

# Population pharmacokinetic and pharmacodynamic analysis of amikacin and gentamicin in hospitalised neonates: a comparative simulation study from two tertiary hospitals in Ghana

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## Research Article

**Keywords:** Neonatal Sepsis, Aminoglycosides, Population Pharmacokinetics, Monte Carlo Simulation, Probability of Target Attainment, Antimicrobial Resistance, Ghana, Resource-Limited Settings

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# Population pharmacokinetic and pharmacodynamic analysis of amikacin and gentamicin in hospitalised neonates: a comparative simulation study from two tertiary hospitals in Ghana

**Running title:** *Neonatal aminoglycoside pharmacokinetics in Ghana*

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## Abstract

### *Background*

Neonatal sepsis accounts for 17–29% of neonatal deaths in sub-Saharan Africa, where the neonatal mortality rate remains approximately 27 deaths per 1,000 live births. In Ghana, infection causes approximately 31% of neonatal deaths. Aminoglycosides are central to empirical management, yet gentamicin resistance among the predominant neonatal pathogen *Klebsiella pneumoniae* now exceeds 90% in Ghanaian NICUs, while therapeutic drug monitoring is unavailable in most neonatal units. No comparative PK/PD analysis of gentamicin and amikacin has previously been conducted in this setting.

### *Methods*

A retrospective cross-sectional study was conducted at two tertiary hospitals in Ghana (37 Military Hospital and University Hospital, KNUST). Population pharmacokinetic modelling and Monte Carlo simulations (n = 500 per regimen) were performed using Pumas.jl (v2.6.0) in Julia. Efficacy was quantified as the probability of target attainment (PTA;  $C_{max}/MIC \geq 8$ ) and safety was assessed using trough concentration thresholds for each drug.

## ***Results***

Amikacin clearance was 0.0492 mL/min (95% CI 0.0430–0.0577) and volume of distribution was 0.865 L (95% CI 0.808–0.918). Gentamicin clearance was 0.0439 mL/min (95% CI 0.0398–0.0483) with volume of distribution 0.837 L (95% CI 0.797–0.877). Both parameters were strongly influenced by body weight and maturational age. Amikacin 7.5 mg/kg q12h achieved PTA  $\approx$ 64% at MIC 2 mg/L with 2% trough toxicity risk; gentamicin 4 mg/kg q24h achieved 100% PTA at MIC  $\leq$ 1 mg/L with 6% trough toxicity risk. Amikacin demonstrated superior pharmacodynamic coverage at higher MIC thresholds.

## ***Conclusions***

Aminoglycoside pharmacokinetics in Ghanaian neonates are substantially shaped by body size and renal maturation. Simulation-derived dosing benchmarks support a risk-stratified approach: gentamicin 4 mg/kg q24h for susceptible organisms and amikacin 7.5 mg/kg q12h where resistance is suspected. Integration of these findings into neonatal antimicrobial stewardship programmes offers a practical pathway to improving sepsis outcomes in resource-limited settings.

**Keywords:** Neonatal Sepsis; Aminoglycosides; Population Pharmacokinetics; Monte Carlo Simulation; Probability of Target Attainment; Antimicrobial Resistance; Ghana; Resource-Limited Settings

## Background

Neonatal sepsis is a major cause of infant mortality worldwide, responsible for an estimated 375,000 neonatal deaths annually and accounting for 17–29% of all neonatal deaths in sub-Saharan Africa (SSA).<sup>1,2</sup> The neonatal mortality rate in SSA remains approximately 27 deaths per 1,000 live births more than double the global target set by the Sustainable Development Goals with infection as the leading cause.<sup>3</sup> In Ghana specifically, infection accounts for approximately 31% of neonatal deaths, and a recent institutional cohort study reported a neonatal sepsis prevalence of 59% among admitted neonates at a Ghanaian tertiary hospital, with early- and late-onset sepsis contributing almost equally.<sup>4</sup> Despite decades of progress in reducing under-five mortality, neonatal sepsis continues to impede gains in neonatal survival, and the burden of disability-adjusted life years attributable to neonatal infection in SSA has been estimated at 5.3–8.7 million per year, representing an economic cost of up to US\$469 billion.<sup>5</sup> Effective, evidence-based antibiotic therapy therefore represents one of the highest-impact interventions available to reduce neonatal mortality in the region.

In resource-limited settings, empirical antibiotic therapy is initiated before microbiological confirmation, placing critical reliance on standardised treatment protocols. Despite the growing challenge of antimicrobial resistance (AMR), the World Health Organization (WHO) continues to recommend a combination of a  $\beta$ -lactam antibiotic and gentamicin as first-line therapy for neonatal sepsis.<sup>6</sup> However, this recommendation is increasingly undermined by the regional AMR landscape. Surveillance data from Ghanaian NICUs have documented gentamicin resistance rates of 91.8% among *Klebsiella pneumoniae* the predominant neonatal bloodstream pathogen while amikacin resistance in the same organism remained substantially lower at 16.4%.<sup>7</sup> A 2024 systematic review of Enterobacterales infections across sub-Saharan African children confirmed that resistance of *Klebsiella* spp. to gentamicin has increased significantly and progressively over the period 2004–2022 ( $p < 0.01$ ), with amikacin identified as a potential alternative that could help preserve carbapenem use.<sup>8</sup> These findings raise urgent questions about the continued adequacy of the WHO-recommended first-line regimen in the Ghanaian NICU context, and underscore the need for evidence-based, locally contextualised guidance on aminoglycoside selection.

Aminoglycosides, particularly gentamicin and amikacin, remain cornerstone agents for Gram-negative neonatal sepsis owing to their concentration-dependent bactericidal activity, low cost, and broad availability in resource-limited settings.<sup>9</sup> Achieving peak plasma concentrations ( $C_{\max}$ )

substantially exceeding the minimum inhibitory concentration (MIC) is essential for efficacy,<sup>10,11</sup> while excessive trough concentrations drive nephrotoxicity and ototoxicity through accumulation in renal tubular cells and cochlear hair cells.<sup>12,13</sup> The toxicity risk is disproportionately elevated in neonates: a hospital-based East African study found that low birth weight neonates were 4.73 times more likely to develop aminoglycoside-associated nephrotoxicity than normal birth weight neonates (95% CI 1.8–12.5,  $p = 0.002$ ), and those with concurrent sepsis faced a 4.91-fold greater risk of acute kidney injury.<sup>14</sup> Therapeutic drug monitoring (TDM) is the standard approach to navigating this narrow therapeutic window, yet it is largely unavailable across Ghanaian and broader West African neonatal units, meaning that toxic exposure frequently goes undetected.<sup>15</sup>

The pharmacokinetic challenge of aminoglycoside therapy in neonates is compounded by the profound physiological variability of this population. Gestational age, postnatal age, body weight, and the maturation of glomerular filtration rate collectively determine aminoglycoside clearance and distribution,<sup>16,17</sup> rendering fixed weight-band dosing regimens inherently imprecise. This variability is particularly pronounced in West African neonatal populations, which have a high prevalence of low birth weight (LBW) and very low birth weight (VLBW) neonate subgroups in whom renal clearance is most immature, inter-individual pharmacokinetic variability is widest, and the risk of both subtherapeutic and toxic exposure is greatest. Yet despite the widespread use of aminoglycosides across this region, population pharmacokinetic (PopPK) data from Ghanaian or broader West African neonatal populations remain sparse. Critically, no comparative pharmacokinetic and pharmacodynamic (PK/PD) analysis of both gentamicin and amikacin has previously been conducted in this setting a gap that prevents quantitative evaluation of whether current dosing practices are achieving adequate coverage against the resistance profiles now prevalent in Ghanaian NICUs.

