Development and Evaluation of Bayesian Software for Improving Therapeutic Drug Monitoring of Gentamicin in Neonates

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PKUK
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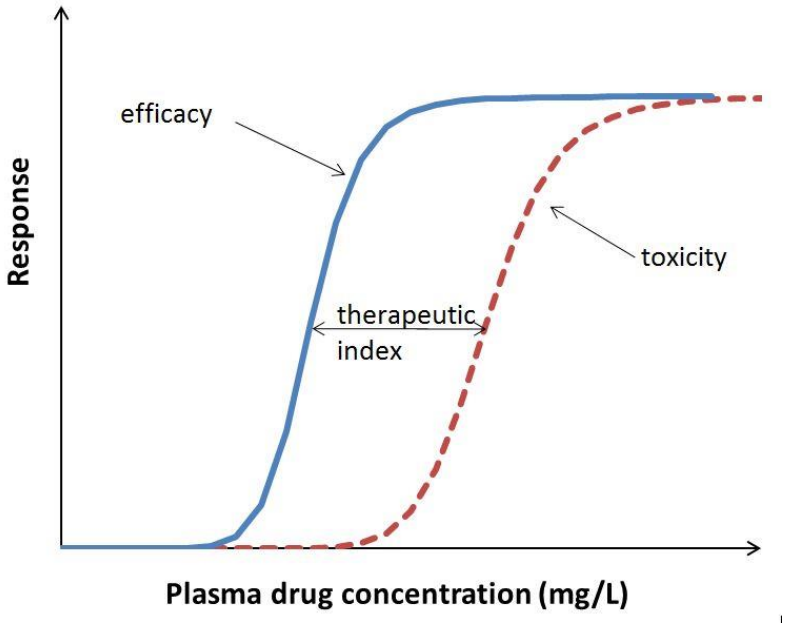
Overview

- Introduction
- Aims
- Methods
- Results
- Conclusions

Introduction

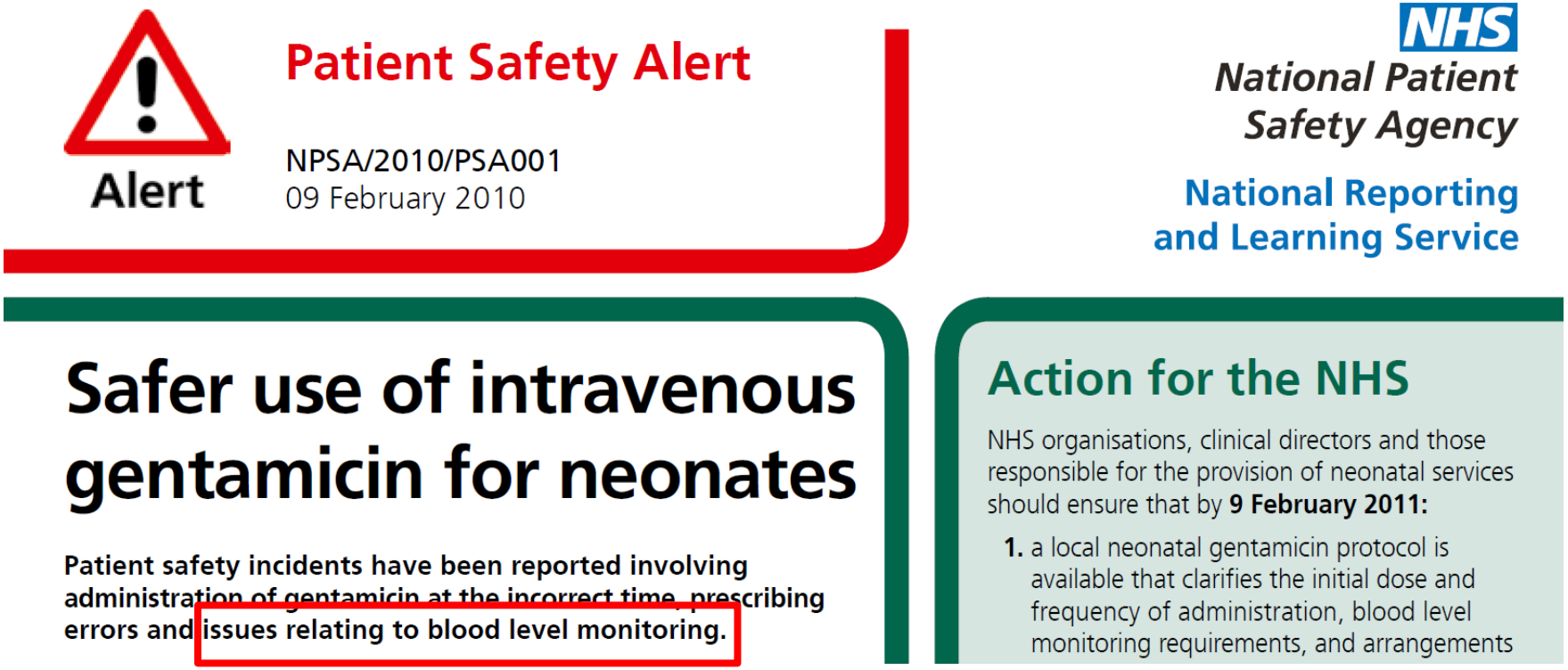
- Neonatal infection → morbidity, mortality
- Gentamicin: antibiotic used for treating newborns
- Narrow therapeutic index
- Small blood volumes
- Renal function not fully developed
- → Need for TDM



