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

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33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
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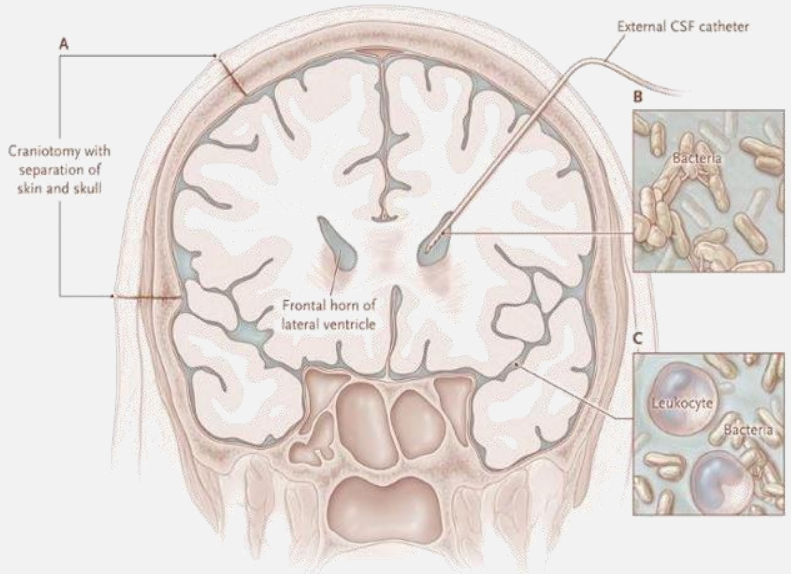
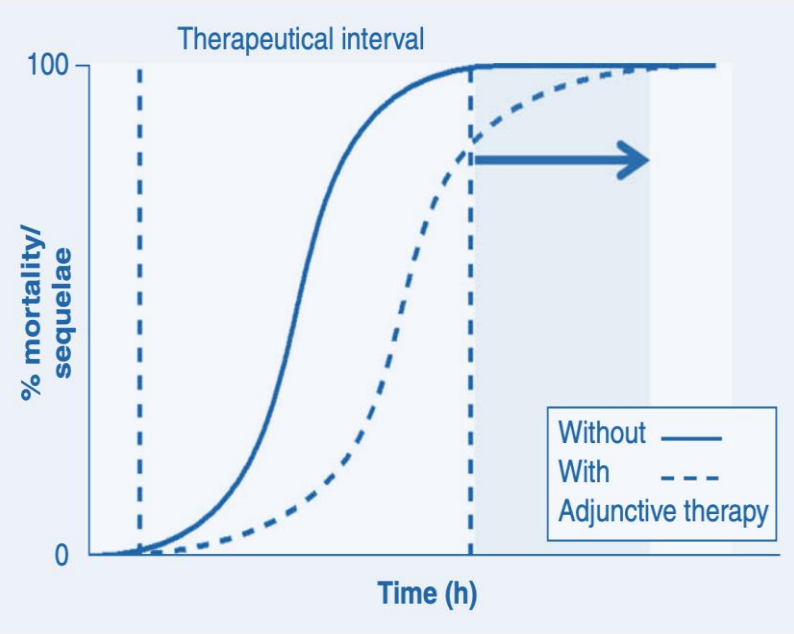
Nosocomial CNS infection



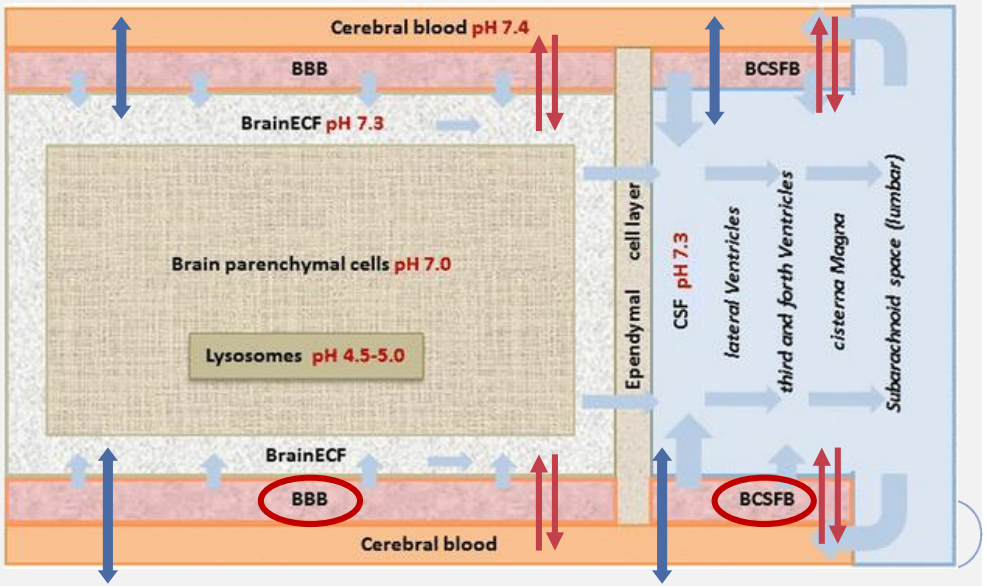
- Incidence of nosocomial cerebro-meningeal infections:
  - **Post-neurosurgery**: 0.3-8.6%
  - **Post EVD**: 0-22%
- High morbidity/mortality: **15 - 23%**

Need to optimize the treatment of CNS infection

Early-targeted antibiotherapy



Limited CSF distribution of antibiotics



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, Vancomycine, Piperacillin-Tazobactam, Daptomycine, Colistin.*

<u>Objective</u> :

