



Accuracy of weight-based artesunate and artemether–lumefantrine dosing among children hospitalised with malaria in Kisumu County, Kenya: a multicentre clinical-record study

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ABSTRACT

Injectable artesunate reduces mortality from severe paediatric malaria, but only when the amount given matches the weight-specific recommendation. Current World Health Organization and Kenyan guidance specify 3.0 mg/kg per dose for children weighing under 20 kg and 2.4 mg/kg for those weighing 20 kg or more, whereas the earlier 2010 Kenyan guideline specified 2.4 mg/kg at all weights; follow-on artemether–lumefantrine is dosed by weight band. How closely routine inpatient practice matches these rules in western Kenya is not well described. Cross-sectional clinical-record study of 333 children aged 6–59 months hospitalised with malaria in eight public hospitals in Kisumu County, Kenya. Recommended doses were recalculated from each child's recorded weight using the World Health Organization guidelines for malaria (2021) and the Kenyan national malaria guidelines (sixth edition, 2020), applicable when data were collected from September 2023. Dose error was the recorded minus the recommended dose, a negative value denoting a dose below the recommendation; signed, absolute and percentage errors were derived and doses classified as accurate (within a prespecified $\pm 10\%$ tolerance), below or above the recommendation. Artemether–lumefantrine tablet counts were compared with the recommended per-dose weight-band count. Proportions are reported with 95% confidence intervals. Confidence intervals for medians were obtained by percentile bootstrap. Results. Injectable artesunate was documented as first-line treatment, with a recorded dose, for 110 of the 333 children, and 97 of these were documented as continuing to artemether–lumefantrine; these formed the evaluable cohorts, and no record was excluded for a missing weight or dose. All 110 artesunate recipients weighed under 20 kg and required 3.0 mg/kg. No dose recorded on the treatment sheet fell within the tolerance; all 110 (100%, 95% CI 96.6–100) were below the recommendation. Median recorded dose was 2.37 mg/kg (IQR 2.22–2.52) and median absolute percentage dose error 20.9% (95% CI 18.1–22.8). Under a uniform 2.4 mg/kg rule, 98/110 (89.1%) would have been within $\pm 10\%$. For artemether–lumefantrine, 86 children fell in the 5 to <15 kg band (one tablet per dose) and 11 in the 15 to <25 kg band (two tablets); 47/97 (48.5%, 95% CI 38.8–58.3) matched exactly, 47/97 exceeded and 3/97 (3.1%) fell below the recommendation; every discordance was a single tablet. Conclusion. Recorded artesunate doses were uniformly below the applicable recommendation, in a pattern consistent with the adult 2.4 mg/kg rule being applied to children under 20 kg. These findings describe an unimplemented dosing rule rather than random calculation error, and point to weight-band dosing charts and independent dose verification as low-cost remedies.

Keywords: Artesunate; Artemether–Lumefantrine; Dose Error; Hospitalised Children; Kenya, Medication Safety; Malaria; Paediatric Dosing

I. INTRODUCTION

Malaria remains a leading cause of illness and death among young children in sub-Saharan Africa, and severe disease progresses quickly: most deaths occur within the first 24 hours of admission.^{1,3} Parenteral artesunate replaced quinine as the treatment of choice for severe malaria after two large randomised trials showed substantial mortality reductions: SEAQUAMAT, which enrolled 1,461 patients, predominantly adults, in Bangladesh, India, Indonesia and Myanmar, and AQUAMAT, which enrolled 5,425 children in nine African countries.^{3,4} Kenya adopted injectable artesunate for severe malaria in 2012 and has since supported the policy with national guidelines, procurement through the Kenya Medical Supplies Authority, administration job aids and in-service training.^{2,7,9,11} Current guidance requires



at least 24 hours of parenteral treatment and continuation until the child can tolerate oral medicine, after which a full three-day course of an artemisinin-based combination therapy — artemether–lumefantrine in Kenya — must be completed.^{1,2}

The benefit of that treatment chain depends on the amount actually given. Children are dosed by body weight, so every dose passes through a measurement, a calculation and a measured administration, and each step can introduce error. Paediatric patients are recognised to be at substantially greater risk of medication error than adults, with dose-calculation mistakes a leading contributor.^{15,17} Weight-based rules are also not always linear: they can change abruptly at a weight threshold, so that two children a few hundred grams apart require different milligram-per-kilogram doses or different tablet counts. Where a threshold exists, an inaccurate or absent weight measurement translates directly into a systematic dosing deviation.