Population pharmacokinetic modelling and Monte Carlo simulation provide established quantitative frameworks for characterising drug disposition, evaluating covariate effects, and estimating the probability of target attainment (PTA) across heterogeneous populations,<sup>18,19,20</sup> including neonates where sparse sampling is the clinical norm.<sup>21</sup> Model-informed precision dosing (MIPD), whereby individual pharmacokinetic parameters are estimated and doses adjusted accordingly, has been shown to substantially improve target attainment in neonates: in one prospective validation study, application of MIPD improved achievement of a therapeutic target from 37% with standard dosing to 62%.<sup>22</sup> However, MIPD requires access to TDM infrastructure

that is largely unavailable in resource-limited settings. Simulation-based pharmacometric analyses therefore offer a practical intermediate: by generating population-level PTA and toxicity risk estimates from existing clinical covariate data, they can provide evidence-based dosing guidance without the need for measured drug concentrations. The Julia-based Pumas.jl platform has further enhanced the accessibility, efficiency, and reproducibility of these analyses in low-resource settings.<sup>23,24</sup>

Against this background, the present study addresses the following research gaps: (i) the absence of comparative PopPK/PD data for gentamicin and amikacin in Ghanaian neonates; (ii) the lack of simulation-based evaluation of whether current dosing practices achieve therapeutic targets against the MIC distribution now prevalent among Ghanaian neonatal pathogens; and (iii) the need for pharmacometrically-derived, locally-contextualised dosing guidance that can be applied at the bedside without TDM infrastructure. We applied a Monte Carlo simulation-based PopPK approach, integrating locally collected clinical data with published regional population models, to compare the pharmacokinetic performance of gentamicin and amikacin and to generate actionable, evidence-based dosing benchmarks for neonatal sepsis management in resource-limited West African NICUs.

## **Methods**

### ***Ethics approval***

Ethical approval for this retrospective study was obtained from the Research Ethics Committee of the University of Health and Allied Sciences (UHAS) for both participating sites: 37 Military Hospital (UHAS-REC A.7[44]22-23) and University Hospital, KNUST (UHAS-REC A.7[52]22-23). All data were de-identified prior to analysis. As this was a retrospective study involving only anonymised, routinely collected clinical data, the ethics committee waived the requirement for individual written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Clinical trial number: not applicable.

### ***Study design and setting***

A retrospective cross-sectional study was conducted at two tertiary hospitals in Ghana: 37 Military Hospital (37MH), Accra, and the University Hospital (UH), KNUST, Ho. Data were collected

from neonates admitted to the paediatric emergency unit (PEU) or neonatal intensive care unit (NICU) of either site between 1 January 2019 and 31 December 2022.

### ***Study population***

Neonates aged 0–28 days with a working diagnosis of bacterial sepsis who received gentamicin or amikacin were eligible. Neonates with concomitant diagnoses other than sepsis or with incomplete medical records were excluded. Convenience sampling was used. Of 641 neonates admitted to the PEU and NICU across the review period, 190 were diagnosed with neonatal sepsis in the reference year (October 2021–October 2022); the study targeted review of more than 50% of patients across the full four-year period.

### ***Data collection***

Eligible participants were identified from hospital electronic medical records (EMR) and de-identified. Demographic and clinical data including gestational age, postnatal age, body weight, Apgar scores, and antibiotic received were collected using Kobo Toolbox. No plasma concentration measurements were performed; the study relied on simulation-based methods with locally collected clinical covariates.

### ***Pharmacometric simulations***

All analyses were performed using Pumas.jl (version 2.6.0) in the Julia 1.10.5 environment.<sup>24,25,26</sup> Descriptive statistics and graphical outputs were generated in R (version 4.3.0; R Foundation for Statistical Computing, Vienna, Austria). Three interdependent analytical components were applied: (i) comparative dose regimen analysis; (ii) individual pharmacokinetic parameter estimation; and (iii) dual-drug comparative analysis with bootstrap confidence intervals.

### ***Population pharmacokinetic models***

Two established one-compartment PopPK models were employed. Amikacin parameters were derived from the Ghanaian neonatal model reported by Amponsah et al.<sup>27</sup> Gentamicin pharmacokinetics were described using a sub-Saharan neonatal model incorporating allometric

weight scaling (exponent 0.75) and maturation of renal clearance using the Rhodin function, as reported by Bos et al.<sup>28</sup>

### ***Simulation design and PK/PD targets***

Monte Carlo simulations used 500 virtual neonates per regimen. Amikacin regimens evaluated: 7.5 mg/kg q12h, 7.5 mg/kg q24h, 10 mg/kg q12h, and 10 mg/kg q24h. Gentamicin regimens: 3, 4, and 5 mg/kg at dosing intervals of 18–24 h. MIC values were derived from the 2024 EUCAST clinical breakpoints for Enterobacterales. For gentamicin, MIC<sub>50</sub> of 1 mg/L and MIC<sub>90</sub> of 4 mg/L were used, consistent with Ghanaian surveillance data.<sup>26</sup> Efficacy was defined as PTA ( $C_{\max}/\text{MIC} \geq 8$ ). Safety thresholds were trough  $>2$  mg/L (gentamicin) and  $>5$  mg/L (amikacin).

### ***Individual parameter estimation***

Subject-specific clearance (CL) and volume of distribution (V) were estimated from pseudo-clinical data generated from simulated population variability, using a one-compartment model with BFGS optimisation. Subjects required at least two concentration measurements and one dosing event for inclusion.

### ***Covariate analysis and weight stratification***

Subjects were stratified by WHO birth weight category: very low birth weight (VLBW,  $<1.5$  kg), low birth weight (LBW,  $1.5$ – $2.5$  kg), and normal birth weight (NBW,  $>2.5$  kg). Covariate effects on CL and V were evaluated using log-linear regression. Parameter uncertainty was assessed by stratified bootstrap (1000 iterations) to derive 95% confidence intervals (CI).

### ***Model evaluation***

Model performance was assessed using standard goodness-of-fit diagnostic plots (observed vs predicted concentrations, residual plots). All models converged without boundary estimates; relative standard errors (RSE) were below 20% for all parameters.

## Results

### *Study population*

The final dataset comprised 122 neonates: 44 amikacin-treated and 78 gentamicin-treated. Demographic and covariate characteristics are summarised in Table 1.

**Table 1 Study population demographics**

| Parameter                               | Amikacin (n=44)  | Gentamicin (n=78) |
|-----------------------------------------|------------------|-------------------|
| Gestational age, median (range) [weeks] | 38 (28–42)       | 39 (35–41)        |
| Postnatal age, median (range) [days]    | 2 (1–22)         | 2 (1–27)          |
| Sex (female), n (%)                     | 20 (45.5)        | 37 (47.4)         |
| Body weight, median (range) [g]         | 2000 (1000–4000) | 2000 (1000–4000)  |
| Samples per patient, median (range)     | 1 (1–1)          | 1 (1–1)           |

*Each neonate contributed a single aminoglycoside concentration measurement (sparse sampling design).*

### *Dose regimen simulations*

Monte Carlo simulations demonstrated distinct efficacy–safety profiles across regimens (Tables 2 and 3; Figures 1–5). For amikacin, 7.5 mg/kg q12h provided the most favourable balance, achieving PTA  $\approx$ 64% at MIC 2 mg/L with 2.4% trough toxicity risk. Higher doses improved PTA at elevated MICs but increased toxicity risk (10 mg/kg q12h: 7.1% trough risk). For gentamicin, all evaluated regimens achieved 100% PTA at MIC  $\leq$ 1 mg/L. The 4 mg/kg q24h regimen provided the most balanced profile (6.0% trough risk), whereas intensified regimens substantially increased predicted trough-associated toxicity (5 mg/kg q18h: 58.3%).

