Paediatric posology and the EMA-endorsed graphical dose justification

or how to best document an adequate paediatric dosing regimen

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How should results/predictions of pharmacokinetic analyses be presented to facilitate decision making about the adequacy of the proposed dosing regimen in paediatric patients? November 2018

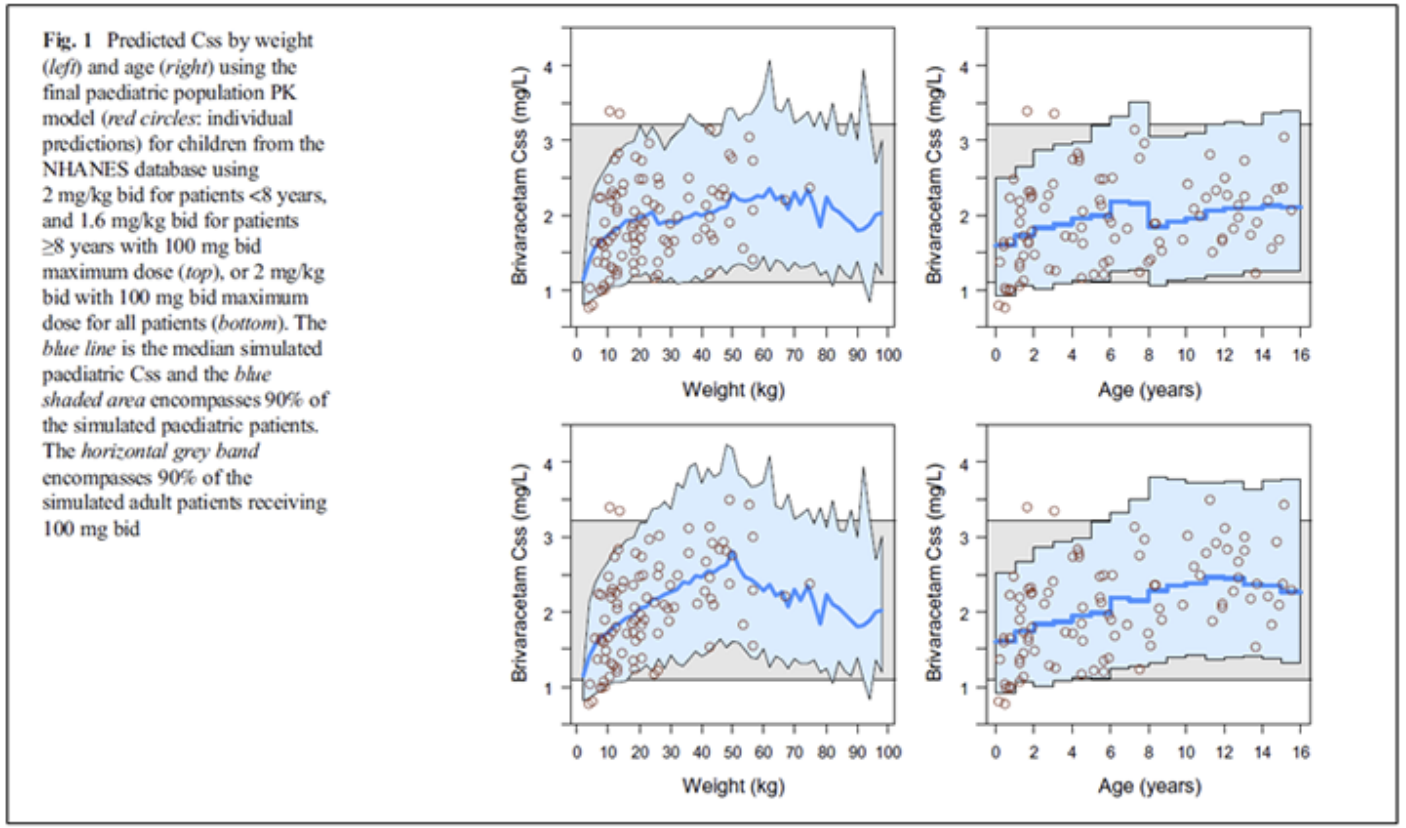

Fig. 1 Predicted Css by weight (*left*) and age (*right*) using the final paediatric population PK model (*red circles*: individual predictions) for children from the NHANES database using 2 mg/kg bid for patients <8 years, and 1.6 mg/kg bid for patients ≥8 years with 100 mg bid maximum dose (*top*), or 2 mg/kg bid with 100 mg bid maximum dose for all patients (*bottom*). The *blue line* is the median simulated paediatric Css and the *blue shaded area* encompasses 90% of the simulated paediatric patients. The *horizontal grey band* encompasses 90% of the simulated adult patients receiving 100 mg bid

Figure 1 Schoemaker et al. 2017 [1]

https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-and-pharmacokinetics/modelling-and-simulation-questions-and-answers

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How to best document an adequate paediatric dosing regimen?

- A graphical representation by both weight and age is very powerful
- Both typical values and the range are important
- Scale from adults to children:
  - Adult PK model and paediatric PK model (possibly combined)
  - Adult recommended dose and paediatric candidate doses
  - Simulate adult and paediatric exposures using a demographic database to link weight or lean body weight to age:
    CDC NCHS National Health and Nutrition Examination Survey (Nhanes[1])
  - Simulate paediatric exposures using EBEs from the children in the paediatric PK data set
- Example from follow-up publication for brivaracetam in children <4 years[2]
- Simple one-compartment first-order absorption model with fixed allometric scaling
- Steady state average concentration for a drug with linear kinetics is trivial:
  C_{av} = (Dose/Clearance)/(dosing interval)

