FULL REPORT

Model-informed dosing of gentamicin – Pediatrics

V1 – Nov 2023

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Disclaimer

This website provides model simulations of dosing regimen for drugs used by pediatric and pregnant patients. These are NOT dosing recommendations for clinical use. Drug dosing recommendations for clinical use in pediatric patients and pregnant patients and/or their fetuses, which may have been supported by modeling and simulation, are provided by the Dutch Pediatric Formulary (www.kinderformularium.nl, or any of its international affiliates) and the Teratology Information Service, Netherlands Pharmacovigilance Centre Lareb (www.lareb.nl), respectively. Final dosing recommendations on these websites are the result of a careful benefit-risk assessment of the model-informed dose in the context of all available clinical evidence and experience. Clinical boards endeavor to implement modeling and simulation information in their recommendations promptly, but a lag time is inevitable. Hence, dosing recommendations on these website may not (yet) take into account results from modeling and simulation.

Important links

Pediatric gentamicin dosing recommendations for clinical practice can be found in one of the European Pediatric Formularies

The Netherlands:	https://www.kinderformularium.nl/geneesmiddel/23/gentamicine
Germany:	https://kinderformularium.de/monographie/5173/gentamicin
Austria:	https://kindermedika.at/monographie/10520/gentamicin
Norway:	https://www.koble.info/legemiddel/8672/gentamicin-parenteral

The scientific publication of this study by De Hoop-Sommen et al. (PMID: 38078320)
"Pragmatic physiologically-based pharmacokinetic modeling to support clinical implementation of optimized gentamicin dosing in term neonates and infants: proof-of-concept"
Front Pediatr. 2023 Nov 21:11:1288376. doi: 10.3389/fped.2023.1288376.

Template for creating a model-informed dosing report: download here.

1. Rationale for model-informed dose

Gentamicin is widely used for the treatment of infections such as pneumonia, urinary tract infections, and sepsis. It is administered on-label to pediatric patients, meaning that this age group is included in the drug label and that the drug is given conform the dosing instructions for this age group on the label. Gentamicin is administered off-label to premature neonates.

Drug labels provide different recommendations regarding dosing frequency despite general consensus on once-daily dosing. The U.S. FDA label still recommends the traditional thrice-daily dosing, while the European label prefers once-daily over twice-daily dosing. In November 2023, the Dutch Pediatric Formulary recommended a once-daily **gentamicin dose of 4 mg/kg for neonates and 7 mg/kg for children ≥1 month of age**. Gentamicin is administered as an intravenous infusion over 30 minutes [(1)].

Rapid changes in body composition and organ maturation may have an effect on the gentamicin plasma level across the pediatric age span. In addition, there is a shift in the therapeutic target above 1 month of age: in neonates it is aimed for a maximum plasma concentration between 8 - 12 mg/L and between 15 - 20 mg/L in older infants.

The following questions arise when looking at this dosing guideline:

- Is the **gentamicin plasma level adequate** when 4 mg/kg is given to neonates and 7 mg/kg to children ≥1 month of age?
- Is this **sudden dose increase at the age of 1 month appropriate**?
- Is a **more gradual increase in dosing** more appropriate from a pharmacokinetic perspective?

These questions are addressed with physiologically-based pharmacokinetic (PBPK) computer model simulations. A PBPK model can be seen as a computerized pediatric body receiving a drug. The effects of development and maturation on the organs are descibred in the model. Also, physical and chemical properties of gentamicin are incorporated. Together, the model can simulate the distribution, metabolism and excretion of gentamicin in a pediatric virtual population with the aim to:

Establish model-informed dosing recommendations for term neonates and infants up to 2 years of age.

More information on physiologically-based pharmacokinetic modeling and the process of model verification can be found in the section Background information: Model-informed dosing of the MELINDA website.

2. Model credibility

The PBPK model that was used in this pediatric dose-finding study is constructed by combining the pediatric population model available from the Simcyp™ software with the gentamicin model of Abduljalil and colleagues [2]. Input parameters were not changed. Credibility of the established PBPK model was evaluated by checking model parameterization and through verification simulations. The framework below was used to navigate through this process.

General information on PBPK model credibility can be found in the section Background information: Model-informed dosing of the MELINDA website.

