

Simulation-based prediction of pharmacokinetic/pharmacodynamic (PK/PD) index for linezolid to treat cerebral infections in critically ill patients

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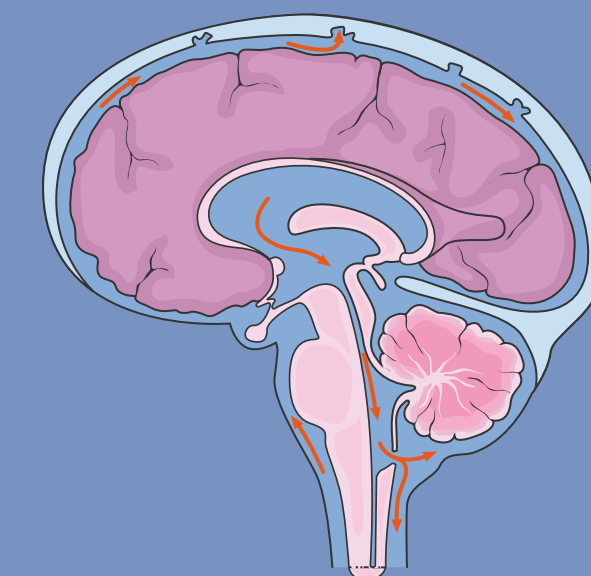
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I - Introduction

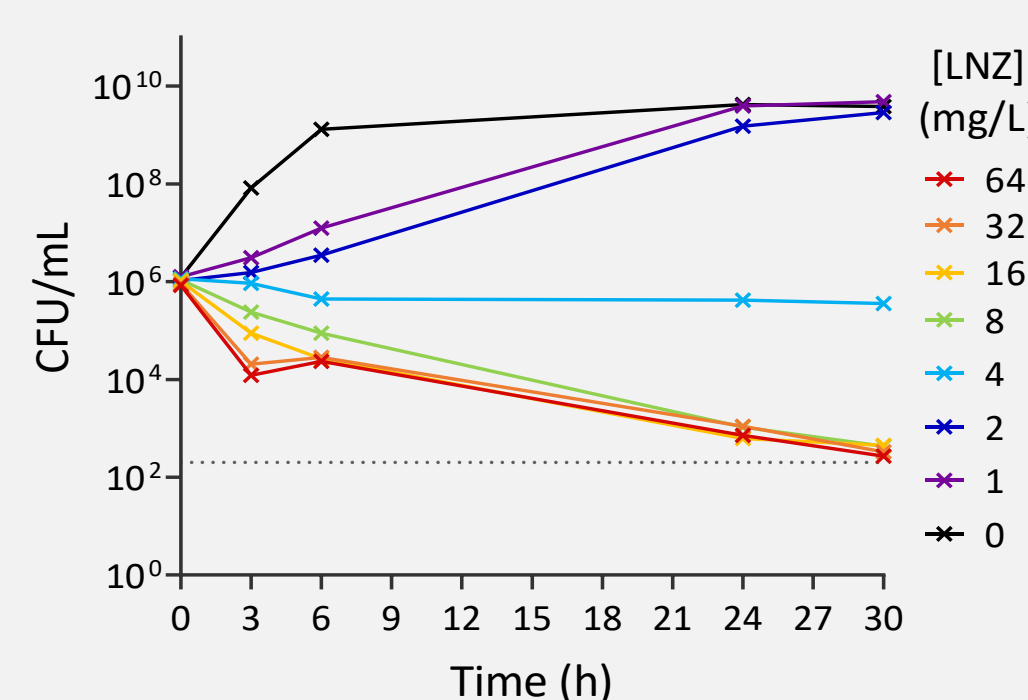
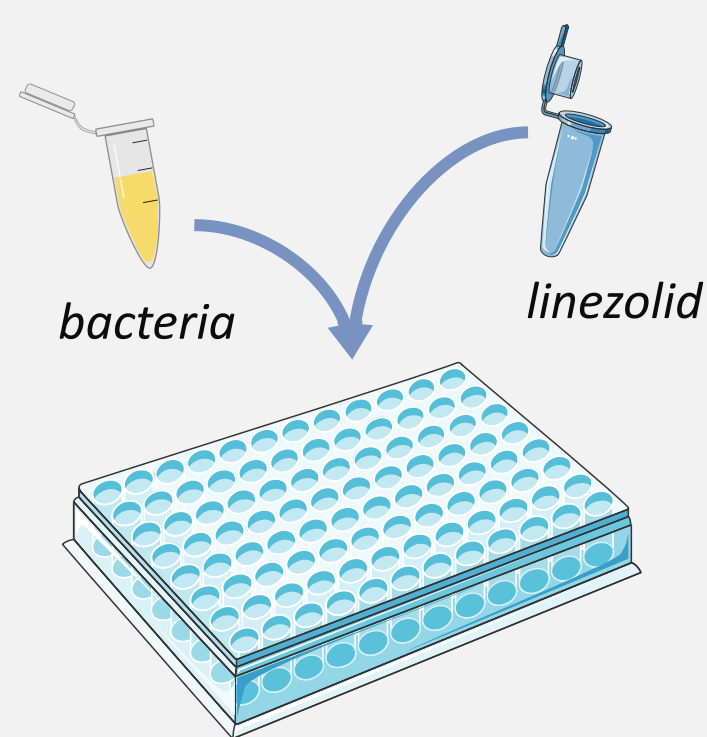
Linezolid is used to treat cerebro-meningeal infections caused by *Staphylococcus* spp. in critically ill patients, but its PK/PD index for efficacy in this context remains unclear. The current PK/PD indices are based on mouse thigh infection models (1) and clinical studies involving patients with bacteremia, respiratory or skin infections (2). Extrapolating these indices to cerebro-meningeal infections, may be unreliable due to the influence of the blood-brain barrier and the blood-cerebrospinal fluid barrier on the antibiotic distribution in cerebrospinal fluid (CSF). Therefore, this study aims to define specific PK/PD targets for linezolid by using PKPD models based on clinical CSF concentrations and *in vitro* time-kill curves.