**Table 2 Amikacin dosing regimens: probability of target attainment and predicted toxicity risk**

| Regimen        | Optimal | C <sub>max</sub> <sup>1</sup> (mg/L) | C <sub>min</sub> <sup>2</sup> (mg/L) | PTA MIC 2 | PTA MIC 4 | Trough risk <sup>3</sup> (%) |
|----------------|---------|--------------------------------------|--------------------------------------|-----------|-----------|------------------------------|
| 7.5 mg/kg q12h | ✓       | 18.52                                | 1.98                                 | 0.635     | 0.082     | 2.4                          |
| 7.5 mg/kg q24h | —       | 12.01                                | 0.91                                 | 0.294     | 0.012     | 0.0                          |
| 10 mg/kg q12h  | —       | 24.85                                | 2.82                                 | 0.918     | 0.247     | 7.1                          |
| 10 mg/kg q24h  | —       | 16.47                                | 1.31                                 | 0.541     | 0.047     | 0.0                          |

<sup>1</sup> Median simulated peak concentration; <sup>2</sup> Median simulated trough concentration; <sup>3</sup> Percentage of virtual neonates with trough  $>5$  mg/L. PTA, probability of target attainment ( $C_{\text{max}}/\text{MIC} \geq 8$ ); q12h, twice daily; q24h, once daily.

**Table 3 Gentamicin dosing regimens: probability of target attainment and predicted toxicity risk**

| Regimen      | Optimal | C <sub>max</sub> (mg/L) | C <sub>min</sub> (mg/L) | PTA MIC 0.5 | PTA MIC 1 | Trough risk (%) |
|--------------|---------|-------------------------|-------------------------|-------------|-----------|-----------------|
| 4 mg/kg q24h | ✓       | 19.56                   | 0.90                    | 1.00        | 1.00      | 6.0             |
| 3 mg/kg q24h | —       | 15.08                   | 0.85                    | 1.00        | 1.00      | 1.2             |
| 5 mg/kg q24h | —       | 25.46                   | 1.45                    | 1.00        | 1.00      | 23.8            |
| 5 mg/kg q18h | —       | 27.83                   | 2.23                    | 1.00        | 1.00      | 58.3            |

*Trough risk: percentage of virtual neonates with trough >2 mg/L. PTA, probability of target attainment ( $C_{max}/MIC \geq 8$ ); q24h, once daily; q18h, every 18 h.*

### ***Pharmacokinetic parameters and bootstrap analysis***

Bootstrap resampling (1000 iterations) confirmed stable parameter estimates for both drugs (Figure 6; Table 4). Amikacin CL was 0.0492 mL/min (95% CI 0.0430–0.0577) with IIV of 38.5%; V was 0.865 L (95% CI 0.808–0.918; IIV 42.1%). Gentamicin CL was 0.0439 mL/min (95% CI 0.0398–0.0483; IIV 35.2%) and V was 0.837 L (95% CI 0.797–0.877; IIV 39.8%). All RSE values were below 10%.

**Table 4 Final model parameter estimates with bootstrap 95% confidence intervals**

| Drug       | Parameter | Estimate | RSE (%) | IIV (%) | 95% CI        | Units  |
|------------|-----------|----------|---------|---------|---------------|--------|
| Amikacin   | CL        | 0.0492   | 8.2     | 38.5    | 0.0430–0.0577 | mL/min |
|            | V         | 0.865    | 6.5     | 42.1    | 0.808–0.918   | L      |
| Gentamicin | CL        | 0.0439   | 9.1     | 35.2    | 0.0398–0.0483 | mL/min |
|            | V         | 0.837    | 7.2     | 39.8    | 0.797–0.877   | L      |

*CL, clearance; V, volume of distribution; RSE, relative standard error; IIV, inter-individual variability; CI, confidence interval.*

CL increased with gestational and postnatal age (Figures 7–9), while V scaled primarily with body size (Figures 10–12). Weight-normalised CL estimates were 0.092 L/h/kg (amikacin; 95% CI 0.077–0.104) and 0.069 L/h/kg (gentamicin; 95% CI 0.054–0.082). Strong allometric scaling of CL was observed (weight exponent  $\approx 0.75$ ;  $R^2 = 0.78$ ). CL increased nonlinearly with postmenstrual age, approaching a plateau at approximately 38 weeks, consistent with neonatal renal maturation patterns (Figures 13–15).

## Discussion

Neonatal sepsis remains a leading cause of morbidity and mortality globally, with a disproportionate burden in low- and middle-income countries, including those in sub-Saharan Africa. In Ghana, the scale of the problem is acute: of 5,416 neonates admitted to two tertiary NICUs in a recent multisite surveillance study, nearly one in five (19.7%) died, with bloodstream infection independently associated with mortality.<sup>7</sup> The predominant neonatal pathogen identified was *Klebsiella pneumoniae*, which accounted for nearly 50% of confirmed bloodstream isolates and critically exhibited gentamicin resistance rates of 91.8% yet retained substantially lower resistance to amikacin (16.4%).<sup>7</sup> This stark contrast between gentamicin and amikacin susceptibility profiles among the most prevalent Ghanaian neonatal pathogen forms a critical epidemiological backdrop for the present pharmacometric analysis and directly motivates the comparative evaluation of both agents. A 2024 systematic review and meta-analysis across sub-Saharan Africa further confirmed that resistance of *Klebsiella* spp. to gentamicin has increased significantly across successive time periods from 2004 to 2022 ( $p < 0.01$ ), whereas amikacin resistance, though rising in neonates, remained substantially lower.<sup>8</sup> These regional trends reinforce the need for evidence-based, pharmacometrically informed dosing guidance to preserve the clinical utility of both agents in West African NICUs.

This study provides the first comparative PopPK/PD analysis of gentamicin and amikacin in Ghanaian neonates. Consistent with established developmental pharmacokinetic principles,<sup>29,30,31</sup> both CL and V were strongly shaped by body weight and maturational age, confirming that uniform dosing approaches are inadequate for a neonatal population characterised by wide physiological variability. Notably, the weight-normalised clearance estimates derived for Ghanaian neonates (amikacin: 0.092 L/h/kg; gentamicin: 0.069 L/h/kg) were broadly comparable to values reported from other sub-Saharan African paediatric populations, suggesting that published regional models may be reasonably transferable within West Africa, while still underscoring the need for locally validated dosing frameworks that account for the specific physiological profile of Ghanaian neonates, including the high prevalence of low and very low birth weight observed in this cohort.

The simulations revealed that regimen selection critically determines both efficacy and toxicity-related exposure. For amikacin, 7.5 mg/kg q12h achieved the most favourable efficacy–toxicity balance, maintaining adequate target attainment at clinically relevant MIC values while

minimising trough accumulation (Table 2; Figure 1). Extended-interval dosing resulted in reduced PTA, whereas higher-dose regimens improved antibacterial exposure at the cost of increased predicted toxicity risk (Figures 3 and 5). For gentamicin, all evaluated regimens achieved full target attainment at  $\text{MIC} \leq 1 \text{ mg/L}$ , indicating preserved activity against susceptible organisms. However, increasing dose intensity was associated with a progressive rise in trough concentrations, narrowing the therapeutic margin (Table 3; Figures 2 and 4). The 4 mg/kg every 24 h regimen provided the most balanced profile, supporting its continued use in this setting. These findings have a direct translation to NICU prescribing practice. At both 37 Military Hospital and the University Hospital KNUST, aminoglycosides are administered according to fixed weight-band protocols without access to routine TDM or real-time pharmacokinetic support. A recent audit of a Ghanaian teaching hospital reported that 76.9% of neonates with suspected sepsis were treated empirically with cefuroxime plus gentamicin, with only 27% of blood cultures yielding a positive result and antibiotic selection rarely conforming to national standard treatment guidelines.<sup>32</sup> In this context, the regimen-specific PTA and toxicity profiles presented here provide actionable, quantitative benchmarks that can directly inform empirical dosing decisions at Ghanaian NICUs without requiring TDM infrastructure: specifically, gentamicin 4 mg/kg q24h for susceptible organisms ( $\text{MIC} \leq 1 \text{ mg/L}$ ) and amikacin 7.5 mg/kg q12h when a higher MIC threshold or resistant pathogen is suspected.

