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Original research paper

External validation of population pharmacokinetic models of gentamicin in paediatric population from preterm newborns to adolescents

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ABSTRACT

The aim of this study was to externally validate the predictive performance of published population pharmacokinetic models of gentamicin in all paediatric age groups, from preterm newborns to adolescents. We first selected published population pharmacokinetic models of gentamicin developed in the paediatric population with a wide age range. The parameters of the literature models were then re-estimated using the PRIOR subroutine in NONMEM®. The predictive ability of the literature and the tweaked models was evaluated. Retrospectively collected data from a routine clinical practice (512 concentrations from 308 patients) were used for validation. The models with covariates characterising developmental changes in clearance and volume of distribution had better predictive performance, which improved further after re-estimation. The tweaked model by Wang 2019 performed best, with suitable accuracy and precision across the complete paediatric population. For patients treated in the intensive care unit, a lower proportion of patients would be expected to reach the target trough concentration at standard dosing. The selected model could be used for model-informed precision dosing in clinical settings where the entire paediatric population is treated. However, for use in clinical practice, the next step should include additional analysis of the impact of intensive care treatment on gentamicin pharmacokinetics, followed by prospective validation.

Keywords: gentamicin, population pharmacokinetics, NONMEM, priors, paediatrics, intensive care

Modelling and simulations continue to evolve in clinical drug development and post-marketing drug research (1, 2). Pharmacokinetic/pharmacodynamic (PKPD) modelling can be applied for rational design and conduct of clinical pharmacology research (1, 2). In addition, PKPD modelling is gaining importance in the field of therapeutic drug monitoring (TDM) and dosing optimisation in patient populations with clinically important PK

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variability (1, 3). Among PK analytical methods, non-linear mixed effect modelling is often used. It is a useful tool for dealing with sparse and unbalanced datasets, as is often the case in paediatric clinical research, where only a small number of samples can be obtained from each individual and both the timing of sampling and the number of samples may vary between patients. This approach also allows for the assessment of various covariates that influence drug PK and accounts for interindividual and residual variability (1, 4).

Gentamicin is a broad-spectrum aminoglycoside antibiotic commonly used to treat severe bacterial infections in the paediatric population (5). It is a hydrophilic drug with a low volume of distribution (Vd) and drug clearance (CL) proportional to the glomerular filtration rate (GFR) (6). The bactericidal effect of aminoglycosides is concentration-dependent and the ratio of peak concentration to minimum inhibitory concentration (MIC) should be 8 to 10 times the MIC when treating severe Gram-negative infections (*7*). Due to a considerable post-antibiotic effect, trough levels below the MIC can be tolerated and less-fractionated dosing regimens may be preferred (3, 8, 9). Available evidence in paediatric patients suggests that extended-interval aminoglycoside dosing is as effective as conventional dosing, and no differences in toxicity were observed (10). Nephrotoxicity and ototoxicity are the most important adverse effects associated with aminoglycoside exposure. Epidemiological studies using more widely accepted definitions of acute kidney injury suggest that acute kidney injury may occur in 20 to 33 % of children exposed to aminoglycosides (11), whereas aminoglycoside-related hearing loss occurs in up to 57 % of children (12). The risk of nephrotoxicity is greater in patients with impaired renal function and in patients receiving high doses or prolonged therapy, therefore the optimal dosing for each patient should be determined by TDM. To reduce the risk of nephrotoxicity, a trough concentration of less than 2 mg L^{-1}, but preferably less than 0.5–1 mg L^{-1}, should be targeted (5, 7, 8).

In the paediatric population, drug dosing should be based on the developmental physiological changes that affect the PK of the drug (13, 14). Variations in gentamicin PK are most pronounced in neonates, especially preterm newborns, due to differences in body composition and immature kidney function. Therefore, extended dosing intervals are recommended in neonates, ranging from 24 to 48 hours, depending on gestational age (GA) and postnatal age (PNA) (5, 15). Drug PK may also be altered in critically ill patients (16, 17). Increased Vd of gentamicin has been reported in critically ill patients, which would require higher doses to reach target peak concentrations. However, as impaired renal elimination of gentamicin has also been observed, longer dosing intervals may be required to prevent renal toxicity (8, 17).

Due to the potential toxicity of gentamicin and the numerous factors that influence its PK, dosing should be individualised based on the monitoring of serum concentration to ensure adequate plasma levels and to avoid potentially toxic levels (5, 18). Although gentamicin concentrations are commonly monitored and doses are empirically adjusted in hospitals, population PK models in the TDM process could contribute to the understanding of the factors contributing to the risk of treatment failure and toxicity.

As reported in the 2019 review of population PK models of gentamicin in paediatric patients, non-linear mixed-effect modelling was the most commonly used approach to examine the gentamicin population PK in paediatric patients (19). The covariates that most often significantly influenced CL and Vd were age (GA, PNA, postmenstrual age (PMA) or post-conceptual age), body mass (birth mass, current or fat-free mass), and serum creatinine

concentration or creatinine clearance (19). Most models were developed for newborns only, in whom the PK of gentamicin varies mostly due to the greater volume of extracellular fluid per kg of body mass and immature renal function compared to children and adults. Only one model included infants, although changes in body composition and immature renal function are also expected in this subgroup. Two studies included the entire paediatric population (newborns, infants, and children). In children over 2 years of age, renal function is already comparable to adult level, while body composition still differs (20, 21). Moreover, the interindividual variability of gentamicin CL at any age could be influenced by parameters affecting renal function, *e.g.* critical illness and nephrotoxic drugs (19).

In population PK analysis, imprecise estimation of some model parameters is often related to sparse datasets, which is frequently the case with the paediatric population. On the other hand, the direct use of a literature model for routine TDM in clinical practice is not appropriate and the transferability of the model to the local population needs to be assessed using external dataset.

