Physiologically-Based Pharmacokinetic (PBPK) Modeling of Fluconazole Using Plasma and Cerebrospinal Fluid Samples from Preterm and Term Infants

FIGURES S1 – S4

Figure S1. Observed dose-normalized CSF concentration after first fluconazole dose for preterm and term infants

Dose-normalized CSF concentration is plotted against time after first dose observed from preterm and term infants enrolled in the prophylaxis and PPRU studies following various treatment and prophylactic fluconazole dosing regimens. Lines along the x-axis represent nominal dosing times for the prophylaxis study. Note that individual variations in dosing time are not reflected in this figure.

CSF: cerebrospinal fluid; PPRU: Pediatric Pharmacology Research Unit

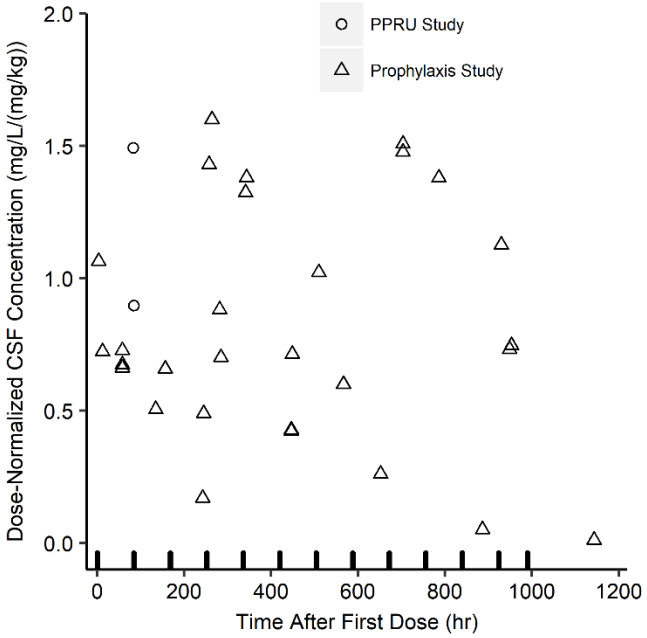


Figure S2. Population simulation using original model in adults (n = 1,000) of CSF fluconazole concentration following oral dosing (800 mg daily) in adults with cryptococcal meningitis

Population simulation of CSF is shown overlaid with observed adult digitized data.[1] The shaded region is the 5-95% range in concentration from 1,000 simulated adults reflective of the study demographics.

