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Title: **Scaling Clearance in Paediatric Pharmacokinetics: all models are wrong, which are useful?**

Authors: Eva Germovsek (1), Charlotte Barker (1, 2, 3), Mike Sharland (2, 3), Joseph F Standing (1, 2)*

Affiliations: (1) Inflammation, Infection and Rheumatology section, Great Ormond Street Institute of Child Health, University College London, London, UK; (2) Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's, University of London, UK: (3) St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London, UK

Eva Germovsek
PhD student
Great Ormond Street Institute of Child Health, University College London
Inflammation, Infection and Rheumatology section
30 Guilford Street, London WC1N 1EH, UK
Phone: 020 7905 2307
Fax: 020 7905 2882
E-mail: eva.germovsek.11@ucl.ac.uk

Charlotte Barker
Clinical Research Fellow
Paediatric Infectious Diseases Research Group
Institute for Infection and Immunity
St George's, University of London
Cranmer Terrace, London SW17 0RE, UK
Phone: 020 8725 5382
Fax: 020 8725 0716
E-mail: cisbark4444@doctors.org.uk

Mike Sharland
Professor
Paediatric Infectious Diseases Research Group
Institute for Infection and Immunity
St George's, University of London
Cranmer Terrace, London SW17 0RE, UK
Phone: 020 8725 5382
Fax: 020 8725 0716
E-mail: mike.sharland@stgeorges.nhs.uk

*corresponding author:
Joseph F Standing

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Principal Research Associate
Great Ormond Street Institute of Child Health, University College London
Inflammation, Infection and Rheumatology section
30 Guilford Street, London WC1N 1EH, UK
Phone: 020 7905 2370
Fax: 020 7905 2882
E-mail: j.standing@ucl.ac.uk

Running head: A comparison of models for scaling clearance in children

Keywords

Allometric scaling, maturation function, children, infants, neonates, NONMEM, allometric exponent, gentamicin, midazolam, pharmacometrics

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Number of tables: 3

Number of figures: 3

Table of links

Ligands
Gentamicin
Midazolam
These Tables of Links list key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan et al., 2016).*

Structured Summary

Aim(s) When different models for weight and age are used in paediatric pharmacokinetic studies it is difficult to compare parameters between studies or perform model-based meta-analysis. This study aimed to compare published models with the proposed standard (allometric weight$^{0.75}$ and sigmoidal maturation function).

Methods A systematic literature search was undertaken to identify published clearance (CL) reports for gentamicin and midazolam and all published models for scaling clearance in children. Each model was fitted to the CL values for gentamicin and midazolam, and the results compared with the standard model (allometric weight exponent of 0.75, along with a sigmoidal maturation function estimating the time in weeks of postmenstrual age to reach half the mature value and a shape parameter). For comparison we also looked at allometric size models with no age effect, the influence of estimating the allometric exponent in the standard model and, for gentamicin, using a fixed allometric exponent of 0.632 as per a study on glomerular filtration rate maturation. Akaike Information Criteria (AIC) and visual predictive checks were used for evaluation.

Results No model gave an improved AIC in all age groups, but one model for gentamicin and three models for midazolam gave slightly improved global AIC fits albeit using more parameters: AIC drop (number of parameters) -4.1(5), -9.2(4), -10.8(5) and -10.1(5) respectively. The 95%CI of estimated CL for all top performing models overlapped.

Conclusions No evidence to reject the standard model was found; given the benefits of standardised parameterisation, it's use should therefore be recommended.

What is already known about this subject:

- In children clearance scales approximately with weight$^{0.75}$ but in neonates and infants maturation also affects clearance.
- A standardised method for scaling size and postmenstrual age has been proposed but is not always used.
- A systematic comparison of all suggested models is lacking.

What this study adds:

- Several published modelling approaches give similar fits to the same data, but no model out-performed the standard for all age groups.
- Standardising scaling to a single method does not compromise model fitting and facilitates information sharing.

Introduction

Smaller people need smaller absolute doses. Since the 1950s paediatricians have recognised that drug clearance, and usually therefore dose requirements (which depend on drug exposure, i.e. area under the curve (AUC)), scale with body surface area rather than body weight [1]. Body surface area can be approximated by raising weight to a power of 0.67, and the approach of relating a biological parameter with weight raised to some power is typically known as allometric scaling. The fact that clearance scales in this way means that children will have higher dose requirements on a (linear) mg/kg basis compared to adults (see Figure 1). In 1950 Crawford [1], and then almost five decades later Holford [2], highlighted the parallels between weight and clearance with the relationship of weight and basal metabolic rate. Basal metabolic rate and how it scales with weight has been studied for over a century and various "correct" values have been derived for the exponent with 0.75 [3] and 0.67 [4] being the two commonly argued "true" values. A comprehensive review summarising various mathematical descriptions of these observations, along with discussion on whether "basal", "field", or any other variety of metabolic rate should be used to infer drug clearance scaling was recently provided by Mahmood [5].

Rather than focusing on cross-species studies of metabolic rate however, when considering drug clearance paediatric pharmacologists will be more interested in how eliminating organ function scales with size, and how drug clearance scaled with size in previous studies. Rhodin *et al* [6] found that in children and adults glomerular filtration scales with weight raised to a power of 0.63, and of course paediatric nephrologists scale their reports of glomerular filtration rate by body surface area [7, 8]. Concerning hepatic clearance, Johnson *et al* [9] found liver volume (and therefore hepatic blood flow [10]) scales with weight raised to a power of 0.78. We can see from this that biological processes concerned with clearance scale with weight raised to a power of 0.63-0.78 in children.

