

Simultaneous modelling of antimicrobial pharmacokinetic data from birth to adolescence: using different penicillins to inform a common maturation function

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Background and objectives:

Developmental physiology and ontogeny are known to affect drug disposition in neonates and children. Therefore improving our understanding of developmental pharmacology is an important component of paediatric dose optimization strategies. The Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study – NAPPA (NCT01975493)¹ – is a multicentre, multi-drug paediatric population pharmacokinetic (PK) study employing opportunistic sampling strategies² to study the PK of several penicillins during routine National Health Service (NHS) care of children and infants. This analysis aimed to use interim data from the NAPPA study to inform a common maturation function (MF) from birth to adolescence for two drugs: benzylpenicillin and piperacillin.

Methods:

Eligible participants were recruited from nine participating hospitals in England. The antibiotic dosing regimen was as per standard care, following local NHS practice in conjunction with the British National Formulary for Children (BNFC) dosing recommendations. After informed consent, study blood samples (approximately 0.5mL each) were obtained, taken either with routine blood samples (required for normal care – termed ‘clinically scavenged’ sampling) or at recommended times.³ After centrifugation all plasma samples were frozen at -80 degrees Celsius and analysed in retrospect using ultra high-performance liquid chromatography with tandem mass spectrometry. PK data from both penicillins were analysed simultaneously with a joint PK model implemented in non-linear mixed-effects modelling software (NONMEM v7.3, Icon plc, Ellicott City, Maryland), with *a priori* allometric weight scaling on both volume (Vd) and clearance (CL), and a shared postmenstrual age (PMA) driven MF on CL.^{4,5} The importance sampling (IMP) estimation method was used to obtain the objective function value (OFV). The NAPPA study protocol was approved by the London Dulwich NRES Research Ethics Committee (REC reference 13/LO/0907).