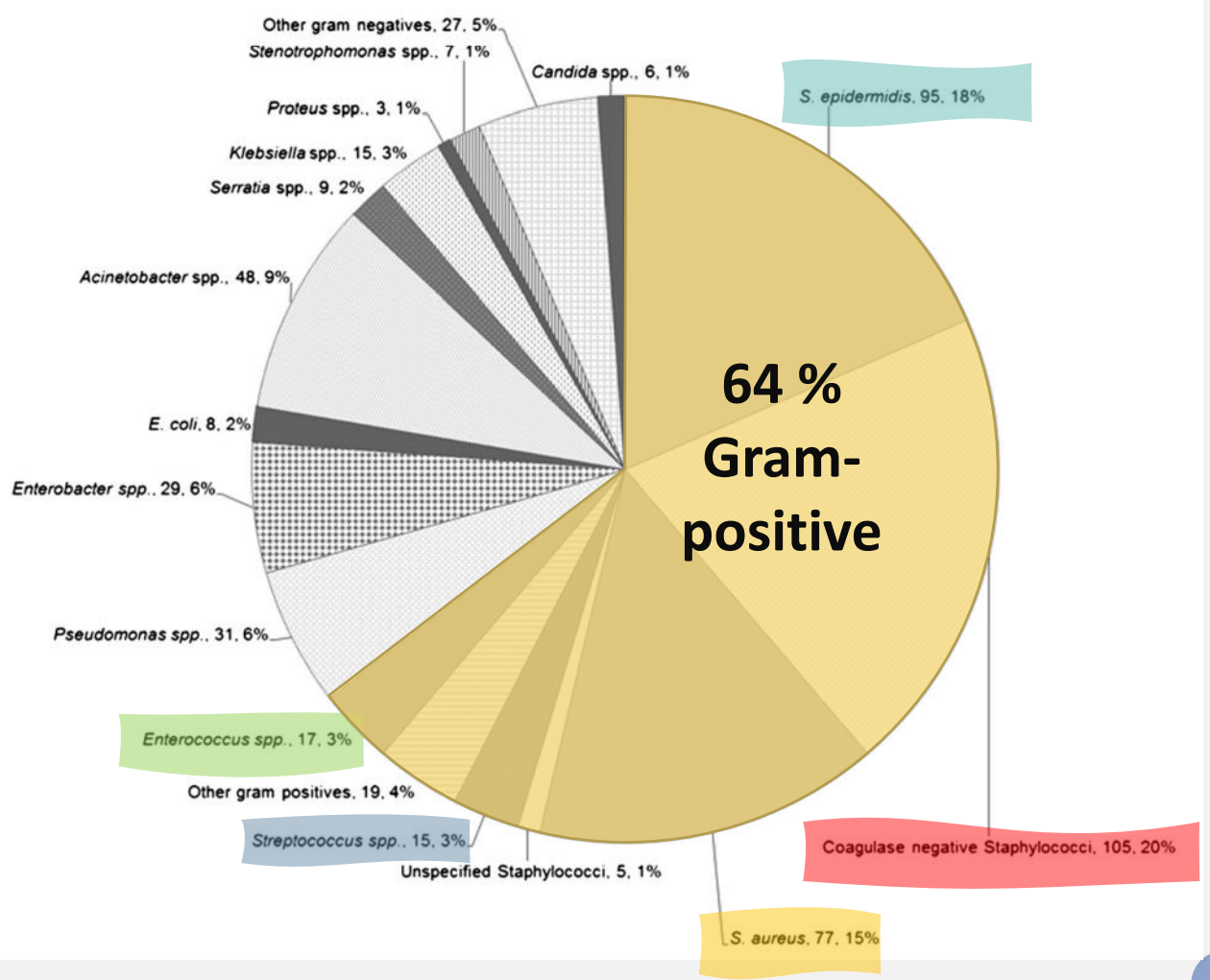
Characterize CSF distribution and **evaluate the efficacy of current dosing regimens** of antibiotics indicated in **nosocomial cerebro-meningeal infections** using a **PK/PD modelling approach**