Whilst allometric scaling for size with an exponent of around 0.63-0.78 is widely accepted to be a useful approach to describe or predict clearance in children [5, 11], it often does not perform as well in neonates and infants due to the maturation of drug eliminating processes. Two main approaches have been developed over recent years to account for this. The first is to use allometric weight scaling with a single fixed or estimated exponent with clearance further multiplied by a maturation factor to adjust for age. This maturation factor is usually a logistic function of age which asymptotes towards 1 with increasing age. The second method is to estimate an allometric exponent which changes with either weight or age, for example with a sigmoidal function [12]. For both of these approaches a wide variety of maturation functions or functions to vary the allometric exponent have been used.

A popular method for scaling for size and maturation is to fix the allometric weight exponent to 0.75, and to use a sigmoidal maturation function driven by postmenstrual age (PMA) (gestational plus postnatal age) such that clearance scales in the following manner:

$$CL = CL_T \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{PMA^{Hill}}{PMA_{50}^{Hill} + PMA^{Hill}}, \qquad \text{(Equation 1)}$$

where CL is drug clearance in an individual, CL_T is the typical clearance for a 70 kg adult, WT is body weight, PMA_{50} is the PMA (usually in weeks) for CL to reach 50% mature, and *Hill* is the shape parameter. The rationale behind using PMA rather is that pre-term neonates may have lower CL in early life due to immaturity of organ function and drug metabolising enzyme expression. This model has been proposed as a standard method for modelling clearance in children [11], and its advantages are threefold: firstly the allometric exponent is fixed to a value within the accepted range of plausible values, thereby adding biological prior knowledge to the model without requiring the addition of a parameter. Secondly the maturation parameters are easy to communicate: PMA_{50} gives the age at which clearance is half-way to being explained solely by weight, and the Hill coefficient describes the steepness of the maturation curve. Thirdly this model is flexible enough to describe slow and rapid (step-like) maturation and anything in between.

This study aimed to seek evidence to reject the model presented in Equation 1. Our hypothesis was that no published model gives superior fit to this model across all age groups. We sought to test this by systematically reviewing the literature to identify models for maturation and/or size, and comparing their fit to the clearance of two typical drugs, gentamicin (cleared almost exclusively by glomerular filtration) and midazolam (cleared almost exclusively by hepatic metabolism).

Methods

Gentamicin and midazolam clearance data collection

The MEDLINE database was searched using PubMed in (search last updated March 2016) to identify clinical PK studies where the clearance of intravenously administered gentamicin and midazolam was reported. The key words for the search strategy were: pharmacokinetics, midazolam, and gentamicin, and the filter "humans" was applied. The reference lists of the identified publications were also manually searched.

For each clearance value the corresponding ages and weights were extracted from the reports. Since it is known that clearance changes rapidly in the first weeks and months of life [6, 13], we did not include CL estimates where a wide age range of subjects (i.e. a few days or weeks up to >10 years of age) were analysed together, with only a mean CL estimate provided for the whole group. Only gentamicin CL values that corresponded to age up to 50 years were kept in the dataset to avoid including adult values affected by declining renal function in older subjects. When only weight or age range was reported, the middle of the range was taken as the mean value of the demographic data. In neonatal studies, if only birth weight was reported, this was assumed as current body weight. A gestational age (GA) of 40 weeks was assigned for children and adults that did not have GA reported. Where only age was reported, typical weight for age was calculated using a published model [14].

We did not include studies where a disease was known to affect the clearance of midazolam or gentamicin.

Systematic search for models used to scale clearance

A systematic literature review was undertaken (last updated in March 2016) using MEDLINE via PubMed, and, additionally, we emailed the NMUsers discussion group (a global discussion forum for users of NONMEM software) [15], to identify models for size and maturation. Search key words were: allometry, allometric, scaling, pharmacokinetic, and pharmacokinetics. All models were compared to the proposed model (Equation 1) with a fixed allometric exponent of 0.75 and a sigmoidal maturation function [11]. For comparison we also tested the parsimonious model of a single weight effect with either estimated allometric exponent or the allometric exponent fixed to 0.75 or 0.67.

Comparison of models for size and maturation

All models were normalized to 70 kg to facilitate parameter comparison. All parameters that were estimated in the original study were also estimated during the model comparison. We also tested the performance of a simple allometric model with either a single fixed (to 0.75 or 0.67) or estimated exponent. Fitting was performed using NONMEM version 7.3 [16]. Since CL is usually assumed to follow a log-normal distribution, an exponential residual error model was used.

The Akaike Information Criteria (AIC), which was given by -2LL + 2p (where -2LL is -2 times the log likelihood reported as the objective function values in NONMEM and p the number of estimated parameters) was calculated for each model to the overall data and split by age as follows: neonates (0-28 days), infants (1-23.9 months), children (2-11.9 years), adolescents (12-18 years) and adults (>18 years). For each age group the -2LL value for that age group only was used. The difference in AIC between the tested model and the proposed standard model was calculated, with a better performing model being defined as one in which the AIC was lower than the standard. We defined a better-performing model as one for which the AIC was lower than the standard model in all age groups. Visual predictive checks were created using R version 3.1.0 [17]. For the 5 best models (lowest AIC values) the typical clearance and 95% confidence interval was generated by simulation of 1000 parameter combinations using the standard errors from the NONMEM covariance step for a typical neonate, infant, child and adolescent.