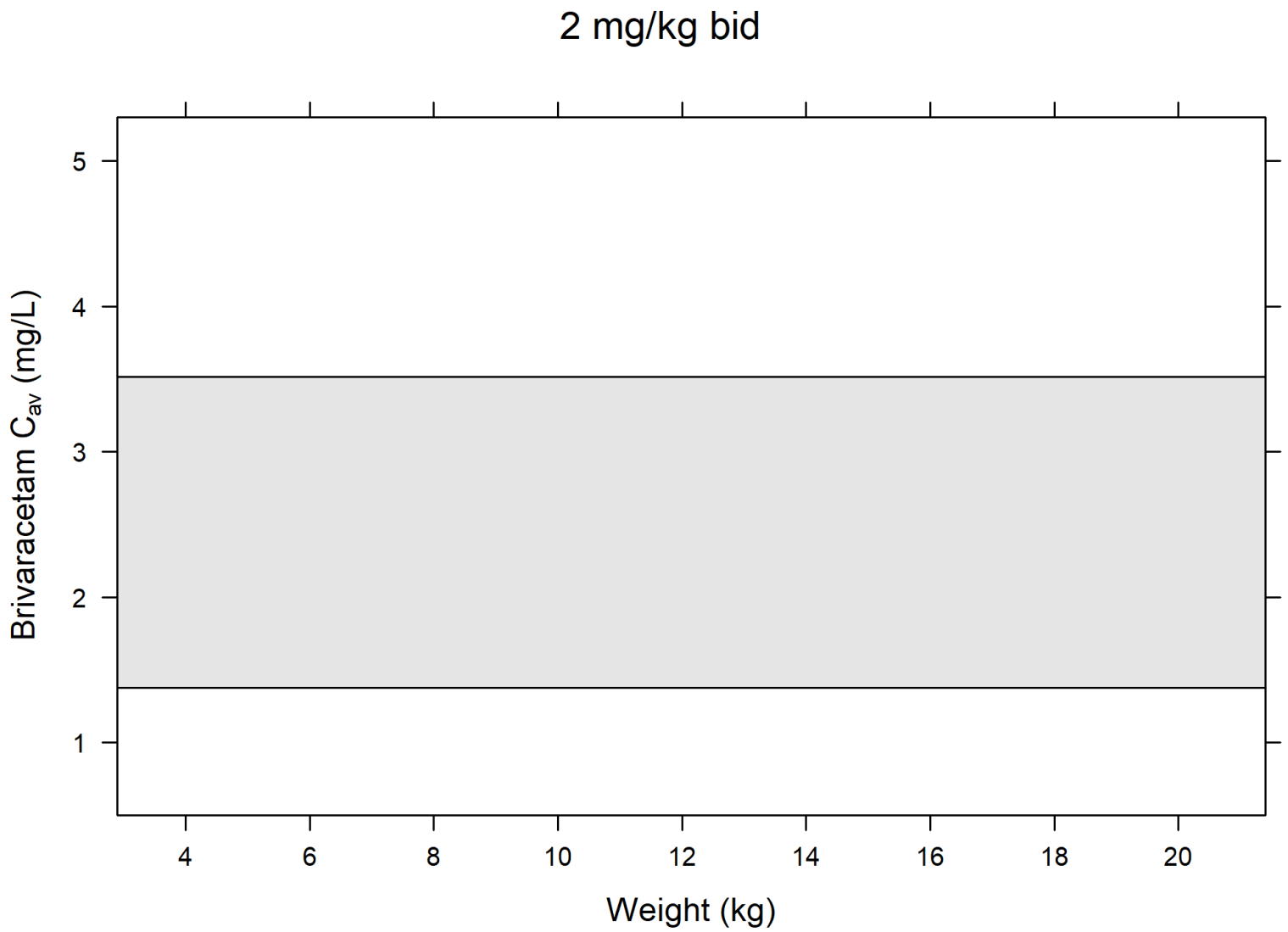
[1]The 1999-2006 Dual Energy X-ray Absorptiometry (DXA) Multiple Imputation Data Files and Technical Documentation dxa data (https://wwwn.cdc.gov/Nchs/Nhanes/Dxa/Dxa.aspx) and The 1999-2006 CDC NCHS National Health and Nutrition Examination Survey bmx and demo data (https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx)

[2]Rik Schoemaker, Walter Krauwinkel, Jan-Peer Elshoff, Armel Stockis. Brivaracetam exposure-response predictions in pediatric patients from age 1 month: Extrapolation of levetiracetam adult-pediatric scaling to brivaracetam. Epilepsy Research 202 (2024) 107332.

Adult 90% reference range for 100 mg bid

- Sample adults from Nhanes database (e.g. 1000)
- Sample PK parameters from the population distribution using the Nhanes weights
- Calculate exposure metrics for the adult reference dose (100 mg bid)
- Derive the 90% range (5^{th} to 95^{th} quantile) and plot result as a horizontal band across the paediatric age or weight range

