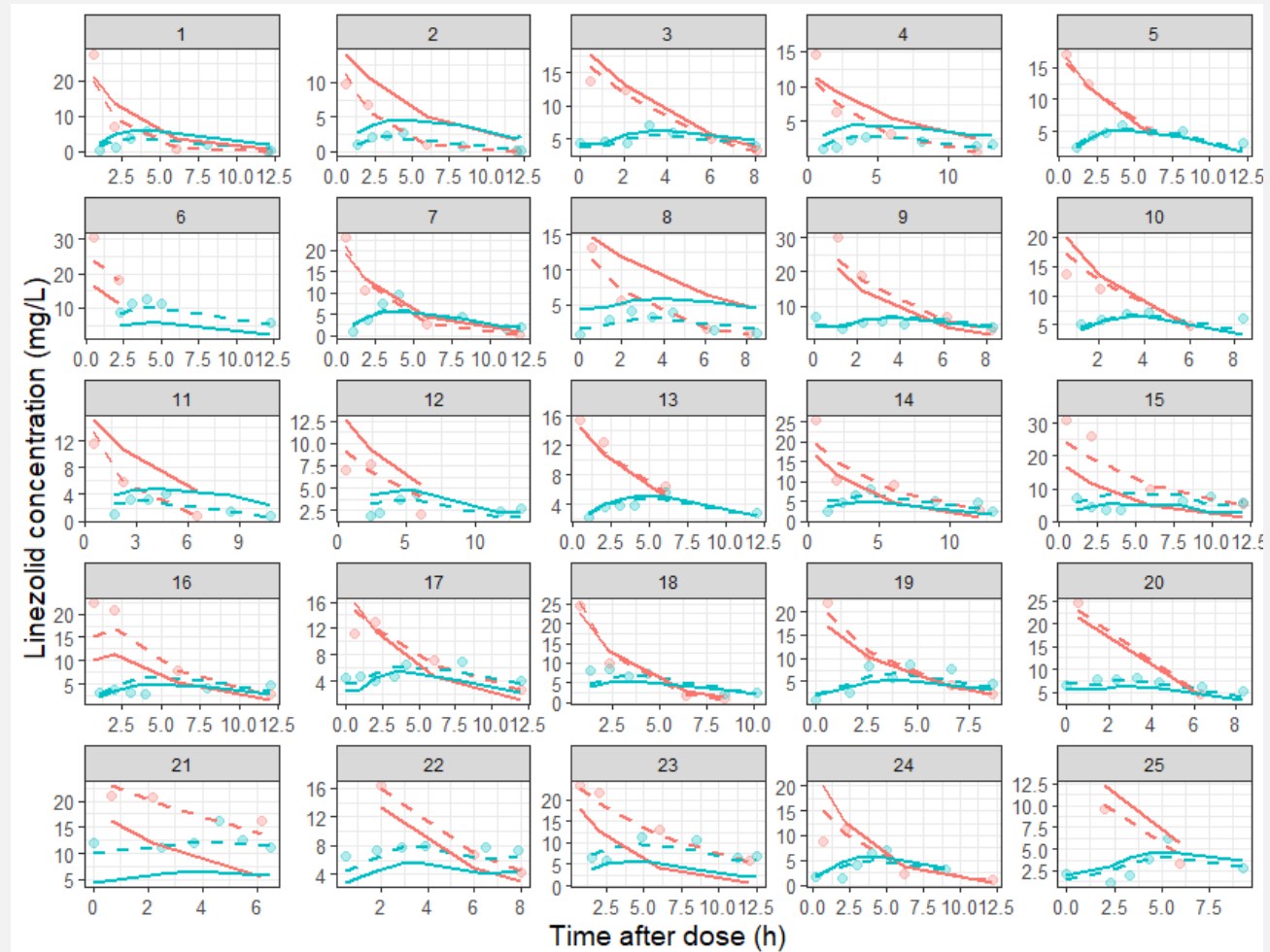
$$\frac{AUC_{CSF}}{AUC_{u,plasma}} = 89.5\%$$

PK modeling of linezolid



Parameter	Value (95% CI)	IIV %CV (95% CI)
CL (L/h)	12.1 (10.0-14.5)	45.4 (35.2-59.9)
V1 (L)	52.8 (47.5-60.5)	23.1 (13.9-34.2)
V2 (L)	0.15 FIX*	-
Q_{in} (L/h)	0.040 (0.033-0.048)	15.0 (6.2-23.8)
Q_{out} (L/h)	0.037 (0.030-0.044)	-
$\sigma_{prop,plasma}$ (%)	22.1 (18.2-27.1)	-
$\sigma_{prop,CSF}$ (%)	32.6 (28.6-37.5)	-

