

## INTRODUCTION

- (Pre)term neonates are dosed based on weight, in combination with gestational age (GA) or postnatal age (PNA).
- Currently, no attention is paid to neonates that are born small for gestational age (SGA).
- **SGA neonates:** neonates with a birth bodyweight (bBW) < 10<sup>th</sup> percentile of the bBW for their GA.

## AIM

1. To determine the influence of being born SGA on the clearance (CL) of vancomycin and gentamicin in neonates.
2. To quantify its influence on exposure (AUC) when dosing vancomycin and gentamicin according to a national dosing guideline.

## METHODS

### Patient demographics

**Table 1:** Patient demographics of vancomycin and gentamicin datasets [1-4].

	Vancomycin [1,2]	Gentamicin [3,4]
Number of patients	437	733
Gestational age (wks)	30 (23-41)	34 (23-42.1)
Postnatal age (days)	12 (1-31)	3 (1-30)
Birth bodyweight (g)	1310 (385-4680)	2320 (440-5240)
Current bodyweight (g)	1368 (415-4860)	2320 (440-5420)
SGA (n (%)) <sup>[5]</sup>	100 (22.9%)	84 (11.5%)

Values are expressed as median [range], except stated otherwise.

### Software

- NONMEM 7.5, PsN 5.2.6, Pirana 3.0.

### Influence Small for Gestational Age (SGA) on CL

- In a two-compartment model for vancomycin and gentamicin [6] SGA was studied together with GA or bBW (as antenatal predictor) and PNA (as postnatal predictor) for CL.

### Model-based simulations of influence of SGA

- Stochastic simulations (n=500).
- **Vancomycin:** dosed on current bodyweight based on 4 subgroups: bBW (< and > 2.5 kg) and PNA (< and > 7 days) (Dutch Pediatric Formulary [7]).
  - Efficacy: AUC 400 – 600 mg\*h/L.
- **Gentamicin:** dosed on current bodyweight based on 4 subgroups: GA (< 32, 32-37, > 37) and PNA (< and > 7 days) (Dutch Pediatric Formulary [8]).
  - Efficacy: AUC > 80 mg\*h/L & peak levels 8 – 12 mg/L.
  - Toxicity: trough levels < 0.5 – 1 mg/L.

## CONCLUSIONS

- Being born **Small for Gestational Age (SGA)** has a **significant impact on CL** of both vancomycin and gentamicin in neonates. SGA neonates have a **higher CL** of these renally excreted drugs, likely due to a higher GA compared to AGA neonates of the same bBW and PNA.
- Model-based evaluations show that **below-target AUC occurs more often in SGA neonates** when dosed according to a national dosing guideline, particularly for **vancomycin**, which requires further attention in neonatal dosing guidelines.