The aim of this study was to externally validate the predictive performance of published population PK models of gentamicin in all paediatric age groups, from preterm newborns to adolescents. In addition to the literature models, the predictive ability of the tweaked models obtained with the "prior approach" was evaluated. We were interested in whether model-informed precision dosing could be achieved in clinical settings treating the entire paediatric population using only one model. We also investigated the influence of critical illness on gentamicin PK.

EXPERIMENTAL

The structured approach was used to meet our objective, consisting of the following steps: *i*) retrospective data collection from a routine clinical practice including details of gentamicin treatment and TDM; *ii*) selection of the published population PK models of gentamicin developed in paediatric population with a wide age range; *iii*) re-estimation of selected literature models with priors and evaluation of their predictive performance; *iv*) model based simulations to evaluate of the impact of the critical illness (defined as treatment in the intensive care unit (ICU)) on gentamicin PK.

Data collected from a routine clinical practice

We included paediatric patients aged less than 18 years, that were hospitalized at the Clinical Department of Paediatric Surgery and Intensive Care, University Clinical Center Ljubljana between the years 2015 and 2017, who received a continuous intravenous infusion of gentamicin during the hospitalization and had at least one available serum gentamicin concentration measurement as part of routine clinical practice. Data were retrospectively collected after approval of the study protocol by the National Medical Ethics Committee (Approval No. 0120-220/2017-4).

Gentamicin treatment was initiated following the Harriet Lane Handbook (22) at the discretion of the treating physician. Based on measured gentamicin concentrations and the patient's clinical status, an empirical adjustment of gentamicin dosing was performed by the physician to maintain the gentamicin trough concentration below 2 mg L^{-1}.

Venous blood samples were collected as part of routine TDM of gentamicin, upon request of the treating physician. Gentamicin serum concentration was measured using a fluorescence polarization method (COBAS INTEGRA Gentamicin Test, Roche Diagnostics). The lower limit of quantification was 0.286 mg L^{-1}. Concentrations reported as below the lower limit of quantification (n = 16) were replaced with LLOQ/2 values and flagged as below the LLOQ.

Besides the information about gentamicin treatment (administered dose, infusion rate, time of administration, duration of treatment) and TDM data (gentamicin serum concentration, blood sampling time), the following data were obtained from hospital medical records: demographic characteristics (sex, age (GA, PNA, PMA), mass, height) and clinical data (serum creatinine concentration, hospitalization in ICU or non-ICU department during the gentamicin treatment).

Patients were sorted into 5 age groups: preterm newborns (0–27 days, GA < 37 weeks), term newborns (0–27 days, GA ≥ 37 weeks), infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 18 years) (23).

Selection of the literature models

Gentamicin population PK models were identified in the literature based on the PubMed database screening using the following combination of terms: gentamicin AND (pharmacokinetic model OR pharmacokinetic analysis OR population pharmacokinetic OR nonlinear mixed-effects modelling OR NONMEM) AND (paediatric OR newborns OR infants OR children). The search was limited to humans and the English language and results were additionally double-checked. All articles published by the end of 2022 were reviewed. The following inclusion criteria were met for accepted articles: *i*) treatment: intravenous gentamicin administration; *ii*) population studied: paediatric population with a wide age range (from newborns to adolescents); *iii*) PK model/PK analysis: nonlinear mixed-effects modelling. In addition, articles were excluded based on the following exclusion criteria: *i*) if gentamicin was not administered intravenously; *ii*) if the study included a narrow age range (*e.g.* newborns only). The population PK models of gentamicin published by the end of 2017 have already been included in the review article by Crcek *et al.* (19).

Validation of the literature and tweaked PK models

PK analysis was performed using NONMEM® (version 7.5., ICON Development Solutions, Ellicott City, MD, USA). NONMEM output processing, data wrangling, and visualizations were performed using packages plyr, dplyr, ggplot2, and xpose in R software version 4.0.2 (R Development Core Team, Vienna, Austria) and RStudio version 1.3.1073 (RStudio Team, PBC, USA).

First, the retrospective data were 5 times randomly split to obtain 5 estimation datasets with 70 % of the subjects and 5 prediction datasets with the remaining 30 % of the subjects. In each dataset, the proportion of patients from each age group was the same as in the whole dataset (as for cross-validation). The estimation dataset was used to re-estimate the parameters of the literature models and the prediction dataset was used to evaluate the predictive performance of the literature and the tweaked models.

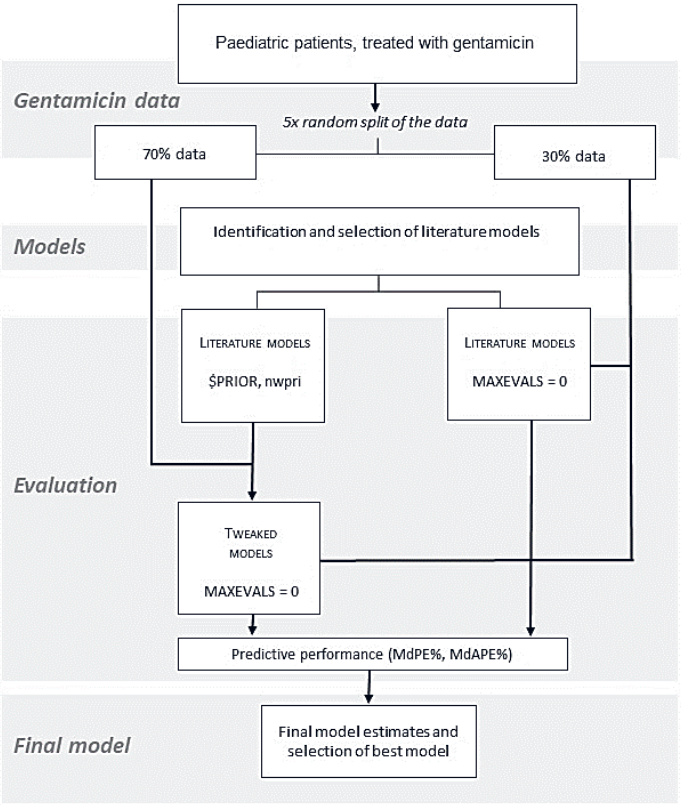


Fig. 1. Modelling strategy.