* Fixed to the physiological volume

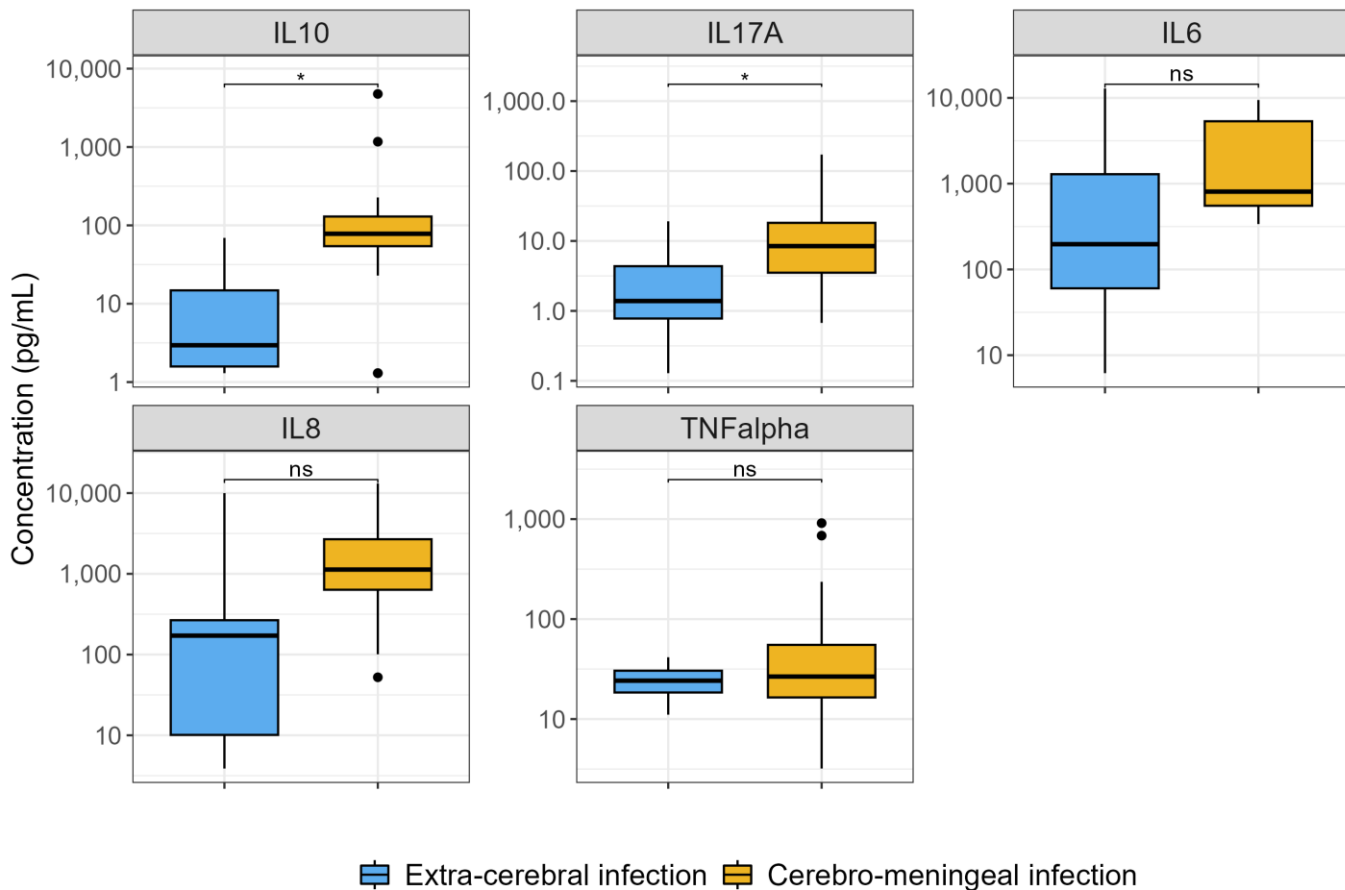


— Plasma — CSF • Observations --- IPRED — PRED

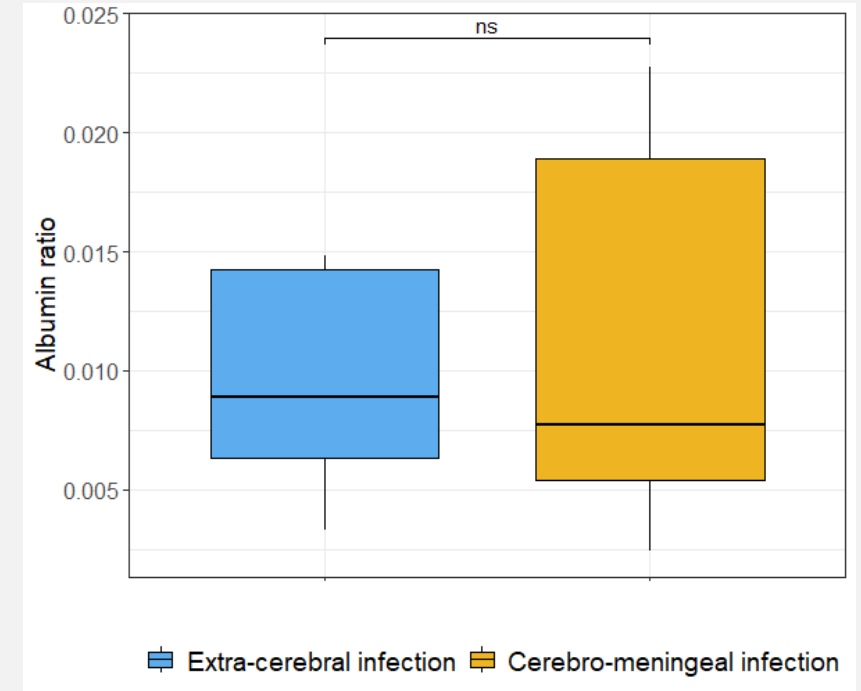
Impact of inflammation on CSF distribution

- 14/25 patients with cerebro-meningeal infections