Results

In total, 38 [18-55] and 44 [56-99] publications that included reported CL values were identified for gentamicin and midazolam, respectively. These papers reported a total of 66 and 57 CL values for gentamicin and midazolam, respectively. Four studies including a wide range of neonates, infants and children with only a mean CL estimate provided for the whole group were excluded [100-103]. Similarly, four gentamicin studies including wide adult age ranges (e.g. 16-96 years) were excluded [104-107]. Of the remaining data a further 10 gentamicin CL values in subjects aged over 50 years were excluded [45, 46, 50-54]. Eight studies [38, 40, 41, 45, 46, 71, 78, 88] did not report subjects' weights, so these were inferred from age as described above. The data used for modelling are presented in Supplementary materials Tables S1 and S2.

The models identified in the literature search that sought to account for changing age and weight relationships in neonates and infants could be split into two main categories: those that, in common with the standard model, add an age function to a fixed or estimated weight function to account for maturation in neonates/infants; and those that use an allometric weight exponent which changes by either age or weight. This change can be fixed pre-determined steps or a continuous function. Model structure and estimated parameters are given in Table 1.

Change in AIC from the standard model are presented in Table 2, and a visual predictive check of observed CL values with model predictions given in Figures 2 and 3. The model comparisons showed that models with a sigmoidal-type relationship for neonatal and infant maturation fitted best and that there was very little difference in the fit of these models to the observed CL values (Figures 2 and 3). No model gave consistently better results than model 1 in all age groups based on AIC (Table 2). In Table 3 the CL values and their uncertainty for each age group from the five best models are presented.

Discussion

We have compared the fit of all the major types of published models for size and age scaling of CL in children to two datasets, and have found that no model gave a superior fit in all age groups to the proposed standard model. Several recent studies have compared the performance of a single or limited range of models for predicting CL in a limited range of drugs [5, 11, 108, 109]. None of these studies has systematically compared all published models, so their relative merits are not apparent, although an impressive number of drugs has been used (44 in the case of Holford *et al* [11]). Prediction of paediatric PK, be it with scaled adult models or PBPK, is useful for study design, but ultimately paediatric PK data needs to be collected in order to make dosing decisions. For data fitting, models need to be parsimonious (not estimate too many parameters) in order that parameters are estimated with a reasonable degree of precision, yet flexible enough to describe observed trends. Since weight raised to a fixed power of 0.75 with a sigmoidal PMA maturation function has been shown to give good predictions for a large range of compounds [11], we have therefore sought to challenge this model by direct comparison of its ability to fit the same data as all previous published models. No published model was able to out-perform the standard model for fitting.

Our result has implications for both new drug development and the study of unlicensed and off-label medicine use, which remains commonplace [110-113]. Patient recruitment to paediatric PK studies remains a challenge in both these settings, and if the same modelling approach was taken for scaling size and age in all studies, this would allow information to be shared across compounds with similar modes of elimination, and facilitate model-based meta-analysis. A body of biological prior information on values for PMA_{50} and Hill would be generated which would have a number of uses: a) allowing the analysts of small datasets to fix size and maturation models based on literature from the same or similar compounds to search for other potential covariates of interest; b) giving journal reviewers and regulators the opportunity to compare estimated parameters with those expected from previous studies on similar compounds; c) facilitating the inclusion of *in vitro* information on maturation of drug eliminating enzymes [114]; and d) allowing the combination of studies without requiring the sharing of raw data using model-based meta-analysis.

Unsurprisingly the models which did not account for age or allow the allometric exponent to change with age or weight (Models 2, 3 and 4 in Table 1) performed poorly, confirming the need to account for both. Also those models with linear or exponential maturation, which tended to have been developed in neonates (Models 5, 6, 7 and 8), did not fit well suggesting the need for the sigmoidal-type shape that the Hill coefficient gives. Importantly, should the true maturation shape be exponential or linear over the entire human age range, the sigmoidal model has the flexibility to fit these by allowing the Hill coefficient to be 1 and the PMA_{50} parameter to be very large. Similarly, if maturation is complete in early gestation, the also has the possibility to account for this with a low estimate of PMA_{50}.

Although no single model gave a reduced AIC in all age groups, model 18 (and in the case of midazolam only, models 17 and 9 also) gave slightly better overall fits. Both model 17 and 18 had five estimated parameters, whereas model 9 had 4 estimated parameters, compared with the 3 estimated parameters of the standard model. The price of this improved fit was an increase in standard errors and indeed Table 3 shows that for model 18 it was not possible to construct 95% confidence intervals (CIs) since the uncertainty on θ_4 meant it could take negative values. We did see a trend towards models having superior fit in infants but worse fit in neonates. The main reasons for this are either models did not account for maturation, or that PNA rather than PMA was used and hence gestation was not accounted for, worsening the neonatal fit. Since no model had a globally improved AIC in addition to improved AIC in each age group, we found no evidence to reject the standard model.

Whilst the 95% CI for all the CL estimates in Table 3 overlapped each other, and hence they do not significantly differ, dosing recommendations are usually based on the typical model prediction, and so different doses would have been recommended based on these top 5 models. To take midazolam as an example of where CL may be used to directly infer dosing, Ince *et al* [115] reported the lower end of the target concentration for sedation with midazolam was 250 µg/L. Multiplying this by the CL values in Table 3 we have predicted dose ranges of: 24-44 µg/kg/h, 144-195 µg/kg/h, 140-165 µg/kg/h and 112-120 µg/kg/h for the typical neonate, infant, child and adolescent in the example (note doses scaled by kg as this is standard practice in paediatric intensive care). Typically for midazolam, neonatal dose rates are titrated to the nearest 25 µg/kg/h whereas in older children titrations are in 50 µg/kg/h. From this it can be seen that all but the neonatal group, the models would all have predicted the same typical dose when scaled to the nearest 50 µg/kg/h. Even in the neonatal group, if we exclude Models 18 and 12 because 95% CI could not be constructed, and Model 11 since the neonatal CL value could take negative values, we are left with a much tighter range of predicted doses (32-44 µg/kg/h).