For the model re-estimation, the parameters of the literature models (fixed and random effects) were first set to published values of the respective study. Each model was then run on the estimation dataset using the $PRIOR NWPRI subroutine in NONMEM (24). Laplacian estimation with interaction was used for parameter estimation. The M3 method was used to handle 16/512 (3.1 %) gentamicin concentrations that were reported as below the lower limit of quantification. The additive, proportional and combination residual error models were tested and the model with the lowest objective function value (OFV) was chosen. Afterwards, the initial estimates of the PK parameters were updated to the re-estimated values, the prior information was removed from the control files of the tweaked models (Fig. 1). Subsequently, the predictive performance of the literature and tweaked models was evaluated on the prediction dataset using MAXEVALS = 0 option. *A priori* and *a posteriori* predictions were computed for each model and for each of the five prediction data splits. *A priori* predictions were computed using typical parameters and covariates only, while *a posteriori* predictions were based on individual patient's PK parameters.

The predictive performance of the models was evaluated with visual and quantitative methods. Bias and imprecision of the model-predicted concentrations were determined as

median relative prediction error (MdPE%) and median absolute relative prediction error (MdAPE%), respectively (24–26). Results were presented for the literature models and tweaked models, for the 5 data splits and age groups, and for *a priori* and *a posteriori* prediction. Additionally, goodness-of-fit (GOF) plots of observed gentamicin concentrations *vs.* individual predicted concentrations were generated for visual evaluation. Moreover, the performance of the model was assessed using visual predictive checks (VPC) with multiple replicates of the study simulation (n = 1000). The model with the best predictive performance represented the final model. The individual PK parameters obtained with the final model were additionally compared between ICU and non-ICU patients in each age group.

Model-based simulations

The final model was used for the simulation of the gentamicin plasma concentration profile in a typical ICU and non-ICU patient in each age group. First, the geometric mean of the individual PK parameters was calculated for ICU and non-ICU patients in each age group. Then, mean parameters and the interindividual variability (IIV) were used for the simulation (repeated 500 times) in which preterm and term newborns received gentamicin dosing of 5 mg/kg/24 hours and 5 mg/kg/36 hours, infants and toddlers received 7.5 mg/kg/24 hours and 7.5 mg/kg/36 hours, and children and adolescents received 7.5 mg/kg/24 hours. Plasma gentamicin concentration after a single dose and at a steady state were predicted. Based on the 500 simulations, the probability of reaching a trough concentration of gentamicin below 1 mg L^{-1} was calculated for ICU and non-ICU patients, in each age group.

RESULTS AND DISCUSSION

The aim of this study was to externally validate the performance of published population PK models of gentamicin in entire paediatric age groups, from preterm newborns to adolescents. Modelling has developed rapidly in routine clinical practice over the last decade, to individualize dosing and optimize the outcomes of pharmacotherapy (27). It seems unreasonable to develop own population PK model for a drug in each clinical setting and a much more rational way is to use the already published literature model. However, errors in dose selection may occur if the selected model is not developed in a population similar to the target population (27). Therefore, the accuracy, robustness, and predictive performance of the selected model in the target population needs to be evaluated (27–29). In addition, to use PK models in daily clinical work they should be as simple as possible. Using separate models for each pediatric age group could be complicated and time consuming, therefore we focused on the population's PK models of gentamicin that could be used for the entire pediatric population.

Adopting literature models with a prior approach improves their predictive ability (24, 25, 30, 31). Namely, the PRIOR subroutine in NONMEM allows estimation of some or all parameters using values from literature models, as an alternative to fixing them or adding data to the sparse dataset (32). Re-estimation of literature models using the prior approach is not widely used. It has already been used for population PK models of gentamicin, but either in adult ICU patients or neonates only (31, 33). Therefore, the present study is the first to use this approach to model gentamicin PK in the whole paediatric population, from preterm newborns to adolescents.

Data from a routine clinical practice

The demographic and clinical data of 308 paediatric patients included in the study are summarized in Table I. Most of the included patients (51.0 %) were newborns, whereas children and adolescents accounted for almost 20 %. Two-thirds of the patients were in the ICU during treatment with gentamicin. The total dataset included 512 gentamicin concentration-time data points with a median of 1 observed concentration per patient (range 1–9). The median gentamicin concentration was 0.91 mg L^{-1} and the median time of blood collection was 60 minutes before the next dose. Doses and dosing intervals of gentamicin treatment used in the included group of patients are summarized in the Supplem. Table S1.

Selection of the literature models

Based on the review by Crcek *et al.* (19), two population PK models of gentamicin developed on the entire paediatric population were considered appropriate (34, 35). Another study was initially excluded from the review article as the authors developed population PK models for different antibiotics. However, in the present study, we included the model of gentamicin as it was developed on the entire paediatric population (36). In addition, four appropriate models were identified that were published after 2017 and were relevant to the entire paediatric population (37–40). In total, seven models were considered appropriate. The general characteristics of the selected studies are listed in Table II, while a detailed description of the models is presented in the Supplem. Table S2. The studies differed greatly in the number of patients included and the total number of gentamicin

Table I. Demographic and clinical characteristics of study patients (n = 308)

