COMPARATIVE EVALUATION OF POPULATION PHARMACOKINETIC MODELS OF VANCOMYCIN IN NEONATES WITHIN DOSOPT FRAMEWORK

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Background and aim

- Despite extensive investigation of vancomycin pharmacokinetics (PK), the transferability of different models remains an open question.
- **Our aim was to externally evaluate performance of neonatal vancomycin PK models (NVM) in a Bayesian framework and assess the effect of including individual concentrations on forecasting accuracy.**

Methods

- Systematic literature search (Ovid Medline + reference lists) established 18 relevant

Neonatal Vancomycin PK models

1 (Allegaert et al. 2007)	**10** (Kimura et al. 2004)
2 (De Cock et al. 2012)	**11**(Le et al. 2013)
3 (Anderson et al. 2007)	**12**(Lo et al. 2010)
4 (Bhongsatiern et al. 2015)	**13**(Marqués-Miñana et al. 2010)
5 (Capparelli et al. 2001)	**14**(Oudin et al. 2011)
6 (De Cock, Allegaert, Brussee, et al. 2014)	**15**(De Cock, Allegaert, Sherwin, et al. 2014)
7 (de Hoog et al. 2000)	**16**(Seay et al. 1994)
8 (Frymoyer et al. 2014)	**17**(Silva et al. 1998)
9 (Grimsley & Thomson 1999)	**18**(Zhao et al. 2013)

- External evaluation was carried out on retrospective dataset (312 concentrations from 121 neonates with mean PMA 31.7(24.6-53.1) weeks) using Bayesian-based framework DosOpt (**http://biit.cs.ut.ee/DosOpt**).
- Simulation based diagnostics such as
  - **adjusted-R^2**
  - **MAPE-** mean absolute percentage error
  - **MPE-** mean percentage error
  - **NPDE**- normalized prediction distribution errors were used to assess fit of models, forecasting accuracy and model goodness.

Results

- **Predictive accuracy**: models described the data decently (global average adjusted-R^2_0.7).
- **Model fit**: number of individual concentrations included in modeling converged values of adjusted-$R^{2's}$ but did not change model fits (min p-value 0.38) **(Fig.1)**
- **Forecasting accuracy:** Inclusion of individual trough concentrations (C_{tr}) showed significant improvement of forecasting performance compared to population PK based model (p<1e-16) **(Fig2)**

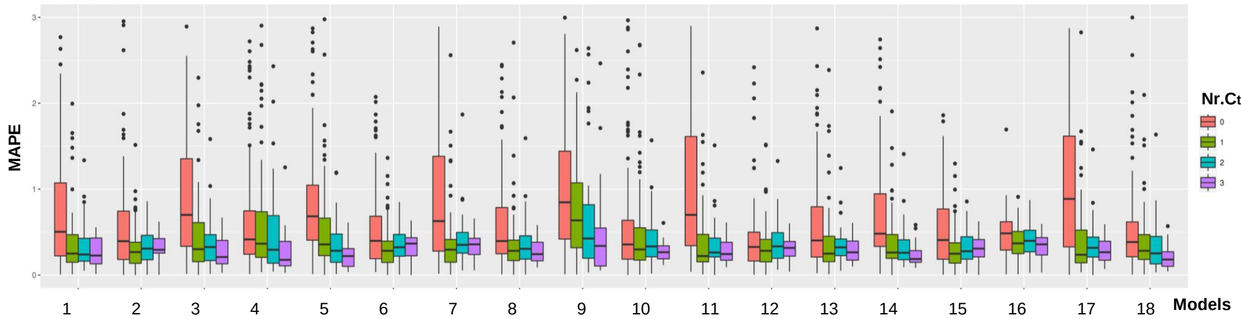

Figure 2: *Decreasing values of MAPE's define the diminution of absolute bias for each model in condition of increasing amount of concentration measurements.*

- **Effect of adding concentrations:** Prediction accuracy increases with increasing number of available concentration points (Ctr), likely improving also probability of target attainment. **(Fig 3)**

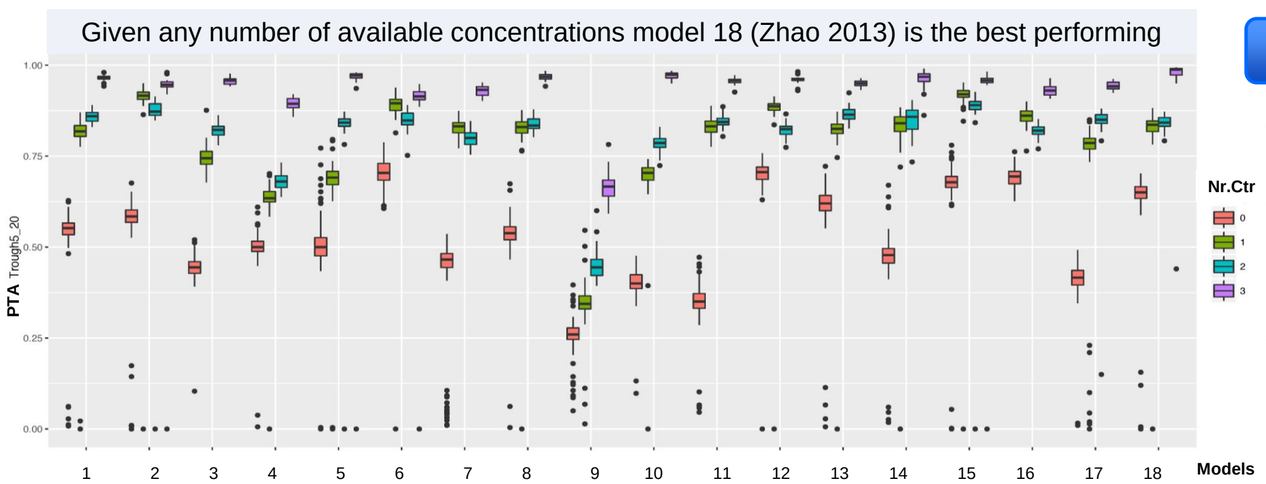

Figure 3: *In this figure the target is set on C_{tr} 10-15mg/L. On y-axis the propability of target attainment (PTA) to achieve concentrations on range C_{tr} 5-20mg/L is shown for each model.*

The proportion of variance explained by the model and included concentrations

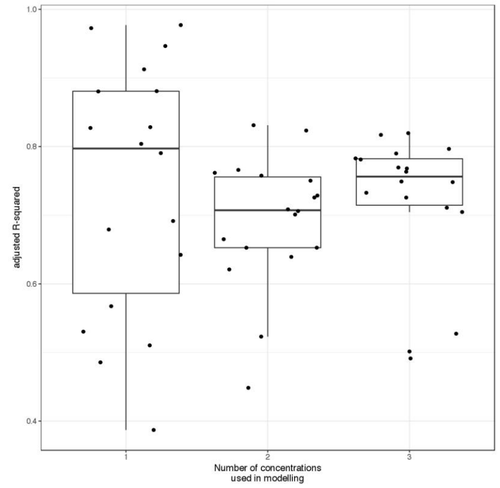

Figure 1*: Boxplots of adjusted –R^2 on predicted vrs observed concentrations in condition of 1, 2 or 3 included C_{tr} measurements over all models*

Conclusion

- Although all models descirbed the data decently, the predictive performance of various NVM differs significantly and need to be considered in the implementation of model-based individual dose prediction into clinical practice
- Adding at least one individual concentration measurement into model-based dose prediction increases significantly prediction accuracy.

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