Predicting antibacterial efficacy of linezolid on *Staphylococcus aureus* in cerebral infections using *in vitro* hollow fiber model and pharmacokinetic-pharmacodynamic modeling

Noémie PREBONNAUD

Inserm U1070, Université de Poitiers, France

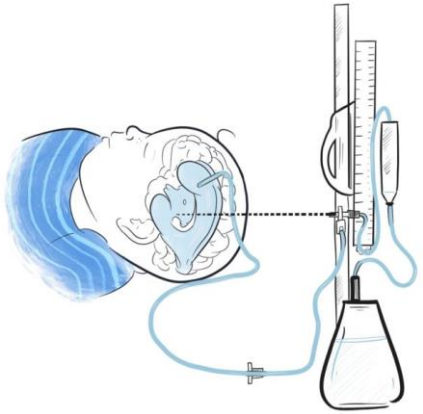
Copenhagen, Denmark
15–18 April 2023

33rd ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

PHRCN 16-0501 « PKPOP-LCR »

Multicenter clinical trial

- Patients in ICU + EVD



- CNS or other sites infection

9 IV Antibiotics

Vancomycin
Daptomycin
Ceftazidime
Meropenem
Colistin
Linezolid
Piperacillin/Tazobactam
Ceftaroline
Cefepime

Objectives

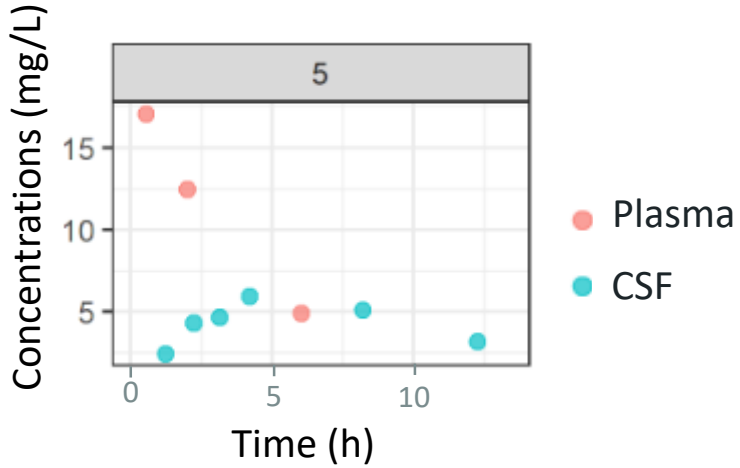
→ Distribution in CSF
→ PKPop study
→ Efficacy of dosing regimens (PTA)

PK/PD of Linezolid – PKPOP-LCR

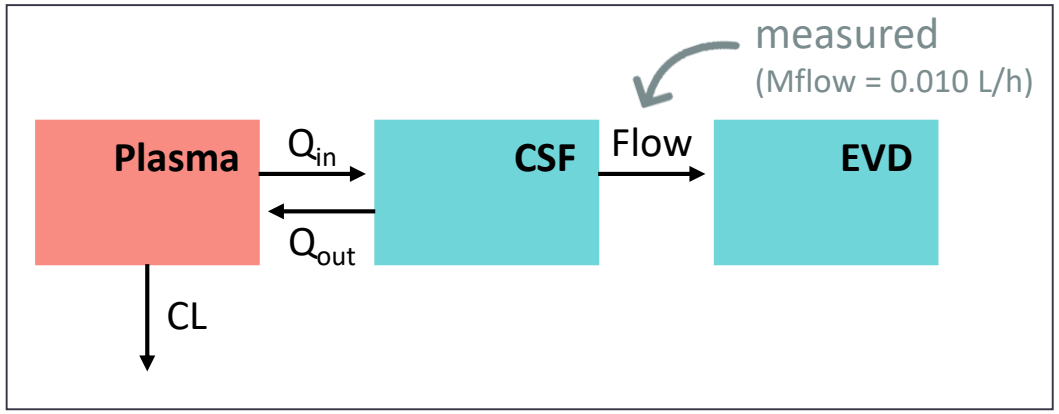
25 patients

≈ 50% with CNS infection

Blood (Plasma) & CSF (via EVD) samples



Ratio of free AUC_{CSF}/AUC_{Plasma}
89.51%



Monte Carlo simulations
(50 000 patients)