Artesunate is a case in point. Population pharmacokinetic work in African children showed that body weight strongly influences clearance and volume of distribution, so that smaller children achieve lower exposure to artesunate and its active metabolite dihydroartemisinin at a uniform milligram-per-kilogram dose.⁵ On that basis the World Health Organization revised its recommendation in 2015 to 3.0 mg/kg per dose for children weighing under 20 kg, retaining 2.4 mg/kg for larger children and adults²⁰; Kenya incorporated the change from 2015 and it is carried in the sixth edition of the national malaria guidelines.^{2,19} The earlier third edition of the Kenyan guideline (2010) specified 2.4 mg/kg as the initial dose at all weights and may still inform practice.²⁷ The revision has since been contested by the United States Food and Drug Administration on the basis of a simulated paediatric population, but recent pharmacokinetic modelling of children given 2.4 mg/kg supports the higher paediatric dose and concludes that younger children given the adult dose do not reach comparable exposure.⁶ The practical difficulty is that the higher dose requires clinicians to remember a threshold rule and to reconstitute and measure a different volume for the commonest group of paediatric patients. Kenyan national hospital surveys found that fewer than two-thirds of inpatient health workers knew the correct dose for children under 20 kg, against roughly four-fifths for patients above that weight.⁷

Artemether–lumefantrine raises a different problem. It is dosed in discrete 20 mg/120 mg tablets according to weight band — one tablet per dose for 5 to under 15 kg, two for 15 to under 25 kg, three for 25 to under 35 kg and four thereafter — given twice daily for three days, a six-dose course.² Because tablets cannot readily be subdivided, accuracy is essentially binary within a band, and errors concentrate at band boundaries and where a reference or estimated weight is used in place of the measured one. Completing the oral course after parenteral therapy matters: an incomplete or misdosed follow-on course leaves the child exposed to recrudescence despite adequate initial parasite clearance.

Evidence on whether these rules are followed in East African inpatient practice is limited and mostly indirect. Studies of paediatric inpatient care in Kenya and Uganda have documented incomplete guideline uptake, over-use of injectable antimalarials and poor documentation of weight^{8,12,13,14,15,16,18}, and Kenyan national hospital surveys reported that, among weighed patients, recommended artesunate dosing rose from 57.3% to 70.0% within a single year, with under-dosing more common below 20 kg.⁷ Those estimates rest on prescriptions rather than participant-level recalculation, come from county referral hospitals only, and predate the current guideline edition. No participant-level audit of paediatric antimalarial dose accuracy has been reported from Kisumu County, a lake-endemic area carrying one of the heaviest malaria burdens in Kenya.¹⁰

1.1 Research Objectives

- i. to determine whether recorded artemether–lumefantrine tablet counts agreed with the applicable weight-band recommendation;
- ii. to compare dose accuracy across weight bands, age groups, sex, facilities and antimalarial-availability categories; and
- iii. to determine the proportion of artesunate recipients documented as transitioning to artemether–lumefantrine.

II. METHODOLOGY

2.1 Study design

This was a multicentre hospital-based cross-sectional clinical-record study of paediatric antimalarial dosing, nested within a parent study of malarial anaemia management. The parent study was itself cross-sectional: each child contributed a single assessment during the index admission, with medication data abstracted from the inpatient file and treatment sheet while the child was on the ward, and there was no follow-up. The analysis is therefore neither a retrospective audit of archived records nor a cohort analysis. Reporting follows the STROBE statement for cross-sectional studies²¹ (Supplementary File 1).

2.2 Study setting



Kisumu County lies in south-western Kenya on the shore of Lake Victoria, within the lake-endemic malaria transmission zone where childhood infection prevalence is among the highest nationally. Of 21 public hospitals identified across the county's seven sub-counties, as listed by the county health department and classified by level in the Kenya Master Health Facility List,²⁸ the single level-six teaching and referral hospital and the principal level-four hospital serving Kisumu city were included purposively; the remainder were selected by simple random sampling from level-four hospitals with paediatric inpatient services, with each sub-county represented. Eight hospitals contributed data. Because the crosswalk between facility codes and hospital names remains provisional, facilities are reported as Facility 1 to Facility 8. These codes are not ordered by hospital level, size or location, and no ranking of named hospitals is offered.

2.3 Study population

Eligible children were aged 6–59 months, admitted to a participating paediatric ward, and were being treated for malaria, with or without anaemia (haemoglobin below 11 g/dL). Malaria was confirmed by microscopy or rapid diagnostic test where testing was available; where it was not, children admitted and treated on a clinician's diagnosis of malaria were also included, and the method of diagnosis is reported in Table 1. A haemoglobin result was not an entry requirement. Children with conditions that confound malarial anaemia, including sickle cell disease and malignancy, were excluded and referred for specialist care. The parent cohort comprised 333 children.