TDM = therapeutic drug monitoring

Background:

- NPSA alert



Alert

Patient Safety Alert

NPSA/2010/PSA001
09 February 2010

NHS
National Patient Safety Agency

National Reporting and Learning Service

Safer use of intravenous gentamicin for neonates

Patient safety incidents have been reported involving administration of gentamicin at the incorrect time, prescribing errors and issues relating to blood level monitoring.

Action for the NHS

NHS organisations, clinical directors and those responsible for the provision of neonatal services should ensure that by **9 February 2011:**

1. a local neonatal gentamicin protocol is available that clarifies the initial dose and frequency of administration, blood level monitoring requirements, and arrangements

Introduction

UK neonatal units:

- No single dosing & monitoring regimen

J Antimicrob Chemother 2011; **66**: 2647–2650
doi:10.1093/jac/dkr351 Advance Access publication 22 August 2011

Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units

S. Kadambari[1]*, P. T. Heath[1], M. Sharland[1], S. Lewis[2], A. Nichols[3] and M. A. Turner[4]

Forty-three units across the ENN responded to the gentamicin questionnaire, revealing 24 different combinations of dose, timing of dose and timing of monitoring. Figure 1 demonstrates

Introduction

Usually:

- Trough levels
  - taken at pre-set intervals (pre-dose)
  - require separate blood test
  - at inconvenient times

Bayesian methods:

- Combine TDM with routine blood sampling
- → ↓invasive

Published PK models:

- Model: 1-, 2-, 3-compartment
- Covariates: weight, age, creatinine, APGAR score, sepsis, gender, co-medication

- → a more mechanistic approach is required

Aim

1. Develop a software neoGent → improve TDM
   - predict safe trough levels from routine blood samples

2. Evaluate the developed software
   - with new prospectively collected data

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Data

- Retrospective: published studies → model building
  - Literature search: data from two studies[a,b]
  - N=174, samples=1163
  - GA=23.3-42.1 weeks, PNA=0-65 days
- Prospective: neoGent study→ model evaluation
  - St George's, Liverpool, Oxford, Portsmouth, Coventry
  - Collected: June 2012 – November 2013
  - N=163, samples=483
  - GA=23.9-42.3 weeks, PNA=0-77 days

GA = gestational age PNA = postnatal age

[a]Nielsen EI., et al, Clin Pharmacokinet 2009; 48: 253-63.
[b]Thomson AH, et al., Dev Pharmacol Therapeut 1988; 11: 173-9.

