

# Evaluation of model-based vancomycin concentration monitoring in neonatology

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## Background and Objective

- To optimize vancomycin use and enhance therapeutic drug monitoring (TDM) in neonatology, **model-informed precision dosing (MIPD)** using suitable population pharmacokinetic (PopPK) models is proposed[1].
- We aimed to **evaluate the potential suitability** (predictive performance) of a published PopPK model for vancomycin concentration prediction in our local population of neonates.

## Methods

### Retrospective data collection

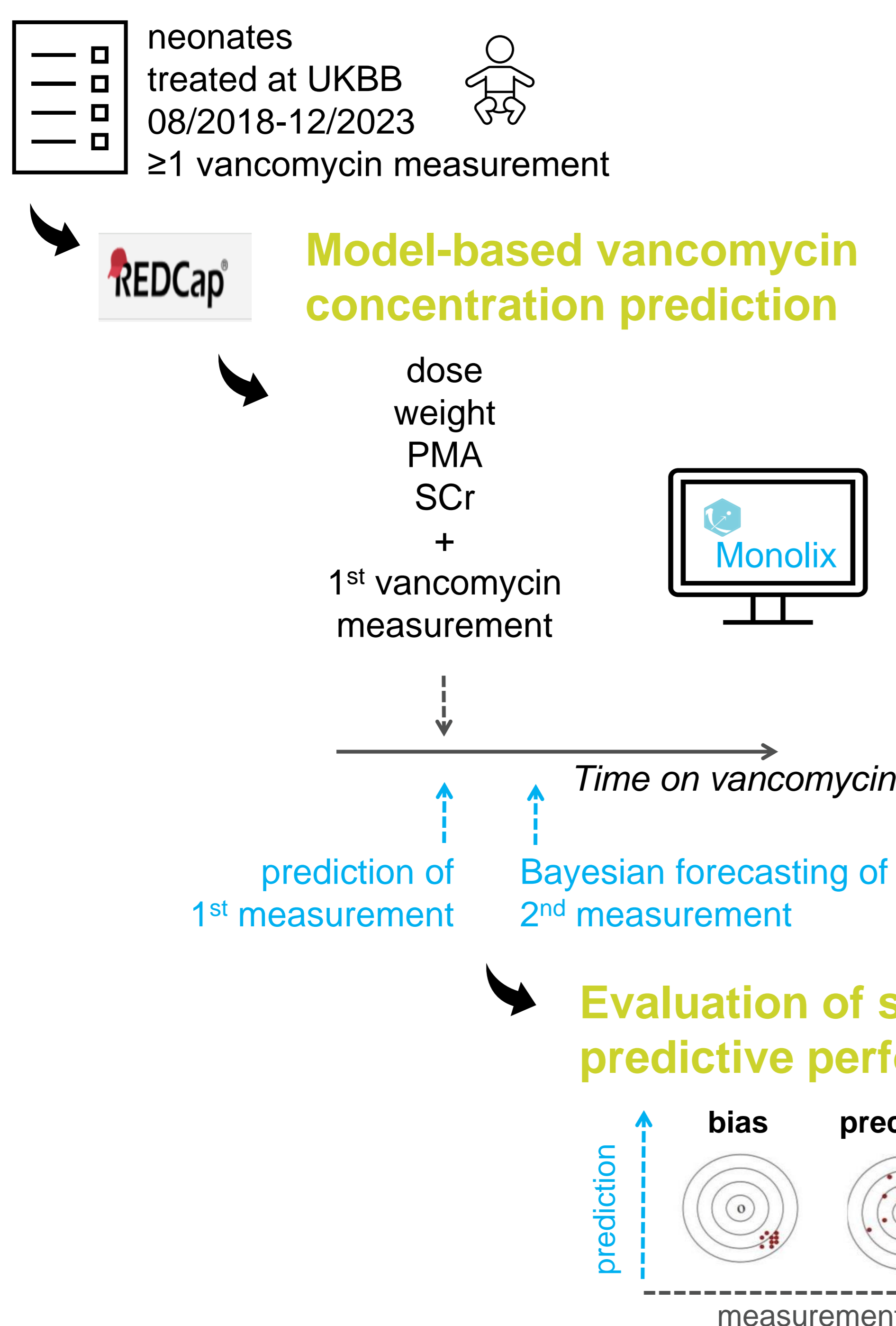


Table 1: Characteristics of 32 neonates included in retrospective analysis

Variable	Value number (%) or median (IQR)
Female / Male	11 (34.4 %) / 21 (65.6 %)
Gestational age (GA) [weeks]	27.5 (24.5 - 35.1)
Birthweight (BW) [g]	1045 (600 - 2480)
Small for gestational age (SGA) (< 10 <sup>th</sup> percentile)	10 (31.2 %)
APGAR at 5 minutes	7.00 (6 - 8)
Postnatal age at start vancomycin [PNA, days]	21 (8 - 45)
Postmenstrual at start vancomycin [PMA, weeks]	32 (29 - 41)
Calculatory weight (WT) [g]	1834 (1170 - 3400)
Treatment days with vancomycin [days]	6 (4 - 10)
Indication for vancomycin treatment	
LOS (Late onset sepsis)	23 (71.9%)
EOS (Early onset sepsis)	9 (28.1%)
Pathogen identified	
MRSE	10 (31.2%)
MRSA	4 (12.5%)
not detected	10 (31.2%)
others	8 (25.1%)
Additional antibiotic treatment	
+ Meropenem	16 (50.0%)
no additional antibiotic	6 (18.8%)
other combinations	10 (31.2%)