MRSA and MRSE

PTA
PK/PD Index
AUC/MIC > 100

1200 mg /d PTA < 10% of patients

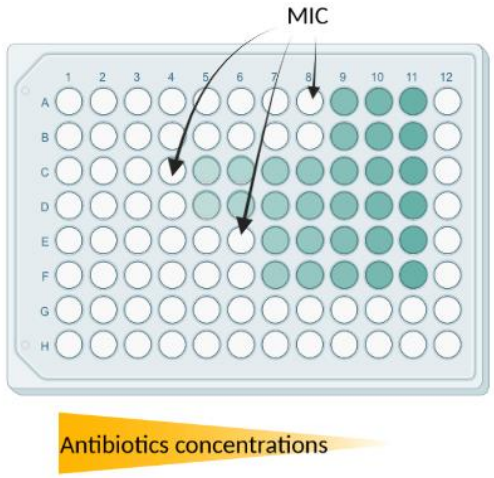
1800 mg /d PTA 20% des patients

Objective

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

Methods

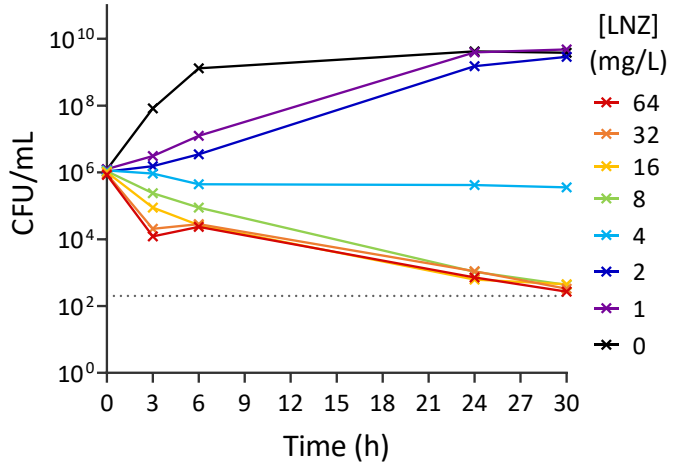
MIC + ATBg



S.aureus *(n = 4)*

S.epidermidis *(n = 3)*

S.capitis *(n = 2)*

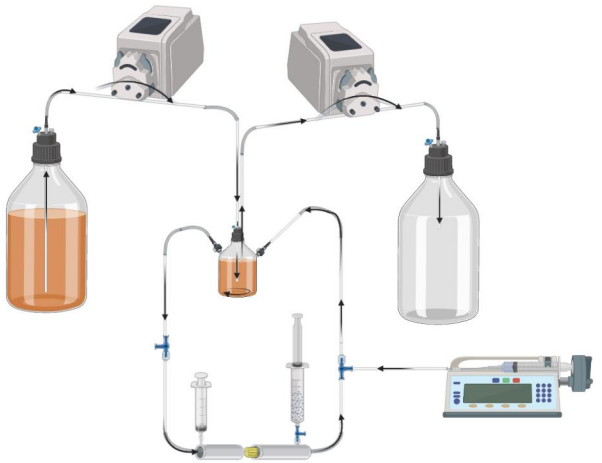


TKC *(n = 3)*

PD model

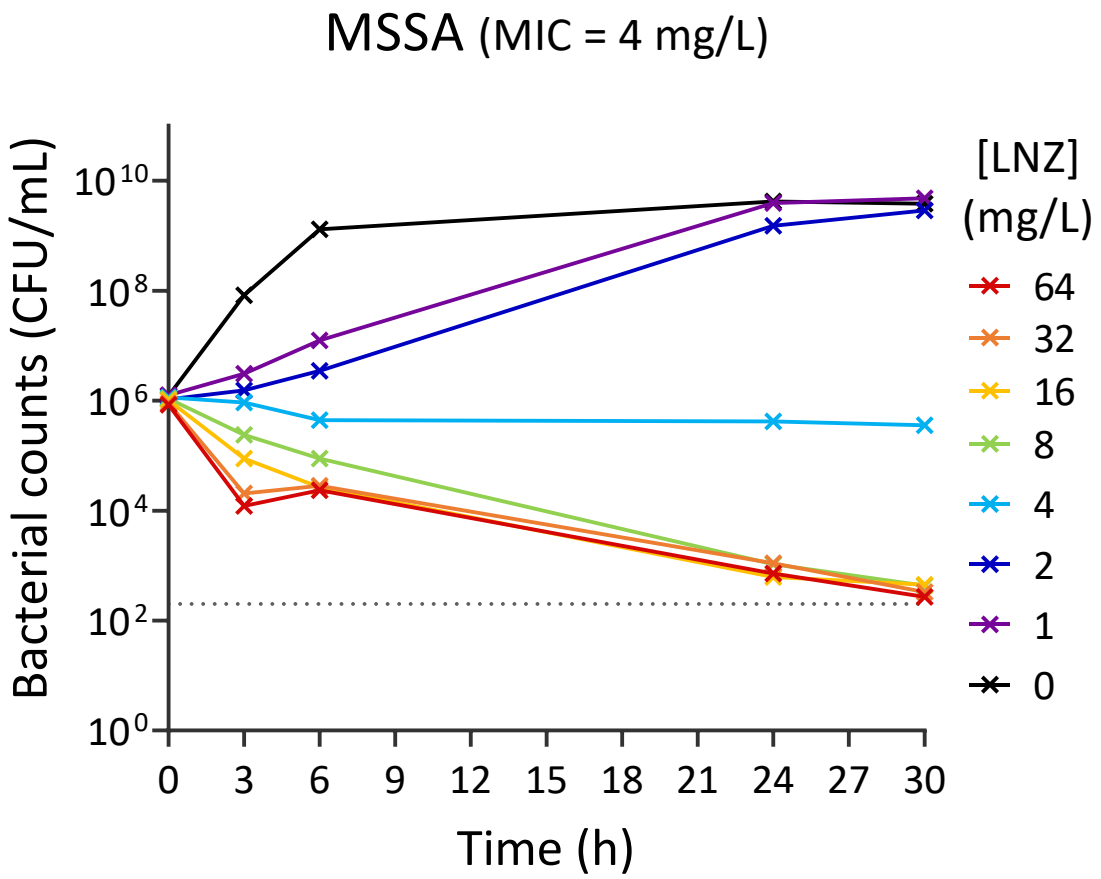
PK-PD model

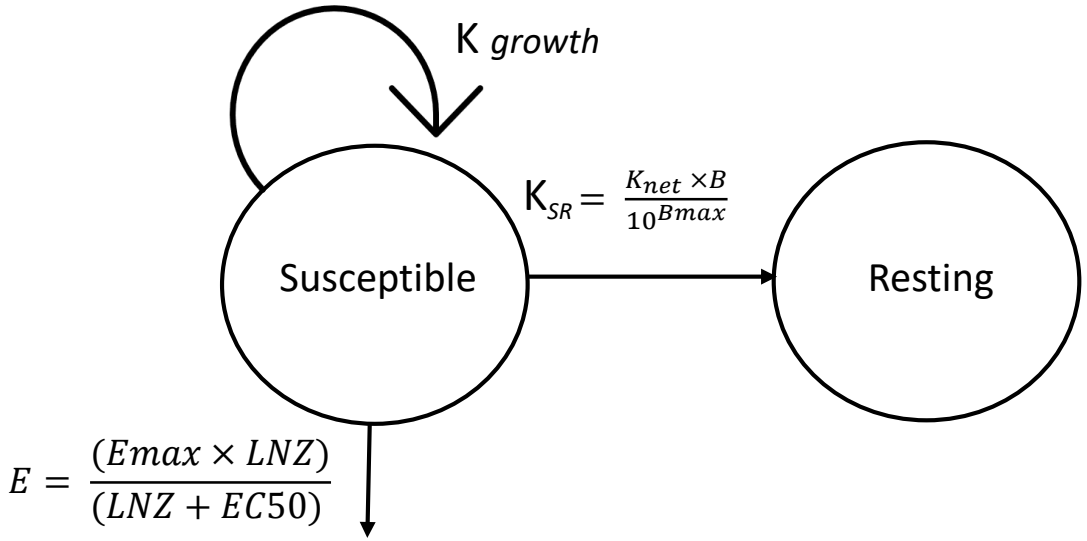
Prediction of dosing regimens



HF *(n = 2)*

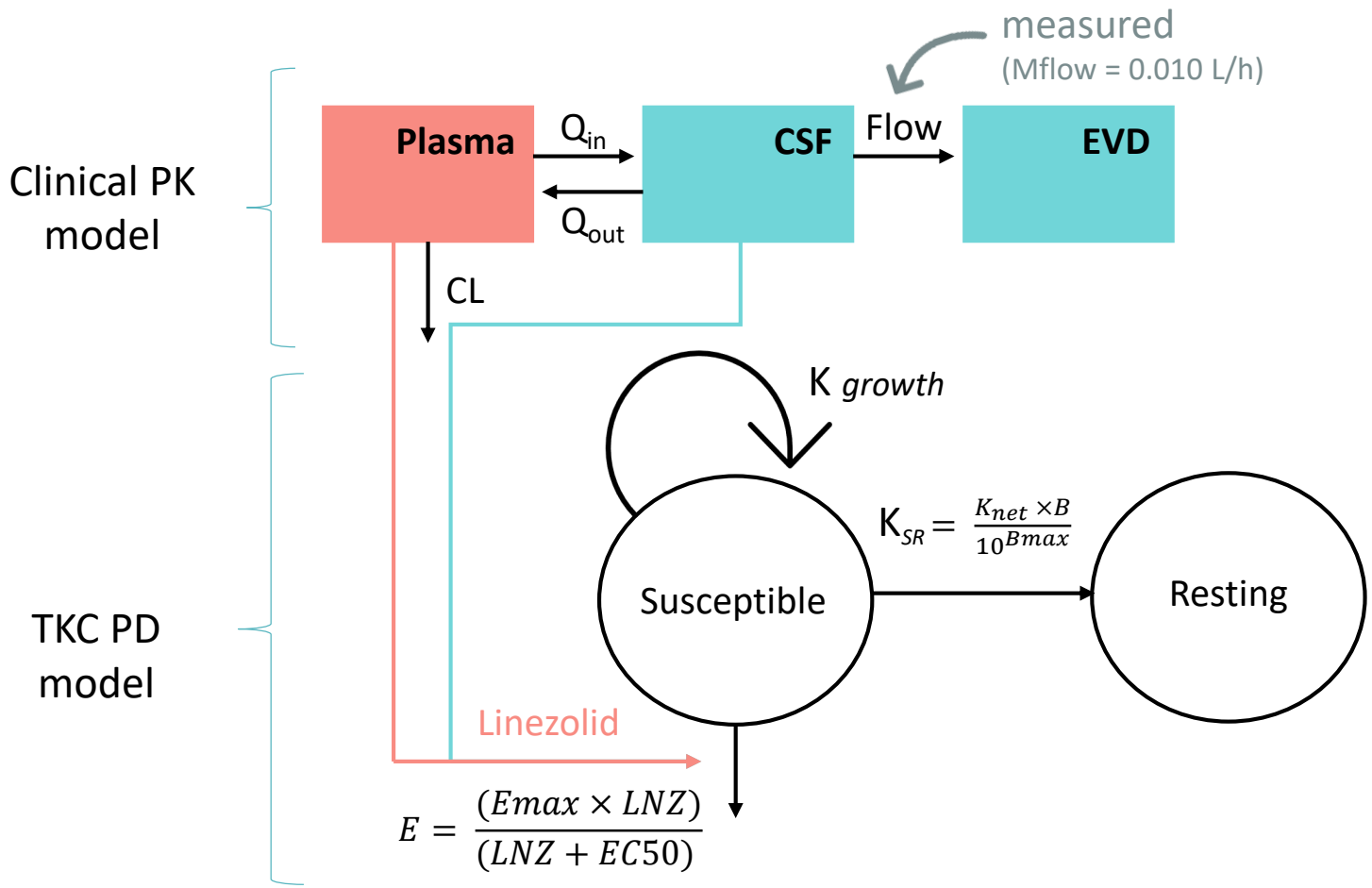
Time Kill Curve – PD model



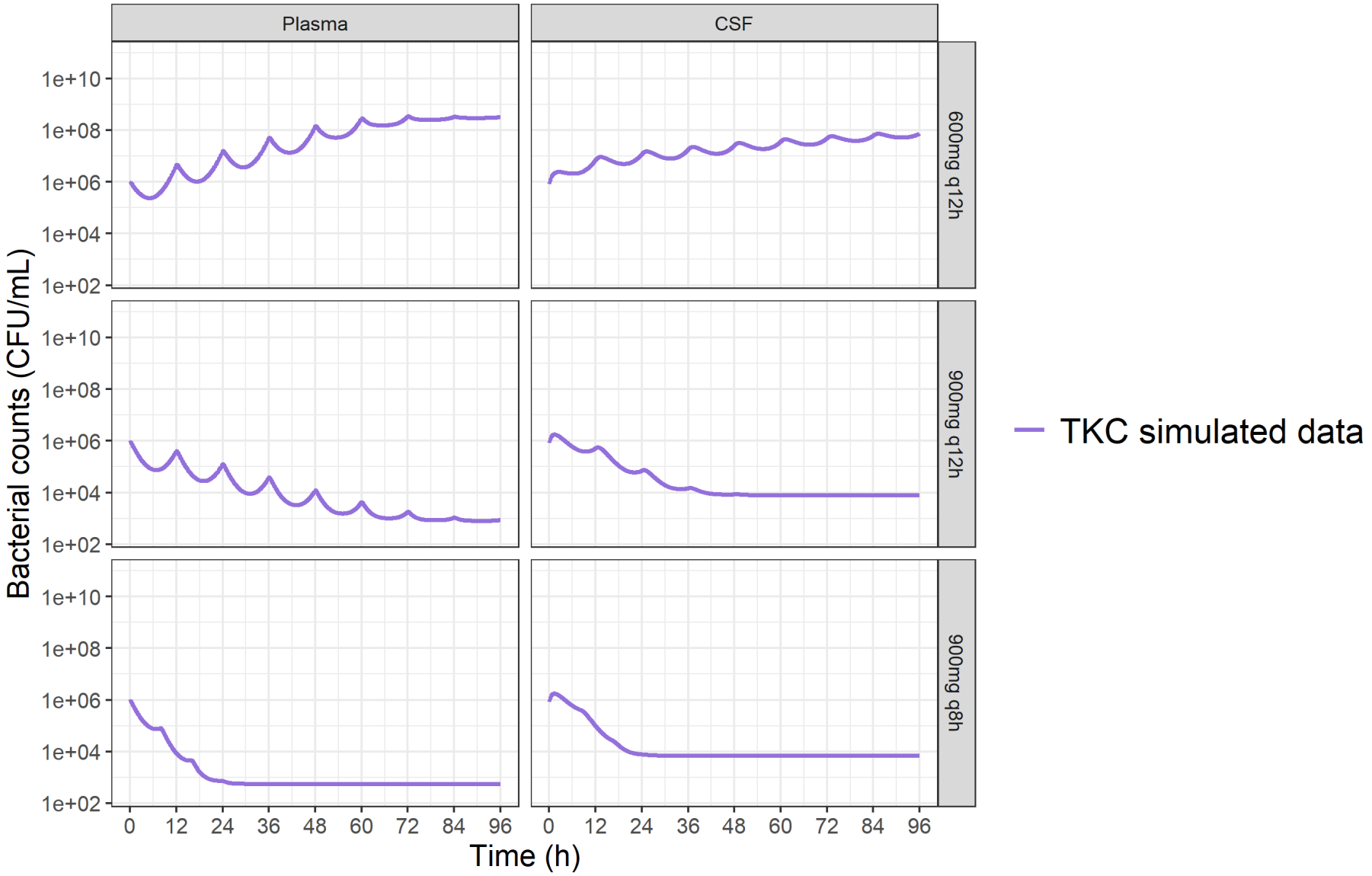


Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Nielsen et friberg. 2013

PK-PD model

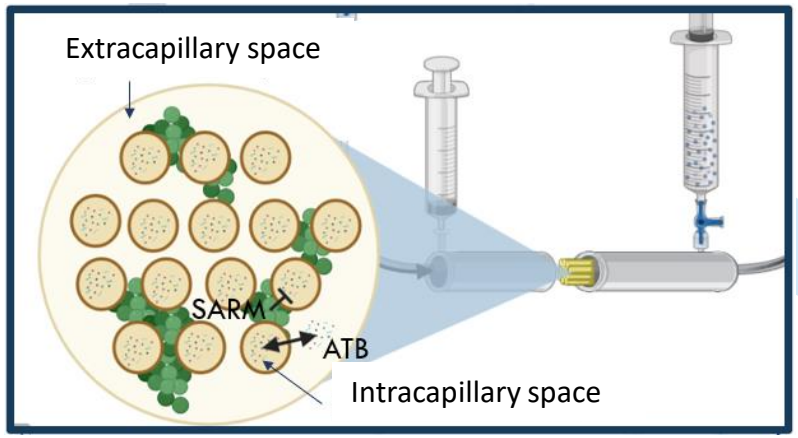

measured
(Mflow = 0.010 L/h)
Clinical PK model
Plasma
Q_{in}
Q_{out}
CSF
Flow
EVD
CL
K *growth*
TKC PD model
$K_{SR} = \frac{K_{net} \times B}{10^{Bmax}}$
Susceptible
Resting
Linezolid
$E = \frac{(Emax \times LNZ)}{(LNZ + EC50)}$