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II - Materials / Methods

1 Figure 1. Experimental representation and typical plots of Time-Kill Curves



Time-Kill Curves (TKC) were performed over 30 h in Mueller-Hinton broth with linezolid concentrations ranging from 0 to 16 x MIC on 9 strains of *Staphylococcus* spp., including clinical and reference strains with a MIC ranging from 1.0 to 4.0 mg/L (4 *S. aureus* / 3 *S. epidermidis* / 2 *S. capitis*) (Figure 1).

- 4 • 3 PK/PD indices were calculated from each simulated plasma and CSF PK profile: fC_{max}/MIC , $fAUC/MIC$ and $fT_{>MIC}$
- The variations between the bacterial density at 24 h and the initial inoculum ($\Delta \log_{10}$ CFU/mL) were also determined from the simulated PD profiles and used as PD endpoints.
- The relationship between the PK/PD index values and the PD endpoints was modelled with a sigmoid Emax function. The most predictive index of linezolid efficacy was selected based on the R^2 and visual predictive checks (VPCs).

- 2 Strain-specific PD models were developed from TKC data using Monolix, with one proliferating susceptible (S) and one resting non-susceptible subpopulation (R). Linezolid increased the death rate of the S subpopulation following an Emax model, with some strains showing adaptive resistance through a binding function (ARon/ARoff) (3).

The structural PD model was combined to a clinical population PK model, describing the linezolid distribution between plasma and CSF with intensive care unit patients (4), to get a complete PKPD model (Figure 2).

