



Introduction

- Viral encephalitis is a severe central nervous system (CNS) infection associated with high morbidity and mortality in patients despite antiviral treatment¹⁻³.
- Current Acyclovir dosing (10 mg/kg three times daily, TID) for treating viral encephalitis is anecdotal and outdated based on two 1980s clinical trials^{4,5}.
- Potential dose-induced toxicity can be caused by acyclovir⁶.
- The efficacy of acyclovir for CNS infections relies on drug exposure in the target site (CNS not plasma).

Aims

- To describe acyclovir CNS PK using a Bayesian PBPK modeling approach.
- To examine the current and propose alternative acyclovir dosing for treating CNS viral infection.

Methods

- We built a CNS PBPK model based on an existing model framework (LeiCNS 3.0)⁷ using a full Bayesian approach (Figure 1) with Stan and Torsten package⁸.
- Human drug concentration data in plasma and subarachnoid space were extracted from literature for model validation.
- PTA (probability target attainment) was calculated to evaluate the therapeutic effect of acyclovir based on 500 simulations.

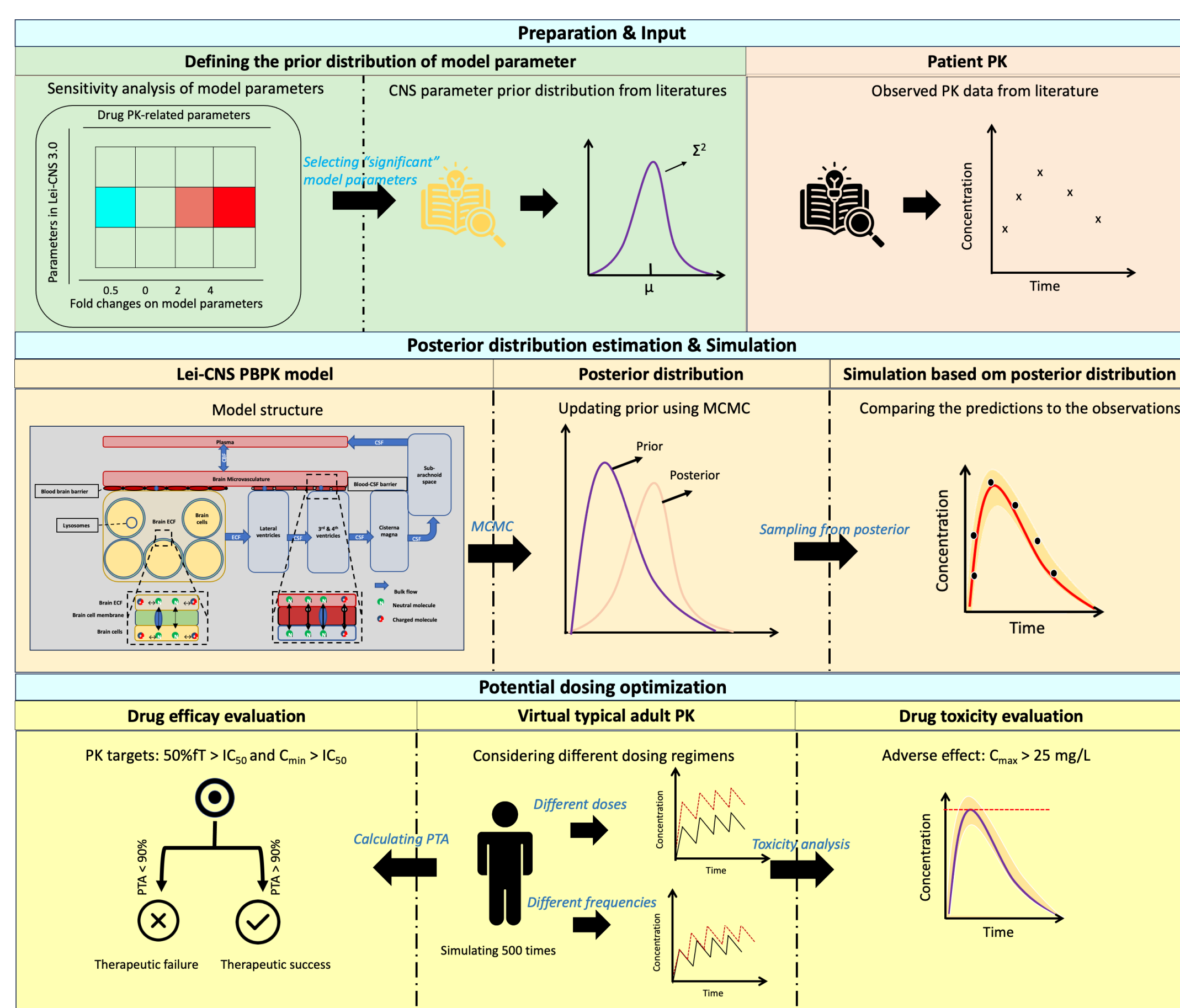


Figure 1. Work flow of Bayesian PBPK model construction.