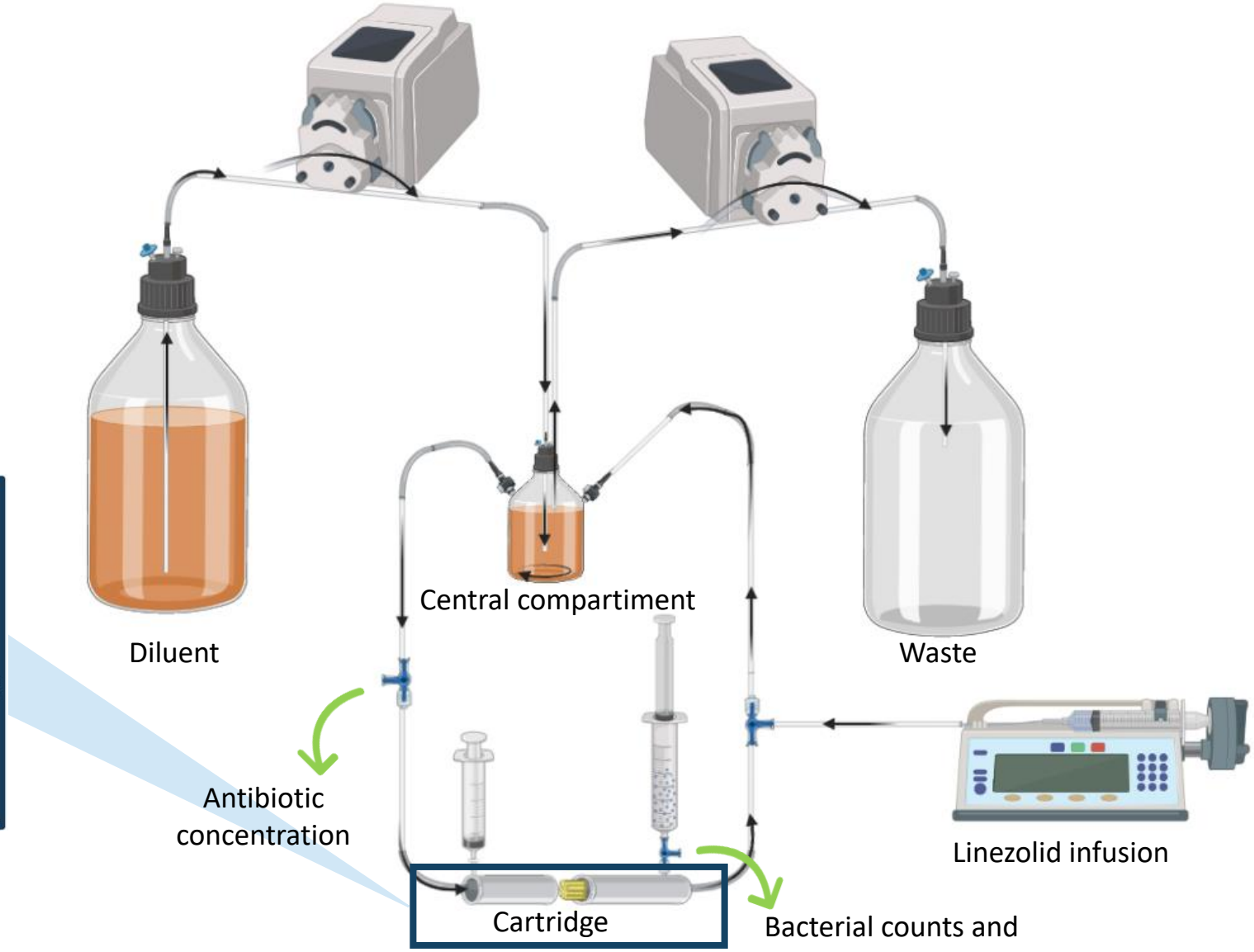
PK-PD simulations



Hollow-Fiber

› Reproduction of human plasma or CSF concentrations for 96h





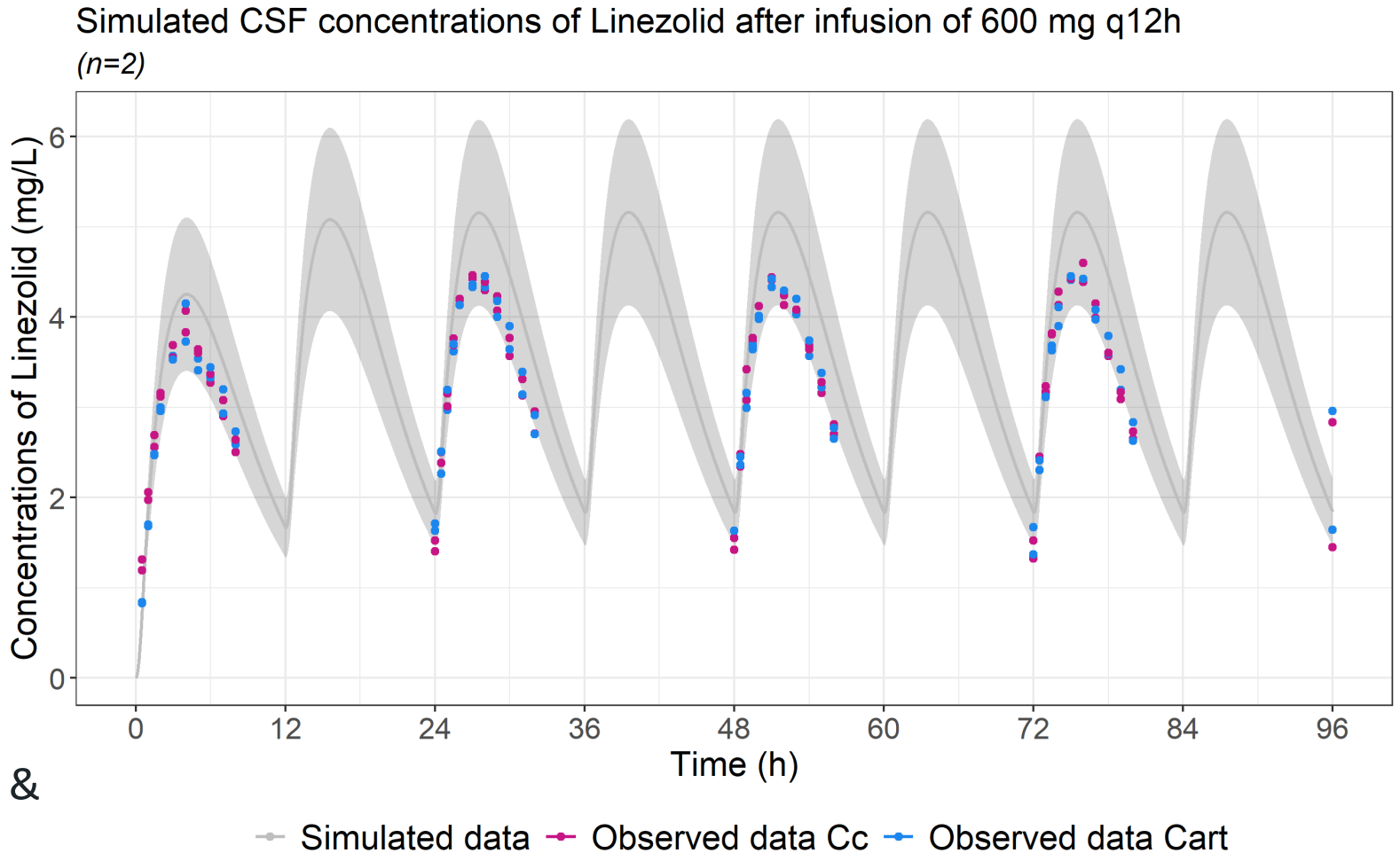
Classical model to simulate a infusion

Hollow-Fiber – PK CSF

Dosing regimen : **600 mg q12h**

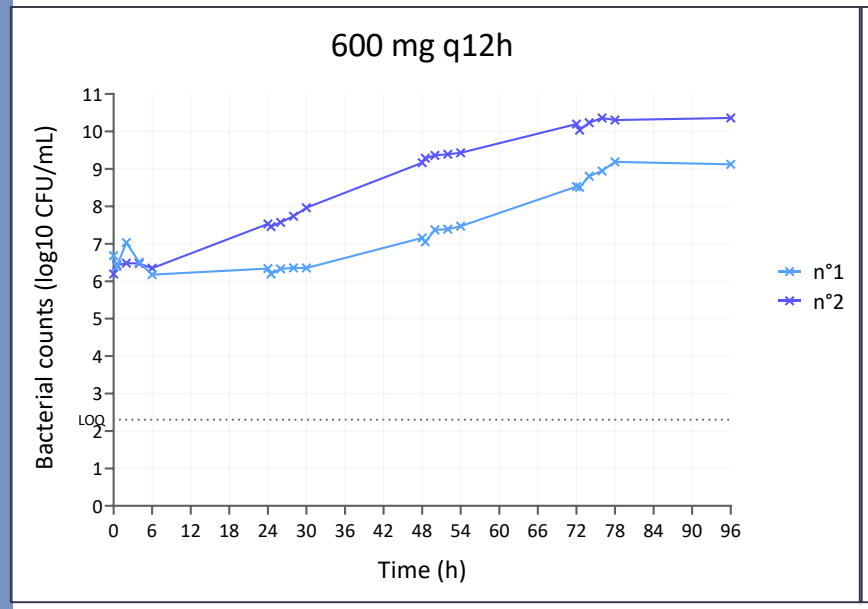
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	5.16	4.44 (-14.0%)	4.39 (-14.9%)
$Tmax_3$ (h)	27.53	27 (-1.9%)	27.5 (-0.1%)
AUC τ (mg/L.h)	44.66	29.37 (-34.2%)	29.34 (-34.3%)
T1/2 (h)	3.67	5.43 (48%)	5.44 (48.2%)