Neuroinflammatory response



Albumin_{CSF} / Albumin_{plasma}



➤ No impact of the cerebro-meningeal infection on the CSF distribution of linezolid

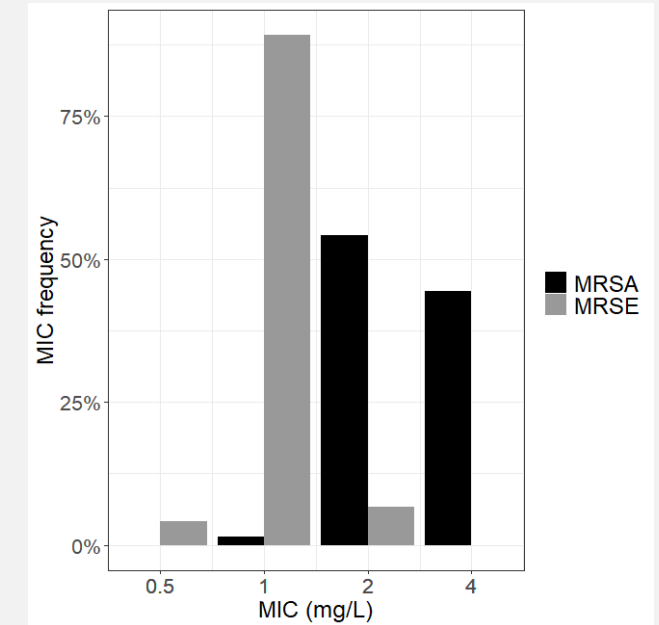
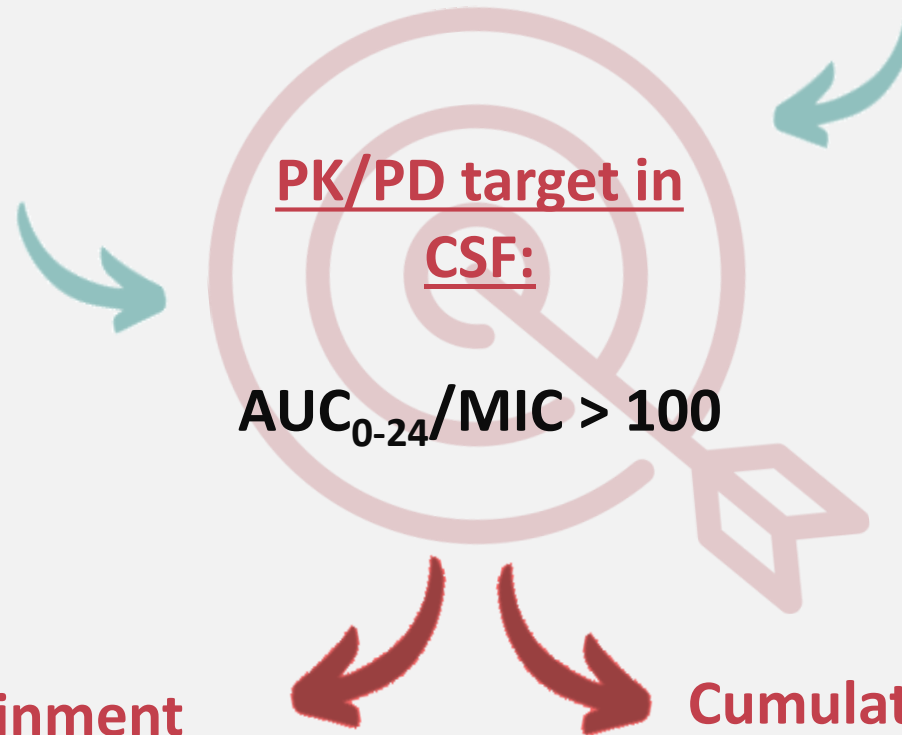
PTA and CFR