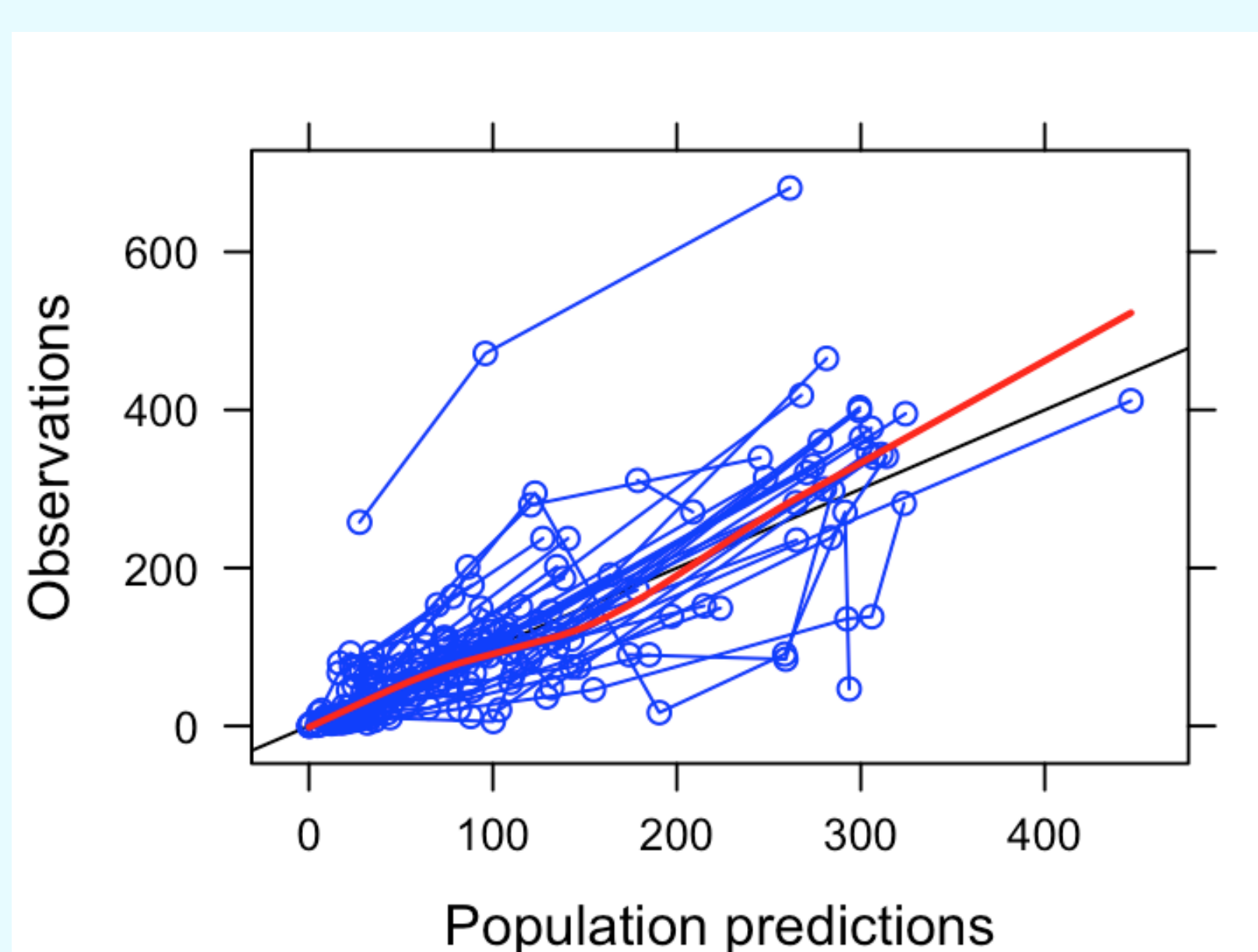


Figure 1: Observed concentrations plotted against the population predictions

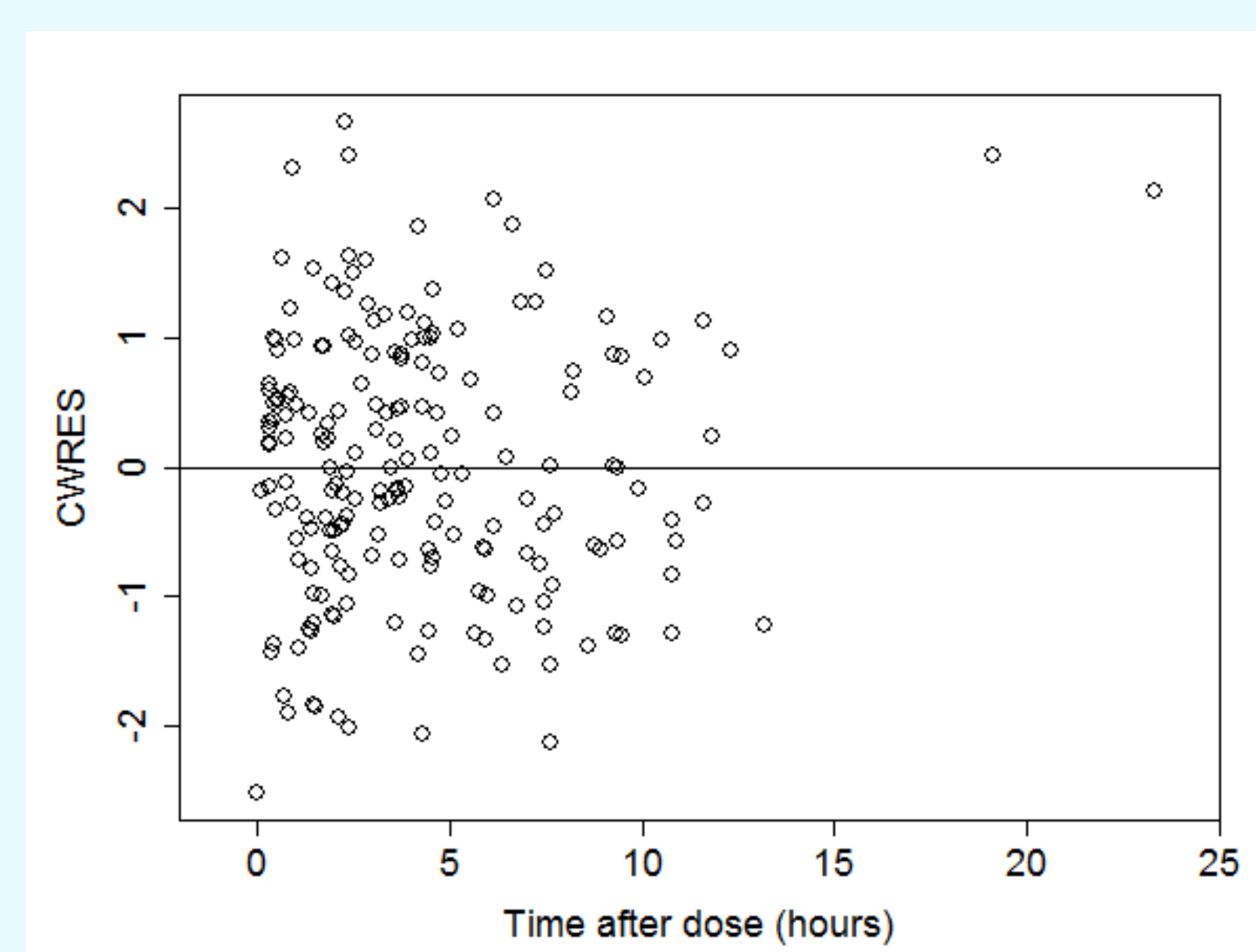


Figure 2: Conditional weighted residual errors (CWRES) plotted against time after dose (TAD)