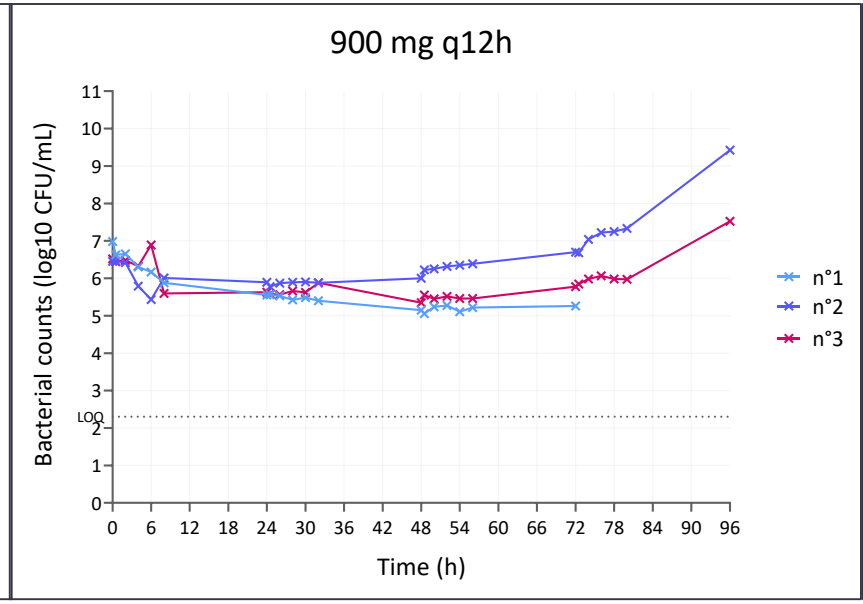
Validated model for **900 mg q12h** & **900 mg q8h**

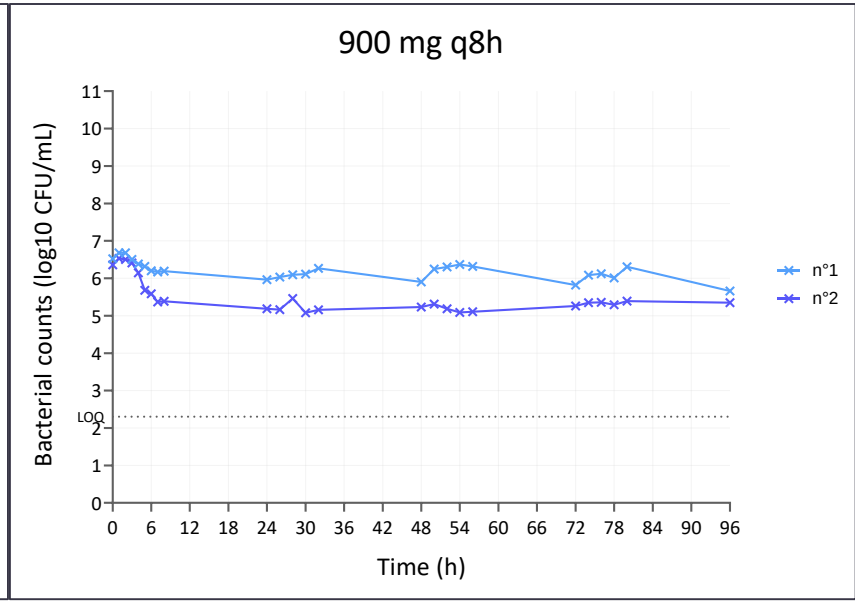


Hollow-Fiber – PD

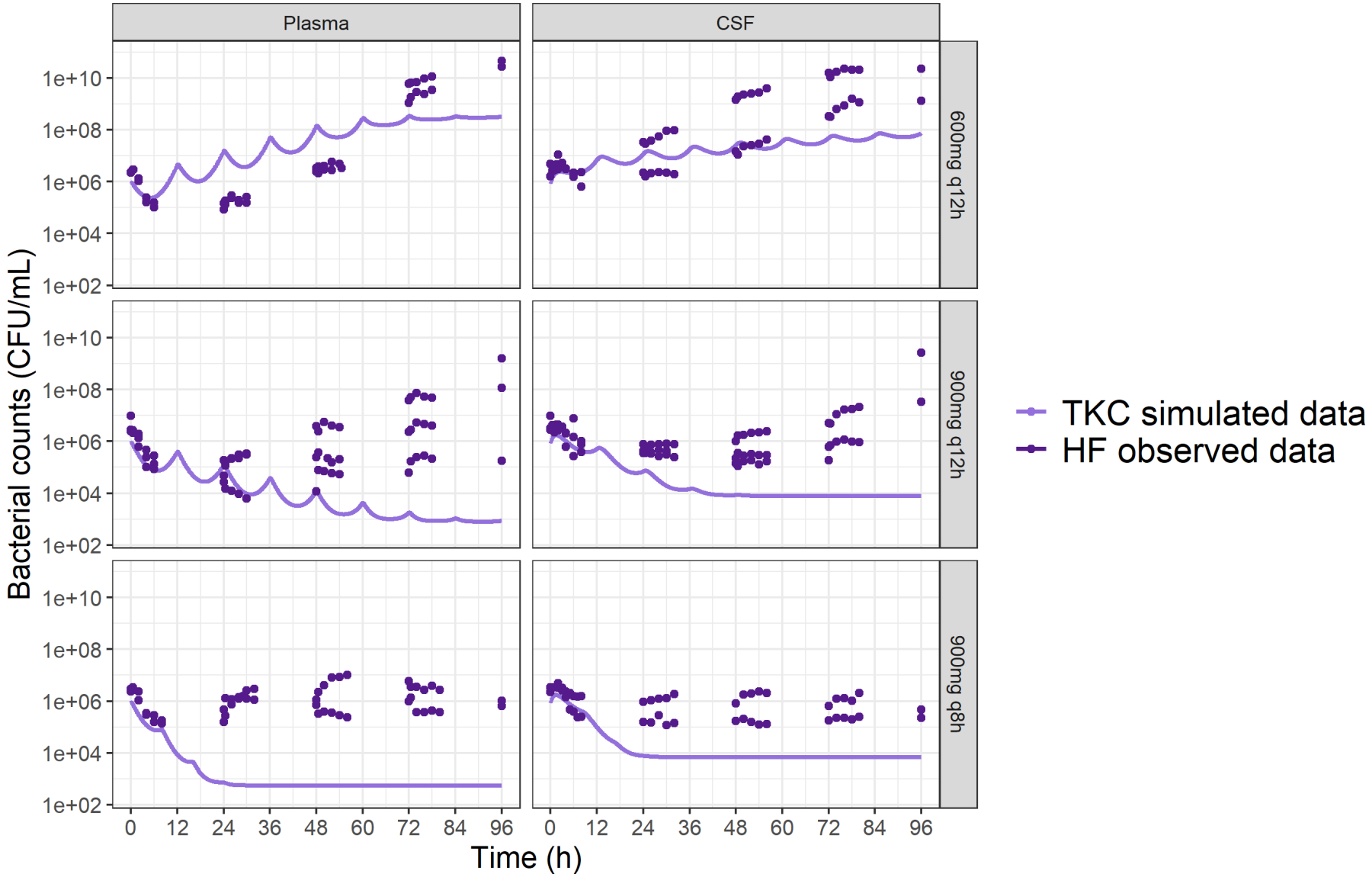
After simulation of CSF Linezolid concentrations



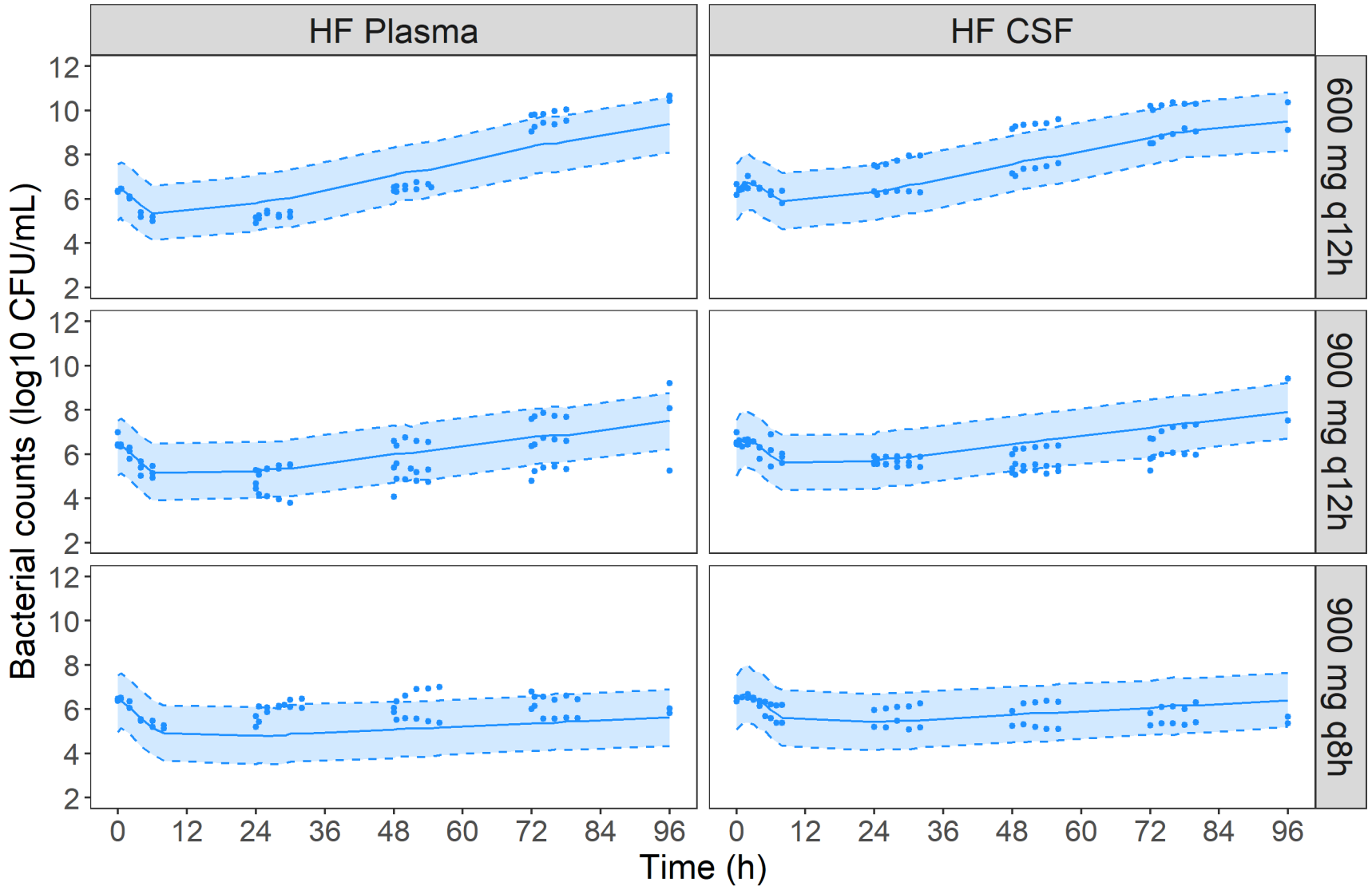




PK-PD simulations – HF data



PD model HF data - Visual Predictive Checks



- HF Observed data
- Median of simulations
- Prediction interval 90%

Conclusion & Prospects

- Increasing dosing regimen ⟶ Limited improvement
- Even at **900 mg q8h** ⟶ Still bacteria