Monte-Carlo simulations for:

- 1200 mg/day = 600 mg q12h
- 1800 mg/day = 600 mg q8h
- 2700 mg/day = 900 mg q8h

Strains:

- Methicillin-resistant *Staphylococcus aureus*
- Methicillin-resistant *Staphylococcus epidermidis*



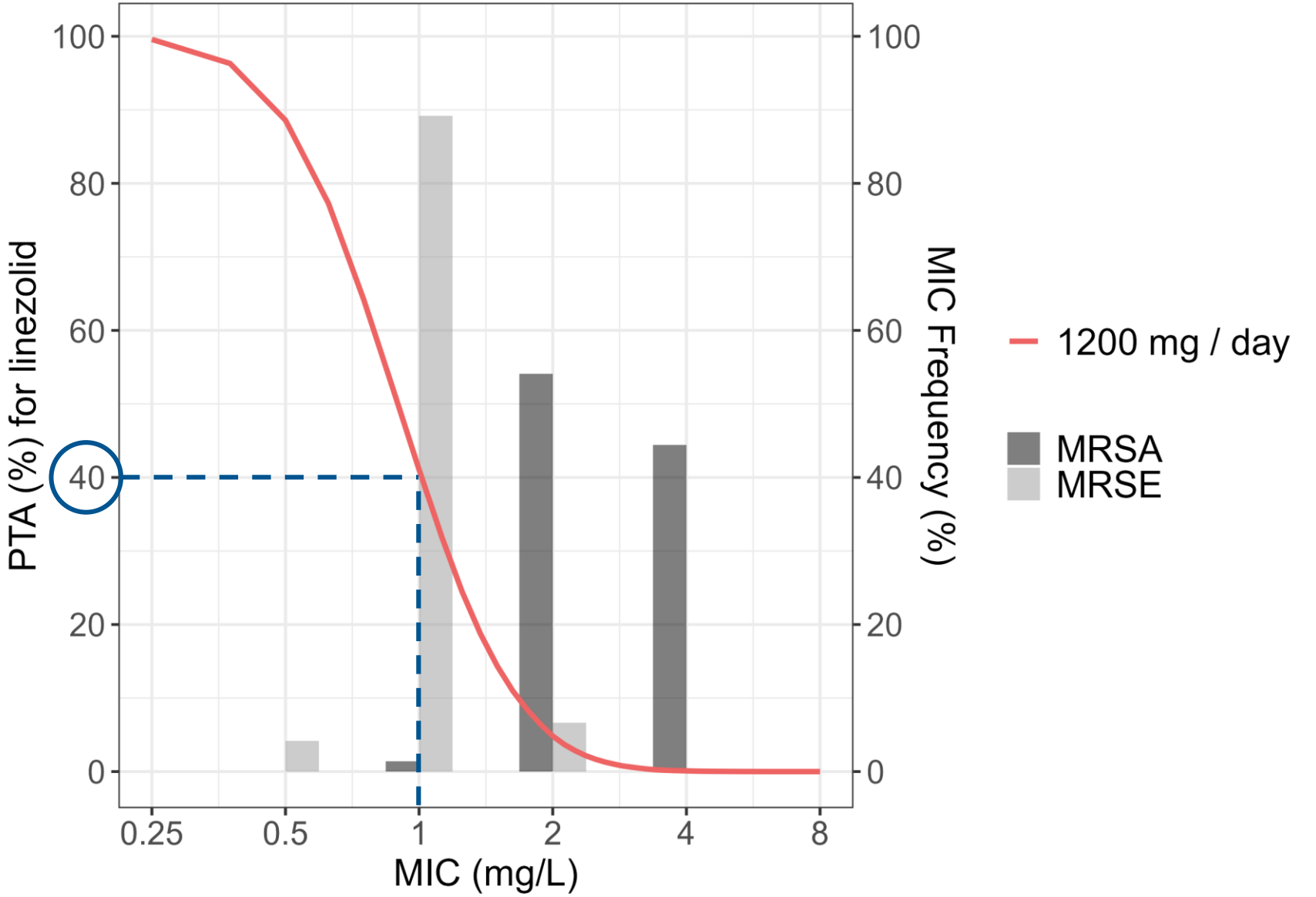
Probability of target attainment
(PTA)