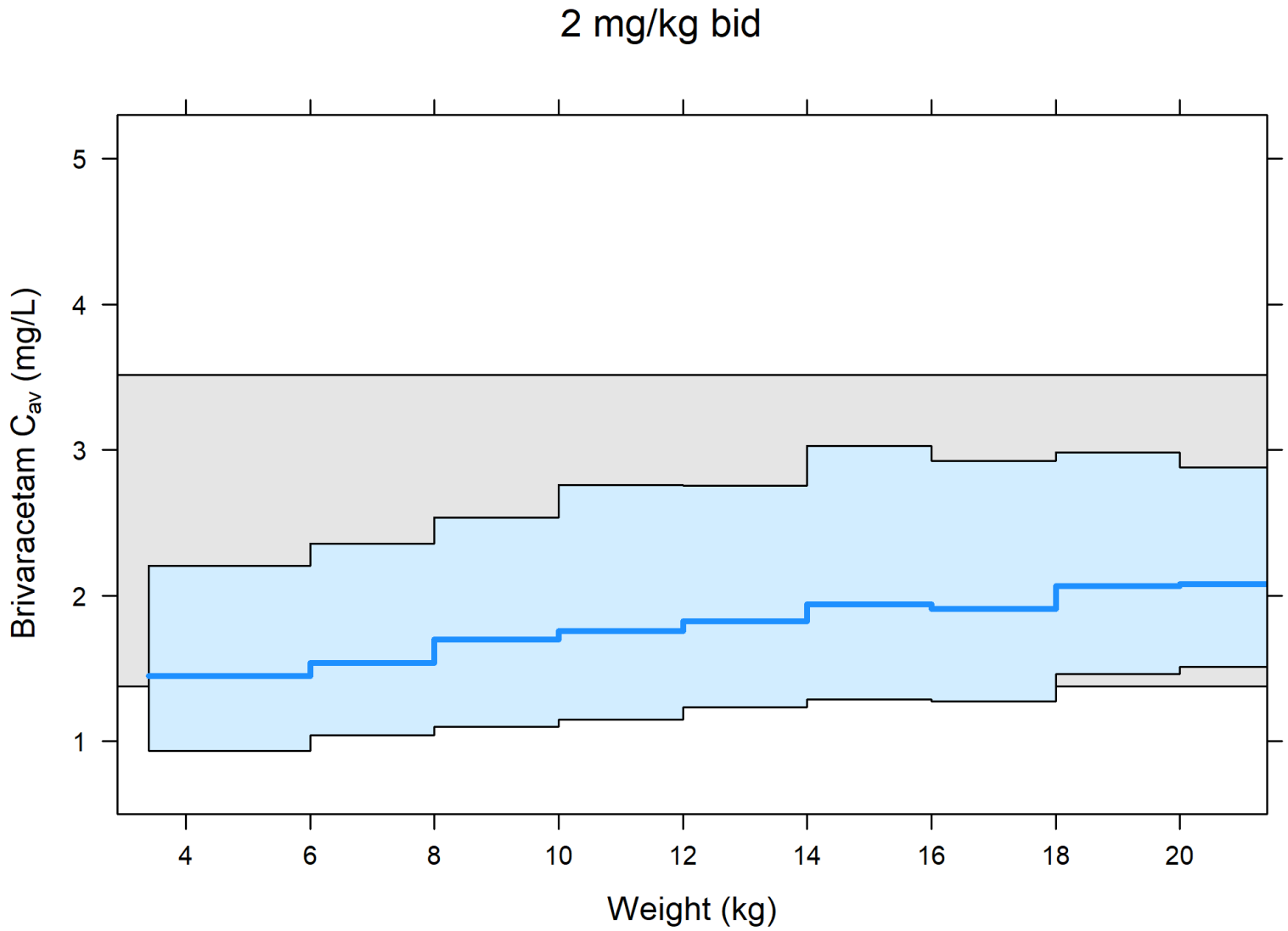
Adult 90% reference range for 100 mg bid



Paediatric median and 90% range for 2 mg/kg bid

- Sample adults from Nhanes database (e.g. 1000)
- Sample PK parameters from the population distribution using the Nhanes weights
- Calculate exposure metrics for the adult reference dose (100 mg bid)
- Derive the 90% range (5^{th} to 95^{th} quantile) and plot result as a horizontal band across the paediatric age or weight range
- Take all kids or sample from Nhanes database
- Sample PK parameters from the paediatric PK distribution using the Nhanes weights
- Calculate exposure metrics for the proposed dose (e.g. 2 mg/kg bid)
- Derive median and the 90% range (5^{th} to 95^{th} quantile) by weight or age bins and plot result as a line and area across the paediatric age or weight range