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



Ramanan et al., BMC Infect Dis, 2015

PK/PD study of linezolid

Patients

25

Brain injured patients
with EVD

Dosing regimens

600 mg q12h
600 mg q8h

IV infusion over 30 min

Sampling

-1 0 1 2 3 4 5 6 7 8 9 10 11 12

4 Plasma / **7 CSF** (over 1h)

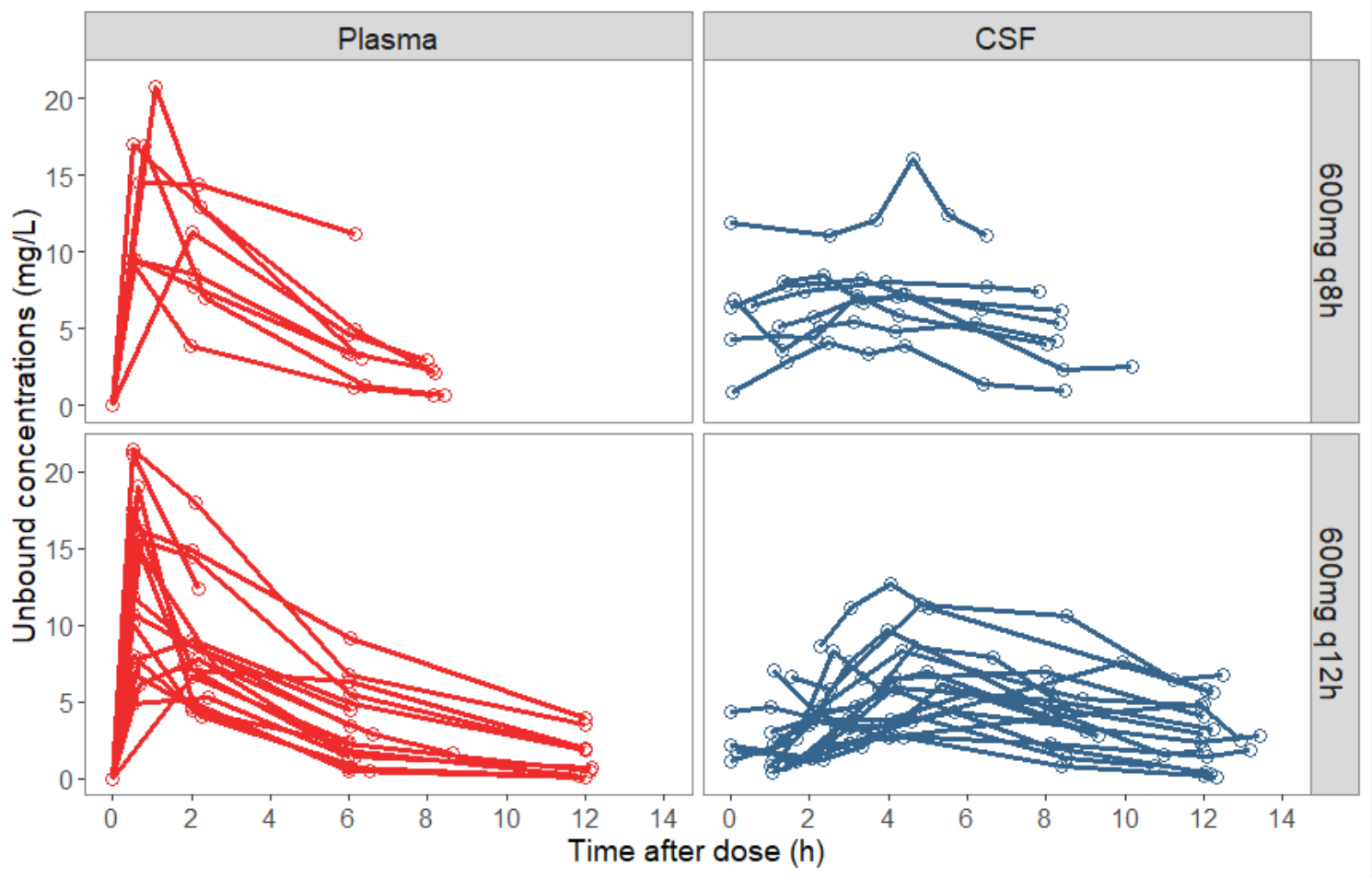
-1 0 1 2 3 4 5 6 7 8

Inflammation markers:
IL-6, IL-8, IL-10,