Cumulative Fraction of Response (CFR)

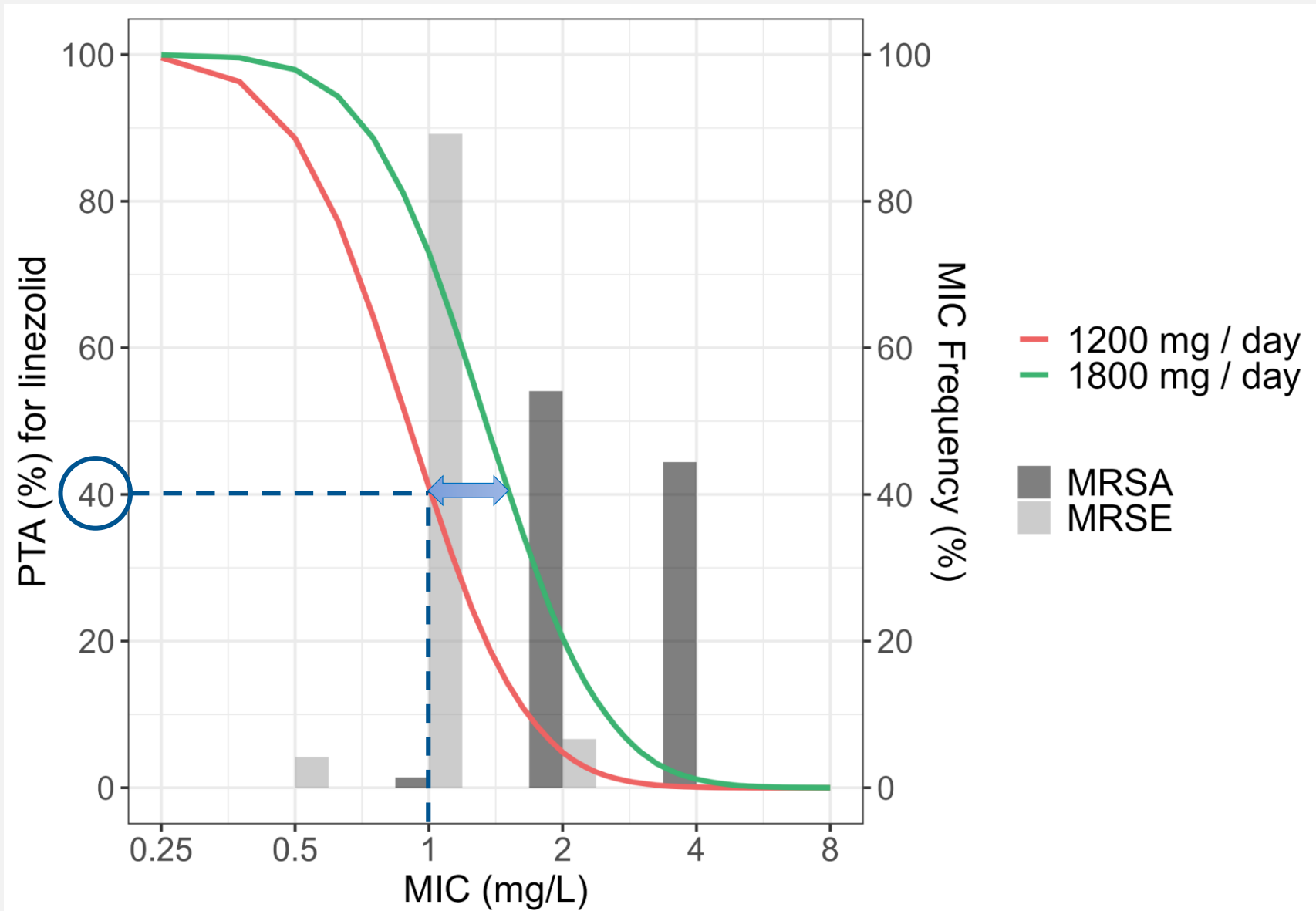
$$CFR = \sum_{i=1}^n PTA_i \times F_i$$

PTA_i : PTA for each CMI