Results

- ❖ Parameter posterior became more informative compared to prior

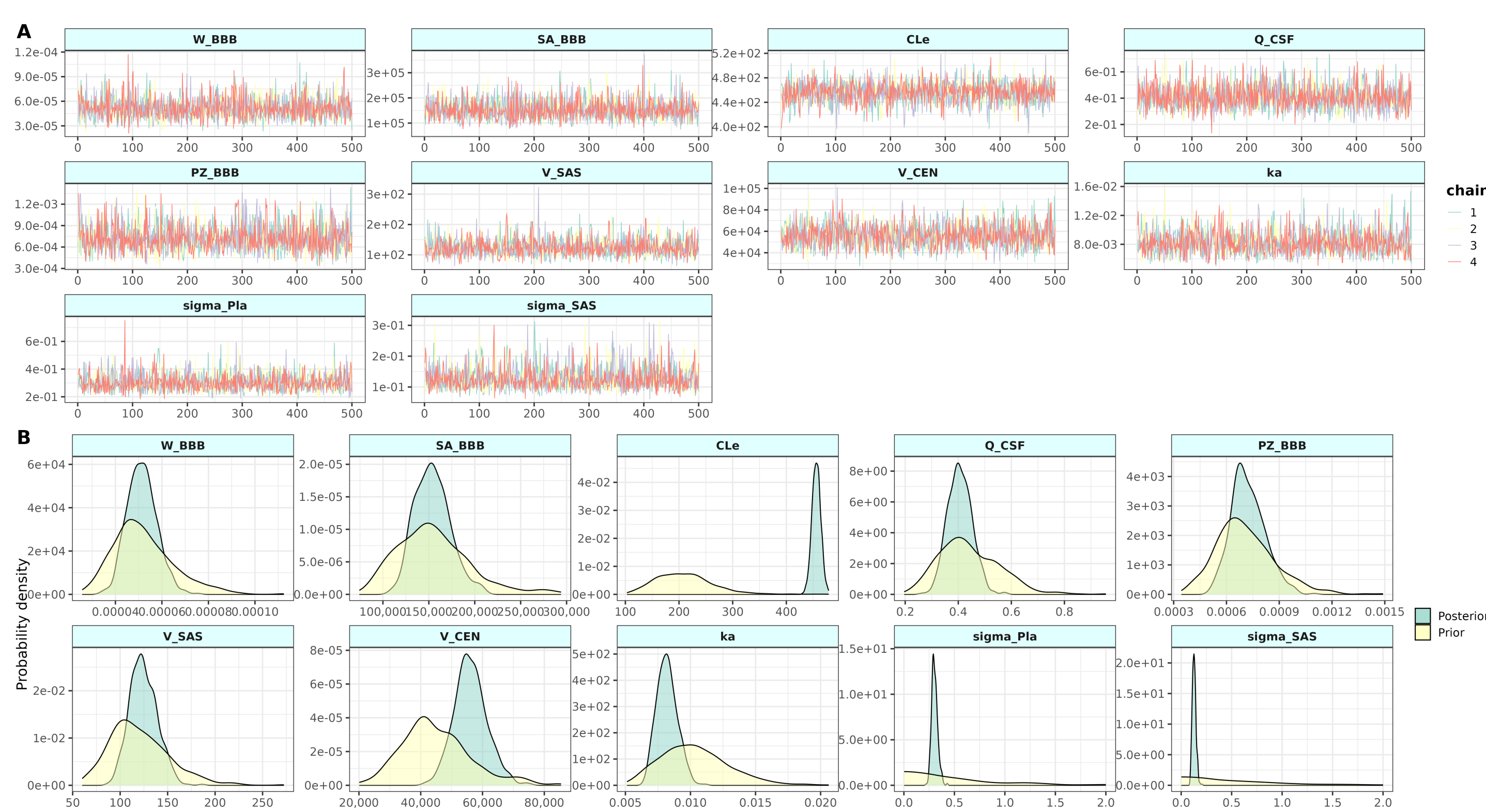


Figure 2. Traceplot and prior/posterior distributions of model parameters.

Results

- ❖ The model successfully predicted observed acyclovir data