Characteristic	Value
Male, *n* (%)	175 (56.8)
Treatment in Intensive Care Unit, *n* (%)	204/308 (66.2)
Age group, *n* (%)	
– premature newborns (0–27 days and GA < 37 weeks)	56 (18.2); ICU = 54/56 (96.4)
– term newborns (0–27 days and GA ≥ 37 weeks)	101 (32.8); ICU = 88/101 (87.1)
– infants and toddlers (28 days to 23 months)	90 (29.2); ICU = 48/90 (53.3)
– children (2 to 11 years)	53 (17.2); ICU = 12/53 (22.6)
– adolescents (12 to 18 years)	8 (2.6); ICU = 3/8 (37.5)
Gestational age (weeks), median (min-max)	38 (23–41)
Postnatal age (days), median (min-max)	26 (0–5017)
Postmenstrual age (weeks), median (min-max)	42 (25–760)
Mass (kg), median (min-max)	3.7 (0.58–56)
Height (cm), median (min-max)	52 (30–176)
Serum creatinine (mg dL^{-1}), median (min-max)	0.39 (0.16–2.51)

Table II. Overview of selected literature models for gentamicin in the entire paediatric population (studies characteristics)

First author and year of publication	Population characteristics			Total number of gentamicin conc.[a]	Base model	Covariates on CL	Covariates on Vd
	Paediatric age group and number of included patients	Type of patients	Age and body mass; mean (± SD) or median (range)				
Alsultan, 2019 (37)	Infants and children (n = 107)	all paediatric patients	AGE: 4.5 ± 3.5 yr BW: 16.7 ± 10.8 kg	306	1-CM	BW	BW
De Cock, 2014 (36)	Newborns, infants, children and adolescents (n = 717)	critically ill patients	AGE 2 d (1 d–15 yr) BW 2.600 g (440 g–80 kg)	1705	2-CM	BW	BW
Ghoneim, 2021 (40)	Infants and children (n = 22)	non-critically ill patients	AGE: 34.88 ± 31.9 (1–72) m BW: 10.13 ± 5.25 (3.98–17.7) kg	–	2-CM	BW	BW
Llanos-Paez, 2017 (34)	Infants, children and adolescents (n = 423)	oncology patients	PNA 5.2 (0.2–18.2) yr PMA 309 (50.9–985) wk BW 19.4 (4.8–102.8) kg	2422	2-CM	FFM, PMA, SCr	FFM
Llanos-Paez, 2020 (38)	Newborns, infants and children (n = 115)	non-oncology patients	PMA: 327.6 (271.3) wk BW: 22.3 (18.8) kg	487	2-CM	NFM, PMA, SCr	NFM
Lopez, 2010 (35)	Newborns, infants and children (n = 50)	critically ill patients	AGE: 5.3 m (1 d–15 y) BW 4.8 (2–80) kg	238	2-CM	BW, AGE	BW
Wang, 2019 (39)	Newborns, infants, children and adolescents (n = 2357)	all paediatric patients	AGE 1d (1 d–19 yr) BW 3.24 (0.35–124) kg	6459	2-CM	FFM, PMA, SCr	FFM, PNA

CL – clearance, Vd – volume of distribution, BW – body mass, PNA – postnatal age, PMA – postmenstrual age, d – days, wk – weeks, m – months, yr – years, FFM – fat-free mass, NFM – normal fat mass, SCr – serum creatinine, 1-CM – one-compartment, 2-CM – two-compartment

[a] serum and/or plasma concentrations.

concentrations. With the exception of one study, gentamicin disposition was described with two compartments. Body mass, age, and serum creatinine concentration were the most frequent covariates for CL and body mass for Vd. In the study by Llanos-Paez (38), the model parameters were estimated separately for oncology and non-oncology patients, and only the latter were included in our study.

Validation of the literature and tweaked PK models

The total data from 308 patients enrolled in the study were randomly split 5 times into an estimation and a prediction dataset. As the number of gentamicin concentration measurements per patient varied, the total number of observed concentrations was also not the same between the splits. It ranged from 358 to 371 for the estimation datasets and from 141 to 153 for the prediction datasets. The patient characteristics of the individual datasets were similar (Supplem. Table S3).

For the literature models, the population parameter estimates of the final model (35–38) or the bootstrap average (34, 39, 40) were used. In some cases, the published data were not complete (missing interindividual variability value for Vd (36) or residual error predictions (37, 39, 40). When residual error parameter values were missing, the residual error model was estimated while keeping all other parameters fixed to the literature values. In one study, the SIR technique was used to calculate the relative standard errors and assess the precision of the model parameters (38). In two studies, the available information was insufficient to correctly mass the priors because the standard error for interindividual variability was missing (37, 40). In these two cases, degrees of freedom of omega prior were set to m+1, where m is the number of terms in the omega matrix (noninformative prior on omega).

A priori and a *posteriori* predictive performance of the literature and tweaked models was assessed for each age group (Figs. 2 and 3 and Supplem. Tables S4–S6). As expected, for most literature and tweaked models, the bias and imprecision, expressed as MdPE% and MdAPE%, were lower for *a priori* predictions than for a *posteriori* predictions, and re-estimation of the models improved their predictive performance. This is consistent with other studies reporting that adopting literature models with a prior approach improves their predictive ability (24, 25, 30, 31). For *a priori* predictions, the range of MdPE% for the literature and the tweaked models was –96.2 to 300.8 % and –29.6 to 286.0 %, respectively. For *a posteriori* predictions, the range of MdPE% for the literature and the tweaked models was –95.9 to 4.0 % and –13.4 to –5.9 %, respectively. The range of MdAPE% for *a priori* predictions was 51.0 to 343.3 % for the literature and 48.1 to 358.0 % for the tweaked models and for *a posteriori* predictions 11.0 to 95.9 % for the literature and 15.2 to 21.3 % for the tweaked models.

The models by Alsultan 2019 and by De Cock 2014 had the highest bias and imprecision. They fit poorly with our data set and although re-estimation significantly improved their performance, it was still worse compared to the other 5 models. When these two models were not considered, the range of MdPE% for *a priori* prediction for the literature and for tweaked models was –55.4 to –19.8 % and –29.6 to 10.1 %. For *a posteriori* predictions, the range of MdPE% was –20.3 to –1.2 % for the literature and –13.4 to –5.9 % for the tweaked models. The range of MdAPE% for *a priori* predictions was 51.0 to 65.4 % for the literature and 45.9 to 55.7 % for the tweaked models, and for *a posteriori* predictions 14.3 to 27.1 % and 19.0 to 21.3 % for the literature and tweaked models.