In the neonatal group the models with lower AIC than Model 1 were Model 9b for gentamicin and model 9 for midazolam (Table 2). Both these models were variations on Model 1, in that Model 9b used an allometric exponent of 0.632 (tested for gentamicin since this was the estimated exponent for GFR maturation by Rhodin *et al* [6]), and Model 9 estimated the allometric exponent, and so in the age group where there is potential uncertainty in the midazolam recommended dose rate (see above), the standard model fits best. A contributing factor to the standard model performing well in neonates is the use of PMA rather than weight alone, or postnatal age (PNA). The reason to use PMA rather than PNA ought to be apparent, in that by using PNA, a baby born prematurely would be treated in exactly the same way as a term baby despite the fact eliminating organ function and enzyme expression will be less developed. Similarly, allowing the allometric exponent to change with weight gives identical treatment to babies of the same weight regardless of their gestational age. There will almost certainly be additional increases in CL in the first few days of life in addition to those predicted by gestation, and in situations where rich neonatal data with a range of PNA and PMA are available, it may be possible to identify this effect separately. Despite the obvious rationale for using of PMA, several published models did not take this approach.

A possible limitation of this work is that despite systematically comparing all models, these were only tested on two datasets, and we also used some model-based predictions of CL. To address this we would argue that the standard model has already been evaluated on data from 44 drugs [11], and so to discriminate between models required comparison on the same data. Gentamicin and midazolam were chosen as they each accounted for an example renal and hepatic clearance respectively, and there was sufficient intravenous data available in the literature to cover the whole age range. Whilst we would have preferred individual non-compartmental $AUC_{(0\text{-}\infty)}$ estimates to infer CL from, these are simply not available in all age groups, particularly neonates. Hence we did use model based CL estimates in narrow age and weight ranges, and consider this should not unduly bias our results since all models were tested on the same data. We also did not only include data from healthy subjects, which are anyhow unavailable for paediatric subjects due to ethical reasons. However, we only included data from studies where a disease did not have a known effect on CL (for example, neonates on extracorporeal membrane oxygenation (ECMO) were shown to have similar midazolam CL to non-ECMO neonates [62]), and also some data from critically ill subjects (such as neonates receiving midazolam [61], which were also shown to have similar clearance (for an infant of the same weight) to non-critically ill neonates [58]).

Whether to estimate an allometric exponent from PK data was recently explored by McLeay *et al* [116] in an extensive meta-analysis. They found an average allometric exponent on clearance of 56 drugs to be 0.65 (precision of this estimate was not reported but a histogram of the estimated values shows a 95% CI of approximately 0.1-1.2). This highlights the fact that that a size-related allometric exponent can be difficult to identify, and indeed Model 9, which was the standard model with estimated allometric exponent, did not give a superior overall fit. Our results support the argument that fixing the allometric exponent, thereby adding biological prior information on the effect of body size *a priori*, will allow delineation of size from other important covariates without adding an uncertain parameter and thereby potentially destabilising parameter estimation. The importance of minimising the number of estimated parameters is highlighted by Model 18 for which 95% CI of dosing predictions could not be constructed due to the uncertainty in parameter estimates. Interestingly, Model 13 with only one estimated parameter and cut-off ages to decrease the allometric exponent with increasing age (effectively fixing both the size and maturation parts of the model) performed well for gentamicin, but less well for midazolam although it did give similar CL values to the standard model in older subjects. From a point of view of model parsimony, this model may be relatively attractive, but the poor fit for midazolam in neonates and infants suggests that fixed cut-offs in the maturation applied to all drugs may not be appropriate. However, the performance of Model 9b for gentamicin, which used fixed allometric and maturation parameters from a previous study on GFR maturation [6], shows that using biological prior information based on the mechanism of CL may be a useful approach.

In conclusion, a systematic comparison was undertaken of all published models for scaling clearance in children, which were tested against the proposed standard model using a fixed allometric weight exponent of 0.75 and an estimated sigmoidal maturation function based on PMA with parameters of 50% mature value and Hill coefficient. We found no evidence to suggest any significant improvement in model fit can be achieved over use of this standard parametrisation. For the two model drugs, midazolam and gentamicin, maturation clearly followed a sigmoidal-type pattern, so linear or exponential age-functions should not be used. Standardising model parameterisation to this single approach will benefit the paediatric PK community by facilitating parameter value interpretation and model sharing across studies of the same drug and between compounds.

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Tables

Table 1: Table of model parameter estimates.