References:  
[1] Rybak MJ et al. 2020. *Heal Pharm.* 77(11):835-63  
[2] Dao et al. 2020. *Pharmacol Res.* 154:104278  
[3] Smits et al. 2018. *Eur J Clin Microbiol Infect Dis.* 37:1503-1510

## Conclusion

- Small overprediction of vancomycin concentrations with limited precision using a literature PopPK model suggests that **MIPD requires careful local evaluation before implementation.**
- There is **room for improvement in neonatal vancomycin use and monitoring**, involving
  - (1) clarification of proposed targets in neonates and
  - (2) a potentially refined MIPD strategy to handle non-steady-state measurements and predict AUC as preferred exposure metric[1].

## Results

### Patient population and concentration measurements

- A total of 78 vancomycin level measurements of 32 neonates were collected (Table 1, Figure 1).

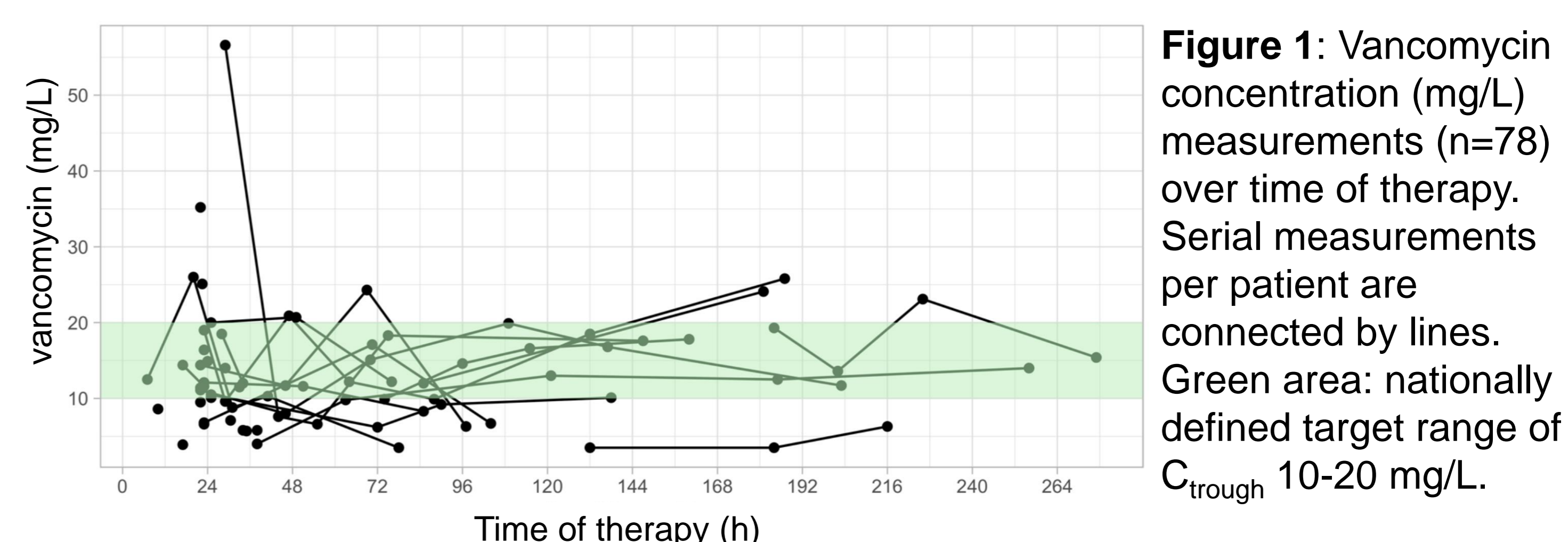


Figure 1: Vancomycin concentration (mg/L) measurements (n=78) over time of therapy. Serial measurements per patient are connected by lines. Green area: nationally defined target range of C<sub>trough</sub> 10-20 mg/L.

### Evaluation of suitability: predictive performance

Table 2: Predictive performance of evaluated population pharmacokinetic model

	prediction of initial vancomycin measurement (n=32)	Bayesian forecasting of 2 <sup>nd</sup> vancomycin measurement (n=16)
<b>Bias</b>	+ 24% (95%CI: 8-40)	+ 12% (95%CI: -14-38)
<b>Precision</b>	±0.57 mg/L ±50%	±0.51 mg/L ±49%
<b>Model-predicted versus measured vancomycin concentration</b>		

### Further secondary outcomes

- Target exposure achievement:** nationally defined target trough concentration was reached in 41/78 (52.6%) of measurements, with similar target achievement projected under current national dosing. It remains however unclear whether lower concentrations should be targeted in neonates due to lower plasma protein binding. [3]
- TDM timing:** Initial measurements: taken at steady state in 17/32 (53%) of cases.
- Safety-related outcome:** Acute kidney injury defined as an increase of serum creatinine >26.5 μmol/L during 48 hours of vancomycin treatment was observed in 2 neonates (6.25%)
- Effectiveness-related outcomes:** Median time of C-reactive protein decline <10 mg/L was 110 hours (~4.5 days, range: 0-268 h) after treatment start with vancomycin. Infection-related mortality was observed in 2 neonates (6.25%)