CSF: cerebrospinal fluid

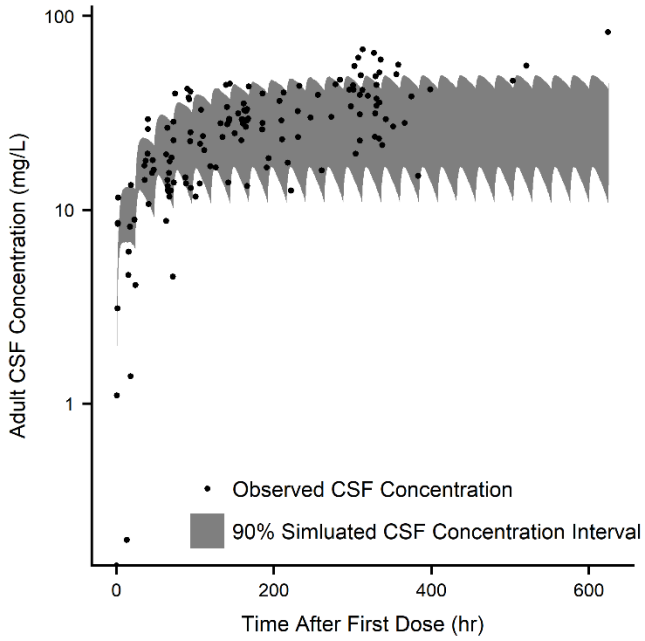
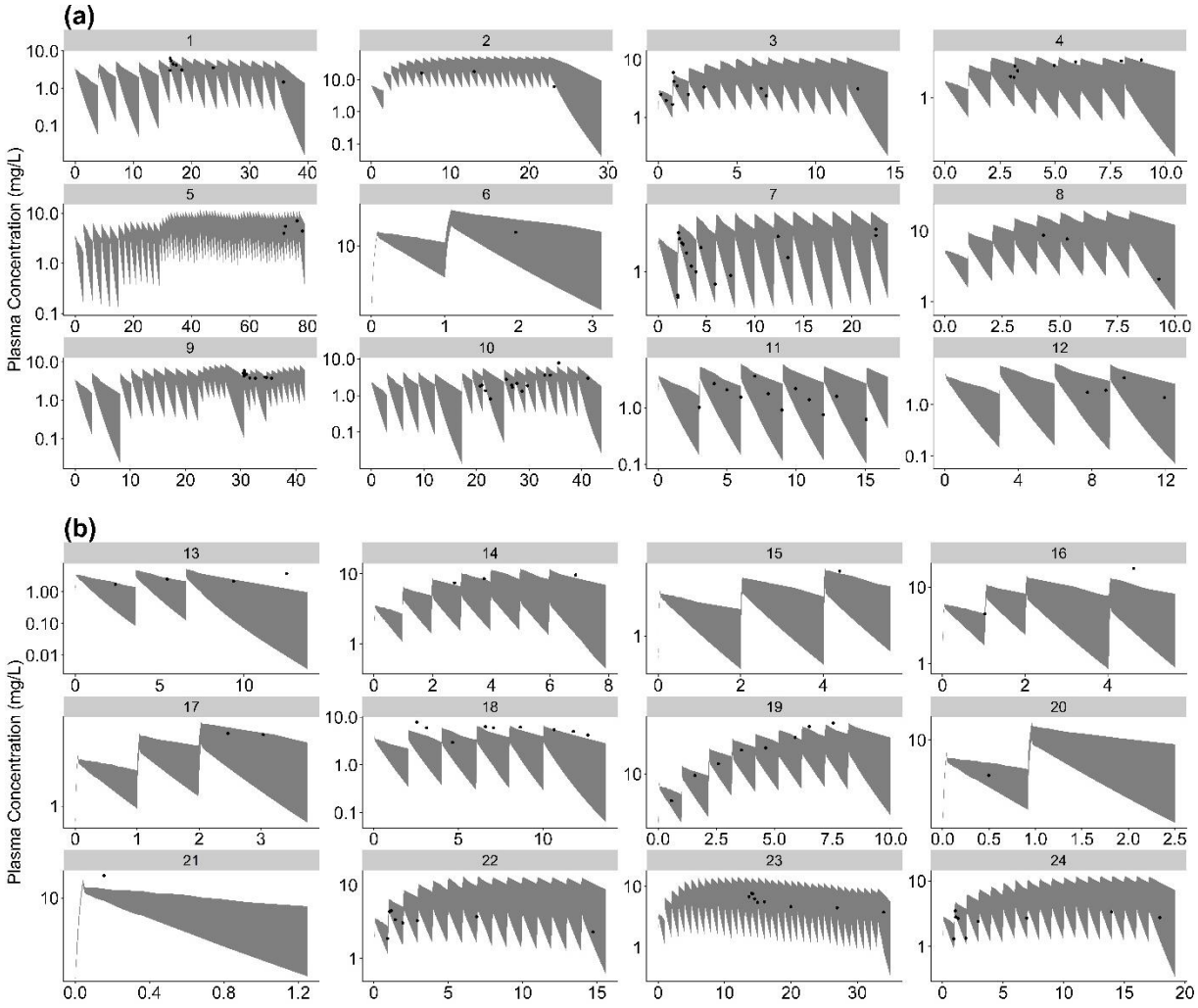


Figure S3. Population simulations (n = 100) of plasma fluconazole concentration following prophylactic or treatment dosing in preterm and term infants from the PPRU study

Population simulations of plasma overlaid with observed data from the PPRU study. The shaded regions are the 5-95% range in concentration from 100 simulated infants reflective of the PPRU study demographics. Due to the wide variation in dosing regimens for the infants in this study, each infant's dosing regimen was simulated individually. Simulation plots are split into four panels (a-d) for ease of visualization where panel a) displays subjects 1-12, b) displays subjects 13-24, c) displays subjects 25-36, and d) displays subjects 37-46.