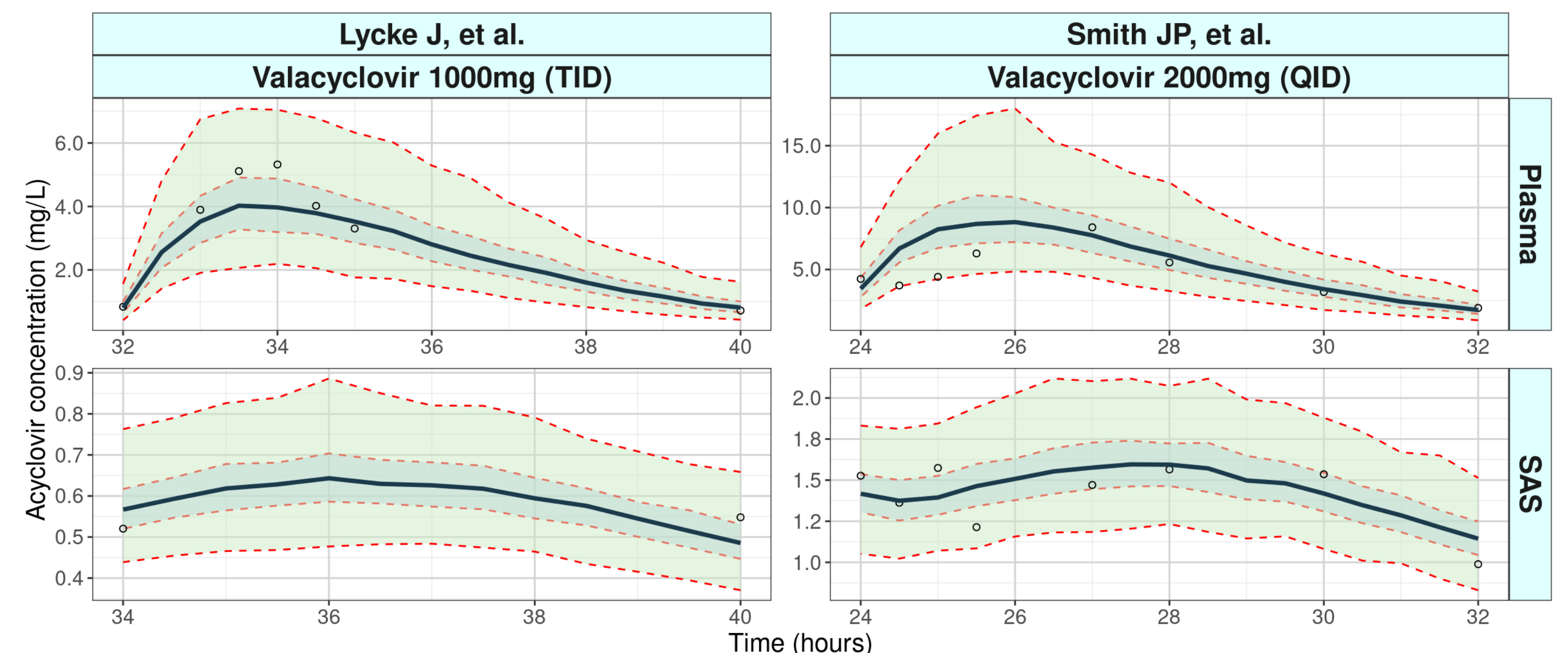


Figure 2. Posterior predictive check (PPC). Predicted acyclovir data (Line, median; dots, mean values; middle band color, 50% interval; outer band, 95% interval) in plasma and brain subarachnoid space (SAS).