From a clinical perspective, these findings carry direct and actionable implications for neonatal prescribing in Ghanaian and West African NICUs. Three structural barriers undermine optimal aminoglycoside therapy in this setting: the near-universal absence of therapeutic drug monitoring, the reliance on fixed weight-band empirical regimens that do not account for the continuous maturation of renal clearance, and the progressive erosion of gentamicin coverage due to rising resistance among the predominant neonatal pathogens. The present pharmacometric analysis addresses all three of these gaps simultaneously.

First, the simulation-derived PTA and toxicity risk profiles presented in Tables 2 and 3 constitute a practical dosing decision framework that requires no TDM infrastructure. For NICU clinicians at 37 Military Hospital and similar institutions, the data support a clear regimen hierarchy: gentamicin 4 mg/kg q24h for early-onset sepsis where susceptible Gram-negative coverage is the primary objective, and amikacin 7.5 mg/kg q12h when *Klebsiella* spp. or other organisms with higher MIC thresholds are suspected or confirmed. The latter regimen achieved a 2% trough

toxicity risk at MIC 2 mg/L a profile that is clinically acceptable in the absence of TDM, provided renal function is monitored clinically.

Second, the marked influence of body weight and gestational maturity on clearance (Figures 7–9) argues against applying uniform dosing to a neonatal population characterised by a wide birth-weight range (1,000–4,000 g in this cohort). Very low birth weight neonates, who represented a significant proportion of admissions at both study sites, had substantially lower predicted clearance values and correspondingly higher trough exposure. This subgroup faces disproportionate toxicity risk under fixed-interval protocols a risk that is currently invisible in the absence of TDM. The weight-stratified pharmacokinetic data in Figures 13 and 14 provide evidence that VLBW neonates warrant dose interval extension or dose reduction, rather than the same weight-normalised mg/kg dose applied uniformly.

Third, at an antimicrobial stewardship level, the quantitative evidence that amikacin provides superior pharmacodynamic coverage against organisms with MIC values above 1 mg/L (Table 2; Figure 1) supports a formal reassessment of the role of amikacin in Ghanaian neonatal sepsis protocols. Given that *K. pneumoniae* the dominant bloodstream pathogen in Ghanaian NICUs now shows >90% resistance to gentamicin in some settings, continuing to rely exclusively on gentamicin as first-line empirical therapy represents a pharmacodynamically and epidemiologically indefensible position.<sup>7</sup> A risk-stratified approach, reserving amikacin for neonates with risk factors for resistant pathogens (e.g. late-onset sepsis, prior antibiotic exposure, healthcare-associated infection), would be consistent with antimicrobial stewardship principles and with the quantitative evidence generated here.

The AMR context in West Africa is no longer one of ‘emerging’ resistance it is one of established, high-level resistance that is actively compromising first-line therapy. A 2024 systematic review of Enterobacterales infections in sub-Saharan African children confirmed significant temporal increases in *Klebsiella* spp. resistant to gentamicin across successive periods from 2004 to 2022, with the greatest acceleration observed in the most recent period (2016–2022,  $p < 0.01$ ).<sup>8</sup> In Ghana specifically, the most recent multisite NICU data document gentamicin resistance among *K. pneumoniae* bloodstream isolates of 91.8%, rendering the WHO-recommended first-line regimen of ampicillin or cloxacillin plus gentamicin pharmacodynamically inadequate for the majority of Gram-negative neonatal sepsis episodes attributable to this pathogen.<sup>7</sup>

Against this backdrop, the pharmacodynamic superiority of amikacin at MIC values of 2 and 4 mg/L (Table 2; Figure 1) takes on considerable clinical significance. At MIC 2 mg/L, amikacin 7.5 mg/kg q12h achieved a PTA of 63.5%, compared with essentially no target attainment achievable with standard gentamicin regimens at equivalent MIC thresholds. The same 2024 SSA systematic review specifically highlighted that amikacin the current WHO-recommended second-line agent for neonatal sepsis in combination with cloxacillin may represent a better alternative for bloodstream infections and could help preserve carbapenem use.<sup>8</sup> The present pharmacometric data provide the quantitative dosing evidence needed to operationalise this recommendation in the Ghanaian NICU context.

Importantly, however, the present analysis also provides a caution against uncritical escalation to higher amikacin doses. The 10 mg/kg q12h regimen, while achieving PTA of 91.8% at MIC 2 mg/L, was associated with a 7.1% trough toxicity risk a near four-fold increase over the 7.5 mg/kg q12h regimen. In a setting without routine TDM or access to nephrotoxicity biomarkers, this margin is clinically unacceptable, particularly in VLBW neonates with already compromised renal clearance. Any protocol shift from gentamicin to amikacin must therefore specify not only the preferred agent but also the specific regimen and the patient subgroup in which escalation is appropriate.

The bootstrap-derived parameter estimates were stable and internally consistent. Drug-stratified comparisons confirmed that observed differences in pharmacodynamic performance are driven primarily by regimen design rather than intrinsic differences in drug disposition, reinforcing the importance of evidence-based regimen selection.

Several limitations should be noted. The study did not include prospectively measured drug concentrations for external model validation. Reliance on published PopPK models and locally collected covariates may not fully capture all sources of variability. Microbiological data, co-administered therapies, and clinical outcome measures were not incorporated. The retrospective, sparsely sampled design limits causal inference. Finally, the absence of concurrent microbiological data from both study sites means that the MIC values used for PTA calculations were derived from published Ghanaian surveillance data rather than institution-specific susceptibility profiles. Future work should incorporate site-specific antibiograms to enable truly local calibration of target attainment thresholds.

Future research priorities should be shaped by the specific structural limitations of Ghanaian and West African NICU practice. Three concrete directions emerge from the present analysis. First, a prospective, multicentre pharmacokinetic study incorporating serial blood sampling, concurrent microbiological data, and aminoglycoside concentration measurement is needed to externally validate and locally calibrate the PopPK models applied here. This priority aligns with active regional efforts: the ICARS-supported Neonatal Infection Prevention in Ghana project is currently implementing antimicrobial stewardship (AMS) and infection prevention interventions across four hospitals in the Volta Region, providing a potential platform for embedded pharmacokinetic sub studies. Second, the development of simplified, locally validated dosing tools such as weight-band-and-age nomograms derived from the present simulation outputs, or lightweight Bayesian dosing calculators requiring only one or two concentration measurements would translate the pharmacometric evidence generated here into a form directly usable by NICU clinicians without specialist training. Such tools have been demonstrated to be feasible and impactful in other low-resource NICU settings.<sup>33</sup> Embedding these tools within the existing AMS infrastructure at 37 Military Hospital and the University Hospital KNUST would allow model-informed dosing to function as a practical complement to empirical protocols. Third, future studies should explicitly evaluate the clinical and economic impact of a risk-stratified aminoglycoside selection policy (gentamicin for early-onset sepsis with susceptible organisms; amikacin for late-onset or healthcare-associated sepsis with higher resistance risk) against the conventional universal gentamicin approach. Patient-level outcome data including treatment failure, toxicity events, length of NICU stay, and mortality would provide the clinical endpoint evidence needed to support guideline revision at the national level in Ghana.

## **Conclusions**

In conclusion, this study demonstrates that aminoglycoside pharmacokinetics in Ghanaian neonates are strongly shaped by body size and renal maturation, and that regimen selection exerts a substantial and quantifiable influence on both efficacy and toxicity-related exposure. Against a background of high-level gentamicin resistance among the predominant neonatal pathogen in Ghanaian NICUs and documented underperformance of current empirical protocols, these findings provide an evidence-based pharmacometric framework for a risk-stratified approach to aminoglycoside prescribing: gentamicin 4 mg/kg q24h for susceptible organisms, and amikacin 7.5 mg/kg q12h where resistance is suspected or confirmed. The integration of such simulation-

derived, locally contextualised dosing evidence into antimicrobial stewardship programmes and national treatment guidelines represents a practical and achievable step towards improving neonatal sepsis outcomes in resource-limited settings across West Africa.