Median and 90% range of simulated pediatric C_{av} values for 2 mg/kg bid



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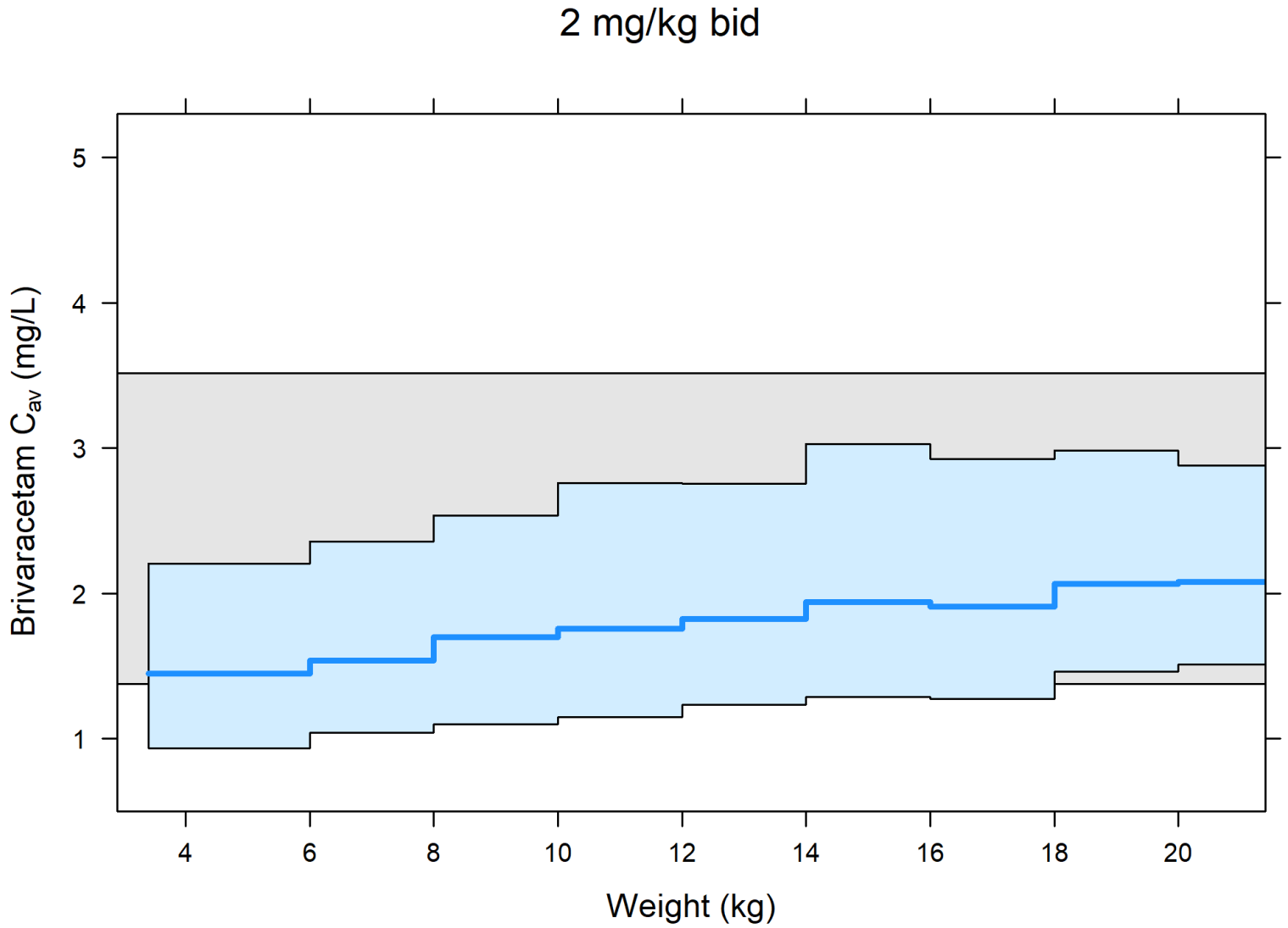
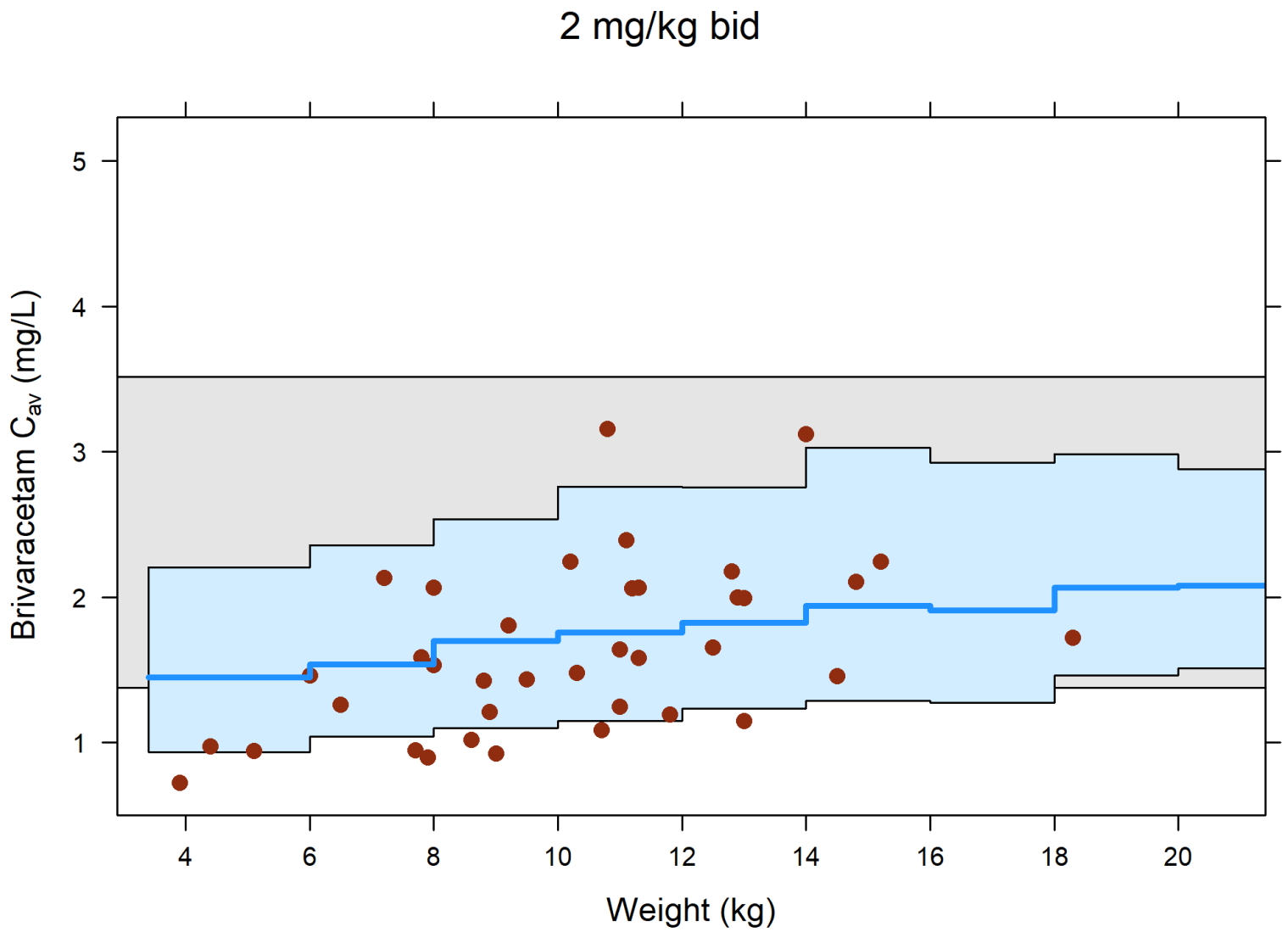
This pattern is a consequence of allometric scaling when using mg/kg dosing



Individual exposures for 2 mg/kg bid

- Sample adults from Nhanes database (e.g. 1000)
- Sample PK parameters from the population distribution using the Nhanes weights
- Calculate exposure metrics for the adult reference dose (100 mg bid)
- Derive the 90% range (5^{th} to 95^{th} quantile) and plot result as a horizontal band across the paediatric age or weight range
- Take all kids or sample from Nhanes database
- Sample PK parameters from the paediatric PK distribution using the Nhanes weights
- Calculate exposure metrics for the proposed dose (e.g. 2 mg/kg bid)
- Derive median and the 90% range (5^{th} to 95^{th} quantile) by weight or age bins and plot result as a line and area across the paediatric age or weight range
- Take EBEs from kids in the analysis and simulate exposures using the proposed dose