- ❖ Four times daily (QID) dosing resulted in higher target attainment than three times daily (TID)

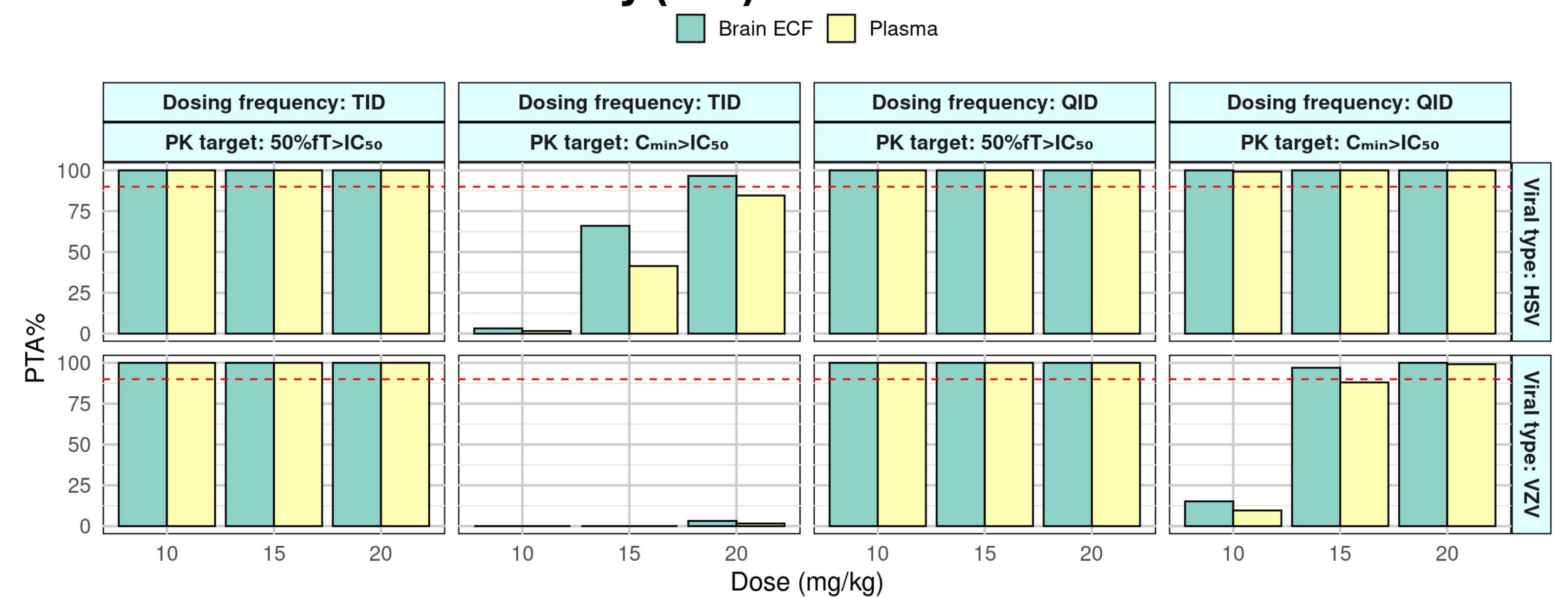


Figure 4. Probability of target attainment (PTA) for different acyclovir dose regimens, considering herpesvirus (herpes simplex virus type, HSV; varicella-zoster virus, VZV) susceptibility in plasma and brain extracellular fluid (ECF). The 90% PTA threshold signifies that 90% of simulations on a typical 70kg adult maintain acyclovir concentrations above the IC_{50} values for at least 12 hours within a 24-hour period, or sustain trough concentrations above the IC_{50} .