## **List of abbreviations**

AMR, antimicrobial resistance; AUC, area under the concentration-time curve; BFGS, Broyden–Fletcher–Goldfarb–Shanno; CI, confidence interval; CL, clearance; C<sub>max</sub>, peak plasma concentration; C<sub>min</sub>, trough plasma concentration; IIV, inter-individual variability; LBW, low birth weight; MIC, minimum inhibitory concentration; NBW, normal birth weight; NICU, neonatal intensive care unit; PEU, paediatric emergency unit; PK/PD, pharmacokinetic/pharmacodynamic; PopPK, population pharmacokinetics; PTA, probability of target attainment; RSE, relative standard error; TDM, therapeutic drug monitoring; V, volume of distribution; VLBW, very low birth weight; WHO, World Health Organization.

## **Declarations**

### ***Ethics approval and consent to participate***

Ethical approval was granted by the Research Ethics Committee of the University of Health and Allied Sciences (UHAS): 37 Military Hospital (UHAS-REC A.7[44]22-23) and University Hospital, KNUST (UHAS-REC A.7[52]22-23). As a retrospective study involving only anonymised, routinely collected clinical data, the ethics committee waived the requirement for individual written informed consent. The study was conducted in accordance with the Declaration of Helsinki. Clinical trial number: not applicable.

### ***Consent for publication***

Not applicable. This manuscript does not contain data from any individual person.

### ***Availability of data and materials***

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. Patient-level data cannot be made publicly available due to ethical restrictions relating to participant confidentiality.

### ***Competing interests***

The authors declare that they have no competing interests.

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### ***Authors' contributions***

C.K.B. and P.E.Y.A. contributed equally as joint first authors; they conceived and designed the study, led the pharmacometric analyses, and drafted the manuscript. A.M., O.F.K., and C.E.A. contributed to data collection and clinical interpretation. P.A.N.A. and A.A.K. contributed to data collection and manuscript review. All authors read and approved the final manuscript.

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FIGURE LEGENDS

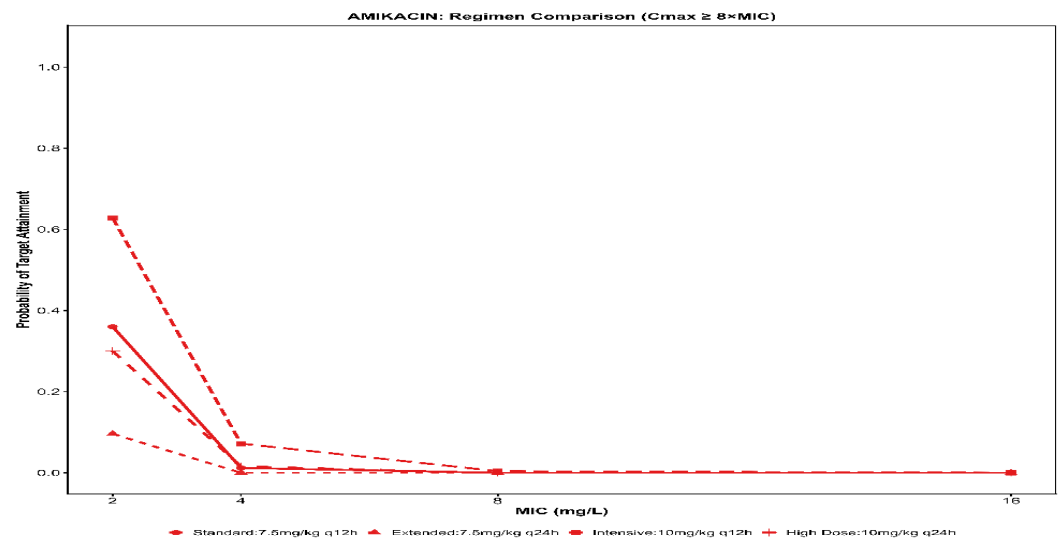


Figure 1. Probability of target attainment (PTA) versus MIC for amikacin dosing regimens. Line plots showing PTA ( $C_{max} \geq 8 \times \text{MIC}$ ) across increasing MIC values. PTA declines with increasing MIC for all regimens; higher-dose or shorter-interval regimens maintain superior target attainment at higher MICs.

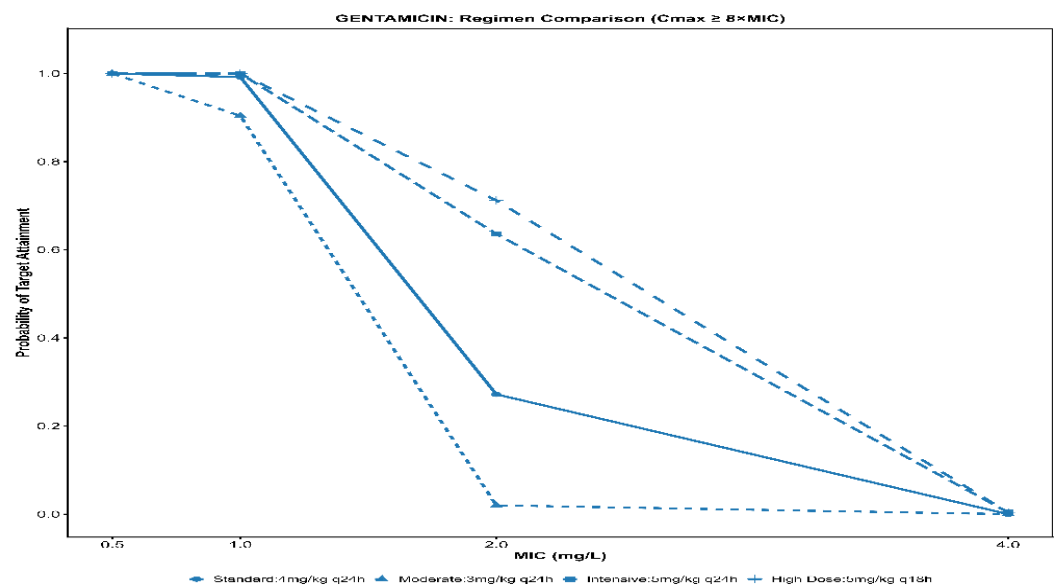


Figure 2. Probability of target attainment versus MIC for gentamicin dosing regimens. PTA decreases with increasing MIC, with intensified regimens achieving higher probabilities of target attainment at clinically relevant MIC thresholds.

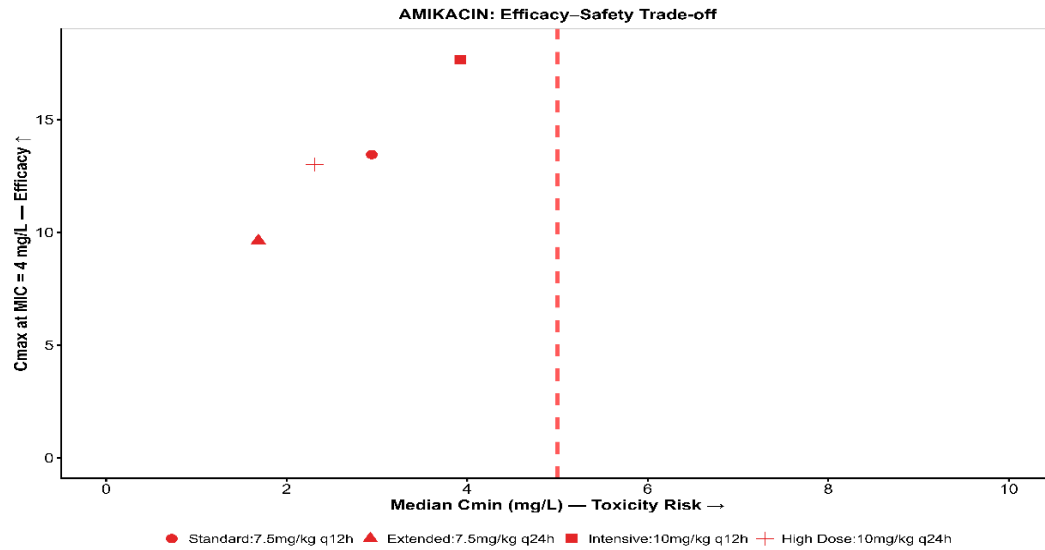


**Figure 3. Efficacy–toxicity trade-off plot for amikacin. Scatter plot of median trough concentration (Cmin) versus peak concentration at target MIC; vertical dashed line indicates the toxicity threshold.**