## RESULTS

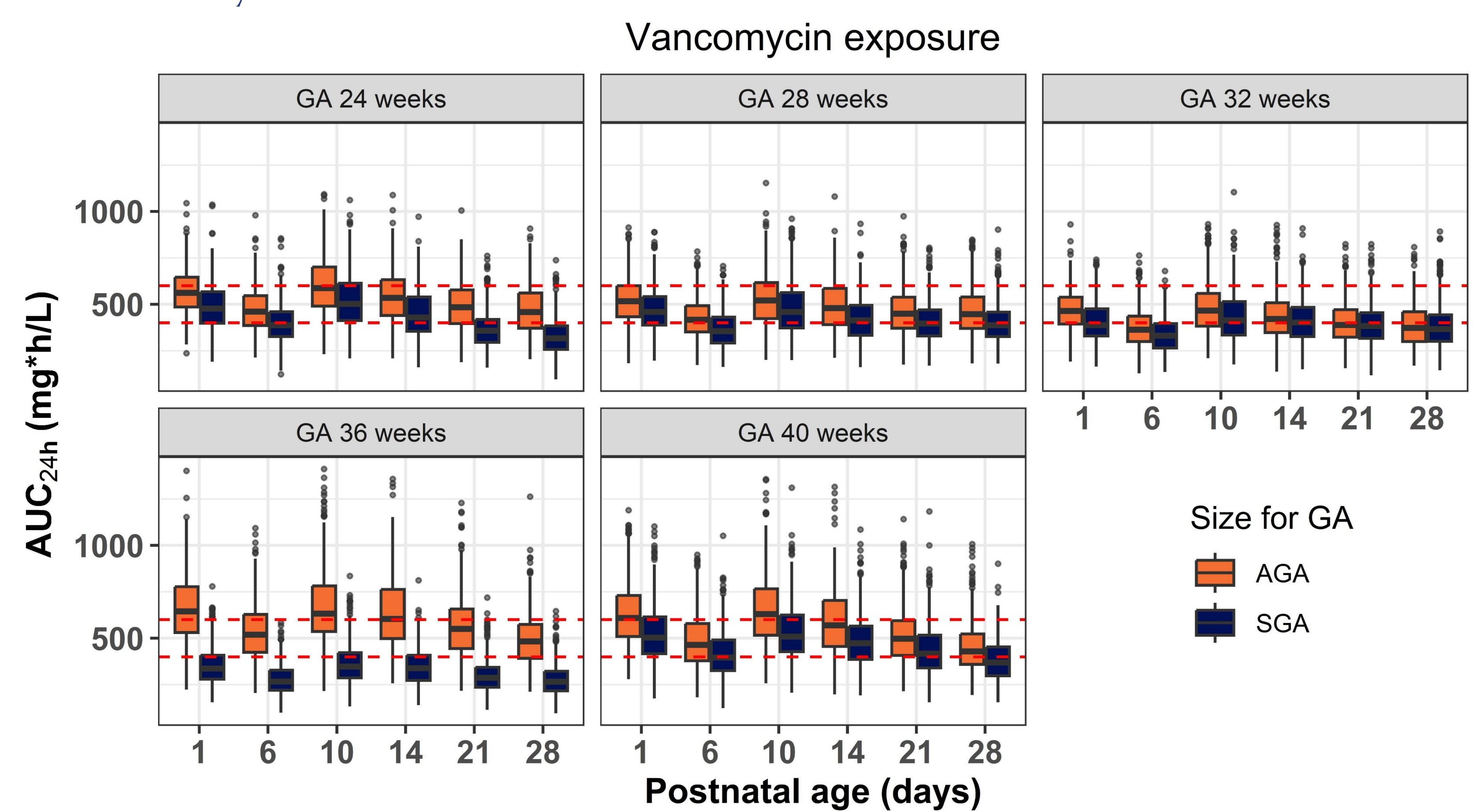
### Influence Small for Gestational Age (SGA) on CL

In a model with birth bodyweight (p<0.001) and postnatal age (p<0.001) as covariates, **SGA proved a significant covariate for CL for both vancomycin and gentamicin:**

- **Vancomycin:** CL **30% higher** (RSE 4%) in SGA vs AGA neonates with the same bBW and PNA (p < 0.001)
- **Gentamicin:** CL **20% higher** (RSE 4%) in SGA vs AGA neonates with the same bBW and PNA (p < 0.001)