Predicted individual pediatric C_{av} values for 2 mg/kg bid



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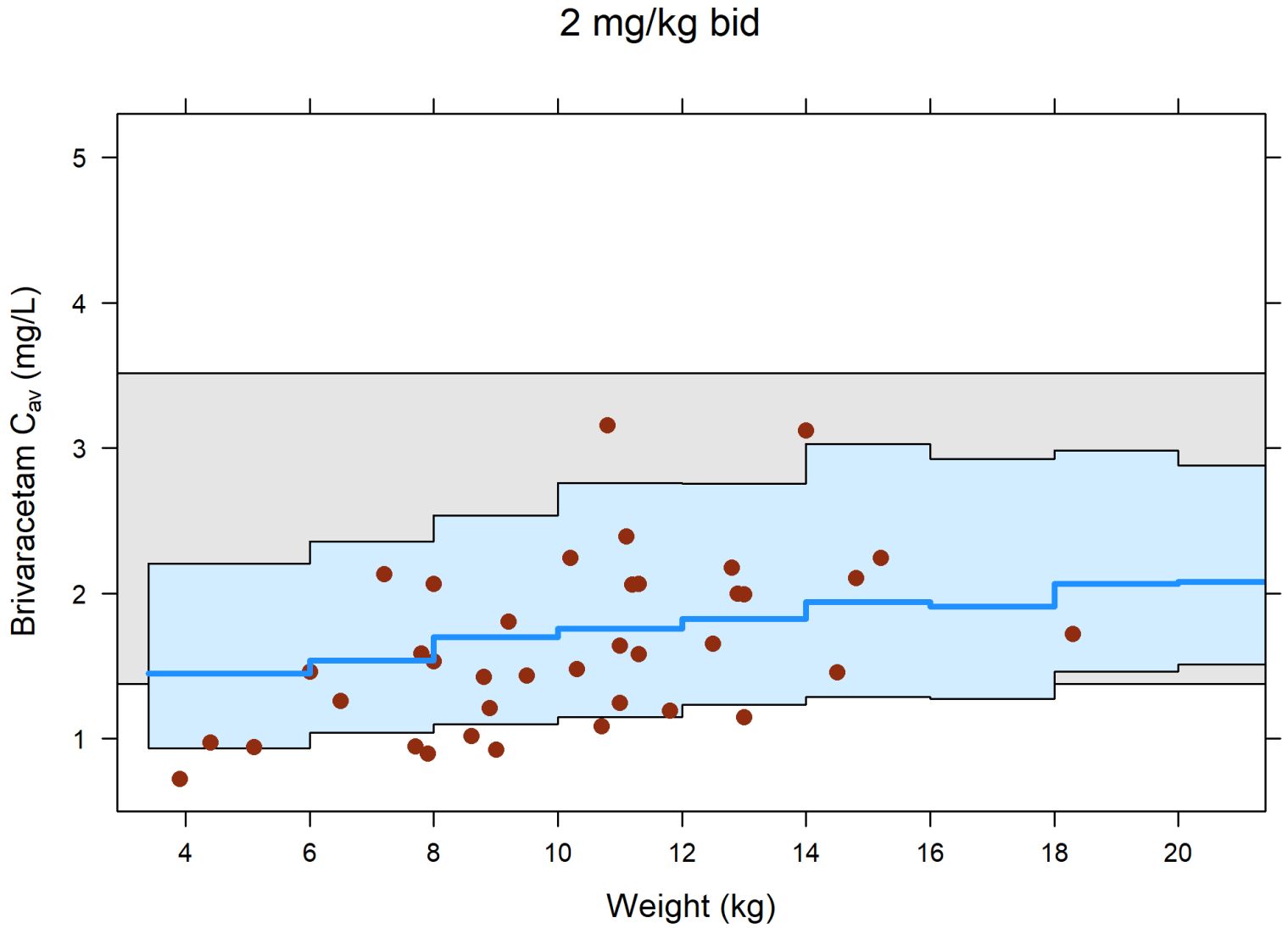
Display provides a posterior predictive check: do the simulated exposures match the data?



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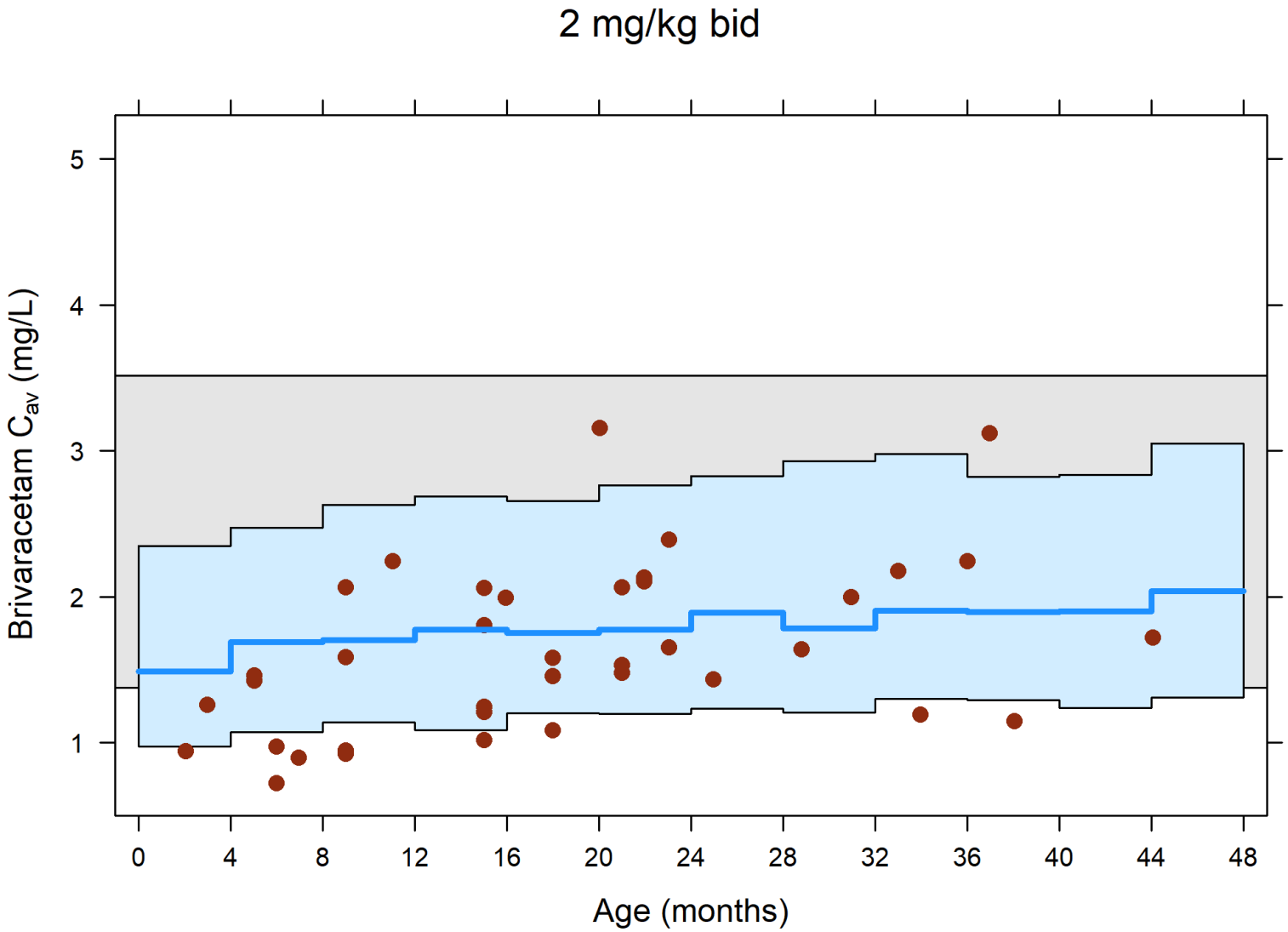
The same graph by age instead of weight