 F_i : fraction of microorganisms at each MIC value

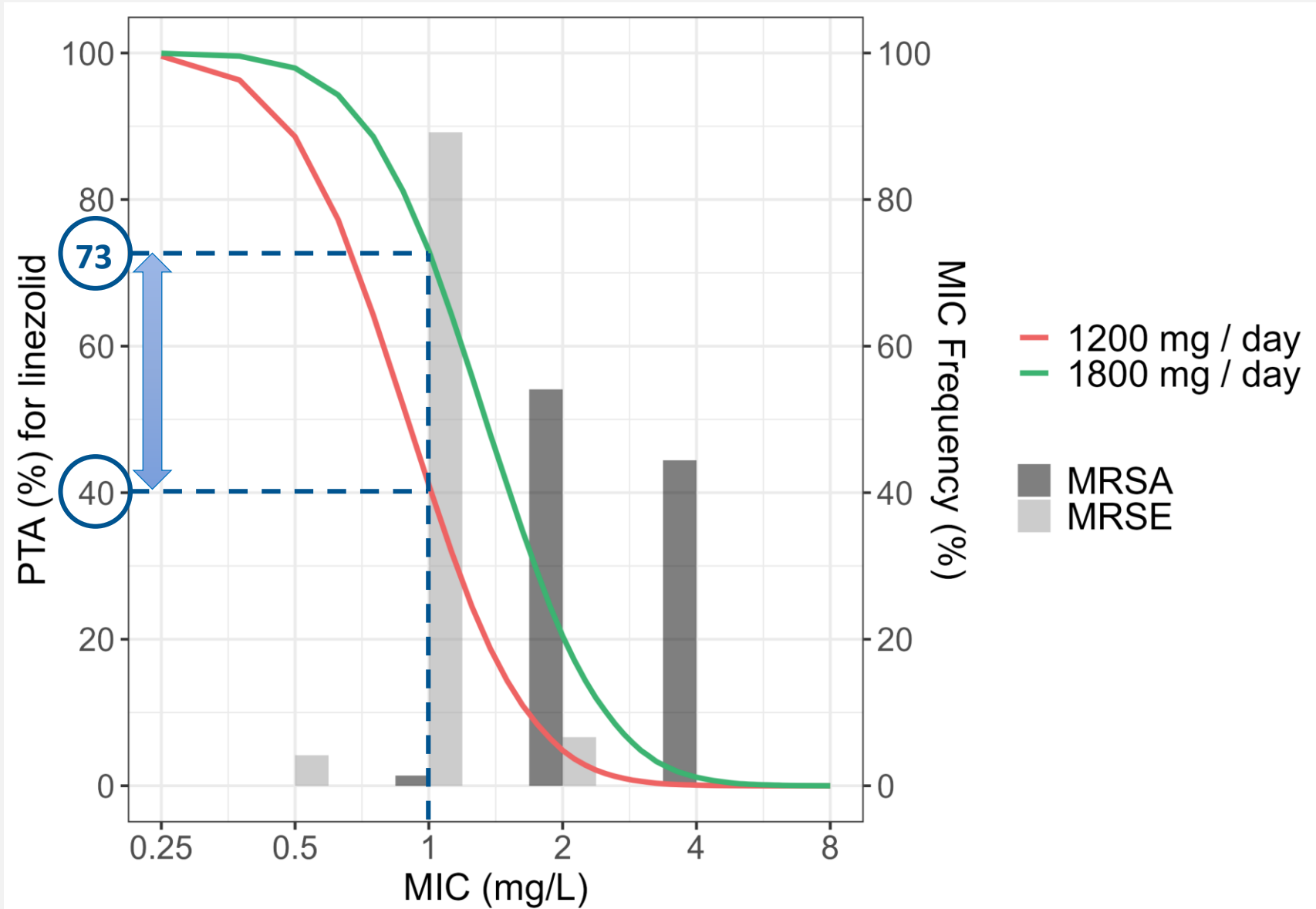
PTA of linezolid in CSF



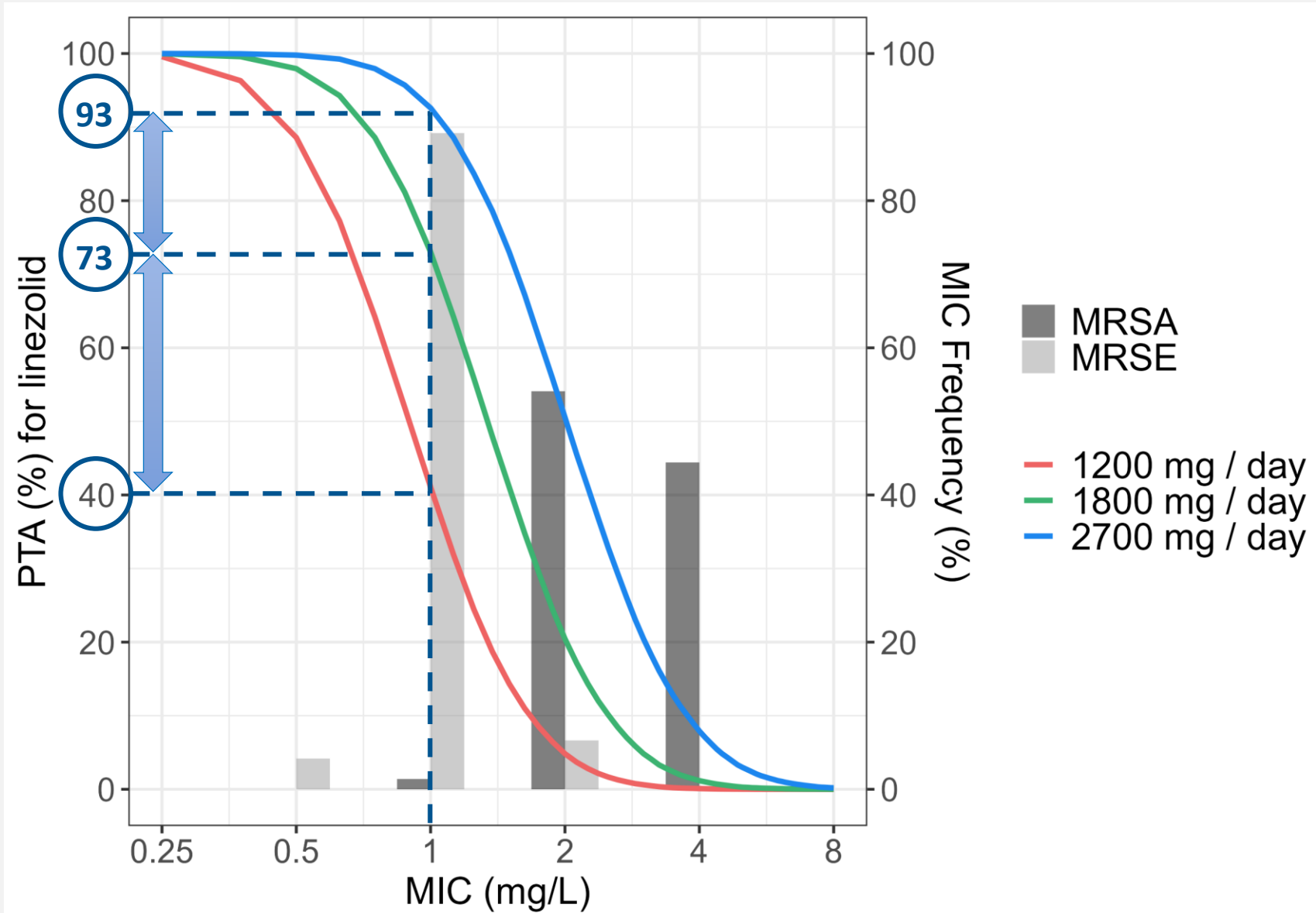
PTA of linezolid in CSF



PTA of linezolid in CSF



PTA of linezolid in CSF



CFR of linezolid

Daily dose	MRSA	MRSE
1200 mg	3.2 %	40.6 %
1800 mg	12.6 %	70.6 %
2700 mg	32.2 %	90.1 %