As expected, for most models the bias and imprecision were larger for *a priori* prediction, when gentamicin PK was predicted only based on covariates, than *a posteriori* prediction. The only exception was the tweaked model by Llanos-Paez 2020. This confirms the importance of measuring gentamicin concentrations also when population models are used in clinical practice to optimize gentamicin dosing in paediatric population. *A posteriori* predictions with tweaked models resulted in MdPE% between ± 15 % and MdAPE% ≤ 25 %, for all seven models tested, which we consider acceptable. Considering the median observed concentration in our dataset (0.9 mg L^{-1}), an absolute PE% of 25 % would correspond to a PE of ± 0.2 mg L^{-1}, which could still be acceptable. In a study by Tong *et al.* (31) trough predictions were considered accurate if they were within 0.5 mg L^{-1} of the actual value. Interestingly, all tweaked models underestimated the predicted concentrations of gentamicin, which could have consequences for the safety of the treatment. It is difficult to find an obvious reason for this underestimation. It could be related to patient' characteristics or the gentamicin plasma concentrations measured in a different clinical center than the one used for model development.

Based on all the results obtained (MdPE%, MdAPE%, and diagnostic plots), the models by Llanos-Paez 2017, Llanos-Paez 2020, and Wang 2019 described well the PK of gentamicin in our cohort of patients, while weaker predictive performance was observed for the models by Alsultan 2019, De Cock 2014, Ghoneim 2021 and Lopez 2010. In general, a model with good predictive performance should recognize the true compartmental structure and include the impact of body size descriptor and maturation-related changes in body composition and renal function (19, 39). The model by Alsultan 2019 was the only one-compartment model, while all other models described gentamicin PK by two compartments. In addition, the models by Alsultan 2019, De Cock 2014, and Ghoneim 2021 included body mass as the only covariate on CL and Vd, and the model by Lopez 2010 additionally included age on CL. All three models with better predictive performance (Llanos-Paez 2017, Llanos-Paez 2020, Wang 2019) were quite similar and included PMA, serum creatinine concentration and normal fat mass or fat-free mass as covariates, and glomerular filtration rate maturation was included in the calculation of CL. For the better predictive performance of gentamicin PK in paediatric population, it is obviously crucial that the model includes covariates that allow assessment of developmental differences in the paediatric population. Namely, higher body water content at lower age influences Vd of hydrophilic gentamicin and immature renal function its CL as renal elimination is the main route of gentamicin elimination (3, 14).

Based on the *a priori* and *a posteriori* predictive performance of the models in the different age groups (Figs. 2 and 3) and in each of the 5 data splits (Supplem. Figs. S1 and S2 and Supplem. Tables S7 and S8), as well as the diagnostic plots (GOF and VPC, Supplem. Fig. S3), the tweaked model by Wang 2019 was chosen as the most appropriate (final model, Table III, Fig. 4, NONMEM control stream in Supplem. Materials). The model was developed with 2357 patients, from newborns to adolescents, and altogether 6459 gentamicin plasma concentrations (39). In comparison, the model by Ghoneim 2021 was developed on only 22 infants and children (40), which could also be a reason for the poor performance of this model on our dataset. Moreover, the median age and body mass of the included patient in the study by Wang 2019 (1 day and 3.2 kg) were the most similar to our cohort of patients (26 days and 3.7 kg). The model includes fat-free mass as a covariate of all parameters estimated and it has been shown to be superior to body mass for the description of glomerular

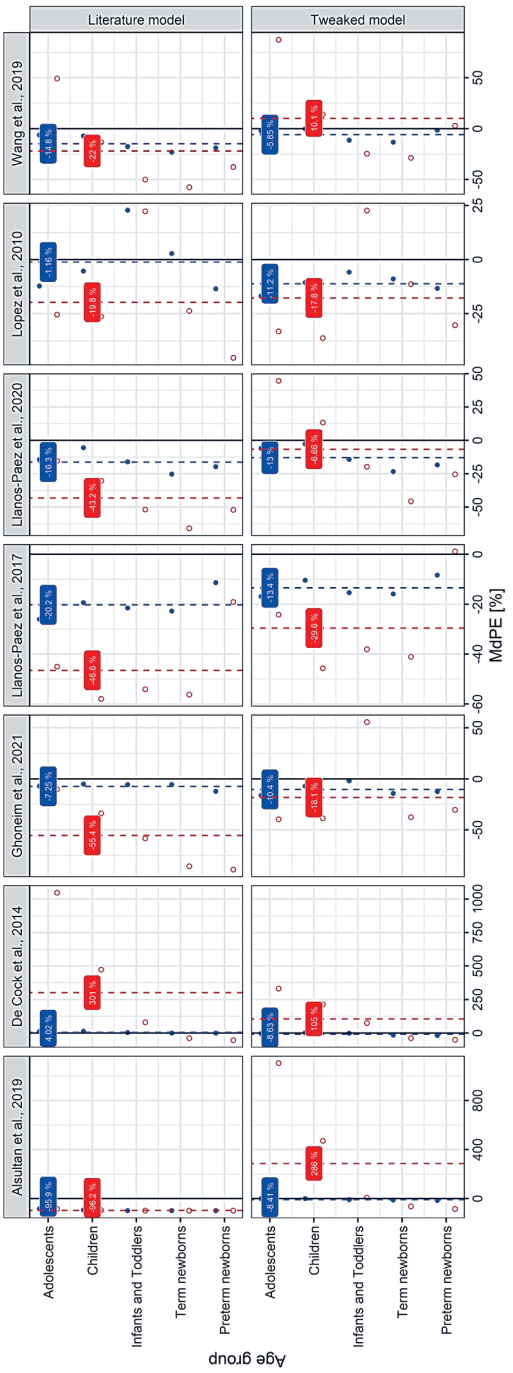


Fig. 2. Median relative prediction error (MdPE%) of the literature (top) and tweaked models (bottom) for *a priori* (red circles) and *a posteriori* (blue circles) predictions. The dashed line represents an average value for the entire paediatric population.