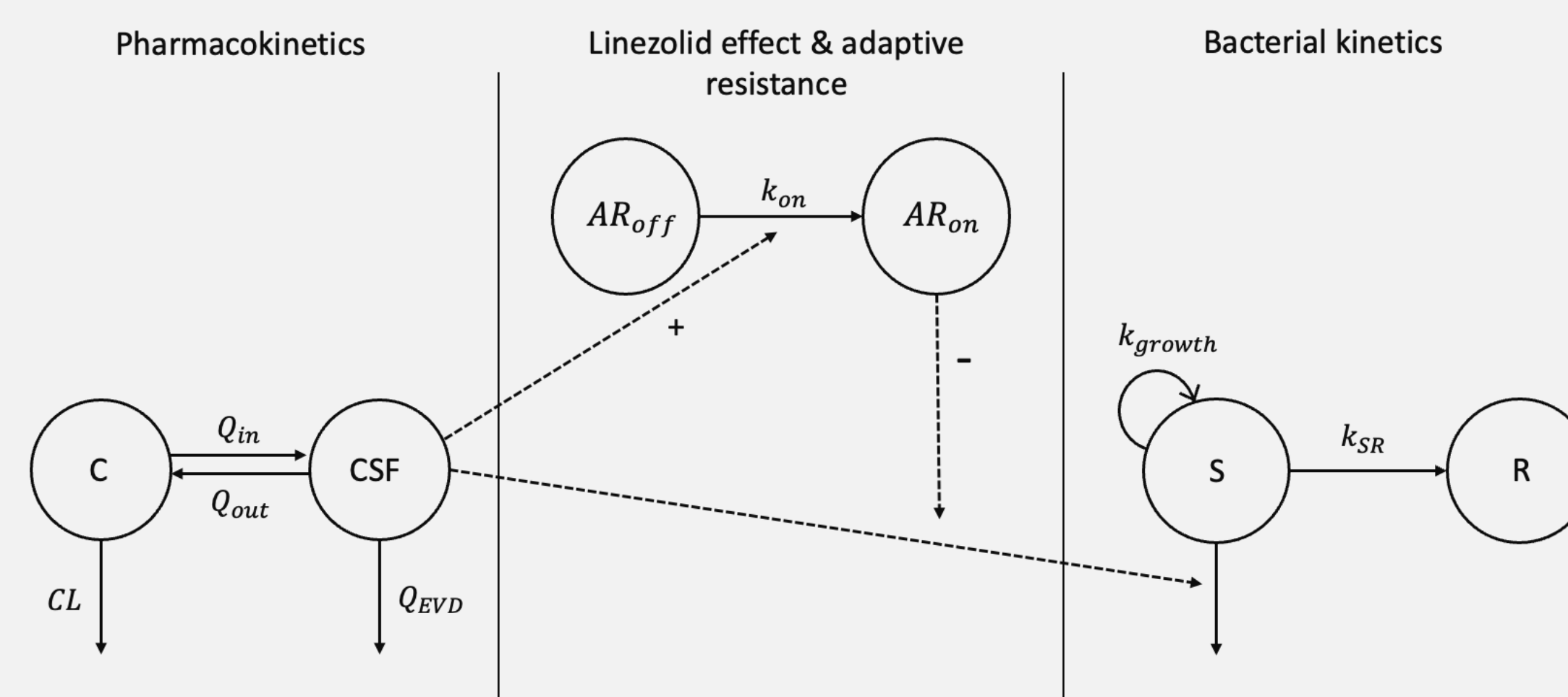


Figure 2. Structure of the PKPD model

- 3 For each strain, a dose fractionation study was simulated over 24 h using human PK parameters and strain-specific PD parameters. A total of 101 dosing regimens were simulated using MrgSolve in R, including intermittent (with various dosing intervals and continuous infusions).



III - Results

- 1 **For CSF-derived PK/PD indices**, $fAUC/MIC$ and $fT_{>MIC}$ were selected as the best predictors of linezolid efficacy, based mainly on VPCs (Figure 3a).

The $fAUC/MIC$ required for bacteriostatic and bactericidal effects ($-2 \log_{10}$ CFU/mL) was estimated to be 30 and 73. Whereas for CSF $fT_{>MIC}$, the corresponding targets were 63% and 91%, respectively.

- 2 **For plasma-derived PK/PD indices**, only the $fAUC/MIC$ stood out as the best predictor of linezolid efficacy in CSF infections, based on both R^2 values and VPCs (Figure 3b).

The plasma $fAUC/MIC$ required for bacteriostatic and bactericidal effects were estimated to be 38 and 91, respectively.

Figure 3a. VPCs of CSF-derived PK/PD indices against *Staphylococcus* spp. in CSF