IL-17α, TNFα, albumin

PK/PD analysis

Population PK modeling
Dosing regimen
optimization

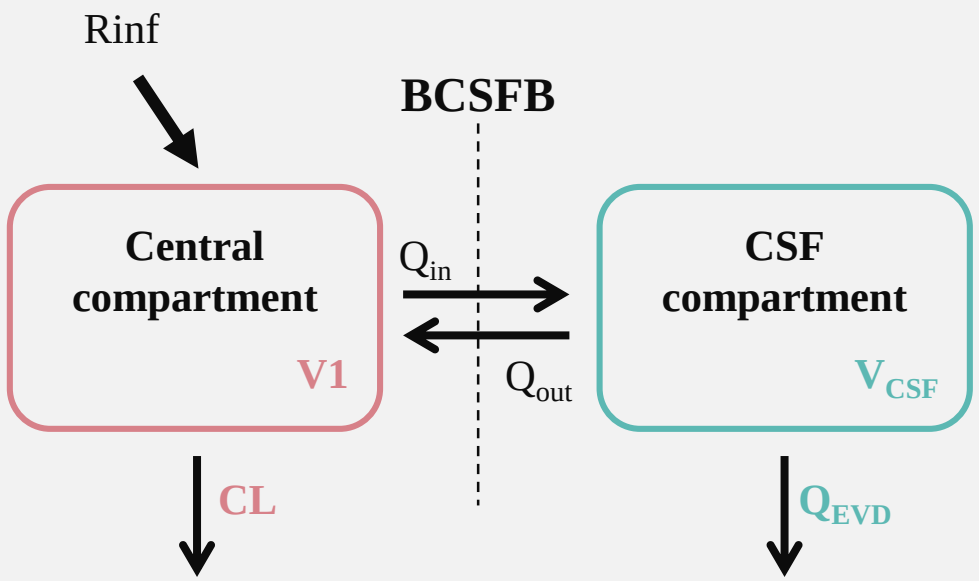
CSF distribution of linezolid



Unbound AUC ratio

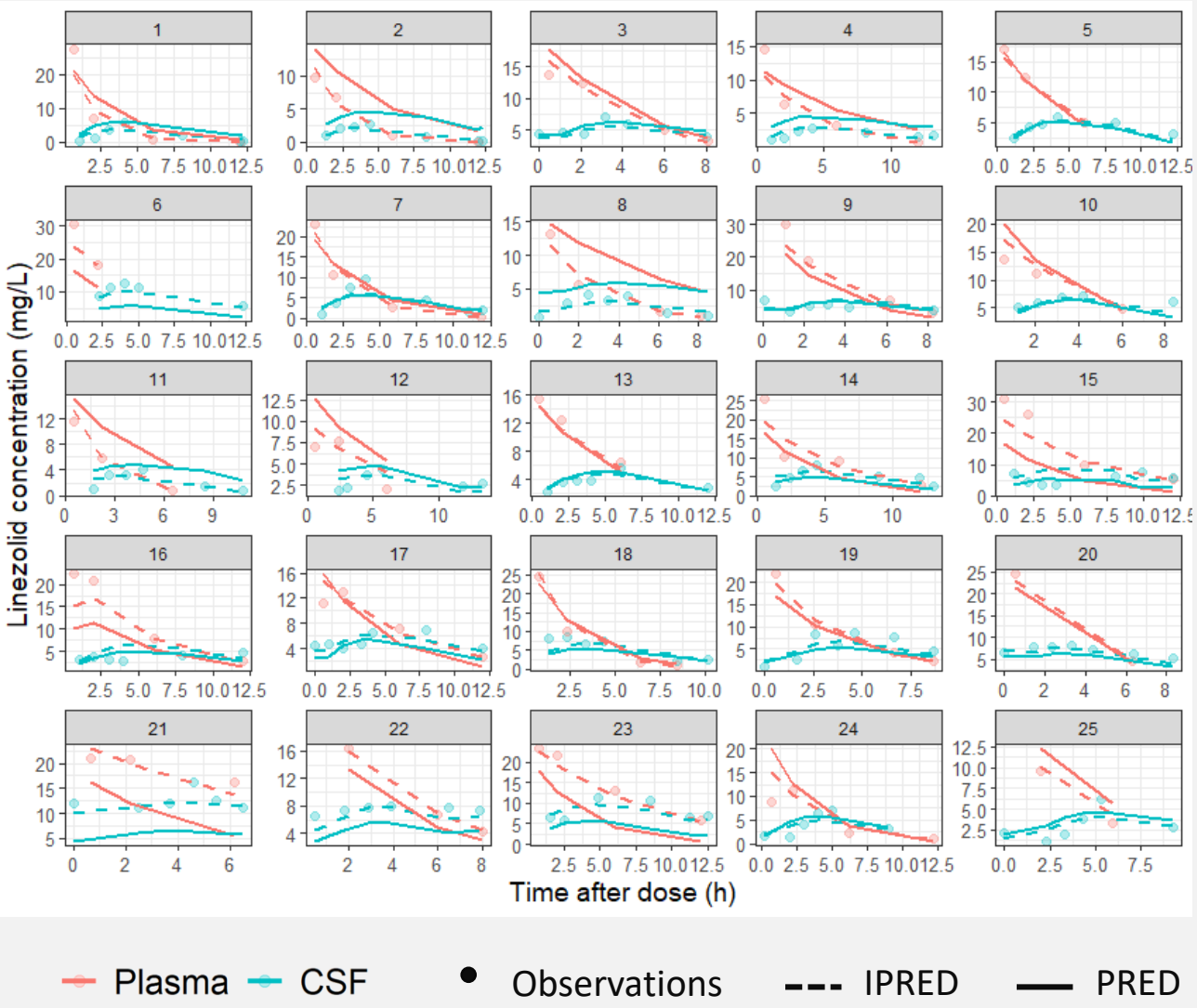
$AUC_{CSF}/AUC_{u,plasma}$ = 89.5%

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)	-

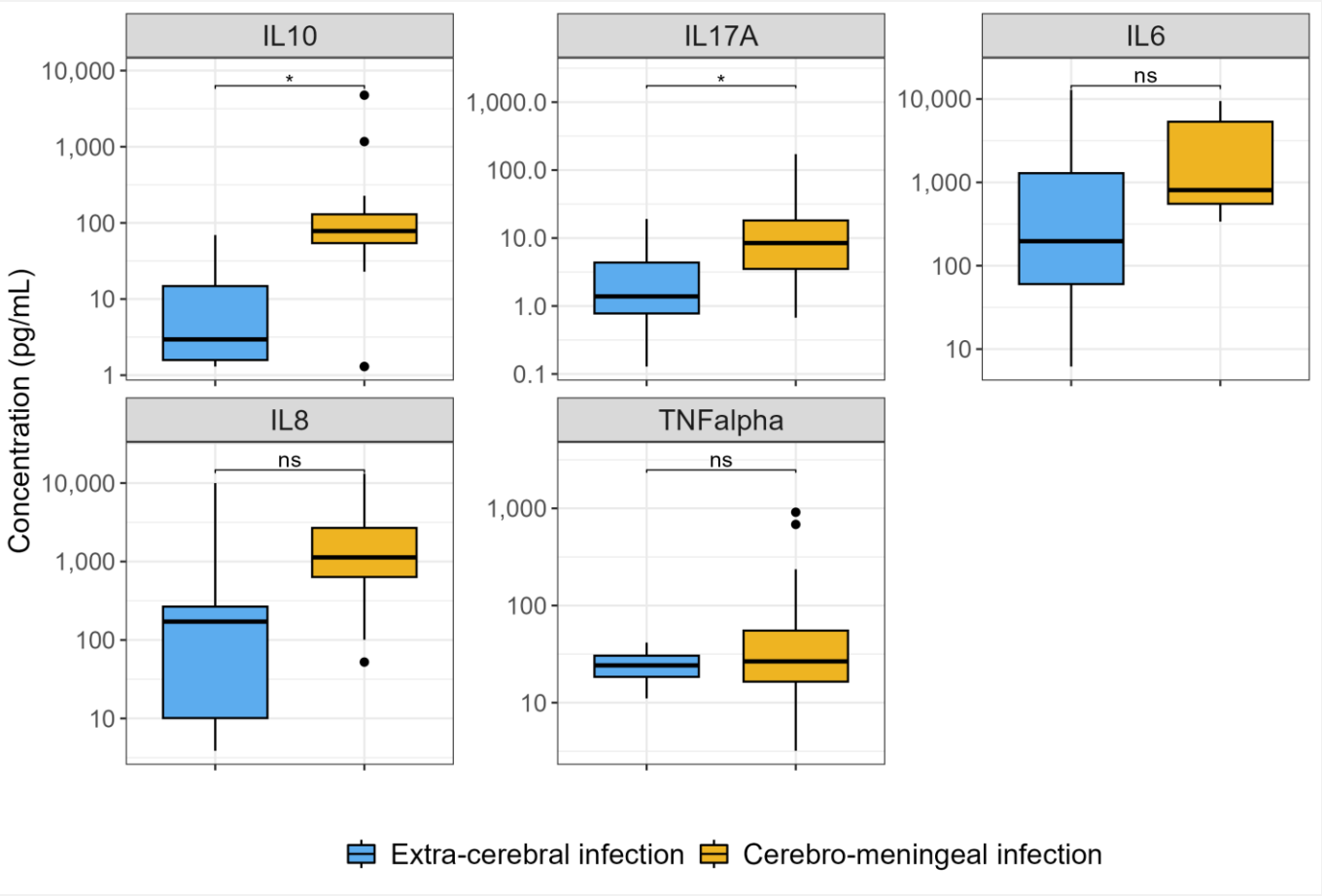
* Fixed to the physiological volume