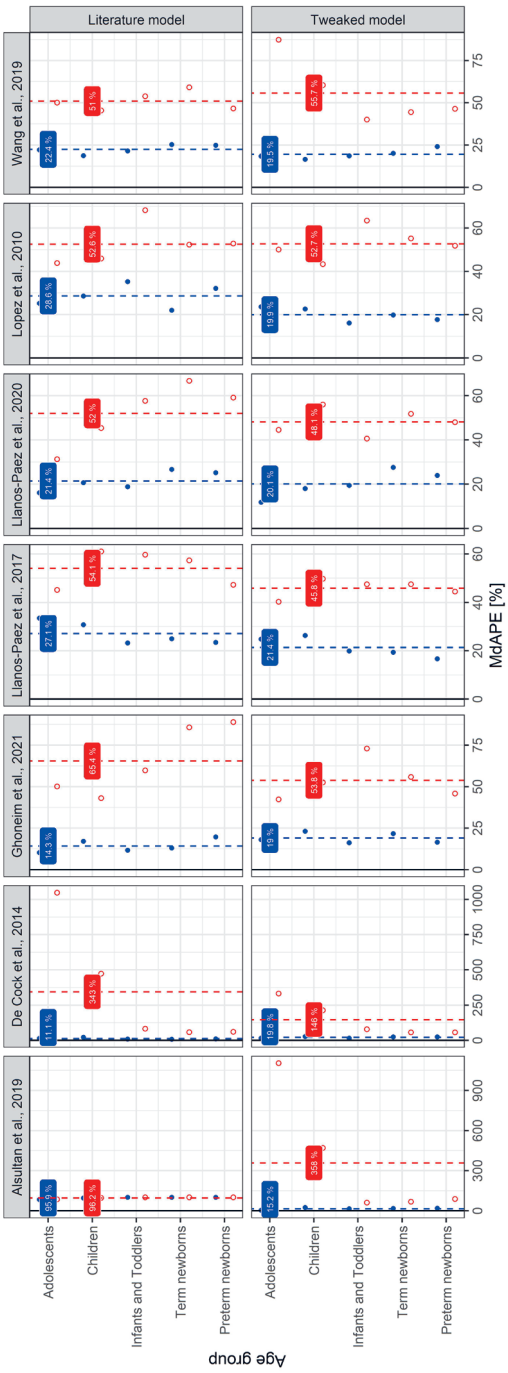


Fig. 3. Median absolute relative prediction error (MdAPE%) of the literature (top) and tweaked models (bottom) for *a priori* (red circles) and *a posteriori* (blue circles) predictions. The dashed line represents an average value for the entire paediatric population.

Table III. Population pharmacokinetic model parameter estimates of the final model (Wang 2019, tweaked model)

Parameter (units)	Final model results		Bootstrap results	
	Estimates	RSE (%)	Mean	Nonparametric 95% CI
CL (L/h/70 kg)	4.17	0.908	4.17	4.10–4.25
Q (L/h/70 kg)	1.13	0.809	1.13	1.11–1.15
V_1 (L/70 kg)	18.5	0.375	18.5	18.4–18.7
V_2 (L/70 kg)	17.2	1.97	17.2	16.5–17.9
PMA50 (wk)	49.0	0.519	49.0	48.5–49.5
Hill	3.39	1.48	3.39	3.28–3.48
SCr power exponent	0.403	5.77	0.402	0.354–0.447
Interindividual variability				
IIV CL (% CV)	40.0	0.631	40.0	39.8–40.3
IIV V1 (% CV)	50.1	0.612	50.1	49.8–50.4
IIV V2 (% CV)	68.9	2.38	68.9	67.1–71.0
Corr CL-V1	0.991	0.627	0.991	0.991–0.991
Residual variability				
Proportional (%)	0.0007	8.58	0.0007	0.0006–0.0008
Additive (mg L^{-1})	38.7	6.26	38.6	34.0–43.4

CL – clearance, Q – intercompartmental clearance, V_1 – volume of distribution in the central compartment, V_2 – volume of distribution in peripheral compartment, PMA50 – postmenstrual age at which GFR is 50 % matured, Hill is the shape factor of the maturation curve, SCr – serum creatinine, IIV – interindividual variability, Corr – correlation coefficient, RSE – relative standard error, CI – confidence interval.

$$\text{CL (L/h/70 kg)} = 4.17 \times \left(\frac{\text{FFM}}{70}\right)^{0.75} \times \frac{\text{PMA}^{3.39}}{\text{PMA}^{3.39} + 49.0^{3.39}} \times \left(\frac{\text{SCr}_{\text{mean}}}{\text{S}_{\text{CRi}}}\right)^{0.403}$$

$$V_1\ \text{(L/70 kg)} = 18.5 \times \frac{\text{FFM}}{70} \times \left(1 + 0.614 \times e^{-\text{PNA} \times \frac{\ln 2}{9.65}}\right)$$

$$\text{Q(L/h/70 kg)} = 1.13 \times \left(\frac{\text{FFM}}{70}\right)^{0.75}$$

$$V_2\ \text{(L/70 kg)} = 17.2 \times \left(\frac{\text{FFM}}{70}\right)$$

SCr_{mean} – mean serum creatinine concentration was calculated using a formula described by Ceriotti *et al.* (45):

$$S_{CRmean}(mg/dL) = -0.02324 - 0.14545 \times \log_e(age) + 0.26964 \times (age)^{0.5}$$