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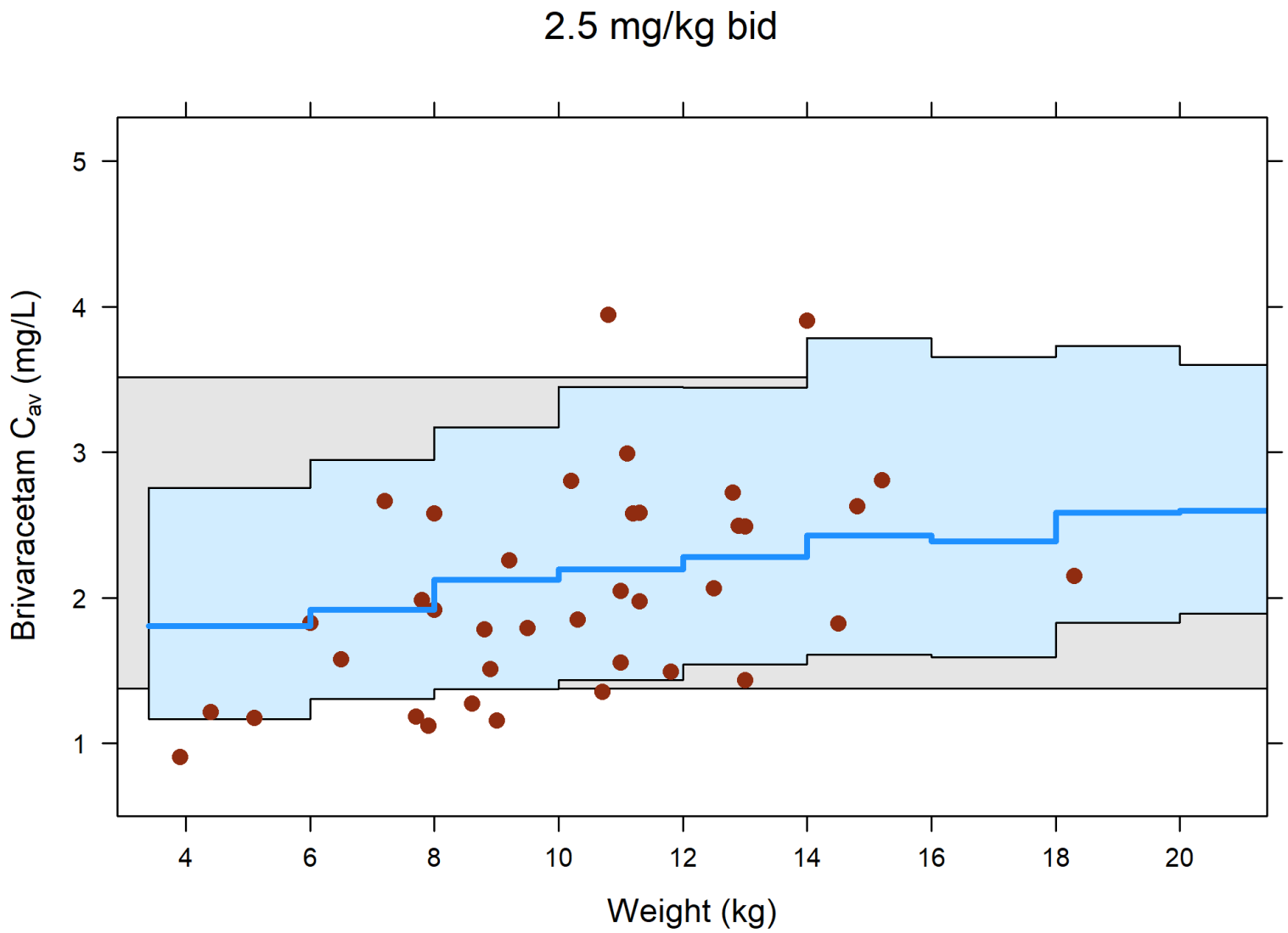
Will a shift to 2.5 mg/kg improve the match with adult exposures?