Framework for assessment of PBPK model credibility				
Model parameterization (defining model input parameters)				
1	Is the drug model of the PBPK model adequately parameterized (e.g. contributing drug eliminating pathways)?	No	Doubtful	**Yes**
	The gentamicin model (full distribution model) used in this study is constructed by Abduljalil et al. [2] without any change of input parameters. It is no issue that the gentamicin model was initially created to study drug pharmacokinetics in preterm neonates, as only the gentamicin model was used which is population-independent.			
2	Is the population model of the PBPK model adequately parameterized (e.g. incorporation of biological interindividual variability and relevant ontogeny profiles)?	No	Doubtful	**Yes**
	Already established and validated population models available from the Simcyp® software are used (v21). These models are constructed by Simcyp® based on a comprehensive literature and database review of pediatric anatomy and physiology. The following models are used: 'Sim-Healthy-volunteer', 'Sim-NEurCaucasian', Sim-Paediatric' and 'Sim-preterm'.			
3	Are there any assumptions made regarding model input parameters? If yes, comment on the potential influence of a change in these model input parameters on modeling output.	Yes	Doubtful	**No**
	The drug model of Abduljalil et al. [2] and population models from the Simcyp® software are used without any change of input parameters.			
Model verification (evaluating the ability of the model to predict PK accurately)				
4	Is model performance verified using clinical PK data* from a similar population (i.e., comparable pediatric age group), using the drug of interest for a similar indication? If no, comment on the data used for model verification (which age, drug, and/or indication) and whether PK may differ between the population from which PK data are derived and the virtual *healthy* individuals. If that is the case, it must be carefully examined whether the model-informed dose is appropriate for the real-life patient population or if dose adjustment is needed.	No		**Yes**
	Model performance is assessed using PK data from IV single and multi-dose studies with adult (eight studies in total) and pediatric subjects (21 studies in total, of which 3 studies in preterm neonates). Subjects included in these PK studies suffer from a variety of infections, hence resembling the population intended to use the model-informed dose.			

5	Is PBPK model performance considered adequate? To answer this question, the predicted and observed* plasma concentration-time curves should be compared and agreement of predicted and observed PK parameter values (e.g., volume of distribution and clearance) should be evaluated. If no, comment on whether this discrepancy can be explained by differences between the populations (e.g., clinically observed PK data are collected from patients that suffer from a severe infection that may have impacted PK, see 4).	No	Doubtful	**Yes**
	Published PK data from intravenous single and multi-dose clinical studies with adult (eight studies in total) and pediatric subjects (21 studies in total, of which 3 studies in preterm neonates) was used to assess the ability of the model to predict PK accurately (i.e., assess 'predictive performance' of the model). Visual predictive checks reveal that the predicted plasma concentration-time curve is comparable to what have been observed clinically, both for adult and pediatric subjects. For adults, 82% of all predicted PK parameters differed less than 2-fold (i.e., within 2-fold lower and 2-fold higher) from the observed value. For pediatric patients this percentage was as high as 91%.			
OVERALL MODEL CREDIBILITY (trustworthiness)				
How credible are the outcomes of the PBPK model considering model parameterization, robustness and verification?		Inadequate	Adequate	**Satisfactory**
Model credibility is considered 'good'. There are no specific insecurities and/or uncertainties that should be taken into account.				

* Clinical observed PK data generally includes plasma concentration-time data and PK parameters such as the volume of distribution and clearance).

Abbreviations: BSA, body surface area; CL_R, renal clearance; GFR, glomerular filtration rate; IV, intravenous; PBPK, physiologically-based pharmacokinetic; PK, pharmacokinetic; Vd, volume of distribution.

Model verification

The ability of the model to predict PK accurately is assessed by conducting verification simulations, using clinical PK data from single and multi-dose IV studies with adults (eight studies in total) and with pediatric subjects (21 studies in total). For illustrative purposes, four verification simulations were selected. Study characteristics are shown in Table 1. Examples are selected based on the number of included subjects and age range covered. All other verification simulations can be found in the publication of this study by De Hoop-Sommen and colleagues [3].

More information on model verification can be found in the section Background information: Model-informed dosing of the MELINDA website.

	ADULT STUDIES		PEDIATRIC STUDIES	
	Boisson et al. 2018	**Triginer et al. 1991**	**Shankar et al. 1999**	**Lares-Asseff et al. 2016**
Reference	(4)	(5)	(6)	(7)
Design	Single dose	Multi dose	Single dose	Multi dose
Proportion of females	0	0.4	Not reported	0.23
Infusion duration	30 min	30 min	30 min	30 min
Number of included subjects	12	10	10	26
Dose	8 mg/kg	3.5 mg/kg every 24h	6 mg/kg	2.5 mg/kg every 8h
Age range	19 - 65 years	32 - 76 years	5 - 13 years	3 - 60 months
Health status	Critically ill	Elective open heart surgery	Cancer patients: infection or sepsis	Children with malnutrition: diarrhoea, pneumonia and septicaemia

Table 1. Clinical pharmacokinetic study characteristics

Figure 1 and 2 show that the established PBPK model was able to adequately predict gentamicin PK: the predicted plasma concentration-time curve is comparable to what have been observed clinically, both for adults and for pediatric subjects.