FFM – fat-free mass was calculated using formulas described by Al-Sallami *et al.* (41):

$$FFM(female) = \left[1.11 + \left(\frac{1-1.11}{\left[1+\left(\frac{age}{7.1}\right)^{-1.1}\right]}\right)\right] \times \left[\frac{9270 \times BW}{8780 + (244 \times BMI)}\right]$$

$$FFM(male) = \left[0.88 + \left(\frac{1-0.88}{\left[1+\left(\frac{age}{13.4}\right)^{-12.7}\right]}\right)\right] \times \left[\frac{9270 \times BW}{6680 + (216 \times BMI)}\right]$$

filtration rate in the paediatric population (41). The *a posteriori* predictions of the tweaked model by Wang 2019 had low bias and imprecision for all tested age groups, from preterm newborns to adolescents, making the model suitable for predicting gentamicin PK in the entire paediatric population.

Model simulations

In clinical practice, the initial dosing of gentamicin in paediatric patients depends on age as well as on some special medical conditions, such as significant asphyxia, poor cardiac output or reduced renal function (22). Monitoring of gentamicin serum concentrations is recommended to ensure efficacy and avoid toxicity. This is particularly important in critically ill patients, as their condition could influence gentamicin PK (5). Moreover, in critically ill patients, treatment failure is associated with increased mortality (42). In our cohort of patients, 66.2 % of them were treated in the ICU, and within all three age groups tested, gentamicin CL and steady-state distribution volume (Vss) were significantly lower in patients hospitalized in the ICU than in non-ICU patients (Supplem. Table S9). Preterm newborns could not be evaluated because they were mostly all hospitalized in the ICU, while the number of adolescents was too small for a meaningful comparison. Other studies also found lower CL of gentamicin in critically ill but higher Vd than in non-critically ill children (17). However, we must emphasise that within the same paediatric age group, the ICU patients were younger and had lower body mass than non-ICU patients (Table S10), which may influence their Vss. In general, changes in Vd during critical illness are a complex result of increased capillary leak associated with sepsis, excessive fluid intake, renal failure, *etc.* (17).

Based on the results, we were interested to explore to which extent these differences are reflected in gentamicin plasma profiles after the administration of the same dosing regimens. Simulated plasma concentrations after a single dose and at steady-state, and the

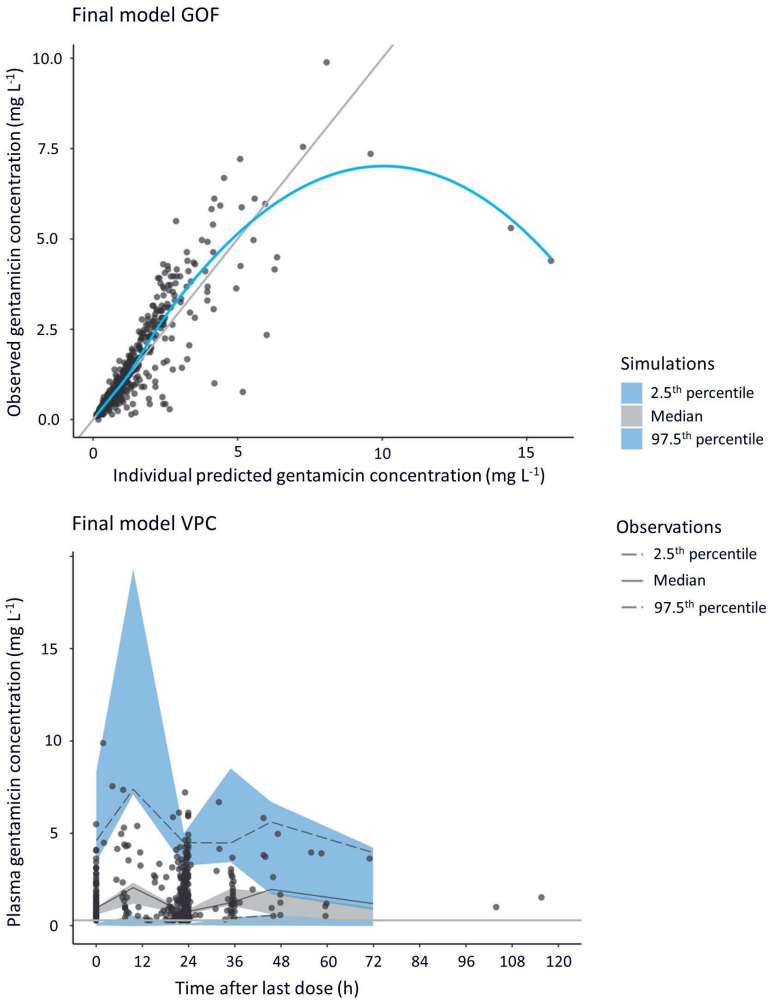


Fig. 4. Diagnostic plots of the final model (Wang 2019, tweaked model): (top) observed *vs.* individual model-predicted gentamicin concentrations (points), LOESS fit (blue) and the line of identity (grey); (bottom) visual predictive check (n = 1000 replicates), observations (points) medians (solid grey lines), 2.5th and 97.5th percentiles (dashed grey lines), 90 % confidence intervals for the corresponding median (grey coloured areas) and 2.5th and 97.5th percentiles (blue coloured areas).

probability of reaching a trough concentration of gentamicin below 1 mg L^{-1}, for all age groups are shown in Fig. 5 (preterm newborns, term newborns, and infants and toddlers) and in Supplem. Fig. S4 (children and adolescents). In preterm and term newborns, infants and toddlers hospitalized in the ICU, lower CL and Vss resulted in higher plasma concentrations. Consequently, there is less likelihood of reaching a trough concentration below 1