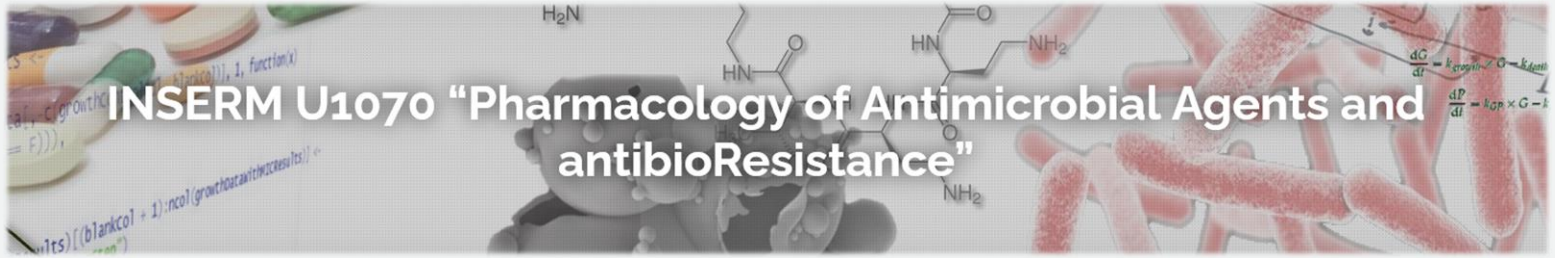
Linezolid ineffective ✗

HF experiments were realized in rich culture medium

Mueller-Hinton Broth 2

Reproduce these experiments into **artificial CSF** in order to be closer to *in vivo* conditions.

Artificial CSF



INSERM U-1070 PHAR2
PHARmacology of antimicrobial agents and antibioResistance

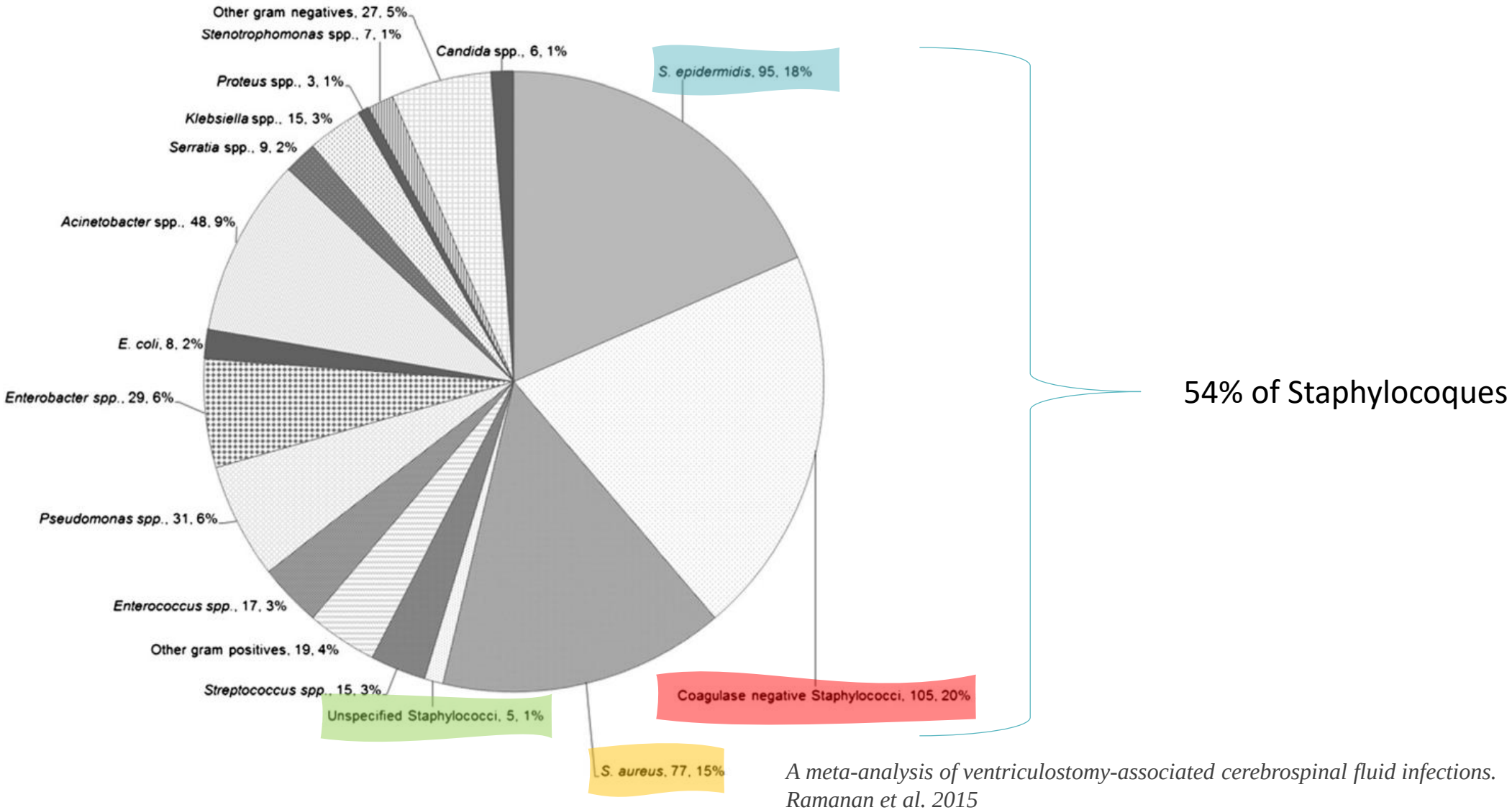
Université de Poitiers

Inserm

CHU Poitiers
CENTRE HOSPITALIER UNIVERSITAIRE

Thank you for your attention

EVD infections

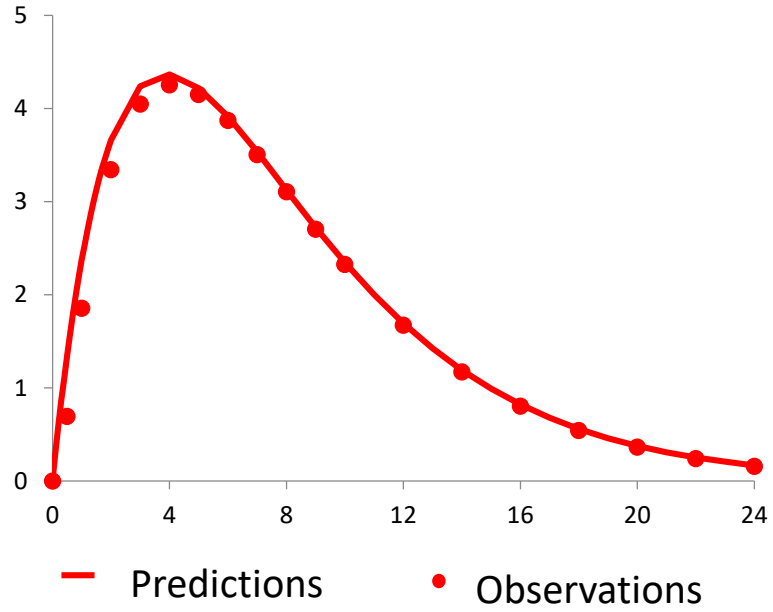


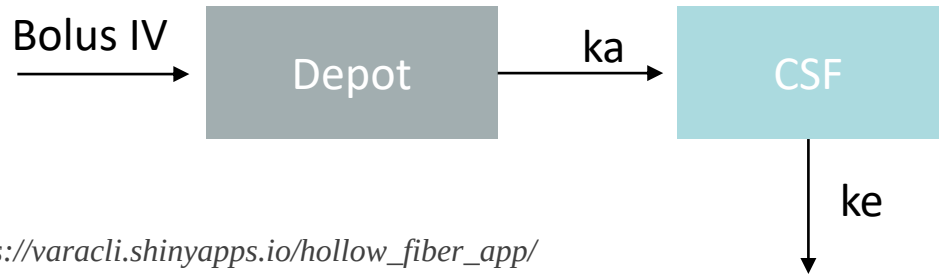
54% of Staphylocoques

A meta-analysis of ventriculostomy-associated cerebrospinal fluid infections. Ramanan et al. 2015