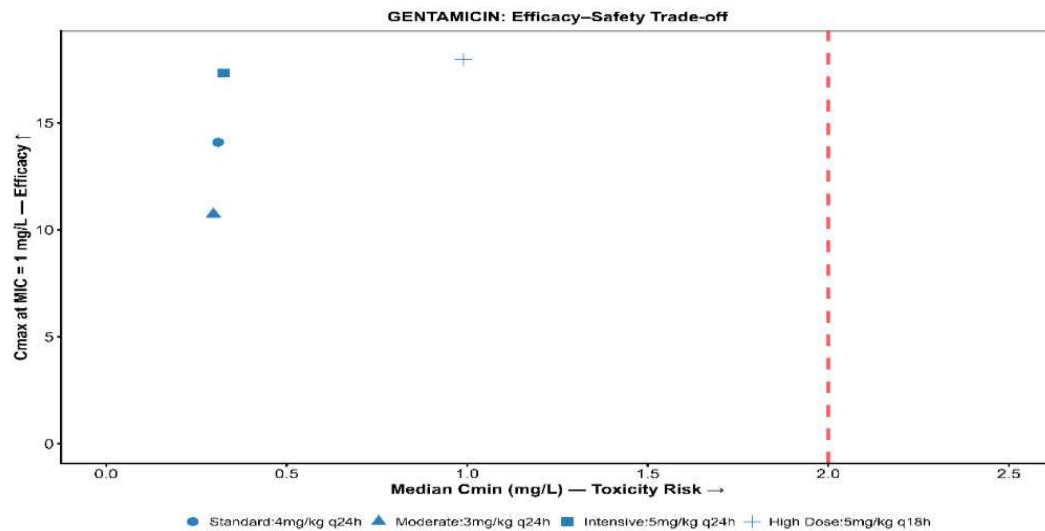


**Figure 4. Efficacy–toxicity trade-off plot for gentamicin. Scatter plot depicting the relationship between median Cmin and efficacy-related peak concentration; several regimens cluster near the toxicity threshold.**

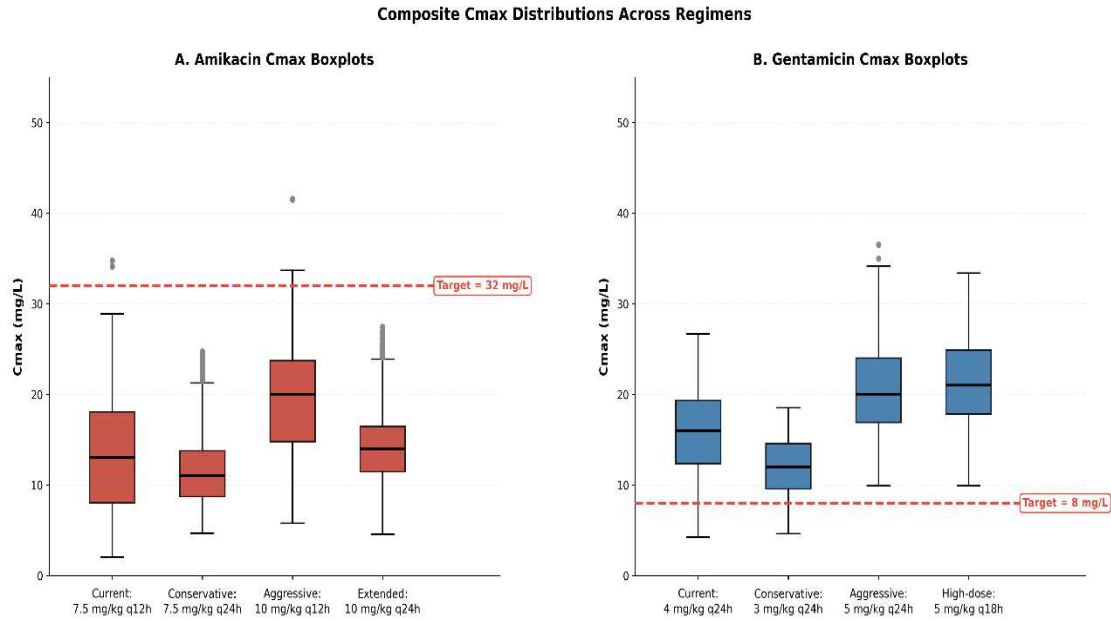


**Figure 5. Simulated peak concentration (Cmax) distributions across dosing regimens. Boxplots for amikacin and gentamicin regimens with dashed horizontal lines indicating target peak concentrations.**

**Bootstrap Distributions of CL and Vd for Amikacin and Gentamicin**

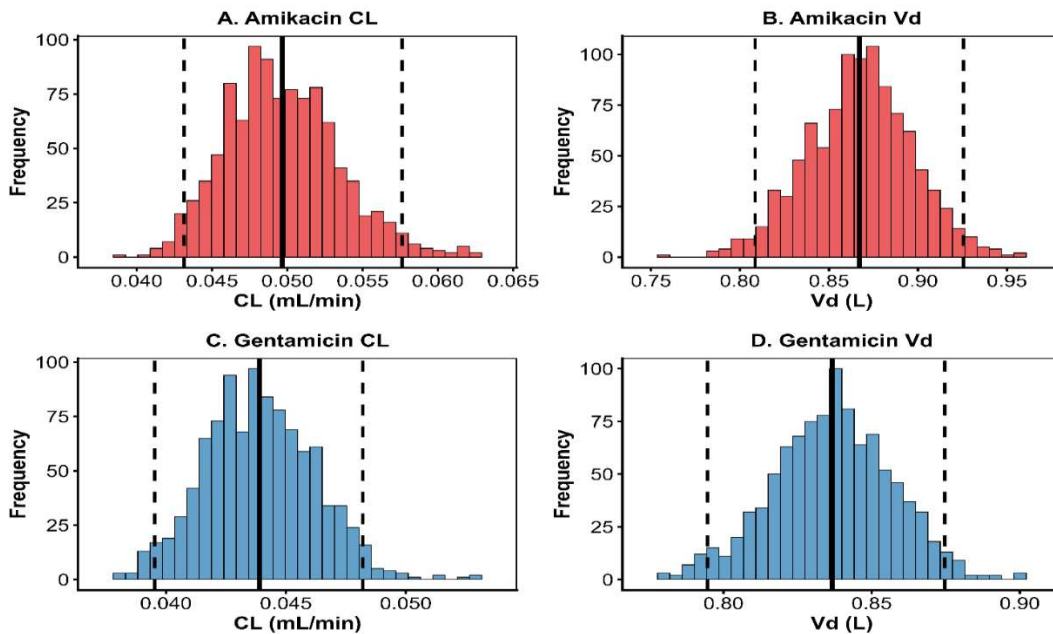


**Figure 6. Bootstrap distributions of clearance (CL) and volume of distribution (V) for amikacin and gentamicin. Histograms with overlaid density curves from 1000 bootstrap iterations; solid vertical lines indicate point estimates and dashed vertical lines represent 95% CI.**