No.	Ref	Model equation	Studied population age range	Parameter	Gentamicin	Midazolam
1	[11]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \frac{PMA^{\theta_2}}{\theta_3^{\theta_2}+PMA^{\theta_2}}$		θ_1	5.97 (0.33)	27.4 (0.95)
				θ_2	4.19 (0.70)	4.04 (0.53)
				θ_3	45.1 (2.96)	55.4 (4.49)
				RUV	0.075 (0.018)	0.071 (0.012)
2		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2}$		θ_1	9.16 (1.42)	24.9 (1.10)
				θ_2	1.28 (0.05)	0.82 (0.10)
				RUV	0.13 (0.027)	0.20 (0.056)
3		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75}$		θ_1	2.90 (0.31)	24.0 (1.39)
				RUV	0.64 (0.087)	0.19 (0.05)
4		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.667}$		θ_1	2.55 (0.31)	23.1 (1.35)
				RUV	0.81 (0.122)	0.19 (0.053)
5	[117]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot (1 + \theta_3 \cdot PNA)$	Neonates	θ_1	9.16 (1.42)	24.9 (1.10)
				θ_2	1.28 (0.05)	0.82 (0.10)
				θ_3	5.8x10^{-9} (1.52x10^{-9})	5.8x10^{-9} (4.13x10^{-9})
				RUV	0.13 (0.027)	0.20 (0.056)
6	[27]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} + \theta_3 \cdot PNA$	Neonates	θ_1	8.56 (1.29)	24.9 (1.10),
				θ_2	1.26 (0.04)	0.82 (0.10)
				θ_3	0.02 (0.064)	6.6x10^{-8} (2.47x10^{-8})
				RUV	0.13 (0.027)	0.20 (0.056)
7	[118]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(1 + \theta_2 \cdot (PMA - 40)\right)$	Neonates	θ_1	1.51 (0.17)	24.0 (1.39)
				θ_2	0.0065 (0.0035)	5.0x10^{-11} (1.43x10^{-10})
				RUV	0.34 (0.087)	0.20 (0.050)
8	[119]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot e^{\theta_2 \cdot (PMA-40)}$	Neonates	θ_1	2.10 (0.37),	24.0 (1.39)
				θ_2	0.00077 (0.00048)	5.0x10^{-11} (2.79x10^{-11})
				RUV	0.55 (0.069)	0.20 (0.050)
9		$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{\theta_2} \cdot \frac{PMA^{\theta_3}}{\theta_4^{\theta_3}+PMA^{\theta_3}}$		θ_1	5.86 (0.58)	25.8 (0.98)
				θ_2	0.72 (0.097)	0.57 (0.053)
				θ_3	4.25 (0.67)	3.9 (0.46)
				θ_4	46.1 (4.88)	68.3 (6.58)
				RUV	0.075 (0.018)	0.059 (0.0090)
9b	[6]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.632} \cdot \frac{PMA^{3.33}}{55.4^{3.33}+PMA^{3.33}}$	Neonates-adults	θ_1	5.59 (0.22)	-
				RUV	0.086 (0.031)	
10	[120]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(1 - \theta_2 \cdot e^{-(PMA-40)\cdot\frac{ln2}{\theta_3}}\right)$	Neonates-adults	θ_1	5.98 (0.34)	27.0 (0.94)
				θ_2	0.65 (0.037)	0.71 (0.060)
				θ_3	27.1 (4.90)	28.9 (8.51)
				RUV	0.08 (0.023)	0.091 (0.019)
11	[121]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot$	Infants	θ_1	5.77 (0.34)	27.1 (0.95)

		$\left(\theta_2 + (1-\theta_2)\cdot\left(1-e^{-PNA\cdot\theta_3}\right)\right)$		θ_2	0.21 (0.018)	0.11 (0.020)
				θ_3	2.39 (1.53)	2.63 (0.74)
				RUV	0.097 (0.017)	0.078 (0.013)
12	[108]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{0.75} \cdot \left(\theta_4 + (1-\theta_4)\cdot\frac{PNA^{\theta_2}}{\theta_3^{\theta_2}+PNA^{\theta_2}}\right)$	Neonates-children	θ_1	5.91 (0.39)	27.2 (0.96)
				θ_2	1.10 (0.17)	7.3 (0.19)
				θ_3	0.29 (0.17)	0.102 (0.0025)
				θ_4	0.21 (0.019)	0.12 (0.015)
				RUV	0.097 (0.016)	0.070 (0.011)
13	[5]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b}$; *b*: 1.2 ≤ 3 mo; 1.0 > 3mo-2y; 0.9 >2-5y; 0.75 > 5y	Neonates-children	θ_1	6.67 (0.25)	27.3 (1.41)
				RUV	0.08 (0.024)	0.15 (0.039)
14	[5]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b}$; *b*: 1.25 ≤ 9kg; 0.76 > 9kg	Neonates-children	θ_1	7.64 (0.337)	27.8 (1.52)
				RUV	0.11 (0.032)	0.17 (0.059)
15	[122]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b}$; *b*: θ_2 ≤ 16.5kg; θ_3> 16.5kg	Neonates-adults	θ_1	8.54 (2.08)	24.6 (1.05)
				θ_2	1.26 (0.075)	0.85 (0.12)
				θ_3	1.12 (0.28)	0.67 (0.070)
				RUV	0.13 (0.027)	0.20 (0.055)
16	[115]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b}, b = \theta_2 \cdot WT^{\theta_3}$	Neonates-adults	θ_1	6.08 (0.57)	25.4 (0.985)
				θ_2	1.25 (0.026)	1.38 (0.033)
				θ_3	-0.13 (0.024)	-0.27 (0.033)
				RUV	0.08 (0.018)	0.10 (0.022)
17	[12]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b},\ b = \theta_3 - \frac{\theta_5\cdot WT^{\theta_2}}{\theta_4{}^{\theta_2}+WT^{\theta_2}}$	Neonates-adults	θ_1	5.31 (0.35)	26.0 (0.98)
				θ_2	1.09 (0.29)	13.2 (8.22)
				θ_3	1.23 (0.058)	1.35 (0.023)
				θ_4	17.8 (3.54)	7.2 (0.39)
				θ_5	1.26 (0.049)	0.74 (0.044)
				RUV	0.07 (0.022)	0.056 (0.0083)
18	[123]	$CL = \theta_1 \cdot \left(\frac{WT}{70}\right)^{b},\ b = \theta_3 - \frac{\theta_5\cdot PNA^{\theta_2}}{\theta_4{}^{\theta_2}+PNA^{\theta_2}}$	Neonates-children	θ_1	5.64 (0.44)	26.1 (1.00)
				θ_2	0.55 (0.26)	19.6 (4.81)
				θ_3	1.21 (0.032)	1.36 (0.025)
				θ_4	2.10 (7.84)	0.017 (0.00046)
				θ_5	0.95 (0.90)	0.72 (0.046)
				RUV	0.07 (0.014)	0.056 (0.0080)

CL is clearance, AIC is Akaike information criterion, θ_1 is the typical value of clearance for a 70-kg adult, b is the allometric exponent, WT is body weight in kilograms, PNA is postnatal age in years, PMA is postmenstrual age in weeks, mo is months, y is years. All θs represent estimated parameters, results are presented as mean (standard error). RUV is residual unexplained variability.