Conclusion

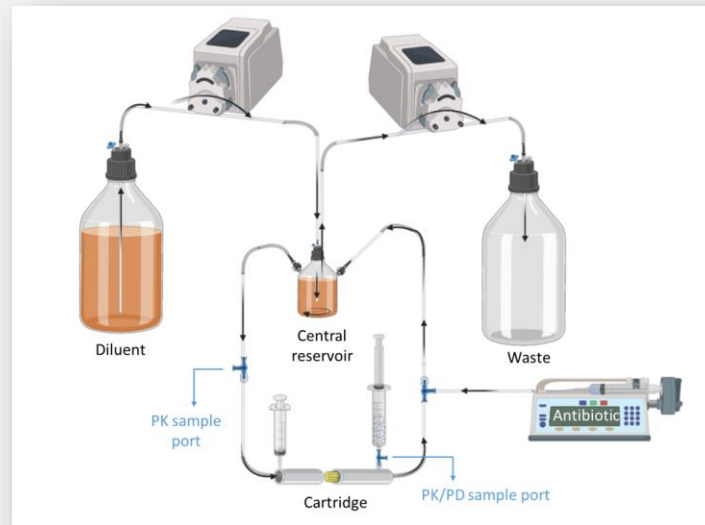
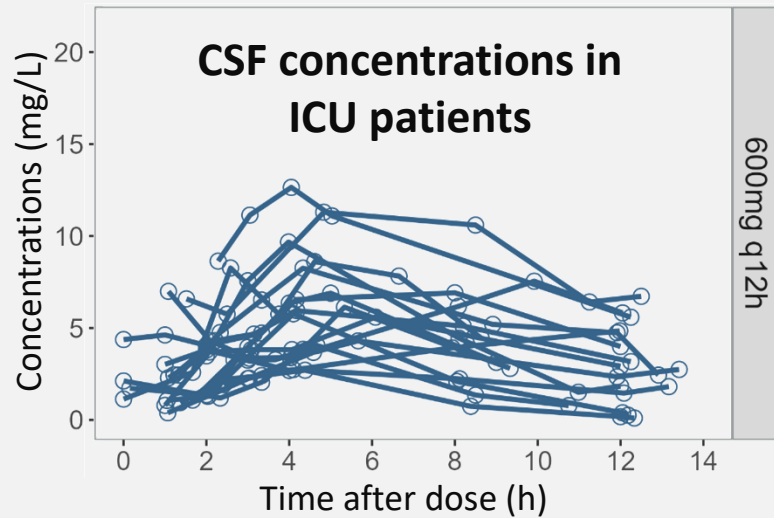
- **PK**
 - **Extensive CSF distribution** simply governed by **passive diffusion**
 - **Therapeutic monitoring of unbound plasma concentrations** to optimize dosing regimen
- **PK/PD**
 - **Current dosing regimens** (600 mg q12h and 600 mg q8h) **seem insufficient** to treat MRSA and MRSE cerebro-meningeal infections
 - 2700 mg / day seems more appropriate but **further investigations are necessary**

Perspectives

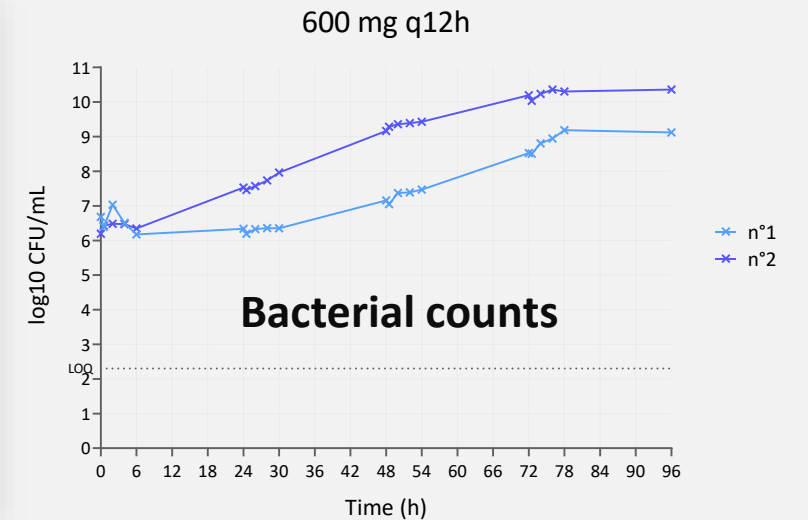
Noémie Prébonnaud
PhD student

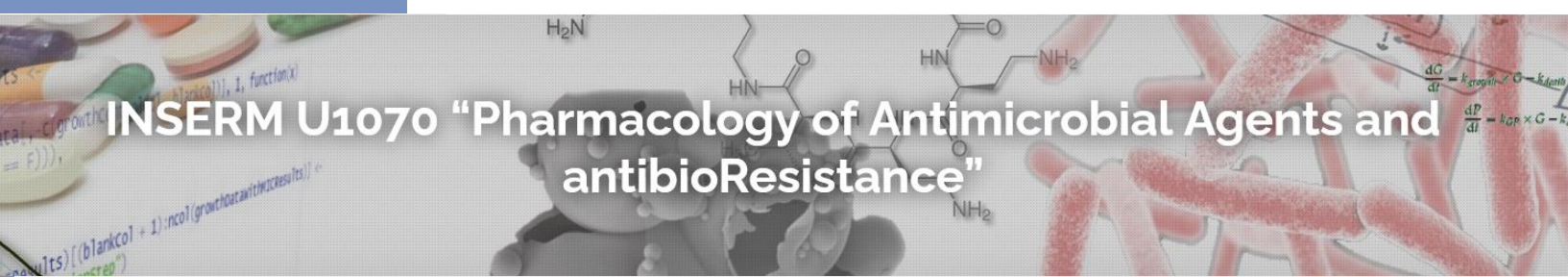


Evaluate the efficacy of Linezolid for multiple dosing regimens in a dynamic *in vitro* Hollow Fiber infection model



**Hollow-fiber
infection model**





INSERM U1070 "Pharmacology of Antimicrobial Agents and antibioResistance"

Thank you for your attention