Hollow-Fiber

To simulate CSF Linezolid concentrations





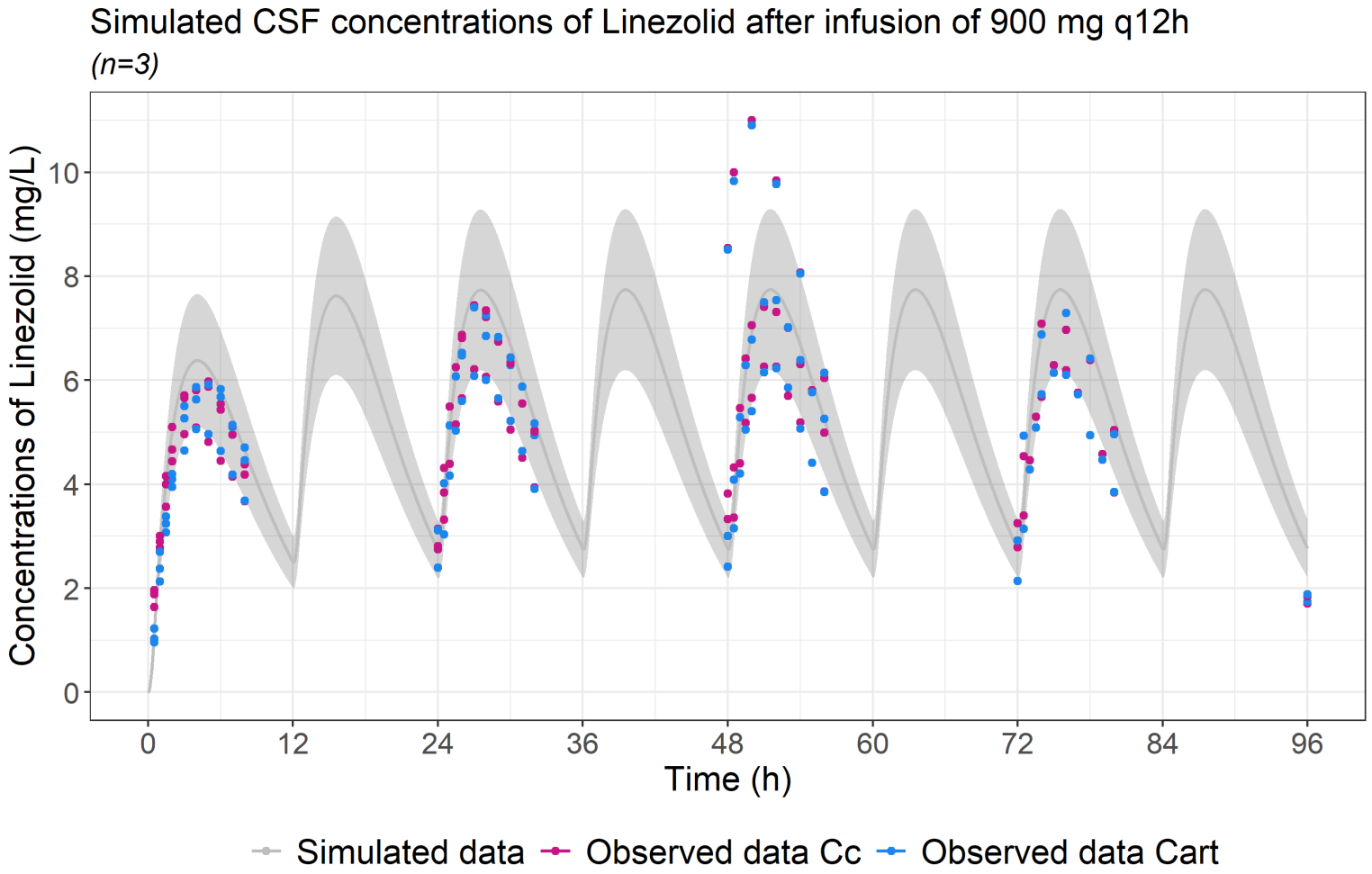
https://varacli.shinyapps.io/hollow_fiber_app/

Interval time possible in the pump	Infusion flow rate (mL/h)	Infused volume (mL)	Infused amount over interval (mg)
NA	NA	NA	0
17 min	7.1	2.01	0.446
19 min	6.5	2.01	0.446
20 min	5.9	2.01	0.446
23 min	5.3	2.01	0.446
26 min	4.7	2.01	0.446
29 min	4.1	2.01	0.446
34 min	3.5	2.01	0.446
42 min	2.9	2.01	0.446
52 min	2.3	2.01	0.446
1h11	1.7	2.01	0.446
1h52	1.1	2.01	0.446
4h35	0.4	2.01	0.446

Hollow-Fiber – PK CSF

Dosing regimen : **900 mg q12h**

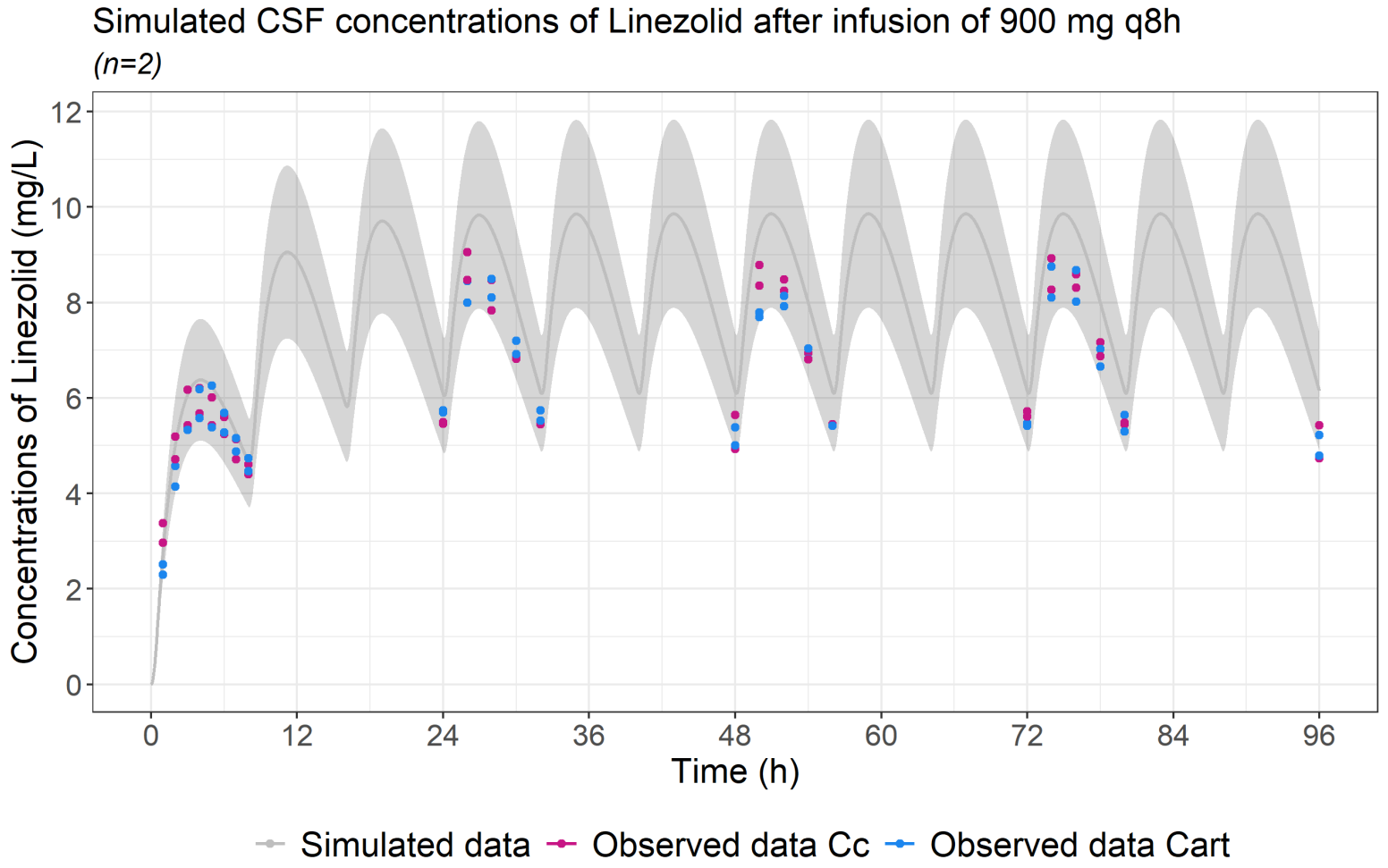
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	7.73	7.34 (-5.1%)	6.85 (-11.4%)
$Tmax_3$ (h)	27.53	27.0 (-1.9%)	27.0 (-1.9%)
AUC τ (mg/L.h	66.98	49.26 (-26.5%)	47.96 (-28.4%)
T1/2 (h)	3.67	5.99 (63.2%)	6.67 (81.7%)



Hollow-Fiber – PK CSF

Dosing regimen : **900 mg q8h**

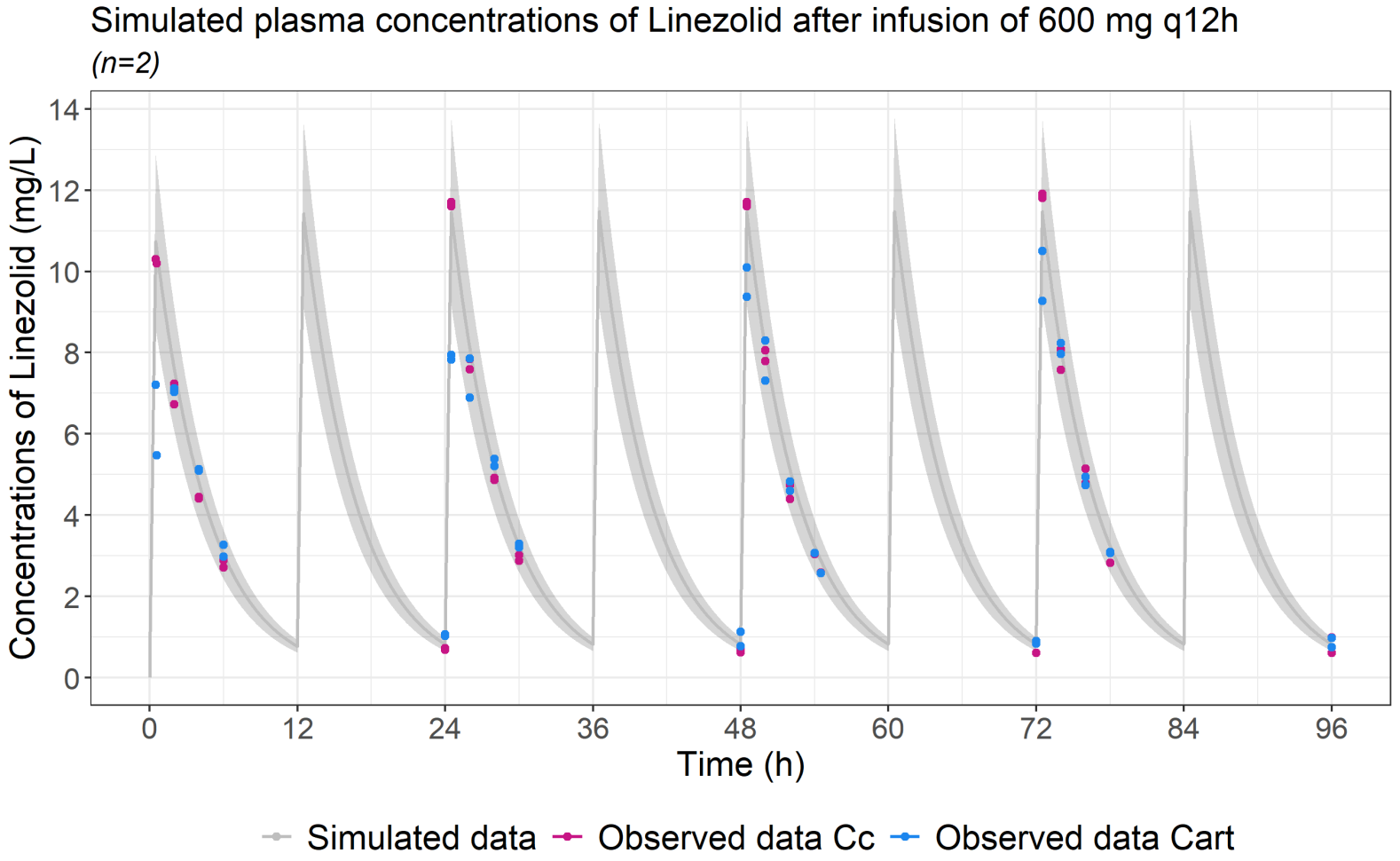
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	9.83	8.76 (-10.9%)	8.3 (-15.6%)
$Tmax_3$ (h)	26.96	26.0 (-3.6%)	28.0 (3.9%)
AUC τ (mg/L.h	66.87	58.47 (-12.6%)	58.5 (-12.5%)
T1/2 (h)	3.67	7.05 (92.1%)	7.16 (95.1%)