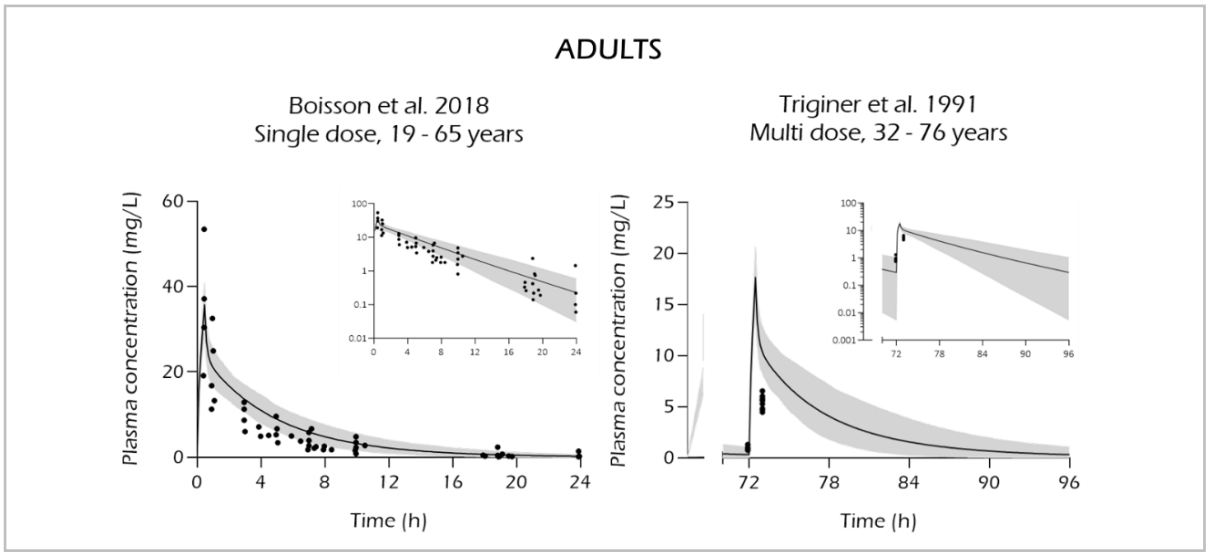


Figure 1. Examples of verification plots in adults. The solid line is the predicted mean plasma concentration of the virtual adult population and the shaded area represents the 5th to 95th percentile. Closed circles are individual datapoints from the clinical pharmacokinetic study. Insets show semi-log plots.

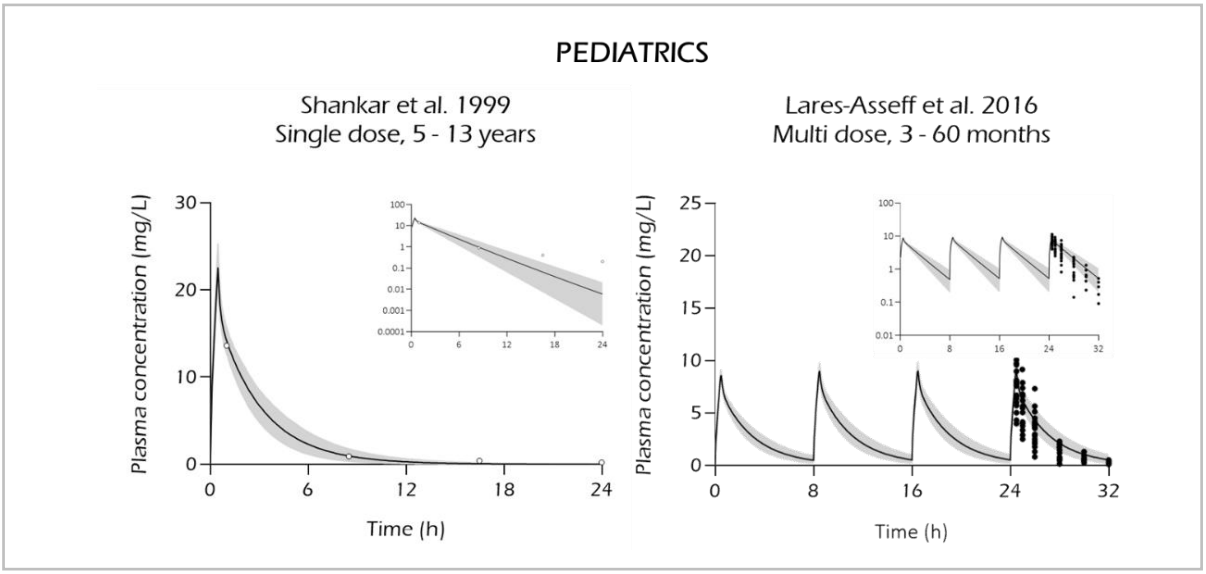


Figure 2. Examples of verification plots in pediatrics. The solid line is the predicted mean plasma concentration of the virtual pediatric population and the shaded area represents the 5th to 95th percentile. Open circles are mean plasma concentration values from the clinical PK study, closed circles are observed individual datapoints. Insets show semi-log plots.