- ❖ A dose of 20 mg/kg was associated with a risk of adverse effect effect

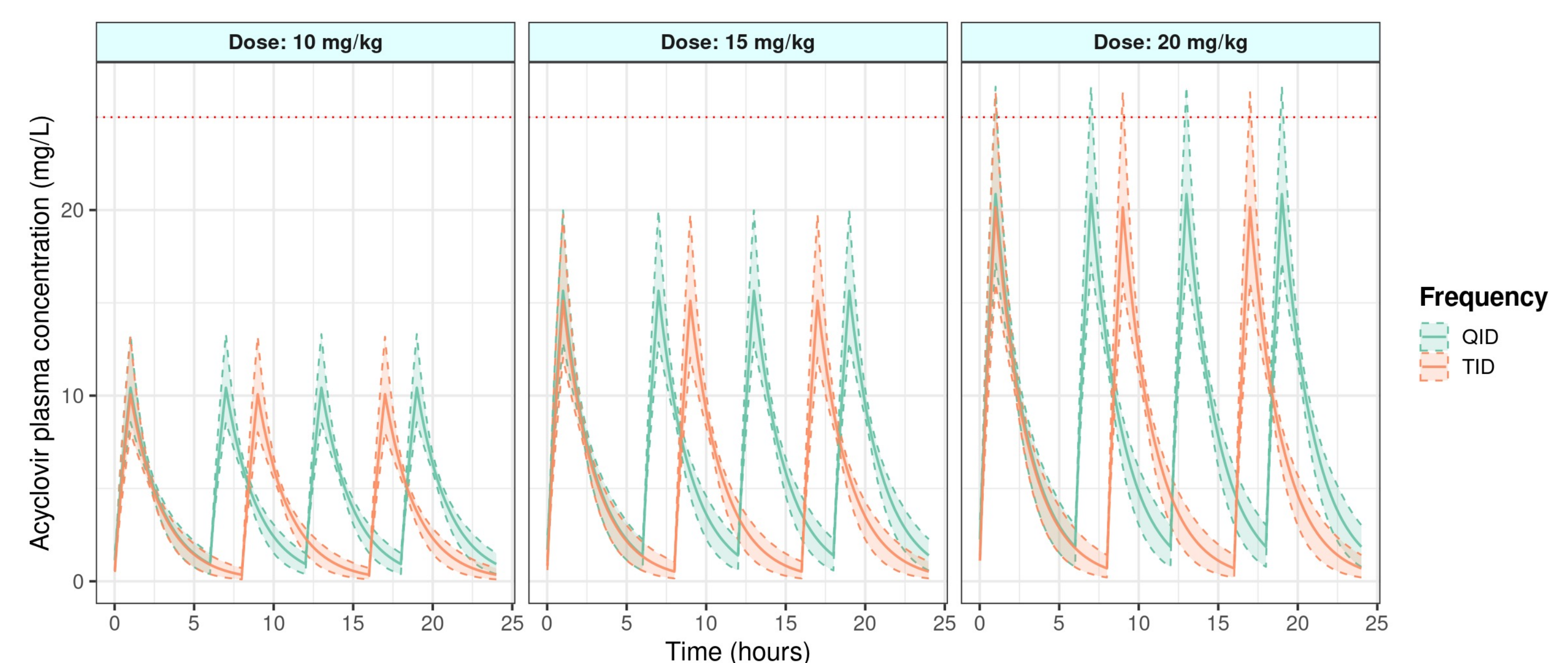


Figure 5. Predicted acyclovir data (Line, median; band, 95% interval) over time in plasma under different dose regimens. C_{max} values under all evaluated dose regimens below the adverse effect level (25 mg/L), except for 20 mg/kg regardless of dosing frequency.

Conclusions

- We developed a Bayesian CNS PBPK model for acyclovir.
- Current acyclovir dosing regimen may not suffice for treating herpesvirus-associated CNS infection, and a dose of 15 mg/kg four times daily (QID) is advised.

References

1. Matthews, E., et al. Curr Trop Med Rep, 2022.
2. Gurgel Assis, M.S., et al. J Pharm Sci, 2021.
3. Raschilas, F., et al. Clin Infect Dis, 2002.
4. Bean, B. and D. Aeppli. J Infect Dis 1985.
5. Sköldenberg, B., et al. Lancet 1984.
6. Whitley, R. J., et al. N Engl J Med 1986.
7. Saleh, M. A. A. Pharmaceutics 2021.
8. Elmokadem, A., et al. CPT:PSP 2023.