Hollow-Fiber – PK Plasma

Dosing regimen : **600 mg q12h**

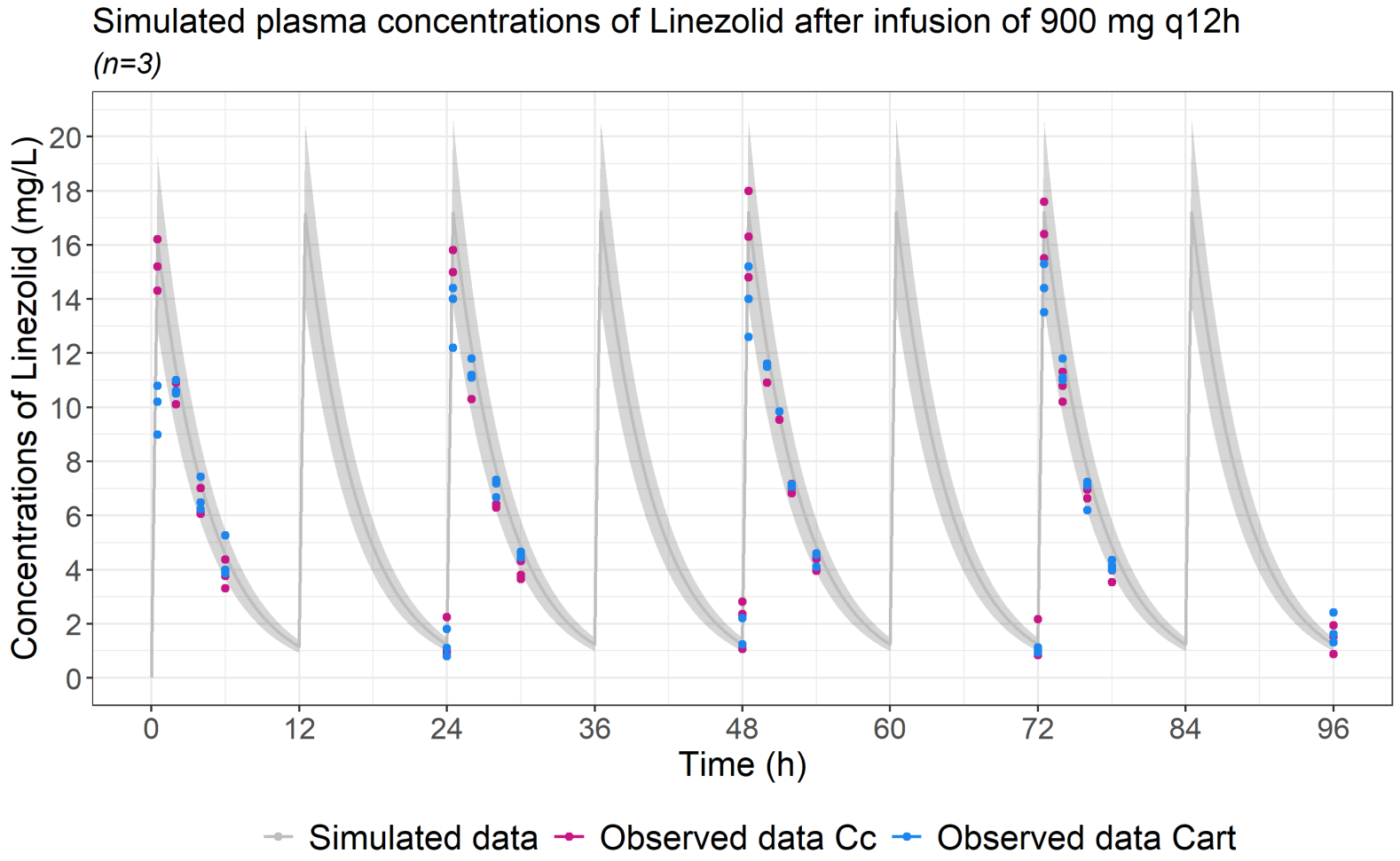
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	11.47	11.65 (1.6%)	7.9 (-31.1%)
$Tmax_3$ (h)	24.5	24.5 (0%)	25.25 (3.1%)
AUC τ (mg/L.h	49.54	38.04 (-23.2%)	34.87 (-29.6%)
T1/2 (h)	3.04	2.88 (-5.3%)	3.40 (11.8%)



Hollow-Fiber – PK Plasma

Dosing regimen : **900 mg q12h**

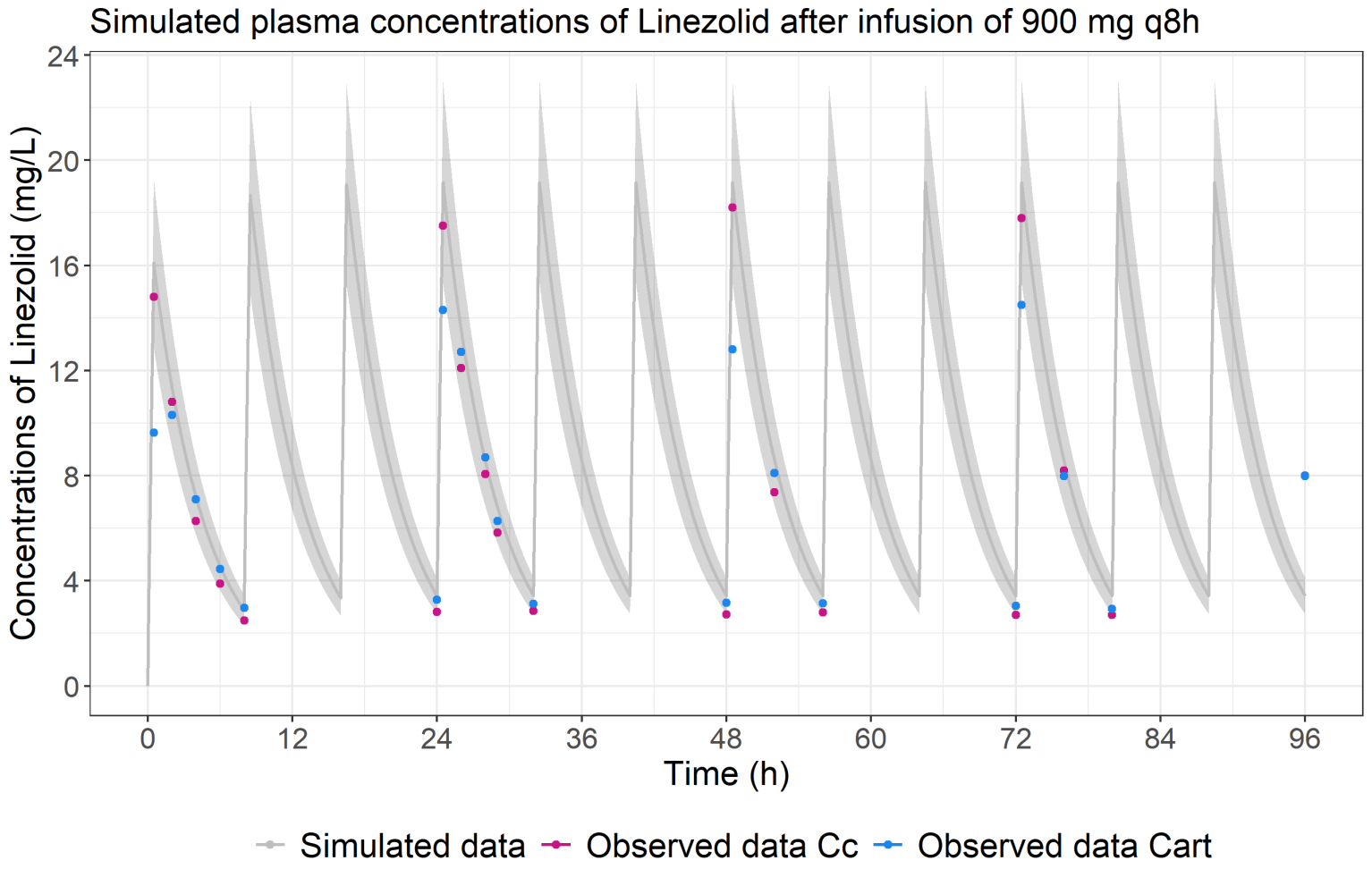
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	17.20	15.80 (-8.1%)	14.0 (-18.6%)
$Tmax_3$ (h)	24.5	24.5 (0%)	25.25 (3.1%)
AUC τ (mg/L.h	74.32	51.21 (-31.1%)	51.8 (-30.3%)
T1/2 (h)	3.04	2.67 (-12.2%)	3.03 (-0.3%)