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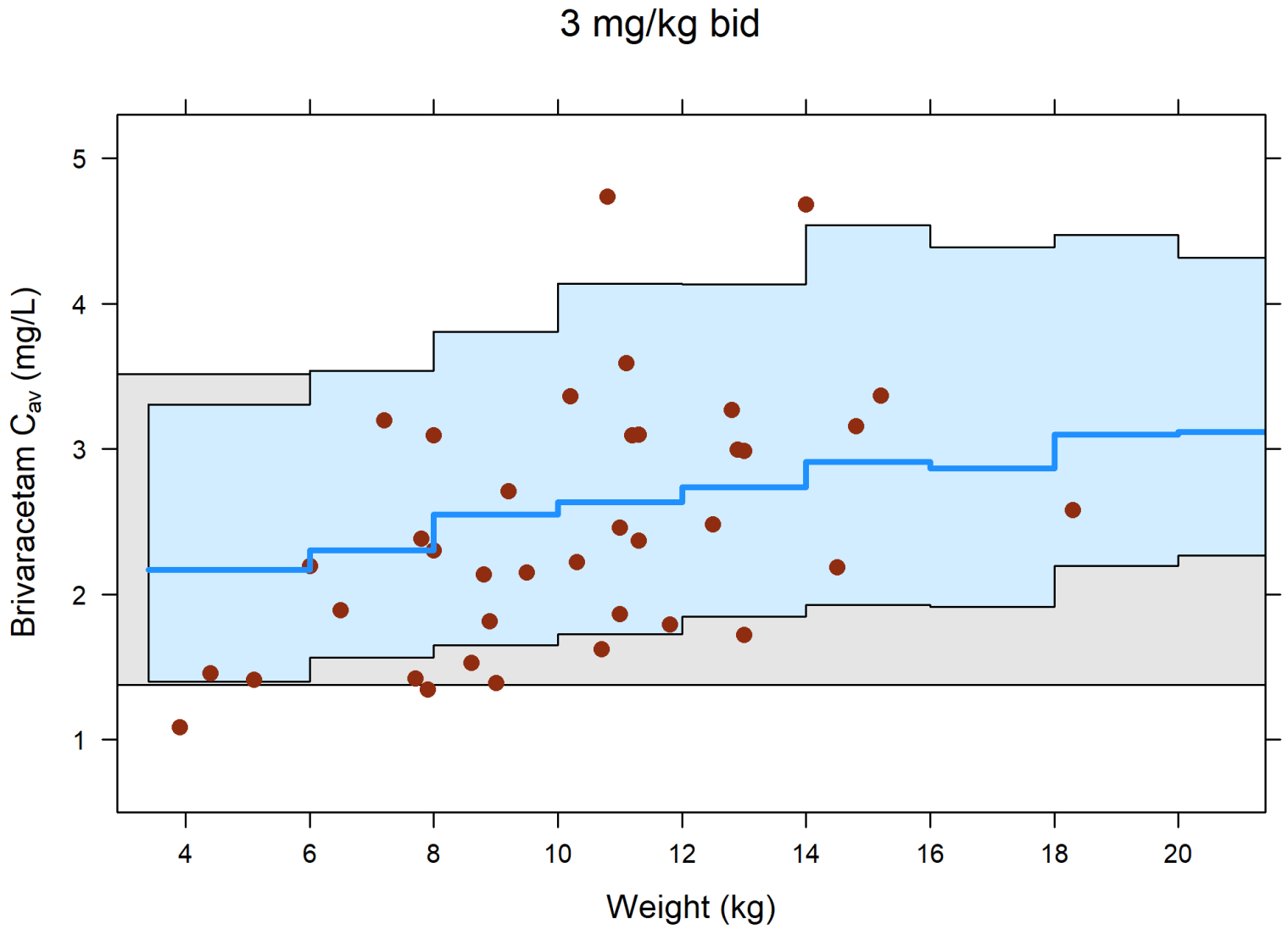
Or do we need to go even higher (3 mg/kg) for small children?



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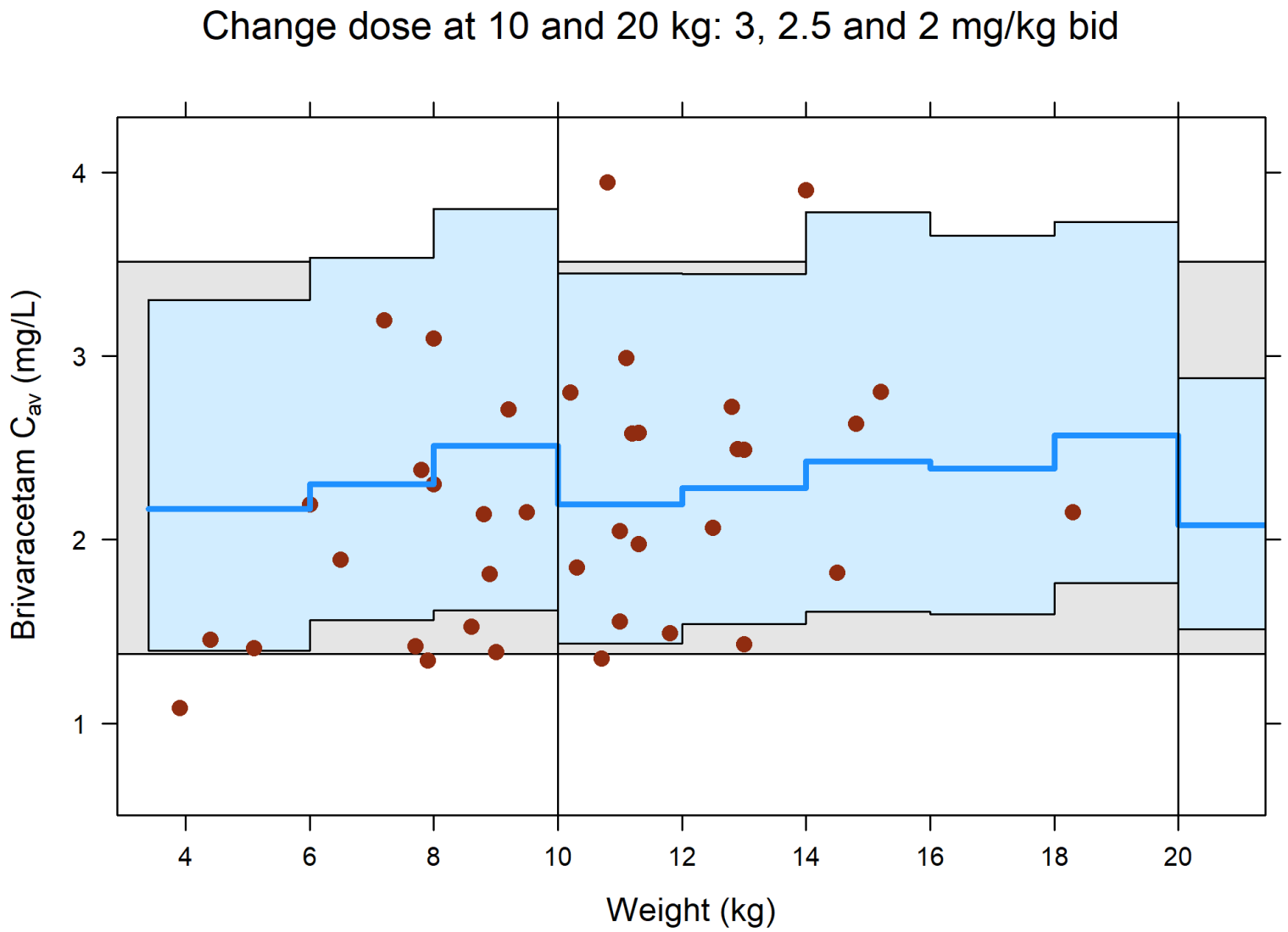
A dose change at 10 and 20 kg best matches adult exposure