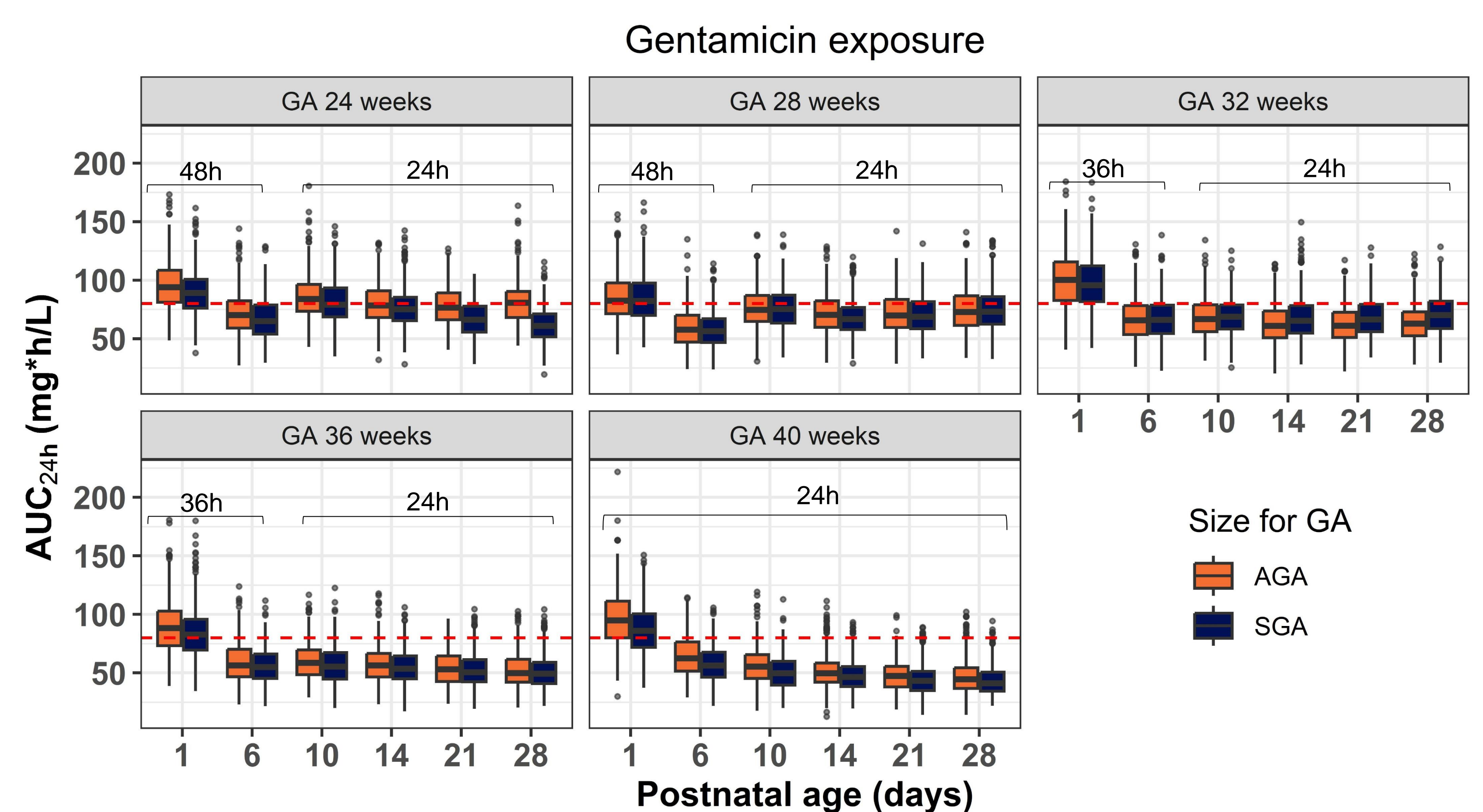
### Model-based simulations of influence of SGA

- **Vancomycin:** lower AUC in SGA vs AGA neonates with 54.1% vs 25.8% of the individuals with an AUC < 400 mg\*h/L on day 3 (**Figure 1**). Particularly for neonates with a GA of 36 weeks because of allocation to different dosing groups based on birth bodyweight between SGA and AGA neonates in the Dutch Pediatric Formulary.



**Figure 1:** Vancomycin exposure (AUC<sub>24h</sub> mg\*h/L) vs PNA for GA of 24, 28, 32, 36 and 40 weeks for SGA and AGA neonates on day 3 of vancomycin treatment according to the Dutch Pediatric Formulary. Target AUC = 400-600 mg\*h/L (red dotted lines).

- **Gentamicin:** small differences in AUC between SGA and AGA neonates were observed (74.7% vs 70.4% < 80 mg\*h/L) (**Figure 2**).
- **Gentamicin:** small differences in peak levels (20.7% vs 8.9% < 8 mg/L) and no major differences in trough levels between SGA and AGA neonates were observed, with 34.5% vs 37.6% showing trough levels > 1 mg/L, respectively (data not shown).



**Figure 2:** Gentamicin exposure (AUC<sub>24h</sub> mg\*h/L) vs PNA for GA of 24, 28, 32, 36 and 40 weeks for SGA and AGA neonates before the second gentamicin dose according to the Dutch Pediatric Formulary. Target AUC > 80 mg\*h/L. 48h, 36h, 24h: patients received gentamicin in a 48h, 36h, 24h dosing scheme as indicated in the panels according to the Dutch Pediatric Formulary.