Hollow-Fiber – PK Plasma

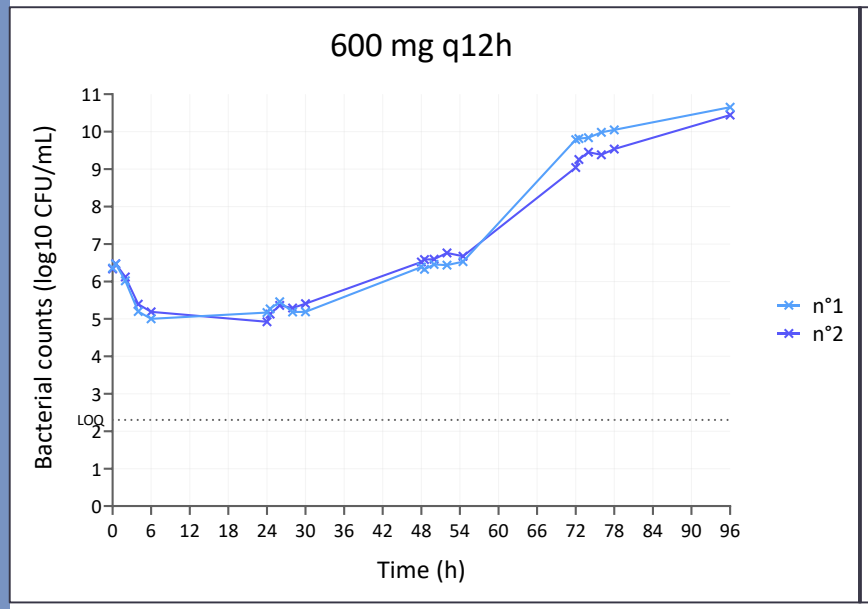
Dosing regimen : **900 mg q8h**

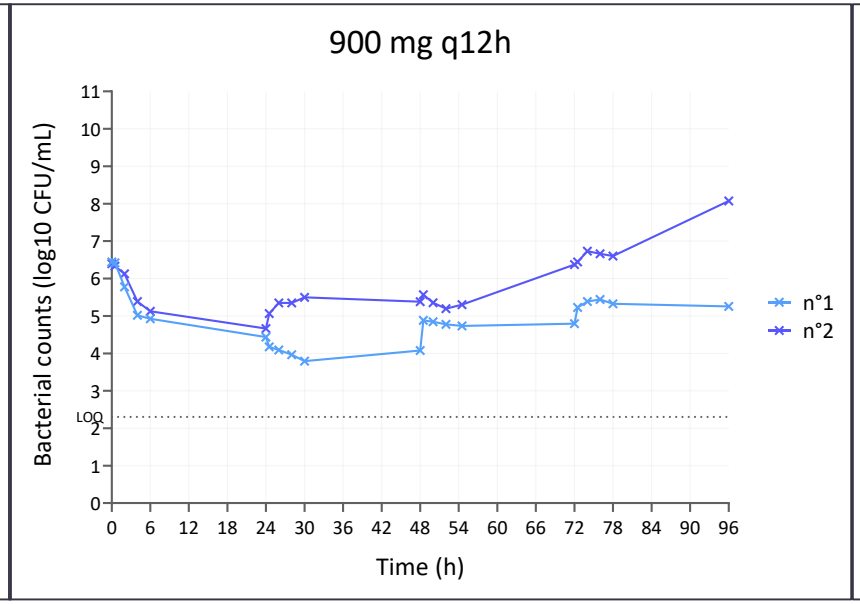
Parameters	Simulate	Observed Cc	Observed Cart
$Cmax_3$ (mg/L)	19.16	17.60 (-8.1%)	16.0 (-16.5%)
$Tmax_3$ (h)	24.5	24.5 (0%)	24.5 (0%)
AUC τ (mg/L.h	74.28	68.57 (-7.7%)	68.68 (-7.5%)
T1/2 (h)	3.04	2.95 (-3.0%)	2.99 (-1.6%)

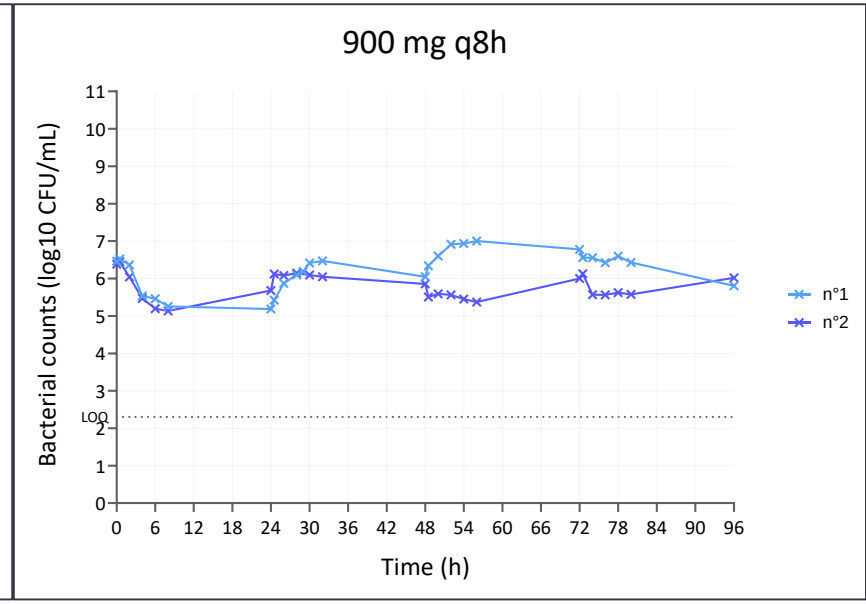


Hollow-Fiber – PD

After simulation of plasma Linezolid concentrations

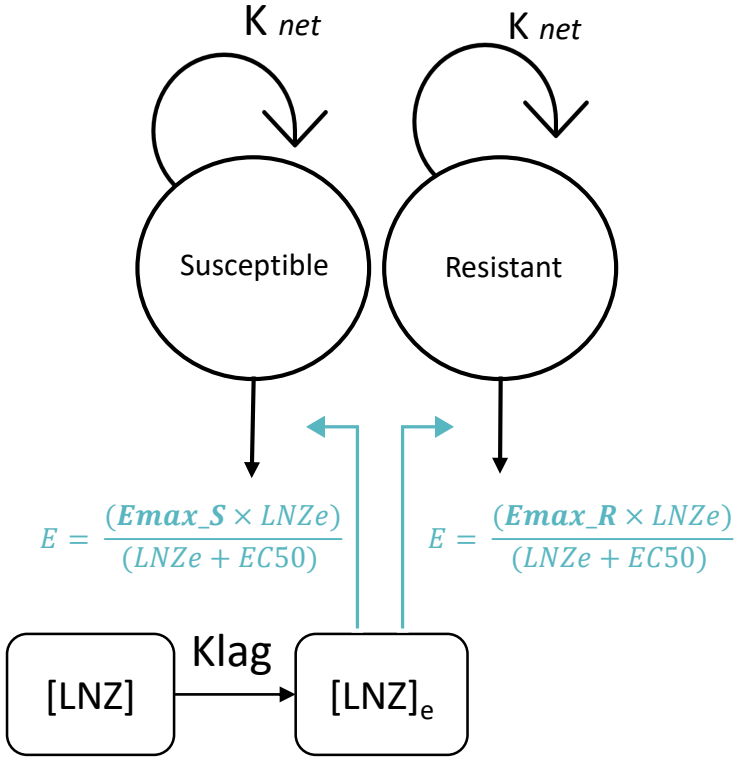






Adapted PD model – HF data (run 49)

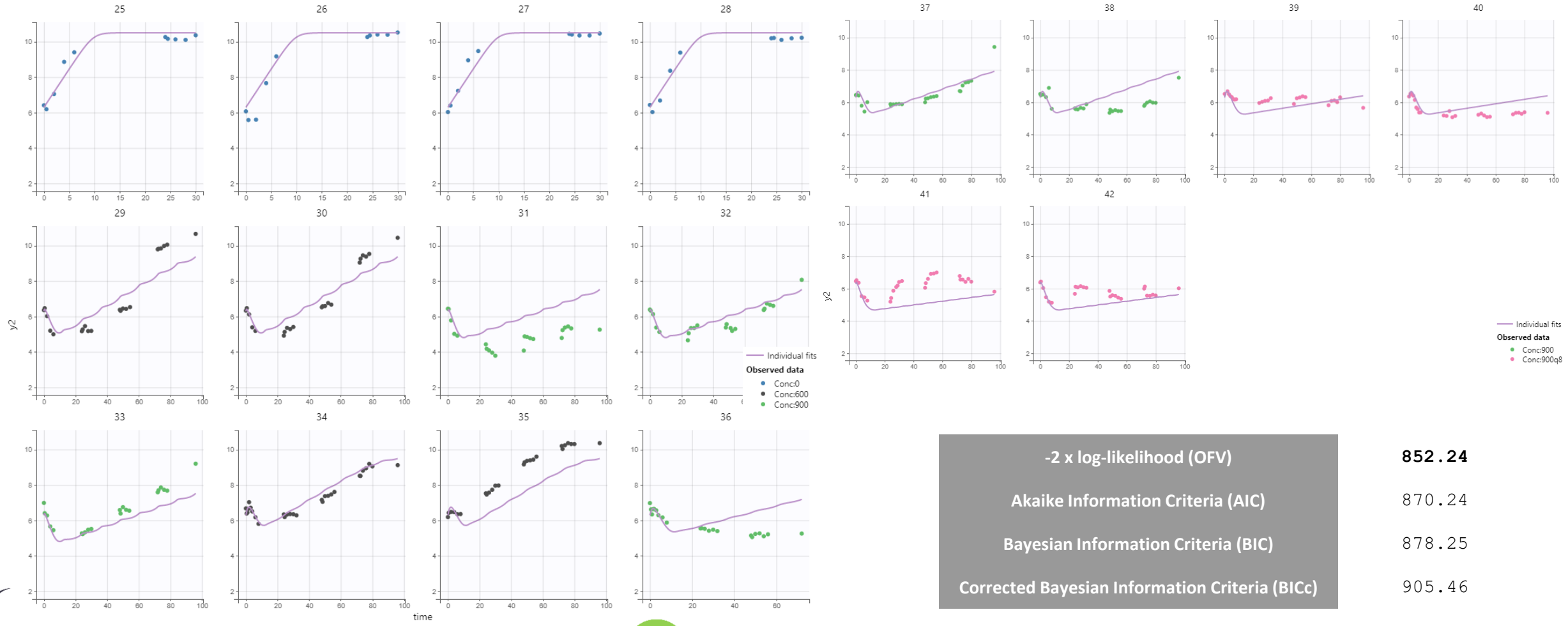
Dataset_002_SA29213_TKC_HF_Plasma_CSF_600q12_900q12_900q8_Cart.csv
Filtré sans les TKC
047_PKPD_SR_HF_only_2Emax_1EC50 (same model as previously)



	VALUE	LINEARIZATION	
		S.E.	R.S.E.(%)
Fixed Effects			
B0_pop	6.3	0.097	1.54
Bmax_pop	10.5	0.21	2.03
Knet_pop	0.99	0.00034	0.0340
fR_pop	2.02	0.17	8.36
Emax_S_pop	1.73	0.13	7.35
Emax_R_pop	1.05	0.0099	0.943
EC50_pop	0.74	0.057	7.66
Cl_pop	12.1		
V1_pop	52.8		
V2_pop	0.15		
Qin_pop	0.04		
Qout_pop	0.037		
Qevd_pop	0.0076		
gamma_pop	1		
Klag_pop	0.4	0.07	17.4
Error Model Parameters			
a	0.77	0.028	3.68

C:\Users\nprebonnaud\Desktop\Modelling\Linezolid\S.AUREUS\SA29213\HF

Individuals fits (run 49)



-2 x log-likelihood (OFV)	**852.24**
Akaike Information Criteria (AIC)	870.24
Bayesian Information Criteria (BIC)	878.25
Corrected Bayesian Information Criteria (BICc)	905.46

Decrease of OFV. Best model for now

C:\Users\nprebonnaud\Desktop\Modelling\Linezolid\S.AUREUS\SA29213\HF