Model development

- PK meta-analysis performed on pooled data from published studies
- NONMEM VII; FOCE with interaction
- Mechanistic covariates:
  - Allometric scaling and a function, describing maturation of the glomerular filtration rate included *a priori*
  - PNA and serum creatinine tested

Model predictions evaluation

- Simulate from final model
  - Internal and external VPC
- Use prospectively collected data:
  - Take the 1st level = opportunistic, study sample
  - Predict the 2nd level = trough sample
  - Compare measured with model predicted trough level

neoGent software (pilot version)

- Individual patient's data put into a file:

ID	GA	SEX	DATE	TIME	PNA	WT	CREAT	RATE	AMT	DV
1	226	1	03/09/2013	12:00	3	1710	59	240	8	0
1	226	1	03/09/2013	15:15	3	1710	59	0	0	6.8

- Read into R; changed to appropriate format
- Predictions: R calls NONMEM
- NONMEM results read back into R
- Prediction of the time when concentration <2 mg/L → safe to give the next dose

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Final model

- 3-compartment model
- Residual error model: proportional + additive
- Inter-individual and inter-occasion variability: exponential model
- PNA and serum creatinine standardized for PMA: significant

$$CL = \theta_{CL} \cdot \left(\frac{WT}{70}\right)^{0.632} \cdot \frac{PMA^{3.33}}{55.4^{3.33} + PMA^{3.33}} \cdot \left(\frac{MSCr}{TSCr}\right)^{\theta_{SCr}} \cdot \frac{PNA}{\theta_{P_{50}} + PNA} \cdot e^{(\eta_{CL} + \kappa_{CL})}$$

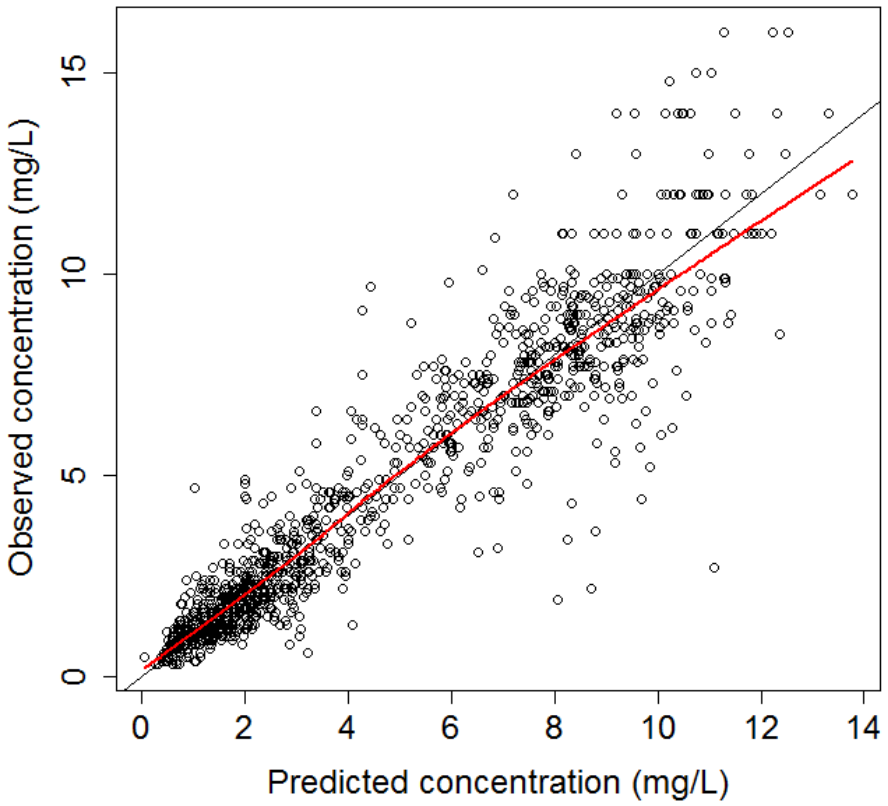
$$V = \theta_V \cdot \left(\frac{WT}{70}\right) \cdot e^{\eta_V} \qquad Q = \theta_Q \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot e^{\eta_Q}$$