Figure 3 shows that for adults, 82% of all predicted PK parameters differed less than 2-fold (i.e., within 2-fold lower and 2-fold higher) from the observed value. For pediatric patients this percentage was as high as 91%.

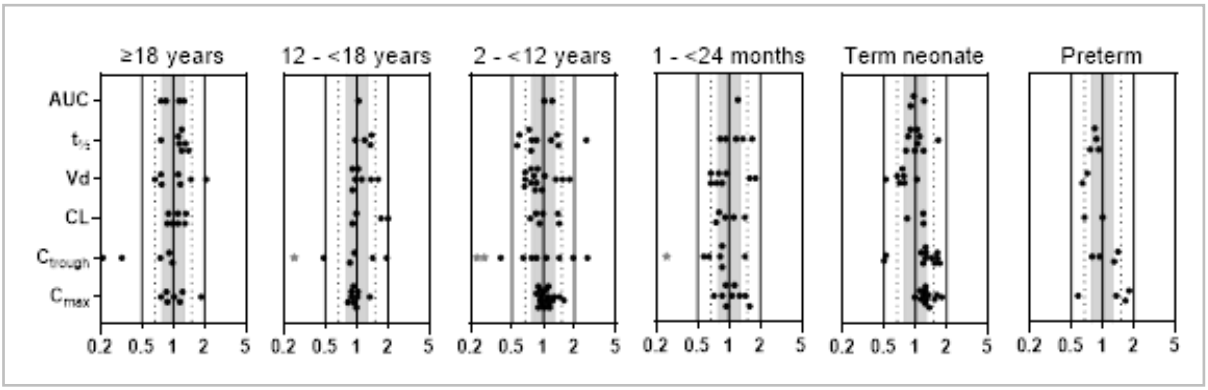


Figure 3. Pharmacokinetic parameter check. Predicted-to-observed PK parameter ratios for gentamicin for distinct age groups are depicted. Solid lines, dotted lines, and the shaded area indicate the 2-fold, 1.5-fold, and 1.25-fold range, respectively. * 1 or 2 (**) datapoints fell outside axis limits. Abbreviations: AUC, area under the curve; $t_{1/2}$, half-life; Vd, volume of distribution; CL, clearance; C_{trough}, trough plasma concentration; C_{max}, maximum plasma concentration.

Based on the verification simulations and assessment of model credibility using the framework above, PBPK model credibility is considered satisfactory.

3. Dose-finding strategy

The established and verified PBPK computer model was used to first:

1) predict gentamicin pharmacokinetics (C_{max} and C_{trough}) in pediatric subjects, with the following dosing regimens as provided by the Dutch Pediatric Formulary in November 2023:
    - neonates: 4 mg/kg every 24h (intravenous infusion over 30 min)
    - infants 1 month - 2 years of age: 7 mg/kg every 24h (intravenous infusion over 30 min)

and subsequently:

2) simulate alternative dosing scenarios to reach the intended C_{max} and C_{trough}. We used this information to decide which dosing regimens will most likely result in the desired gentamicin plasma concentration.

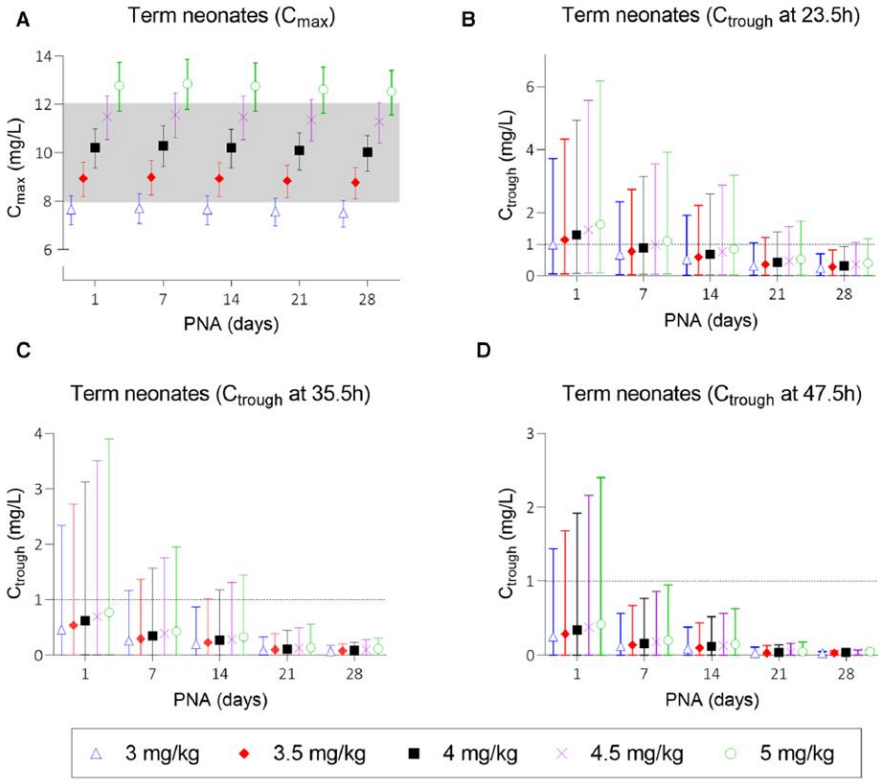
Questions that are addressed are displayed in the framework below.