PPRU: Pediatric Pharmacology Research Unit



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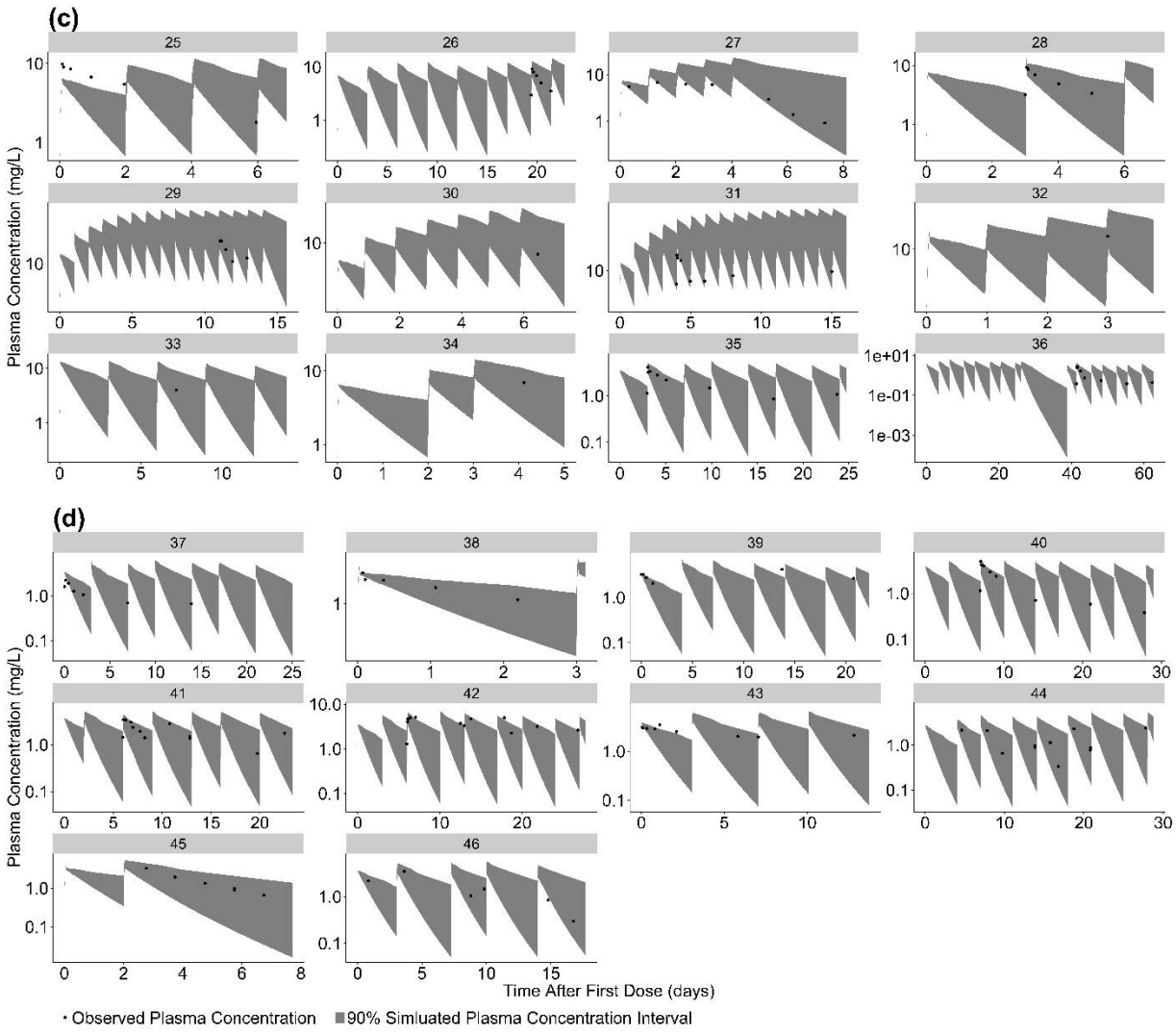
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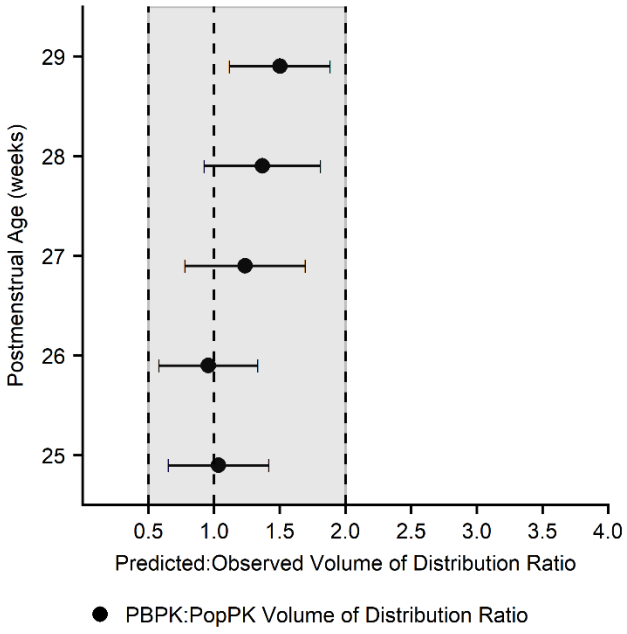
Plasma Concentration (mg/L)
Time After First Dose (days)
Observed Plasma Concentration
90% Simluated Plasma Concentration Interval

Figure S4. Comparison of PBPK model-derived fluconazole volume of distribution to volume of distribution derived from a PopPK model

Circles represent the mean ratio of PBPK-derived volume of distribution to PopPK-derived volume of distribution estimates from a previous study.[2-4] The model parameters from the PPRU study PopPK model were used to generate the PopPK-derived estimates. Tails represent ±1 standard deviation ratio[5], and the shaded region represents the two-fold error range. Mean ratios were calculated as the mean PBPK value divided by the mean PopPK value, and standard deviation ratios were calculated using the method published by Zhou et al.[5]

PBPK: physiologically-based pharmacokinetic; PopPK: population pharmacokinetic



References

1. Stott, K. E. *et al.* Population pharmacokinetics and cerebrospinal fluid penetration of fluconazole in adults with cryptococcal meningitis. *Antimicrob. Agents Chemother.* **62**, e00885-18 (2018). https://aac.asm.org/content/62/9/e00885-18
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5. Zhou, W. *et al.* Predictive performance of physiologically based pharmacokinetic and population pharmacokinetic modeling of renally cleared drugs in children. *CPT Pharmacometrics Syst. Pharmacol.* **5**, 475–483 (2016).