Table 2: Numerical results showing the change in Akaike Information Criteria (AIC) between the tested models and the standard model.

No.	Gentamicin						Midazolam					
	AIC	AIC Neonates	AIC Infants	AIC Children	AIC Adolescents	AIC Adults	AIC	AIC Neonates	AIC Infants	AIC Children	AIC Adolescents	AIC Adults
1	0	0	0	0	0	0	0	0	0	0	0	0
2	31.8	6.9	-6.0	10.2	-3.8	16.5	73.8	53.2	-3.7	4.4	-1.5	13.4
3	147.1	111.5	-7.3	18.4	3.5	5.0	72.9	57.4	-7.1	0.4	-3.2	9.4
4	170.5	131.9	-6.2	17.2	4.4	7.2	76.8	63.4	-7.7	-0.8	-3.0	9.0
5	33.8	8.9	-4.0	12.2	-1.8	18.5	75.8	55.2	-1.7	6.4	0.5	15.4
6	33.7	8.6	-3.9	11.6	-1.8	19.3	75.8	55.2	-1.7	6.4	0.5	15.4
7	97.9	36.0	3.4	18.5	-1.4	33.3	74.9	59.4	-5.1	2.4	-1.2	11.4
8	129.9	78.5	-5.3	31.0	0.7	17.0	74.9	59.4	-5.1	2.4	-1.2	11.4
9	1.9	2.1	2.3	1.9	2.3	1.3	-9.2	-1.8	0.2	1.3	3.0	-3.9
9b	3.8	-4.4	4.4	-3.3	-3.5	-5.4	-	-	-	-	-	-
10	4.1	-0.6	4.2	0.4	-0.2	0.4	15.6	9.0	3.3	1.1	-0.1	2.3
11	16.7	18.2	-3.4	1.5	0.2	0.2	6.1	7.6	-2.0	0.0	0.1	0.3
12	18.7	19.7	-1.5	3.8	1.9	2.7	0.6	5.0	-1.7	1.9	2.3	1.2
13	0.8	3.2	-11.4	-1.7	-5.9	0.6	43.3	11.9	7.7	3.1	-4.7	9.3
14	18.2	3.1	-3.2	1.8	-6.1	6.7	49.3	5.8	19.9	-1.1	-4.8	13.6
15	33.2	9.2	-3.5	13.9	-1.9	15.5	73.7	52.1	-0.1	7.4	0.2	14.1
16	6.7	8.3	-6.3	4.3	-0.6	1.0	20.6	23.3	-2.9	1.4	-0.3	-1.0
17	0.4	9.4	-1.6	4.5	3.9	0.1	-10.8	1.5	-1.7	1.9	5.3	-1.8
18	-4.1	3.8	-0.4	3.4	4.1	1.1	-10.1	0.7	-0.3	1.5	5.4	-1.4

AIC is Akaike information criterion (values are relative to AIC values for model 1, negative values indicate a better fit than model 1).

Table 3: Parameter estimates (95% CI) for the 5 models with lowest global AIC for a 1 day old term neonate weighing 3.5 kg, a 1-year old infant weighing 9 kg, a 5-year old child weighing 18 kg and a 12-year old adolescent weighing 39 kg

		Typical CL (95%CI) L/h			
	Models in order of overall AIC	Neonate	Infant	Child	Adolescent
Gentamicin	Model 18	0.16*	1.03*	2.42*	4.15*
	Model 1	0.24 (0.17,0.32)	1.21 (0.96,1.44)	2.15 (1.76,2.55)	3.85 (3.13 4.59)
	Model 17	0.25 (0.05,1.52)	1.00 (0.30,3.00)	2.36 (1.07,4.83)	4.25 (2.82,6.44)
	Model 13	0.18 (0.16,0.21)	0.86 (0.73,0.98)	1.97 (1.68,2.25)	4.28 (3.65,4.88)
	Model 9	0.23 (0.04,1.54)	1.27 (0.35,4.50)	2.16 (0.93,5.03)	3.84 (2.47,6.00)
	Model 9b	0.34 (0.25,0.45)	1.54 (1.22,1.86)	2.53 (2.06,2.99)	4.12 (3.38,4.92)
Midazolam	Model 18	0.44*	7.02*	10.9*	18.0*
	Model 17	0.46 (0.19,1.10)	6.48 (2.49,16.7)	11.6 (5.56,24.1)	18.3 (13.6,24.4)
	Model 9	0.51 (0.11,2.12)	6.07 (2.25,16.5)	11.9 (6.56 20.7)	18.7 (14.4,25.0)
	Model 1	0.62 (0.38,0.92)	5.20 (4.49,5.73)	9.88 (9.22,10.6)	17.6 (16.4,19.0)
	Model 12	0.35*	5.84*	9.82*	17.5*
	Model 11	0.34 (-0.44,1.12)	5.42 (3.74 5.99)	9.78 (9.00,10.5)	17.5 (16.2,18.7)

*95%CI cannot be constructed because uncertainty on a parameter raised to some power means possible values are less than zero

Figure legends.