More information on dose-finding methods can be found in the section Background information: Model-informed dosing of the MELINDA website.

Framework for establishing a model-informed dose	
Simulations of PK with DPF dosing regimen	
1	Is exposure adequate with the DPF dosing recommendations of November 2023?
	Current dose advice – Term neonates With the current dose advice (4 mg/kg every 24h), the PBPK computer model predictions show that an adequate C_{max} in term neonates up to 1 month of age is reached.. This is visualized in **Figure 4A** below, where black squares (indicating 4 mg/kg every 24h) show that the C_{max} falls within the desired plasma concentration range for term neonates. A therapeutic effect can therefore be expected. With 4 mg/kg every 24h, the C_{trough} level is not optimal. In **Figure 4B**, it can be seen that the 24h C_{trough} level is too high (>1 mg/L) in the majority of the term neonates of 1 day (postnatal age) when 4 mg/kg is given every 24h (black squares). It should be noted that the risk of having such high C_{trough} levels decreases with increasing postnatal age (all neonates of 28 days have an adequate C_{trough} level). Current dose advice – Infants up to 2 years of age With the current dose advice (7 mg/kg every 24h), C_{max} levels are expected to be within the therapeutic range in infants up to 2 years of age. This is visualized in **Figure 4E**, where black squares represent the 7 mg/kg every 24h dosing schedule. Though, the 5th percentile for infants ≥21 months of age just dipped below the lower limit, meaning that a few infants at this age may in fact have C_{max} levels below the lower limit of the effective range (<15 mg/L). **Figure 4F** shows that a large proportion of the infants around 1 month of age have suboptimal C_{trough} levels (>1 mg/L). Adequate C_{trough} levels are seen in older age (infants ≥2 months). Taken together, these predictions show that the gentamicin dosing recommendations for term neonates and infants up to 2 years of age can be improved.
2	Which dose-finding method is applied? Note: If the MID is based on exposure matching, comment on the population for which the plasma exposure target (AUC or C_{max}) is established. Also, comment on whether the plasma level serves as a surrogate measurement of an organ concentration] (e.g., lungs) and hence a similar plasma:organ concentration is assumed between the populations.
	For optimal treatment, a defined C_{max} should be reached upon dosing. The target C_{max} is dependent on the MIC of the micro-organism involved. Based on literature, we aimed to reach a C_{max}/MIC ratio of 8 to 10 [8-11]. Most

	micro-organisms involved in neonatal infections have an MIC of less than 1 mg/L [8, 11-15] while infections in older age groups are generally caused by micro-organisms with MICs up to 2 mg/L [8, 10, 11, 16]. The C_{trough} is a better predictor for toxicity (nephro- and ototoxicity) than total exposure (AUC). To prevent toxic effects, the C_{trough} should be below 1 mg/mL [8-11, 17, 18]. Based on this information, the most optimal dosing regimen had to fulfill the following requirements: □ the C_{max} should be between 8 - 12 mg/L in neonates and between 15 - 20 mg/L in infants <2 years of age □ the C_{trough} should be below 1 mg/L in children of all ages			
3	How wide is the therapeutic window of the drug?	**Narrow**	Intermediate	Wide
4	How wide is the interindividual variability in PK? If narrow, comment on whether you expect that some individuals will reach the efficacy or safety limit of the therapeutic window.	**Wide**	Intermediate	Narrow
	Variability in PK is mainly due to age and disease/condition which may result in sub- or supratherapeutic gentamicin plasma levels (see section 'Considerations for implementation' of this report).			
Simulations of PK with alternative dosing regimens				
5	Do alternative dosing regimens result in more adequate exposure?			
	PBPK computer model predictions with various alternative dosing strategies showed that the total dose does not need to be changed (4 mg/kg) but that the dosing interval for term neonates up to 6 weeks of age should be extended from once every 24h to 36 - 48h to keep C_{trough} levels below 1 mg/mL. This suggestion is based on modeling predictions visualized in **Figure 4B-D** show that a higher proportion of term neonates have adequate C_{trough} levels (<1mg/L) when the dosing interval is extended, as depicted by the trough level at 35.5h and 47.5h as compared to 23.5h. For infants, a dose of 7.5 mg/kg every 24 hours will result in adequate C_{max} levels. This suggestion is based on modeling predictions visualized in **Figure 4E**, showing a more adequate C_{max} with 7.5 mg/kg every 24h (red squares) as compared to 5 mg/kg every 24h (black squares). Predicted PK parameter values for defined age groups are shown in **Table 2**.			