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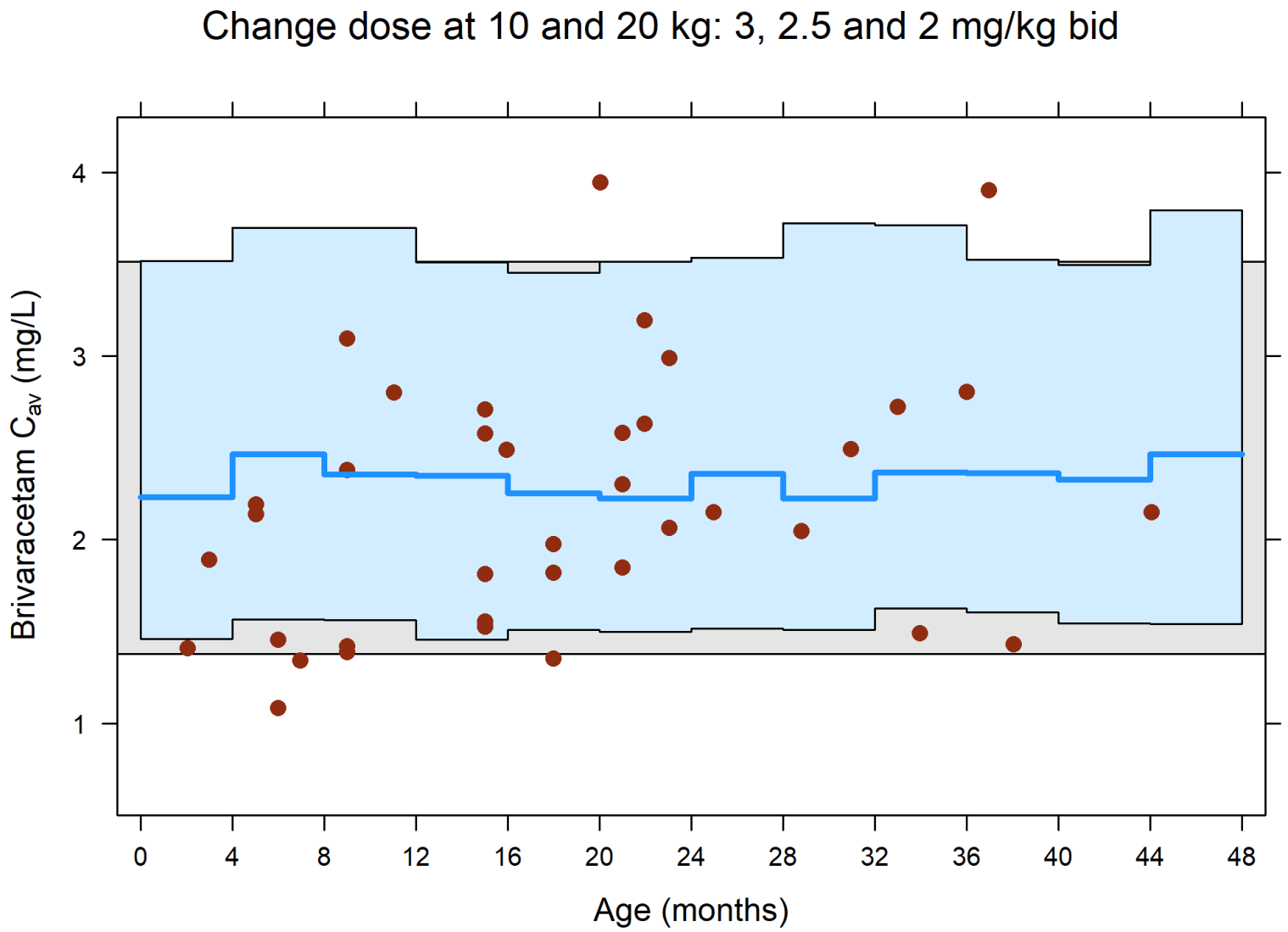
The same graph by age instead of weight



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Conclusions

- Graphs of exposure by weight and age are highly illustrative of potential adequacy of pediatric posology
- They additionally provide a check for model adequacy

- Code for generating graphs (using lattice or ggplot2) and rxode2 simulations for exposure measures is available at github.com/GitOccams