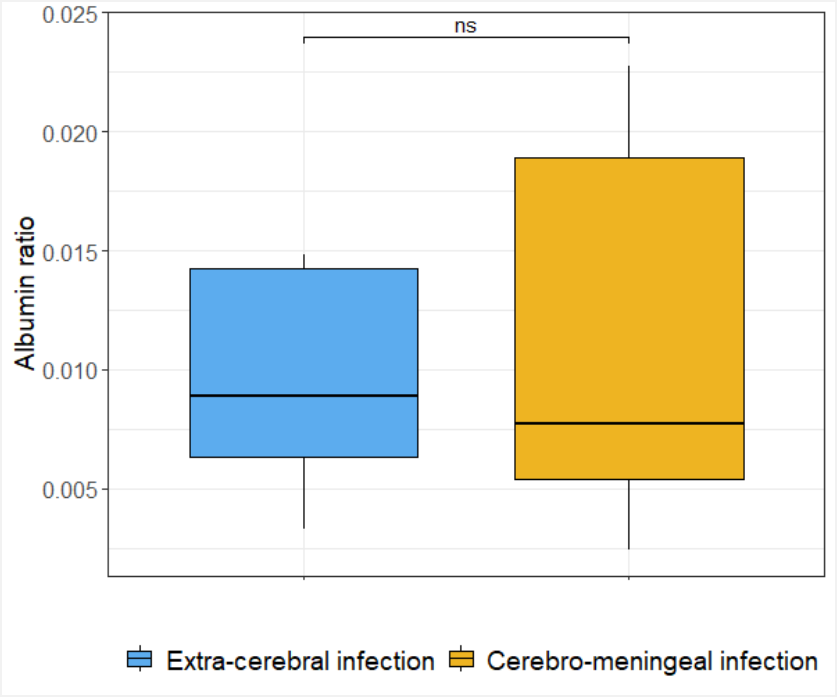
Impact of inflammation on CSF distribution

- **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

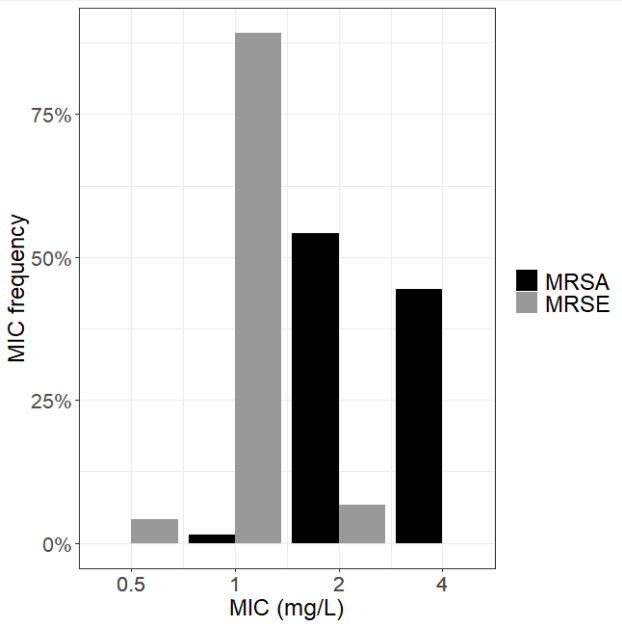
PTA and CFR

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*



PK/PD target in CSF:

$AUC_{0\text{-}24}/MIC > 100$

Probability of target attainment (PTA)

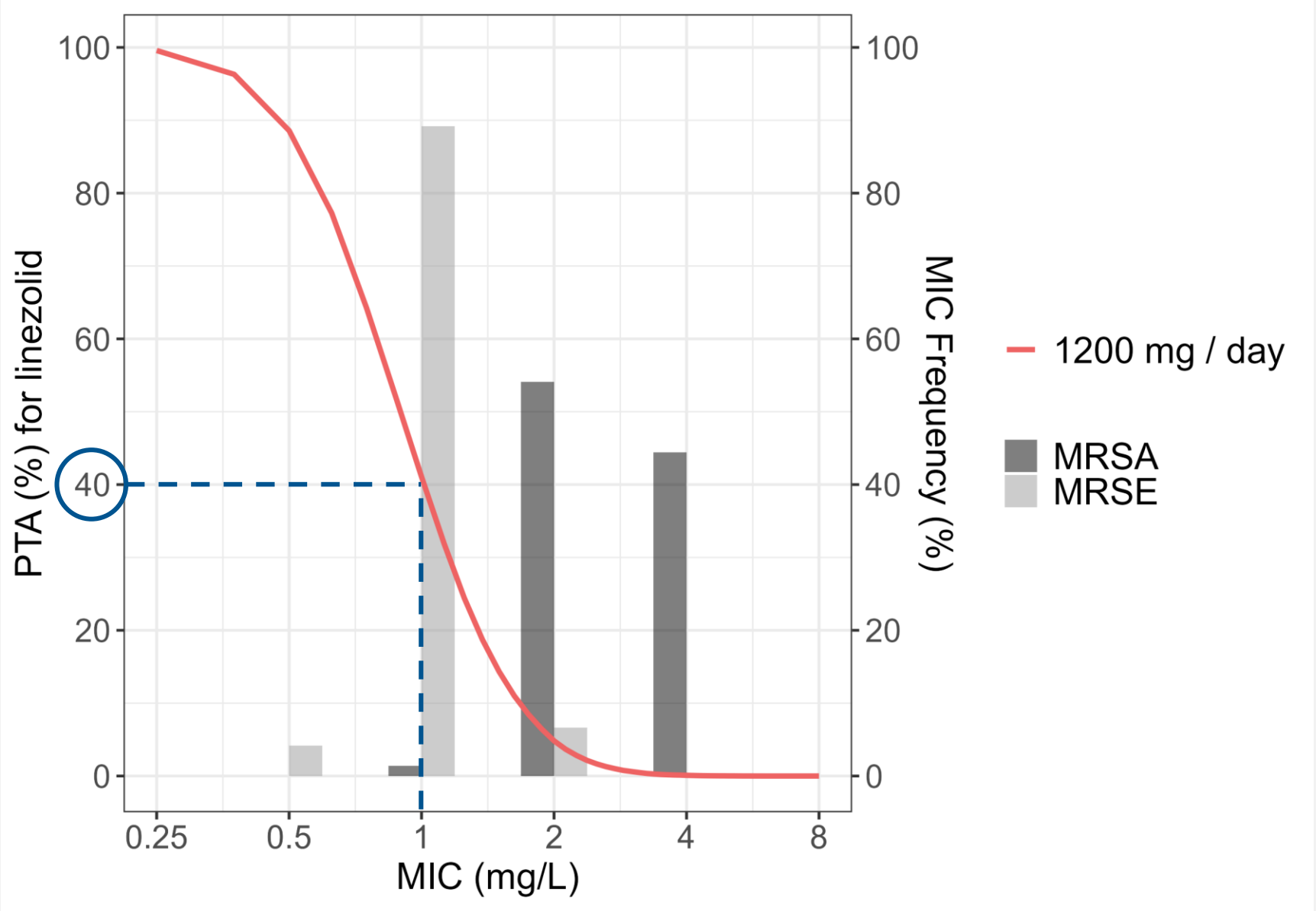
Cumulative Fraction of Response (CFR)