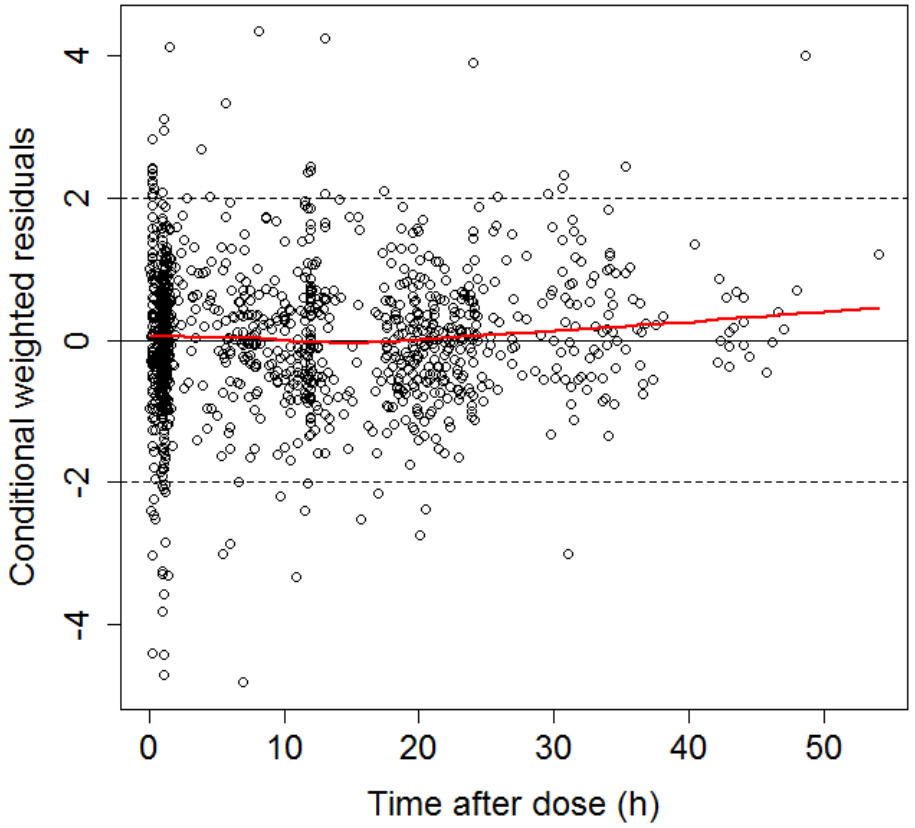
$$\mathrm{TSCr} = -2.8488 \cdot PMA\ [weeks] + 166.48$$

Cuzzolin L, et al., Pediatr Nephrol 2006; **21**: 931-8.
Rudd PT, et al., Arch Dis Child 1983; **58**: 212-5.

Rhodin, M.M., et al., Pediatr Nephrol, 2009. **24**(1): 67-76.