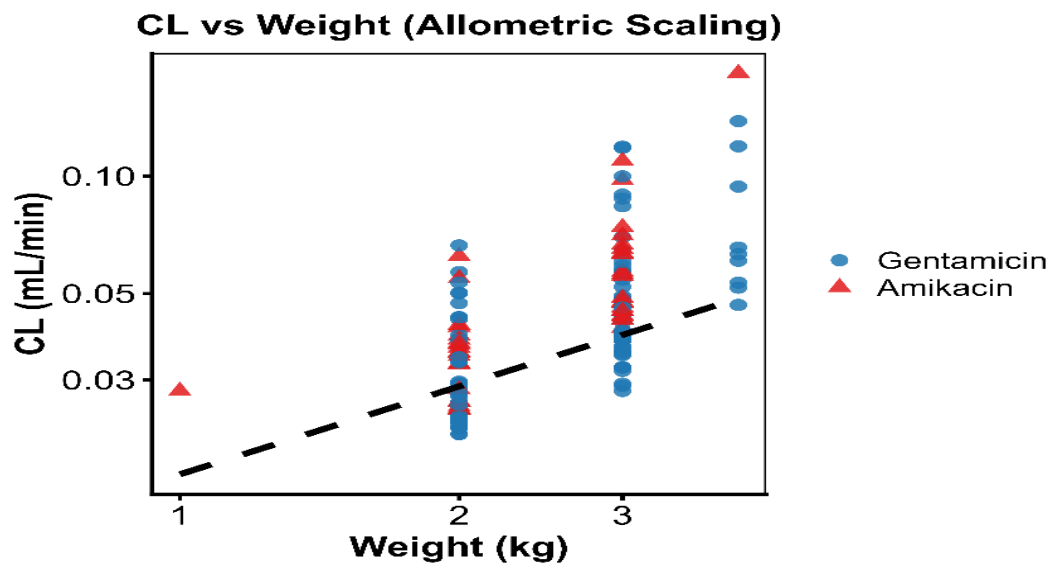


Figure 7. Log-log plot of individual clearance estimates versus body weight with the theoretical allometric reference line (exponent 0.75).

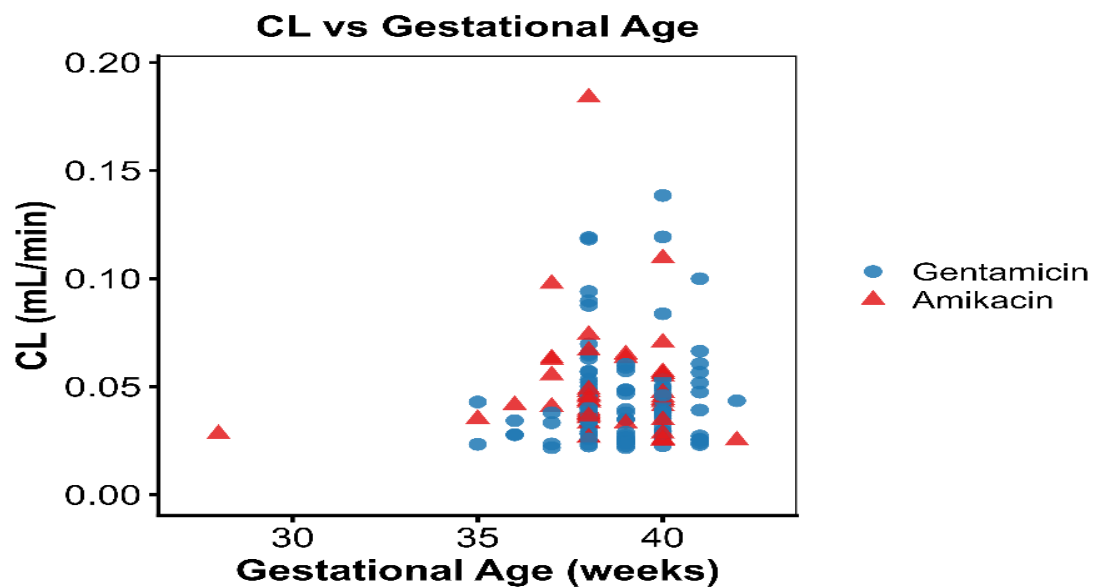


Figure 8. Scatter plot of clearance versus gestational age, showing increasing clearance with advancing gestational maturity.

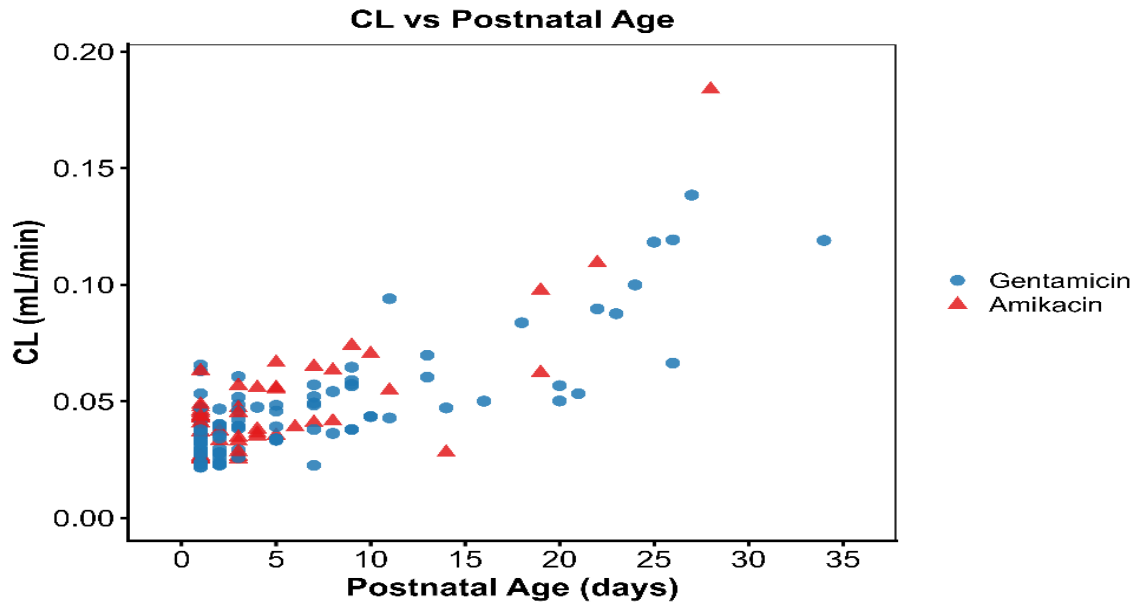


Figure 9. Scatter plot of clearance versus postnatal age, demonstrating age-related increases in clearance during early life.

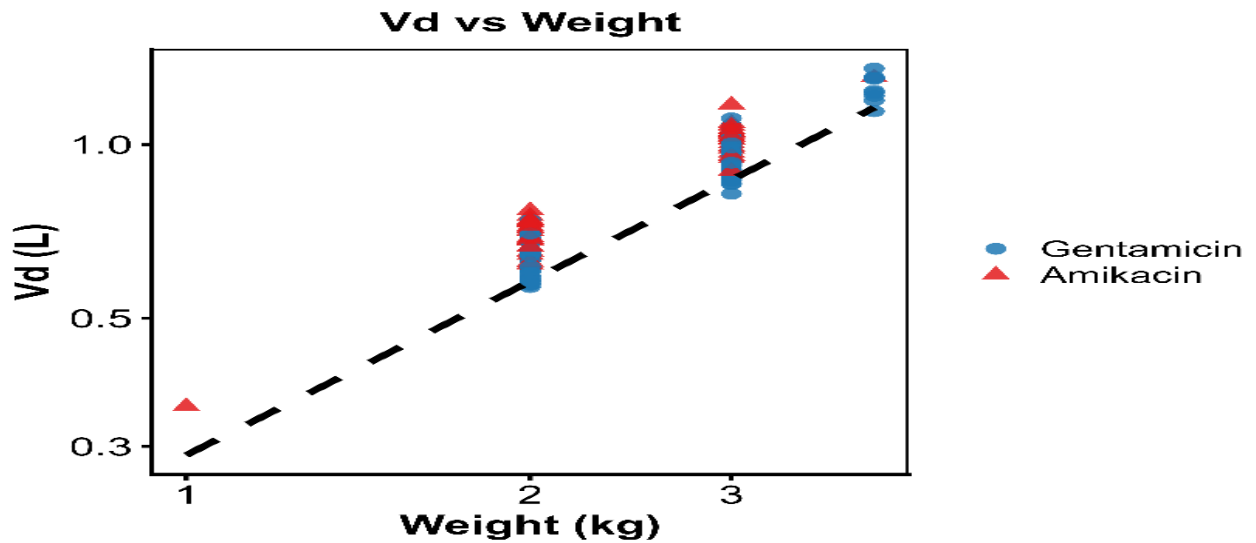


Figure 10. Log-log plot of volume of distribution versus body weight with proportional scaling (exponent 1.0).