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

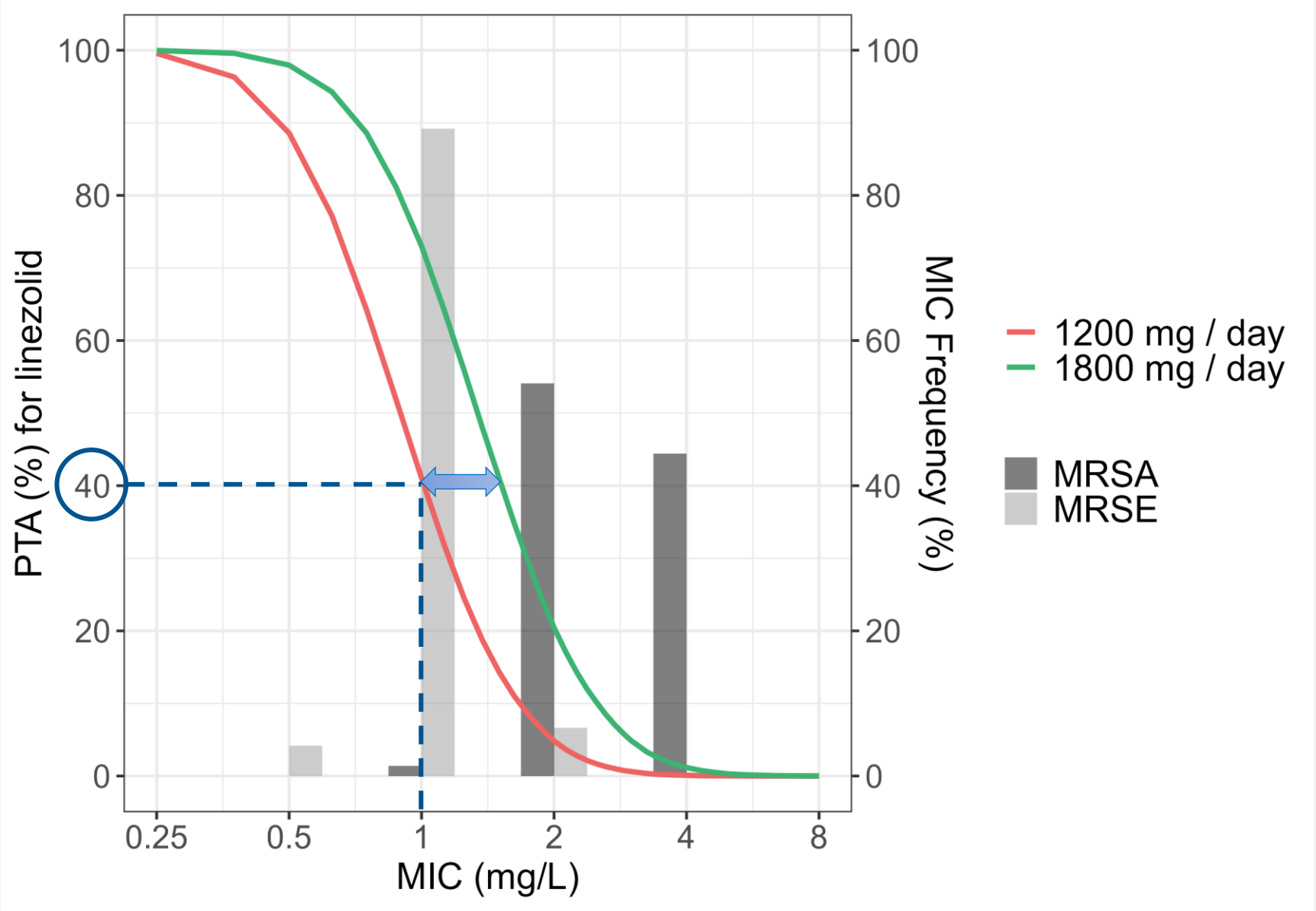
PTA_i : PTA for each CMI
F_i : fraction of microorganisms at each MIC value

Rayner et al., Clin Pharmacokinet, 2003
https://eucast.org/ mic_distributions_and_ecoffs/