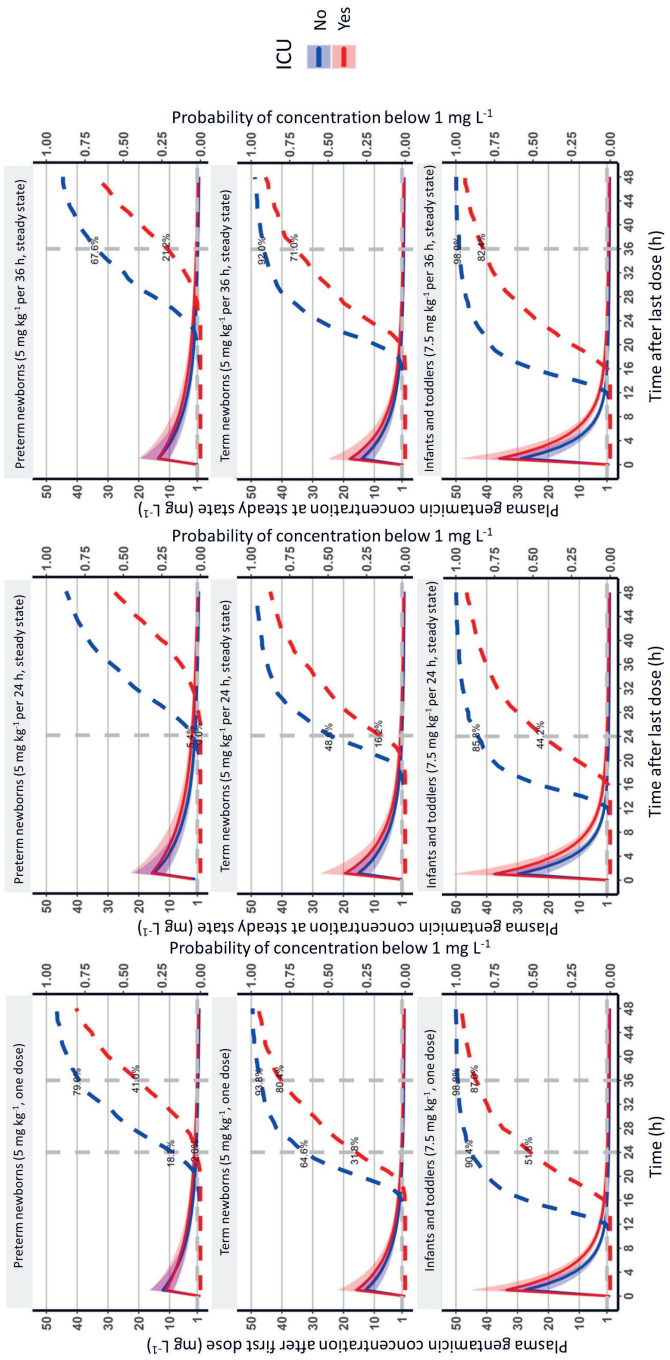


Fig. 5. Simulated plasma gentamicin concentrations (full line) and 50 % prediction interval (ribbon) after the first dose (left) and at steady state (middle and right) in preterm newborns (top), term newborns (middle) and infants and toddlers (bottom), and the probability of reaching trough gentamicin concentration below 1 mg L^{-1} (dashed lines) in Intensive Care Unit (ICU) patients (red) and non-ICU patients (blue).

mg L^{-1}. At doses of 5 mg/kg/24 hours, none of the preterm newborns in the ICU reached the target steady-state trough concentration and only 5 % in the non-ICU, while at a 36-hour dosing interval the probability increased to 21 and 68 % for ICU and non-ICU patients, respectively. Not only in preterm newborns, but also in term newborns, infants and toddlers, especially those treated in the ICU, a dosing interval of 36 hours seems more appropriate to avoid gentamicin toxicity. To maximize the bactericidal effect, a peak concentration to minimum inhibitory concentration (MIC) ratio of 8–10 is generally recommended (22, 43, 44). A 36-hour dosing interval is expected to result in slightly lower peak concentrations at a steady state than a 24-hour dosing interval. Whether these peak concentrations at the extended dosing interval would be high enough to not reduce treatment efficacy depends on the MIC of the susceptible bacteria. For most susceptible bacteria, the MIC is 0.5–2 mg L^{-1}, justifying a level of 5 to 20 mg L^{-1} for the peak concentration of gentamicin (15, 43, 44). In children and adolescents, the probability of reaching a trough concentration below 1 mg mL^{-1} was similar in patients treated in the ICU as in patients not treated in the ICU. However, higher peak concentrations, close to or even higher than 30 mg mL^{-1}, could be expected in patients treated in the ICU.

There are some limitations in our study. Models were evaluated using routine therapeutic drug monitoring data. Most measured gentamicin concentrations were trough levels (326/512; 63.7 %, measured within 1 hour before the next dose), while for other concentrations the median time of blood collection was 1.7 hours before the next dose. Only 35.7 % of patients (110/308) had more than one gentamicin concentration measured during hospitalization. In addition, relatively few adolescents were included. The influence of concomitant therapy on gentamicin PK was also not evaluated. The most common concomitant therapy was vancomycin (126/308; 40.9 %), dopamine (89/308; 28.9 %), and furosemide (79/308; 25.6 %).

CONCLUSIONS

This is the first retrospective validation of published population PK models of gentamicin in the entire paediatric population using the PRIOR approach. We evaluated seven models, and the models that included covariates allowing assessment of developmental differences in the paediatric population had better predictive performance, which further improved after model re-estimation. The tweaked model by Wang 2019 performed best, with suitable accuracy and precision in the entire paediatric population, from newborns to adolescents. In patients treated in the ICU, the gentamicin PK was altered, which could importantly affect the treatment safety. Therefore, the selected model could be applied for model-informed precision dosing in clinical settings where the entire paediatric population is treated. However, to be used in clinical practice, the next step should include additional analysis of the impact of the ICU patients' characteristics on gentamicin PK, followed by a prospective validation of the model.

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