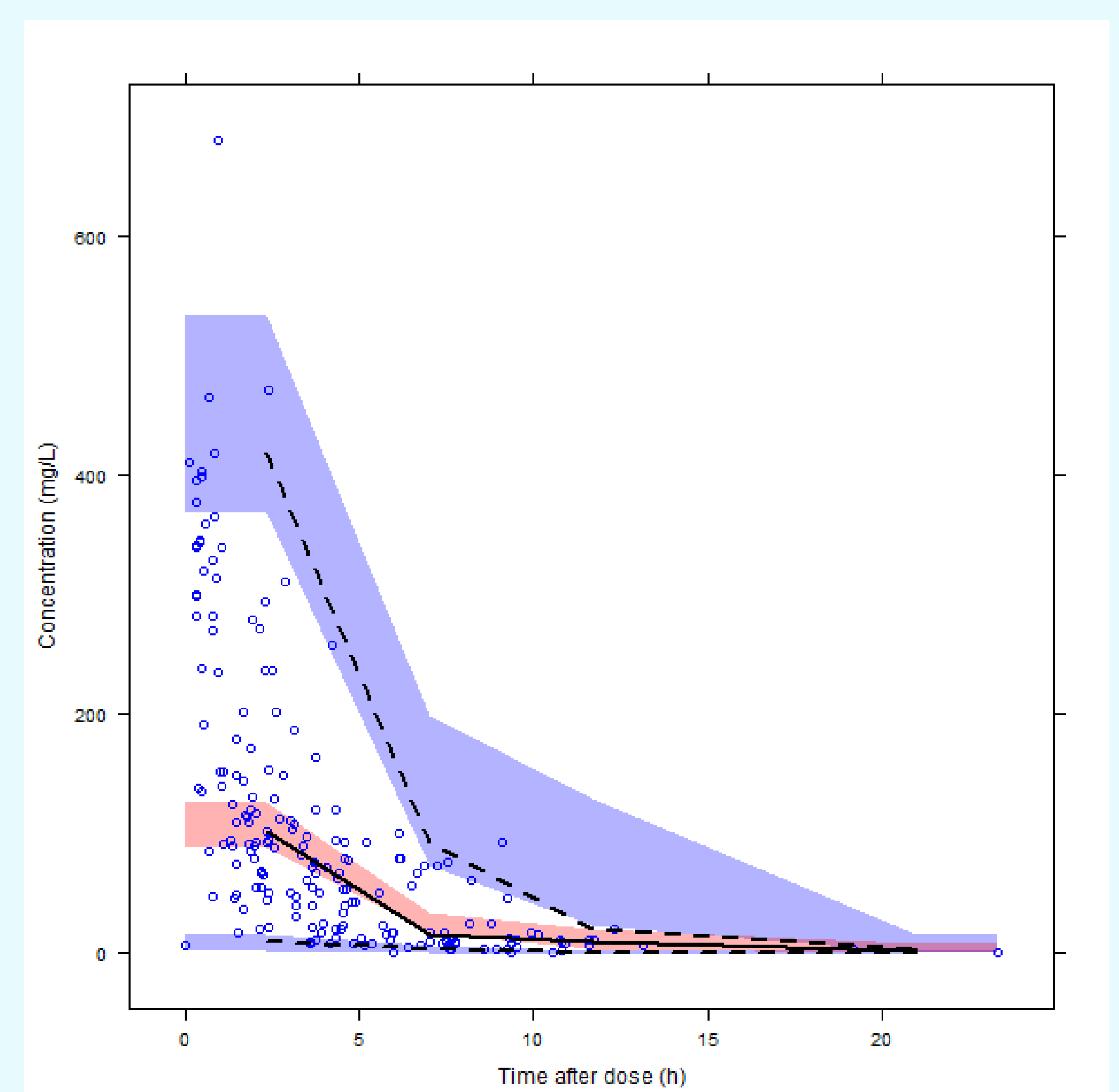


Figure 3: Visual predictive check, showing observations (dots) and prediction intervals (shaded areas) against TAD

Results:

For this analysis, interim NAPPA PK data were available for participants on benzylpenicillin (n=45) and piperacillin/tazobactam (n=29). The study population included 46 neonates (25 preterm), and 28 infants and children (up to 12 years-old). Using a joint one compartment population PK model, the combined data were analysed simultaneously in NONMEM. The optimization was completed with successful convergence. The OFV was 1522.3. The final parameter estimates were: 3.4 L/h/70 kg for benzylpenicillin CL and 11.4 L/70kg for Vd; 7.9 L/h/70 kg for piperacillin CL and 16.3 L/70kg for Vd, and for the common MF, the final parameter estimates were: 3.2 for the Hill coefficient and a PMA of 41.3 weeks for the maturation half-time (TM50). Selected diagnostic plots for this model are shown in figures 1-3. Study limitations: data from only two different penicillins were analysed.

Conclusions:

- Interim paediatric PK data from benzylpenicillin and piperacillin were successfully analysed simultaneously using a joint model with a common MF.
- Allometric weight scaling with a sigmoidal MF was used as standardised parameterization to facilitate extrapolation.⁶
- This approach also supports learning across drugs with similar PK, which can be helpful to further characterise developmental pharmacology.⁶
- Future work will include data from additional NAPPA study penicillins and retesting of the model with the final study dataset.