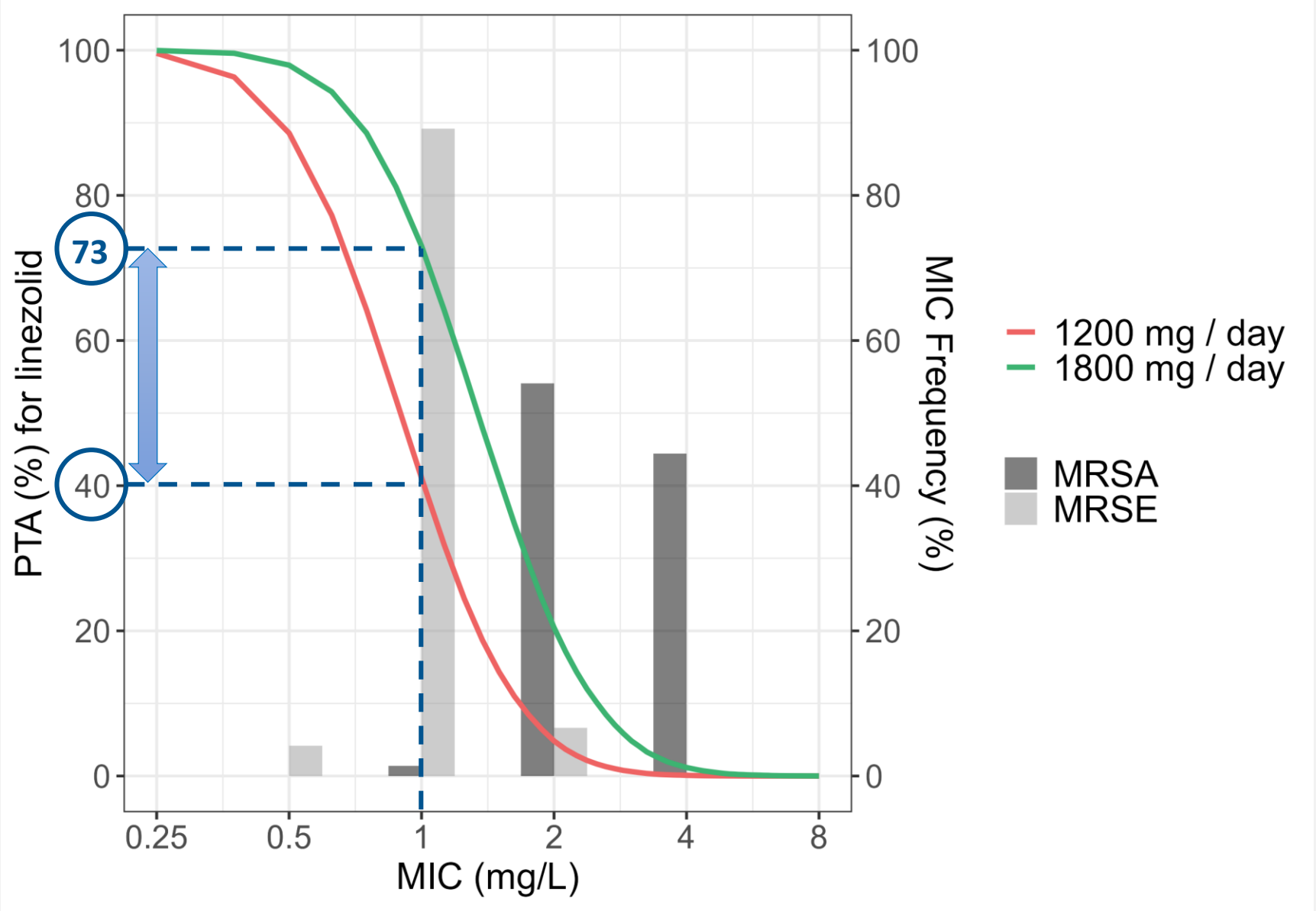
PTA of linezolid in CSF



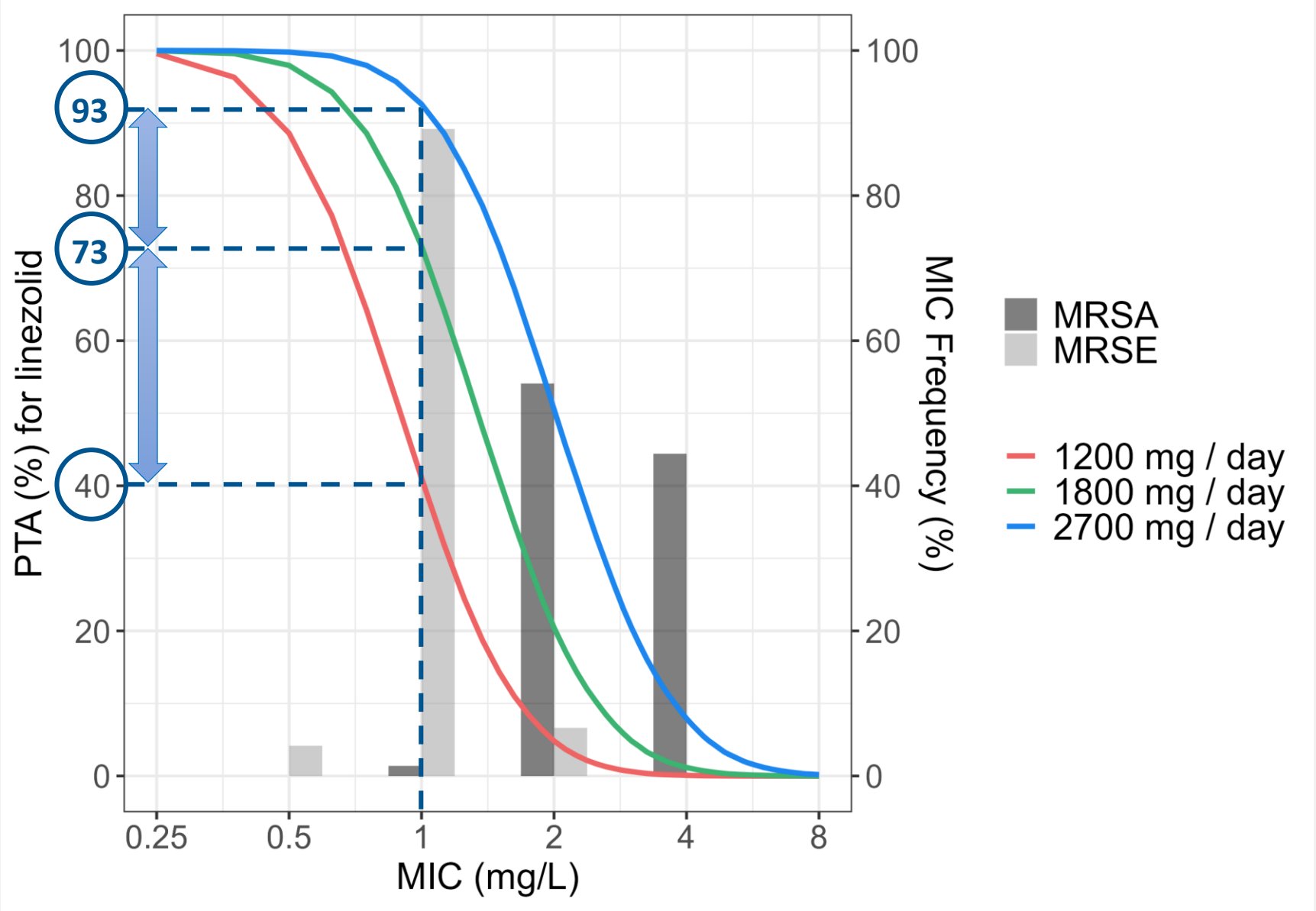
PTA of linezolid in CSF



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

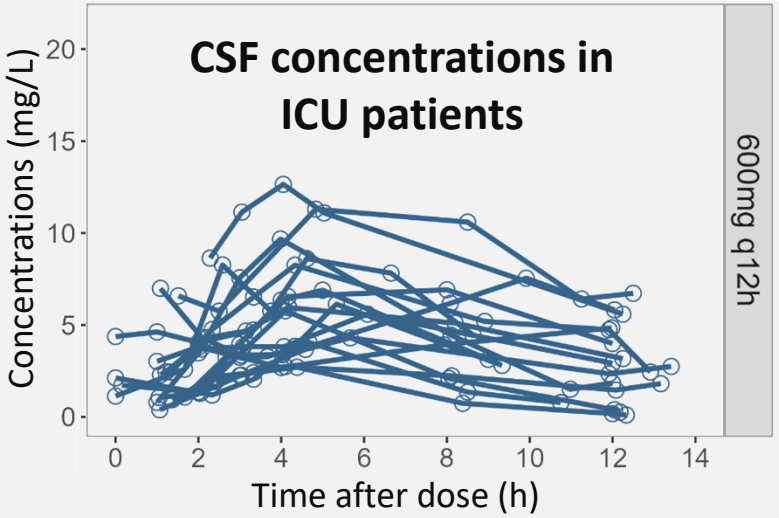
- **PK**
  - **Extensive CSF distribution** simply governed by **passive diffusion**
  - **Therapeutic monitoring of unbound plasma concentrations** to optimize dosing regimen

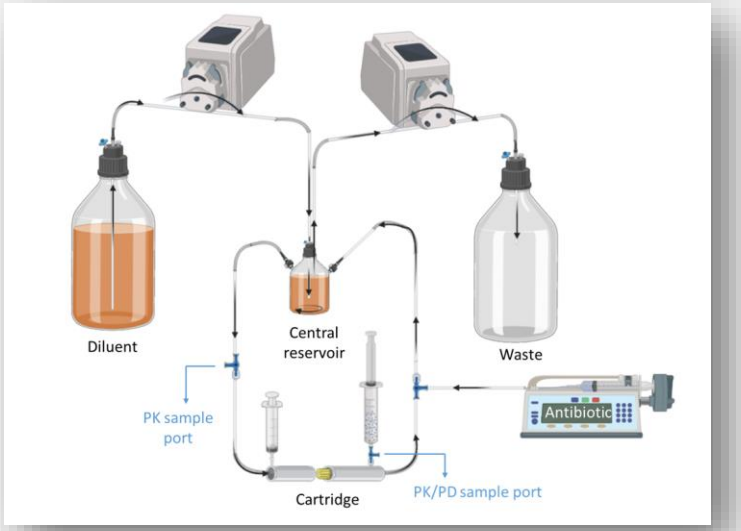
- **PK/PD**