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; PK, pharmacokinetic.



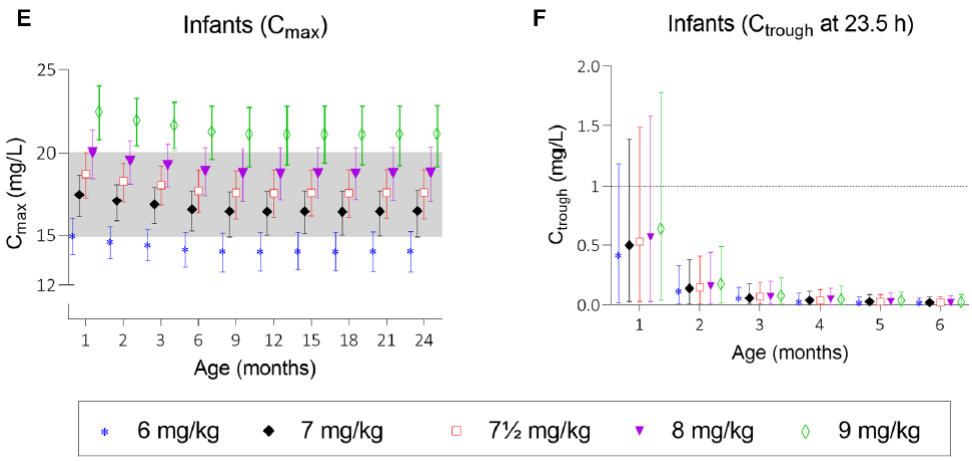


Figure 4. Predicted gentamicin plasma levels in different age groups upon various dosing strategies. Predicted C_{max} and C_{trough} levels and corresponding 5th and 95th percentiles are shown. Graph **(A)** shows C_{max} levels after doses of 3, 3.5, 4, 4.5, and 5 mg/kg for neonates and graph **(E)** shows C_{max} levels after doses of 6, 7, 7.5, 8, and 9 mg/kg for infants. Graph **(B-D)** show C_{trough} levels at 23.5, 35.5, and 47.5 hours after start of infusion for neonates and graph **(F)** shows C_{trough} levels for infants until the age of 6 months; older infants all have C_{trough} levels below 1 mg/L and are therefore not depicted. Black squares (■) in graphs **(A - D)** and black diamonds (◆) in graphs **(E-F)** represent the Dutch Pediatric Formulary dose of November 2023. Abbreviations: C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; PNA, postnatal age.

Table 2. Predicted pharmacokinetic parameter values for different age groups

Age group	Pharmacokinetic parameter				
	C_{max} (mg/L)	**t_{max} (h)**	**Vd (L/kg)**	**CL (mL/min/kg)**	**$t_{1/2}$ (h)**
<3 weeks	13.22	0.50	0.34	0.95	4.80
3 to <4 weeks	13.31	0.50	0.34	1.08	4.00
4 to <6 weeks	25.06	0.49	0.33	1.17	3.62
6 weeks to <2 years	26.43	0.49	0.30	1.87	2.00
Adults	23.16	0.50	0.28	1.31	2.47

Abbreviations: CL, clearance; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; Vd, volume of distribution; $t_{1/2}$, elimination half-life.

4. Model-informed dose

With PBPK computer modeling, we simulated gentamicin plasma levels over time with various dosing strategies. We used this information to decide which dosing regimens are most appropriate for the age groups of interest.

More information on PBPK modeling and dose-finding can be found in the section Background information: Model-informed dosing of the MELINDA website.

We propose age-range appropriate dosing regimens, which are depicted in Table 3. More information on how these model-informed dosing regimens are selected can be found in the section 'Dose-finding strategy'.

Table 3. Gentamicin dosing regimen for neonates and infants as suggested by PBPK modeling

Age	**Dosing regimen as suggested by the DPF in November 2023**	**Dosing regimen as suggested by PBPK modeling**
<3 weeks	4 mg/kg every 24 hours	4 mg/kg every 48 hours
3 to <4 weeks		4 mg/kg every 36 hours
4 to <6 weeks	7 mg/kg every 24 hours	7.5 mg/kg every 36 hours
6 weeks to 2 years		7.5 mg/kg every 24 hours

Note that the dose regimens displayed here concern an intravenous infusion over 30 minutes. Abbreviations: DPF, Dutch Pediatric Formulary, PBPK, physiologically-based pharmacokinetic.

Note that dosing regimens as suggested by modeling do not necessarily represent final dosing recommendations for clinical practice. Final dosing guidelines are the result of a careful assessment of the benefits and risks of the model-informed dose in the context of all available clinical evidence and experience of healthcare providers. Consult the website of the Dutch Pediatric Formulary for gentamicin dosing recommendations for clinical practice.

5. Considerations for implementation

Implementing the model-informed dose in clinical practice is NOT STRAIGHTFORWARD. Several aspects should be taken into consideration. Using the framework below, the model-informed dose can be evaluated in the context of model extrapolation, model influence, decision consequence and practical considerations.