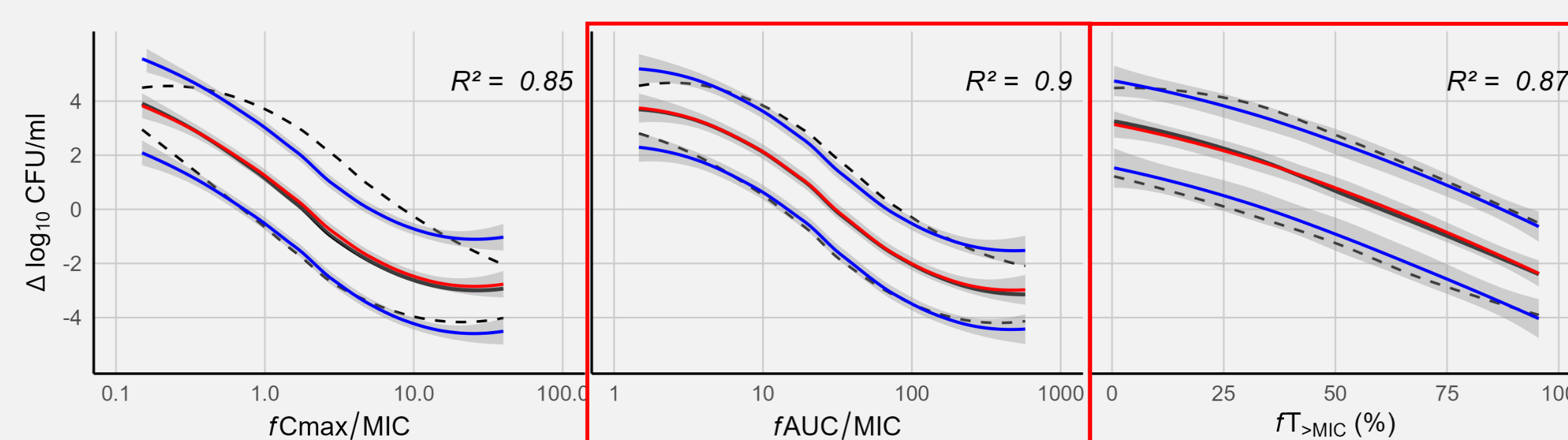
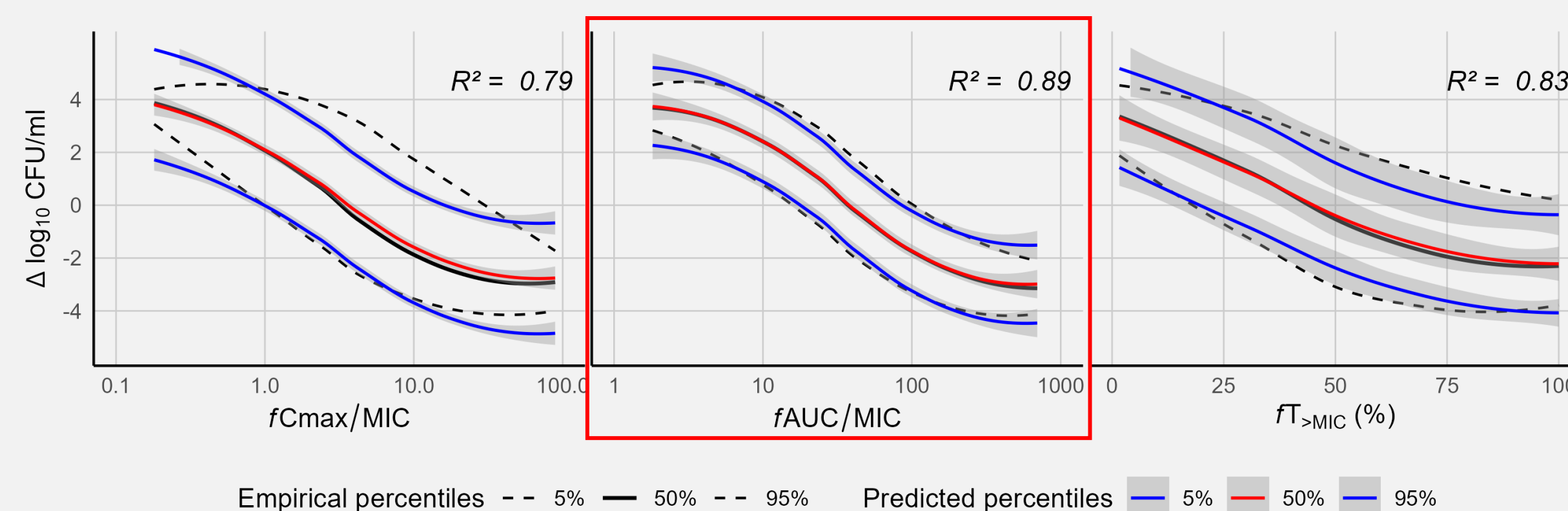


Figure 3b. VPCs of plasma-derived PK/PD indices against *Staphylococcus* spp. in CSF



IV - Conclusion

This study showed that plasma-derived $fAUC/MIC$ was as good a predictor as CSF-derived $fAUC/MIC$ of linezolid efficacy in the treatment of cerebro-meningeal infections caused by *Staphylococcus* spp., facilitating its therapeutic monitoring in practice. Plasma $fAUC/MIC$ of 80-120 has been associated with higher clinical success rates in ICU patients with other infections (2). According to the simulation, achieving this PK/PD target in a context of cerebro-meningeal infection would result in a bactericidal effect ($fAUC/MIC$ of 91 associated with 2-log kill). These findings relied on PK/PD modelling based on *in vitro* studies and therefore need to be confirmed through clinical outcomes.