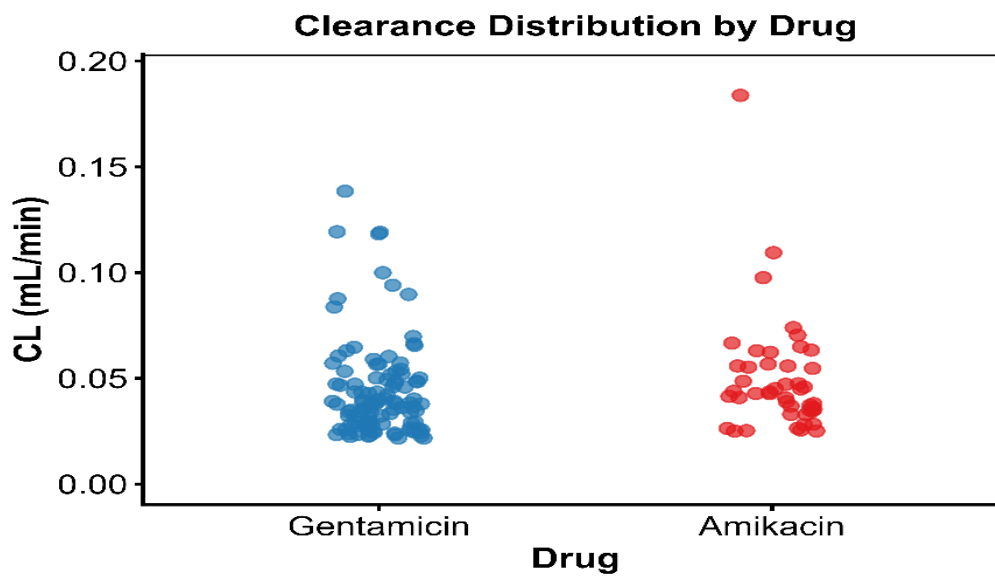


Figure 13. Jittered scatter plots of individual clearance estimate by drug with mean values indicated, showing overlapping distributions and comparable variability between gentamicin and amikacin.

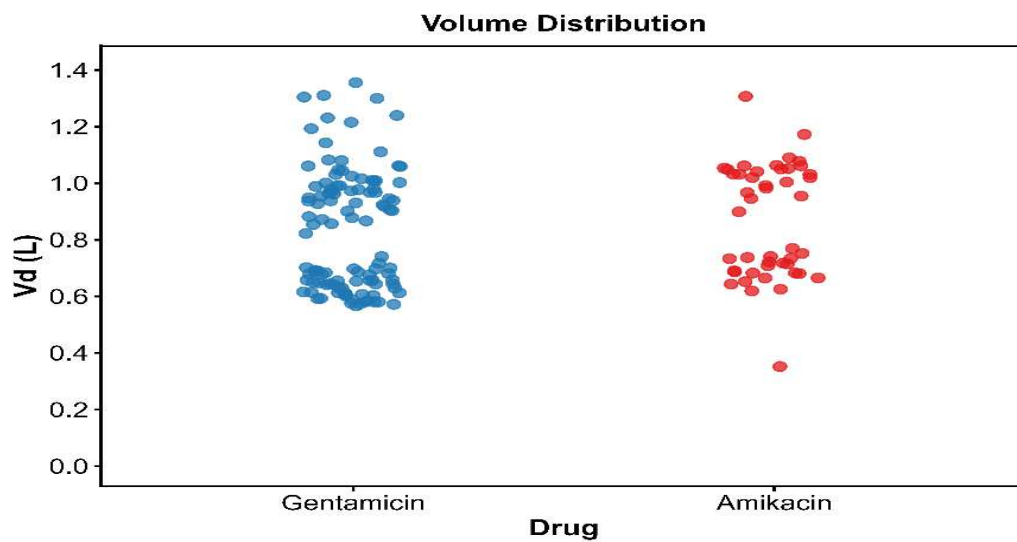


Figure 14. Jittered scatter plots of individual volume of distribution estimates by drug with mean values indicated.

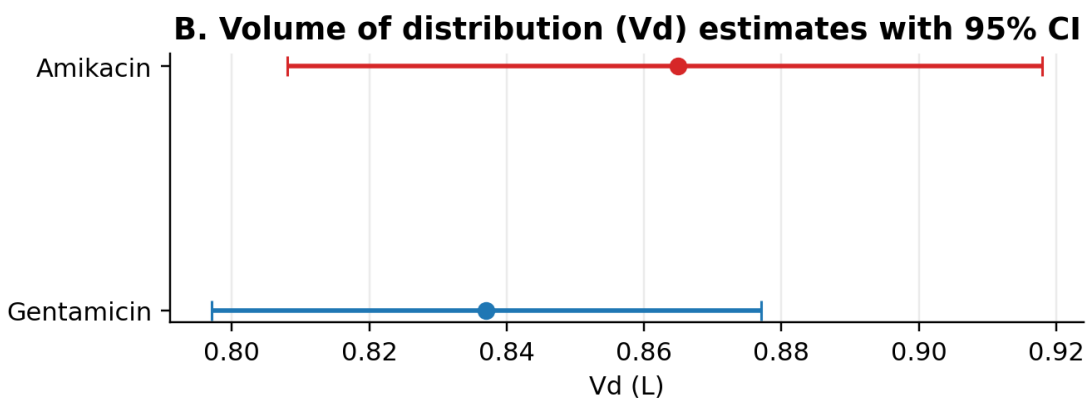
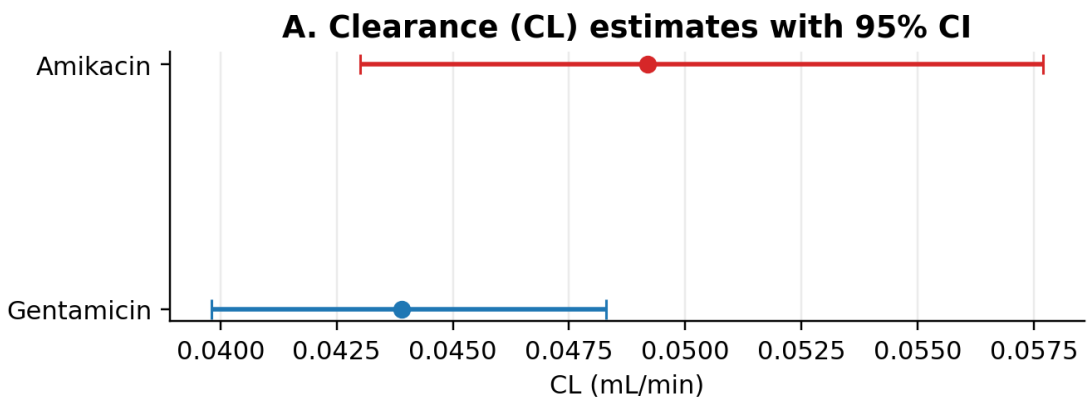


**Figure 15. Forest plots for clearance (A) and volume of distribution (B) with 95% CI by drug.**

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