Framework for implementation of the model-informed dose				
Model extrapolation				
1	Are there any differences expected in drug pharmacokinetics (i.e., absorption, distribution, metabolism and excretion) between the virtual population and the real-world population intended to receive the model-informed dose? * If yes, comment on the disease, co-morbidity, treatment, etc., that is likely to affect pharmacokinetics.	Yes	**Minimal**	No
	Real-world pediatric patients intended to receive the model-informed gentamicin dose suffer from an infection and may undergo treatment that may affects the gentamicin plasma level. In these cases, the model-informed dose may not be appropriate and an adjusted dose is needed. Examples of scenarios which may require an altered gentamicin dosing regimen are given in Table 4.			
2	Are there any differences expected in drug pharmacodynamics (i.e., pharmacological effect) between the virtual population and the real-world population intended to receive the model-informed dose? * If yes, comment on how pharmacodynamics may be different in the real-world population.	Yes	Minimal	**No**
	-			
Model influence (the weight of the model in the totality of all evidence)				
3	Does the model-informed dose deviate from the dosing advice of the DPF (November 2023) or from dosing strategies applied in clinical care (incl. expert opinion, scientific clinical studies and dosing handbooks)?	**Yes**	No	
	Model simulations show that the DPF dose (November 2023) could be optimized: the dose should be increased and/or the dosing interval should be prolonged. The model-informed dosing regimen will likely result in more adequate C_{max} and C_{trough} levels in neonates and infants up to 2 years of age. The model-informed dose thus slightly deviate from the DPF doses (November 2023).			
Decision consequence (the significance of an incorrect decision)				
4	What is the level of certainty of the accuracy of the pharmacokinetic therapy goal that is used to establish the model-informed dose? #	Low	Doubtful	**High**
	There is a high level of certainty in the target concentration as the model-informed dosing recommendations provided here are based on established MIC values of micro-organisms involved in typical infections and a widely accepted target C_{max}/MIC ratio range (reported in literature). The model-informed dosing regimens for gentamicin are based on the assumptions that: 1) the micro-organism causing the infection has a certain minimum inhibitory concentration (MIC) ○ an MIC <1 mg/L in case of neonatal infections and an MIC of ≤2 mg/L in case of infections in infants up to 2 years of age and that: 2) a maximum plasma concentration (C_{max}) to MIC ratio of 8 - 10 should be reached during the dosing period for the drug to be effective. This results in a C_{max} between 8 - 12 mg/L in case of neonatal infections and a C_{max} of 15 - 20 mg/L in case of infections in infants up to 2 years of age. As such, the model-informed dose may not be appropriate when the MIC value is different (e.g., other type of micro-organism involved) and/or when the target C_{max}/MIC ratio is different (e.g., because of novel insights. The most optimal dosing regimen may in that case deviate from the model-informed dosing regimen.			

5	Is the risk at and consequences of under- or overdosing deemed acceptable?	No	Doubtful	**Yes**
	High gentamicin C_{trough} levels (>1 mg/L) may result in nephrotoxicity. Also, ototoxicity is of concern when high plasma levels are reached. Though, the relationship between a high C_{trough} and ototoxicity is weak [19]. Despite the fact that there is a higher chance of pediatric patients having C_{trough} levels that are too high as compared to suboptimal C_{max} levels, the chance remains small. Our proposed model-informed doses likely result in an adequate C_{max} and C_{trough} in the vast majority of the patients. Patient-specific conditions may, however, cause higher-than-expected C_{trough} levels and the prescribing physician should be that a different dose may be needed in such cases (Table 4).			
6	Is it possible to monitor exposure (e.g., with TDM or a clinical measurable effect) to assess whether the dose is adequate?	No		**Yes**
	TDM of gentamicin plasma levels is routinely conducted and the dose can be adjusted if deemed necessary [8].			
7	Is it practical and feasible to administer the model-informed dose? Take into account the drug formulation, difficulty of dose calculation, and excipient safety.	No		**Yes**
	The model-informed dose is practical, but entails dosing recommendations for four pediatric age groups (<3 weeks, 3 to <4 weeks, 4 to <6 weeks, 6 weeks to 2 years) instead of two (term neonate vs. children 1 month to 12 years of age).			

* Note that in this study, model-informed dosing regimens are established based on *healthy* pediatric physiology. These doses are hence most optimal for pediatric subjects that do *not* suffer from any condition (e.g., comorbidity and/or treatment) that may impact gentamicin plasma levels. If an effect of the patient's condition(s) on the gentamicin plasma level is expected, an adaptation of the model-informed dose may be needed to reach the desired plasma concentration.

The most optimal dosing regimen is the regimen that results in an effective and safe plasma level. In some cases, knowledge is limited and there is either a minimum or a maximum plasma level to target (instead of a full therapeutic range). The level of evidence supporting the validity of the pharmacokinetic therapy goal may differ (e.g., based on *in vitro* fundamental research or based on a large *in vivo* clinical study).