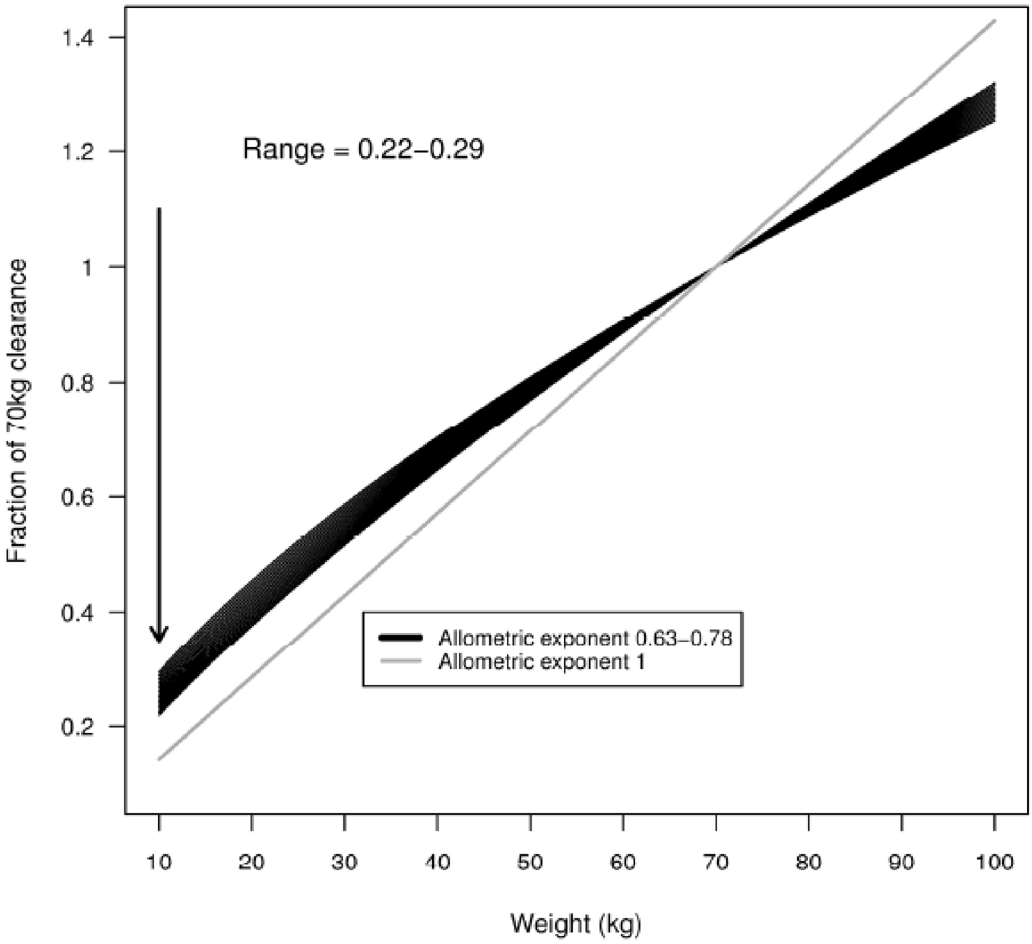

Figure 1: Illustration of the fractional change in clearance compared with using an allometric weight exponent of 0.63 to 0.78