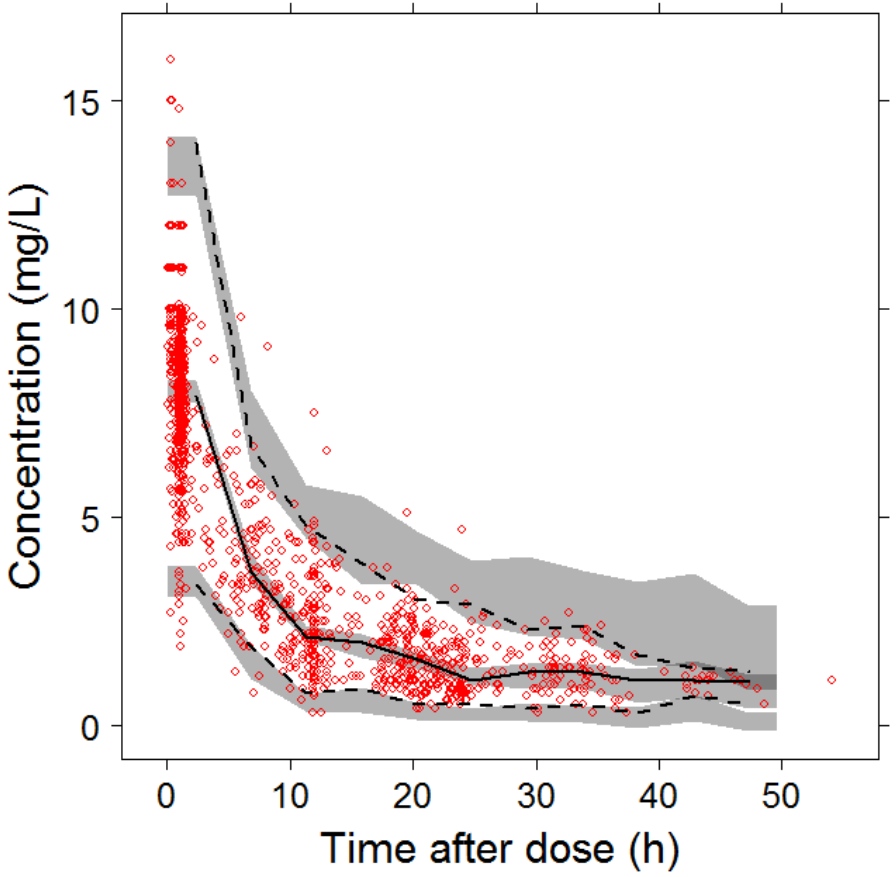
Internal evaluation



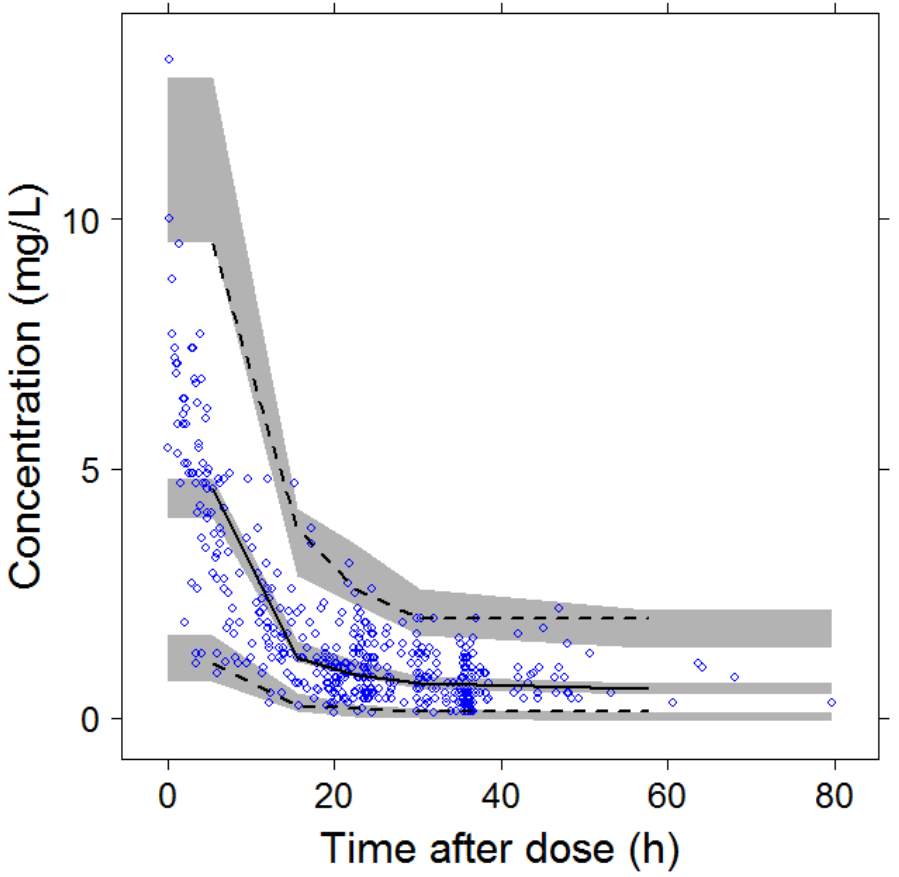


Visual predictive check

Internal VPC

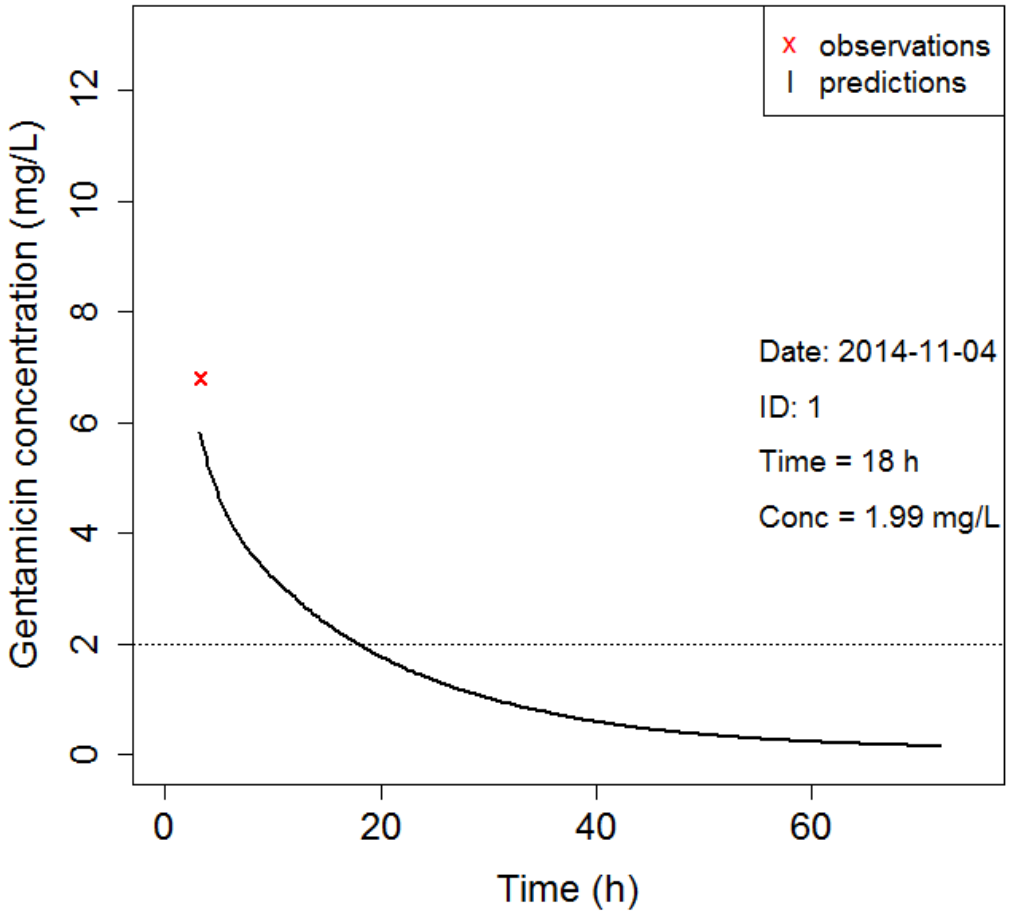


External VPC



An example of the neoGent output

SubjectID	Time(h)	PredConc(mg/L)
1	18	1.99



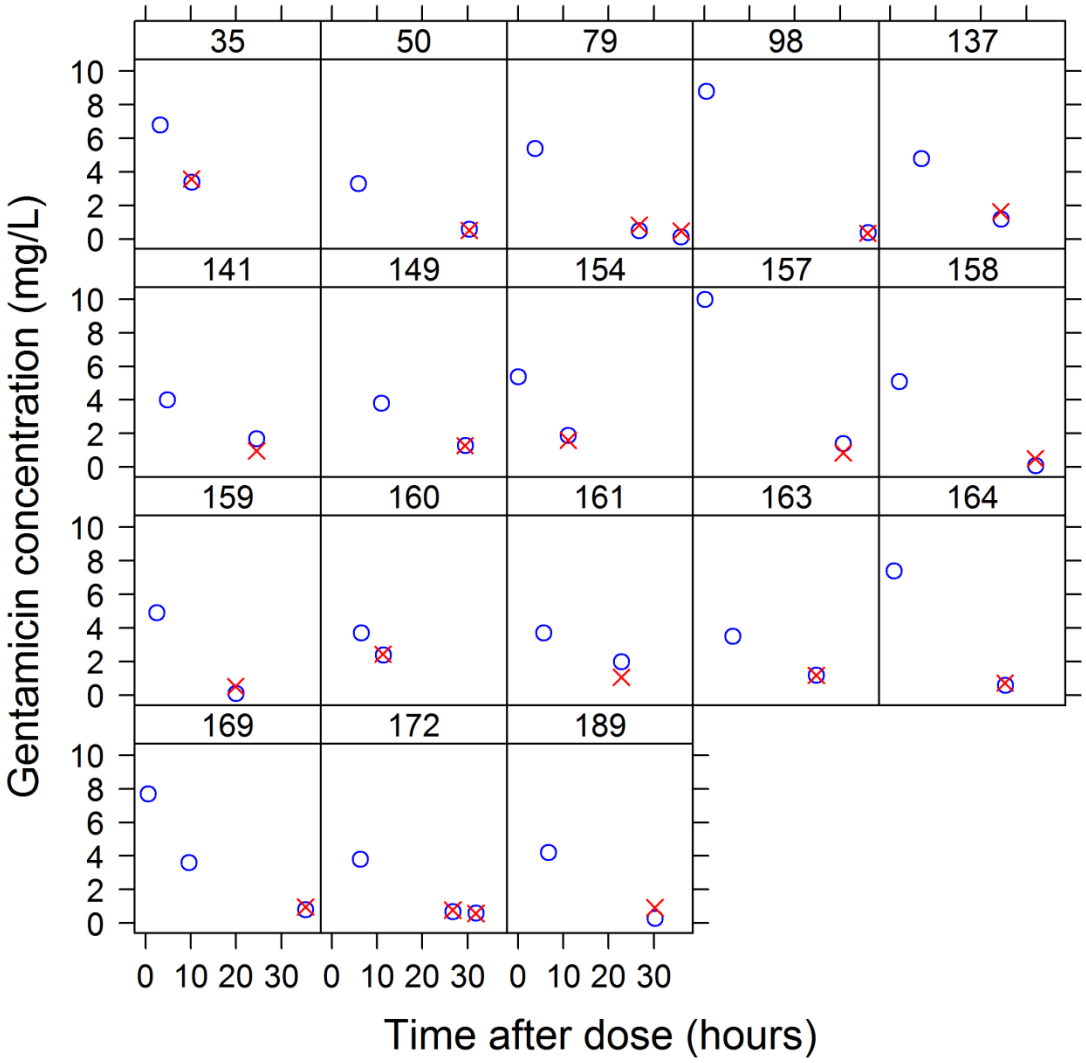
Predictions

$$PE = observed - predicted$$

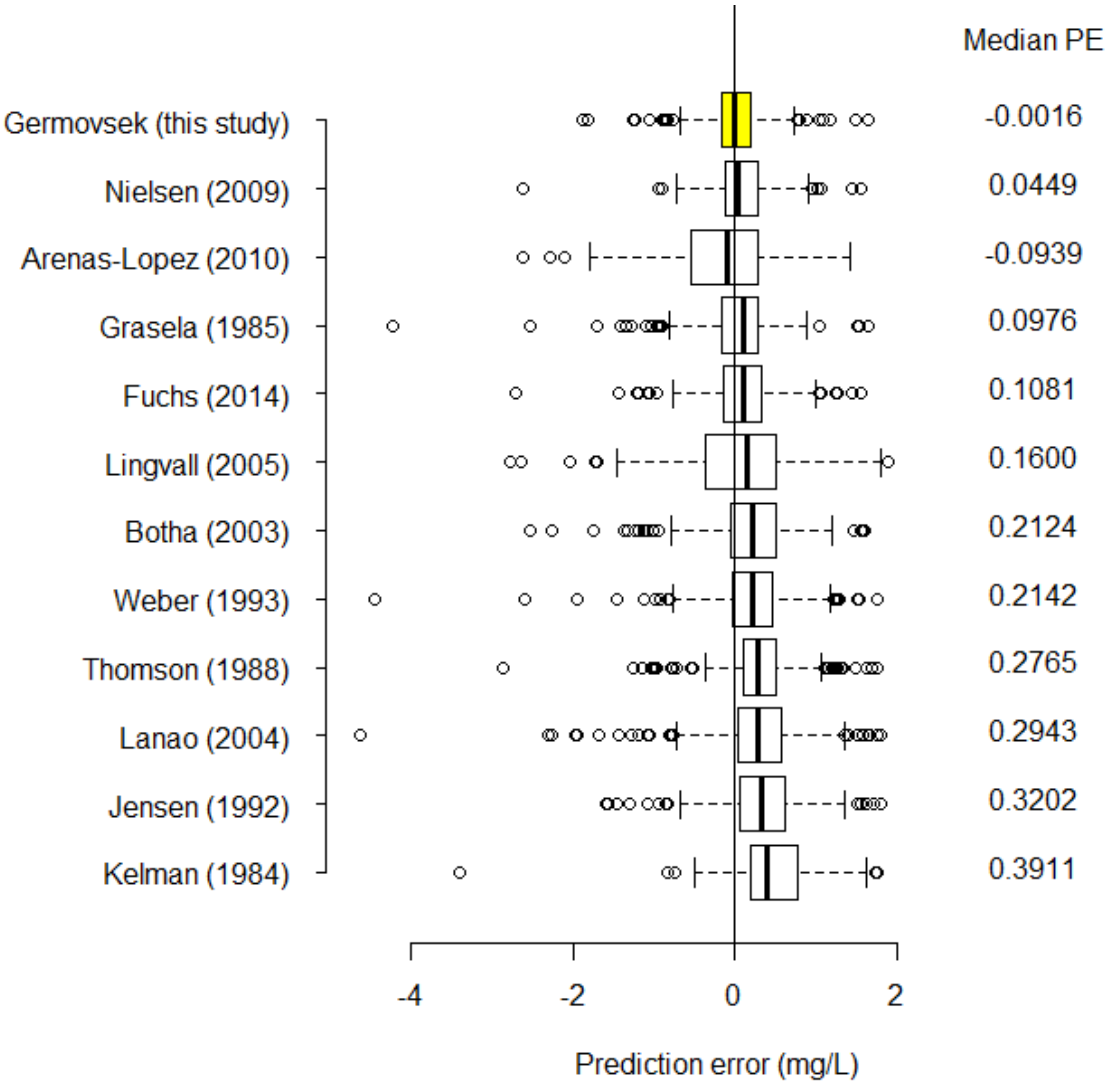
dataset	Limit = 1 mg/L			Limit = 2 mg/L			Median	95% CI	
	n correct (%)	OP	UP	n correct (%)	OP	UP	PE (mg/L)	2.5%ile	97.5%ile
paired + unpaired	215/254 (84.6)	17	22	246/254 (96.9)	6	2	-0.0016	-0.87	0.85
paired: study≥3mg/L	18/20 (90.0)	0	2	20/20 (100)	0	0	-0.061	-0.53	0.84
XV: paired: study≥3mg/L	428/456 (93.9)	13	15	421/456 (92.3)	20	15	-0.062	-1.55	1.04

OP is overprediction, UP is underprediction; PE is prediction error, CI is confidence interval for the prediction errors, XV is cross-validation

Paired samples with study level ≥3 mg/L



Comparison with other published models



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Conclusions

- Final model good descriptive & predictive properties
- Provisional version of neoGent software developed

Future work

- Develop user-friendly interface
- Further clinical trial

Acknowledgements

Patients, who participated in the neoGent study

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рахмат
danke
謝謝
spas
ngiyabonga
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
gracias
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nandri
dhanyavad
thank you
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shukriya
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rahmat
তোমাকে ধন্যবাদ
감사합니다
xièxie
merci

Questions?