Abbreviations: C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; DPF, Dutch Pediatric Formulary; MIC, minimum inhibitory concentration; TDM, therapeutic drug monitoring.

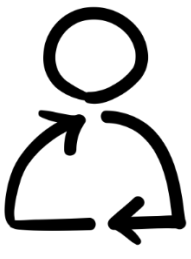
Patient-specific characteristics and conditions may require an altered dose

In addition to interpatient biological variability, conditions such existing comorbidities and/or treatment may influence gentamicin plasma levels. Table 4 shows examples of scenarios which may cause an altered plasma concentration and therefore require a dosing regimen that deviates from the model-informed dosing regimen. Other conditions that may impact PK, such as augmented clearance in critically ill patients, dehydration/hypovolemia and congenital heart disease, can generally be scrutinized by TDM.

Whether the treated condition of the real-life patients affect the gentamicin plasma level, and hence warrant a dose adjustment, should be evaluated on a case-by-case basis by the clinical team, as this depends on the severity of infection and type of treatment.

Table 4. Scenarios potentially resulting in an altered gentamicin plasma concentration

Decreased plasma concentration?
Renal replacement therapy
Increased plasma concentration?
Acute kidney injury
Therapeutic hypothermia
Extracorporeal membrane oxygenation (ECMO)*



It should be noted that a higher volume of distribution is accompanied by a decrease in clearance in case of ECMO, which complicates dosing.

6. Relevant literature

PBPK modeling studies

PubMed, 11 Oct 2023: **9**

1. Zazo et al. *Physiologically-based pharmacokinetic modelling and dosing evaluation of gentamicin in neonates using PhysPK.* Front Pharmacol. 2022 Sep 28;13:977372. doi: 10.3389/fphar.2022.977372. PMID: 36249803. Link.
2. Ferreira et al. *PBPK modeling and simulation of antibiotics amikacin, gentamicin, tobramycin, and vancomycin used in hospital practice.* Life (Basel). 2021 Oct 23;11(11):1130. doi: 10.3390/life11111130. PMID: 34833005. Link.
3. Neeli et al. *Application of physiologically based pharmacokinetic-pharmacodynamic modeling in preterm neonates to guide gentamicin dosing decisions and predict antibacterial effect.* J Clin Pharmacol. 2021 Oct;61(10):1356-1365. doi: 10.1002/jcph.1890. PMID: 33945155. Link.
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10. De Hoop-Sommen et al. *Pragmatic physiologically-based pharmacokinetic modeling to support clinical implementation of optimized gentamicin dosing in term neonates and infants: proof-of-concept.* Front Pediatr. 2023 Nov 21:11:1288376. doi: 10.3389/fped.2023.1288376. PMID: 38078320. Link.
    The publication of this dose-finding study.

Other relevant papers

While many studies focused on gentamicin dosing in preterm neonates, data on the use of gentamicin in term neonates and young infants were more scarce.

Two review papers on gentamicin in neonates and infants:

- Crcek et al. *A review of population pharmacokinetic models of gentamicin in paediatric patients.* J Clin Pharm Ther. 2019;44(5):659-74. doi: 10.1111/jcpt.12850. PMID: 31102287. Link.
- Kato et al. *Gentamicin pharmacokinetics and optimal dosage in infant patients: A case report and literature review.* Int J Environ Res Public Health. 2022;19(22). doi: 10.3390/ijerph192215360. PMID: 36430078. Link.

Four Pop-PK studies on gentamicin in neonates and infants:

- Alsultan et al. *Optimizing gentamicin dosing in pediatrics using Monte Carlo simulations.* Pediatr Infect Dis J. 2019;38(4):390-5. doi: 10.1097/INF.0000000000002120. PMID: 30882729. Link.
- Bijleveld et al. *Population pharmacokinetics and dosing considerations for gentamicin in newborns with suspected or proven sepsis caused by gram-negative bacteria.* Antimicrob Agents Chemother. 2017;61(1). doi: 10.1128/AAC.01304-16. PMID: 27795373. Link.
- Ghoneim et al. *Optimizing gentamicin dosing in different pediatric age groups using population pharmacokinetics and Monte Carlo simulation.* Ital J Pediatr. 2021;47(1):167. doi: 10.1186/s13052-021-01114-4. PMID: 34362436. Link.
- Valitalo et al. *Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates.* J Antimicrob Chemother. 2015;70(7):2074-7. doi: 10.1093/jac/dkv052. PMID: 25766737. Link.

7. Abbreviations and references

Abbreviations

AUC	area under the curve
CL	clearance
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration
MID	model-informed dose
MIC	minimum inhibitory concentration
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PNA	postnatal age
TDM	therapeutic drug monitoring
Vd	volume of distribution

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