  - **Current dosing regimens** (600 mg q12h and 600 mg q8h) **seem insufficient** to treat MRSA and MRSE cerebro-meningeal infections
  - 2700 mg / day seems more appropriate but **further investigations are necessary**

Perspectives

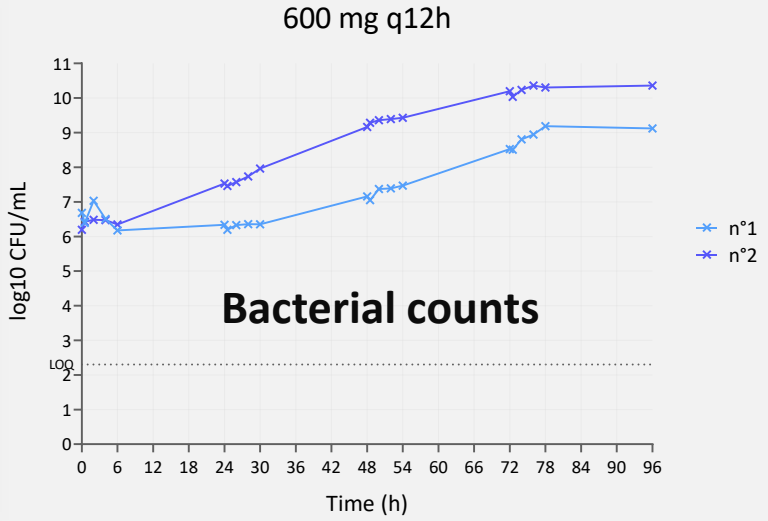
Noémie Prébonnaud
PhD student

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

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INSERM U-1070 PHAR2 PHARmacology of antimicrobial agents and antibioResistance

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