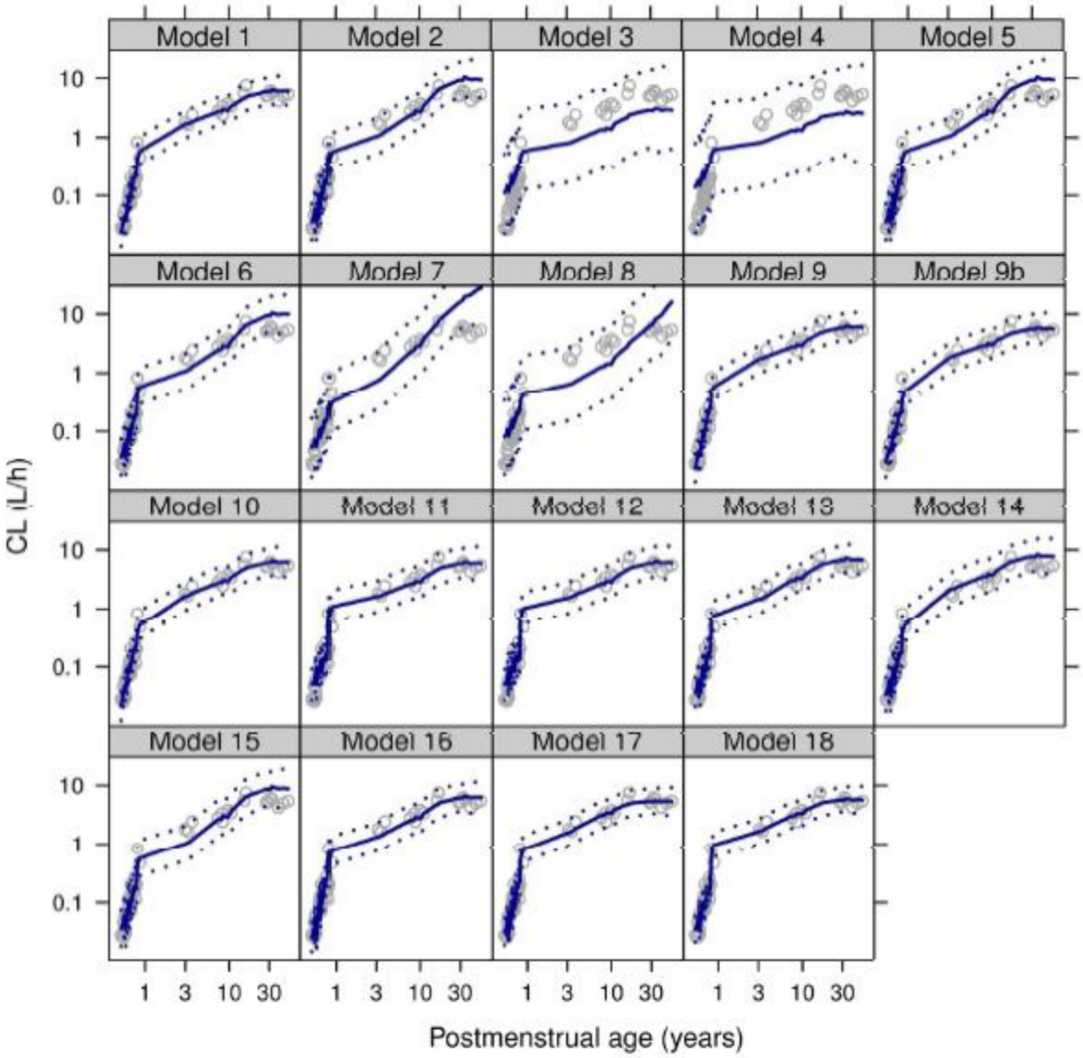

Figure 2: Gentamicin visual predictive checks for each model. Grey open circles are the observed clearance values, the blue solid line is the median simulated model prediction, the dotted blue lines are the 2.5th and 97.5th percentiles of the simulated model predictions. Log-log scale used to aid visualisation of the neonatal period.

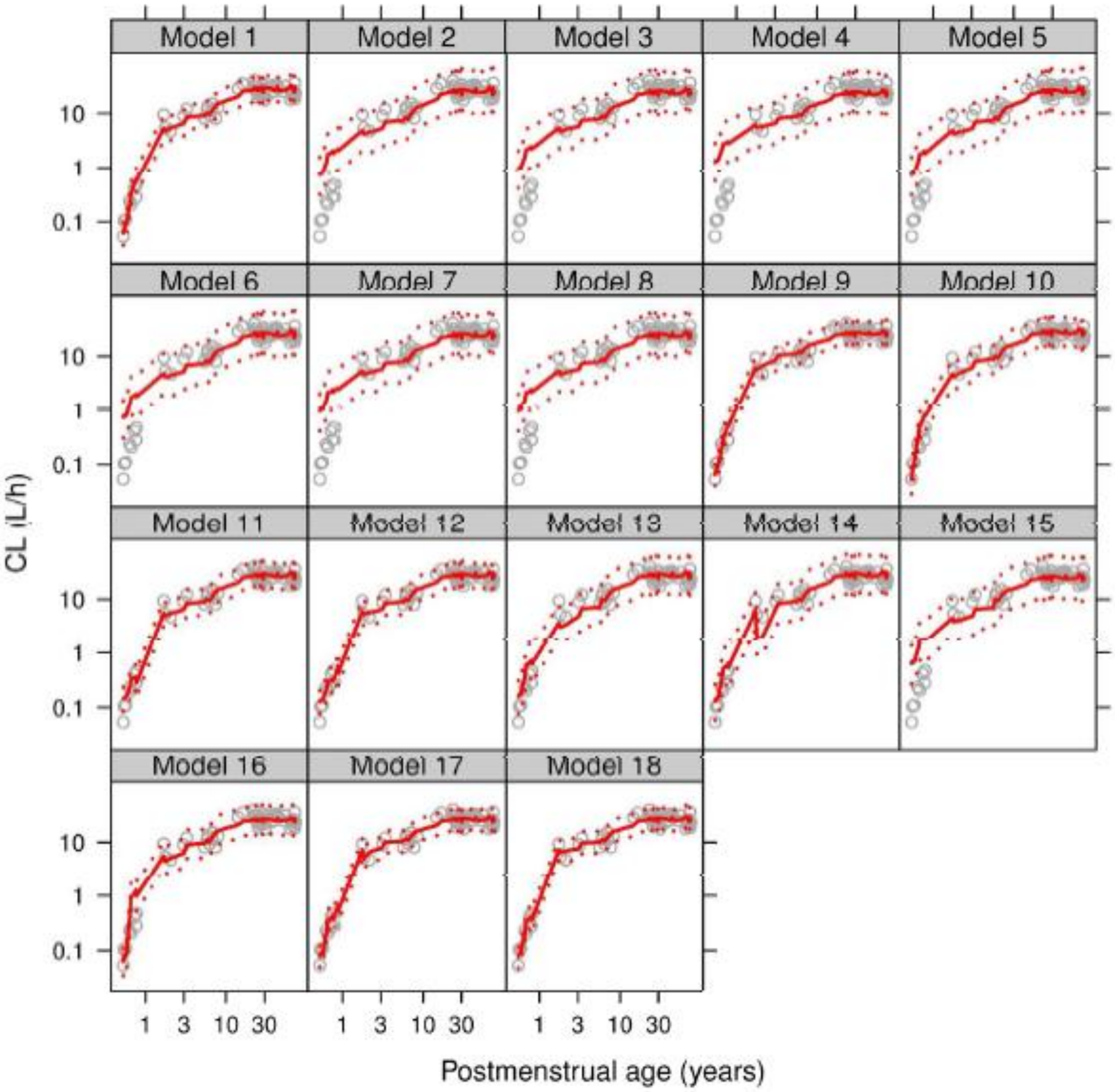

Figure 3: Midazolam visual predictive checks for each model. Grey open circles are the observed clearance values, the red solid line is the median simulated model prediction, the dotted red lines are the 2.5th and 97.5th percentiles of the simulated model predictions. Log-log scale used to aid visualisation of the neonatal period.