Medication-analysis populations

Two analysis populations were defined separately, and the two medicines were never combined into a single dosing measure. A primary artesunate recipient was a child recorded as receiving injectable artesunate as first-line treatment with a valid recorded dose in milligrams per injection, a valid recorded weight and a guideline-determinable recommendation. A valid weight was a positive, biologically plausible weight in grams recorded in the admission file; a valid dose was a numeric amount in milligrams per injection entered on the treatment sheet, excluding the missing-value code 999. A primary artemether–lumefantrine recipient was a child documented as receiving artesunate followed by artemether–lumefantrine with a valid recorded weight and an interpretable per-dose tablet count. The count was the number of tablets per dose written on the treatment plan for the six-dose course; ticks against the scheduled doses showed those given in hospital, but completion of all six doses was not assessed. Children coded “no” or “not known” for first-line artesunate were not automatically included; a dose-record-based sensitivity cohort was prespecified for any child with a credible numeric dose regardless of that indicator, and a broader artemether–lumefantrine cohort for children receiving the medicine without preceding artesunate.

2.4 Data sources

Data were abstracted from clinical records using a structured checklist developed from the Kenya national paediatric protocols and an adapted malaria case-management checklist, and captured electronically using KoboCollect. The recorded artesunate dose was the amount in milligrams per injection entered on the treatment sheet; the instrument did not separate the amount prescribed from the amount drawn up and given, and for children on the ward abstraction was supplemented by observation of care. Vial strength and reconstitution were not captured at any facility, so doses were analysed in milligrams as recorded and the same rounding assumption was applied at all eight facilities. Items relevant to this analysis were the recorded weight in grams, whether injectable artesunate was first-line treatment, the recorded artesunate dose in milligrams per injection, whether artesunate was followed by artemether–lumefantrine, the recorded artemether–lumefantrine dose as a number of tablets, whether another antimalarial was used, and whether the prescribed antimalarial was recorded as available. Analyses used a frozen, de-identified participant-level dataset of 333 records opened read-only, with its SHA-256 hash recorded in the analysis log (Supplementary File 4). All recoding and derivation were performed by script.

Dosing guideline verification

No dose-error outcome was defined before the applicable guideline was identified. Data collection was authorised from September 2023 and the ethical approval and national research licence covered August 2023 to September 2024, so the guidance in force was the sixth edition of the Kenyan *Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya* (revised 2020)² together with the World Health Organization guidelines for malaria of 16 February 2021, whose artesunate and artemether–lumefantrine dosing recommendations were unchanged in the subsequent updates.¹ Both specify, for severe malaria, parenteral artesunate at 3.0 mg/kg per dose for children weighing less than 20 kg and 2.4 mg/kg per dose for patients weighing 20 kg or more, given at 0, 12 and 24 hours and then daily until oral therapy is tolerated. Both specify artemether 20 mg/lumefantrine 120 mg tablets dosed per weight band as one, two, three or four tablets per dose for weights of 5 to <15, 15 to <25, 25 to <35 and ≥35 kg respectively, twice daily for three days. The complete extraction, including issuing body, version, applicable period, formulation, dose basis, rounding and tolerance rules, is given as a Medication Dosing Rule Matrix in Supplementary Table 1. The current World Health Organization guidance was not substituted for the version applicable during the study; it did not differ for either



medicine in the respects relevant here. The third edition of the Kenyan guideline (2010), which specified artesunate 2.4 mg/kg as the initial dose irrespective of weight,²⁷ was treated as superseded and was examined only through the alternative-rule sensitivity analysis.

2.5 Dose recalculation

Independent recalculation of the recommended dose, derivation of dose errors and testing of the classifications against alternative rounding and tolerance rules were prespecified analytical procedures rather than study objectives, and are set out here and under Dose-accuracy classification. The recommended artesunate dose was calculated as the applicable milligram-per-kilogram figure (3.0 mg/kg below 20 kg and 2.4 mg/kg at 20 kg or more)^{1,2} multiplied by the child's actual recorded weight, without premature rounding; an unrounded value was retained for all error calculations and a value rounded to the nearest 1 mg for the exact-match classification, 1 mg being the smallest increment reliably measurable from artesunate reconstituted to 10 mg/mL. Signed dose error was the recorded dose minus the unrounded recommended dose, so that a negative value denotes a dose below the recommendation; absolute error was its magnitude and percentage error the signed error divided by the recommended dose. The recorded dose in milligrams per kilogram was also derived. For artemether–lumefantrine, the recommended per-dose tablet count was derived from the applicable weight band using the actual recorded weight; because recommended tablet numbers are small, tablet differences rather than percentage errors are emphasised.

The recorded artemether–lumefantrine variable is labelled as a number of tablets and is potentially ambiguous between a per-dose count, a daily count and a six-dose course total. Recorded values ranged from one to three and the expected-dose variable carried in the source dataset took only the values one and two, whereas a course total would require six or twelve tablets and a daily total two or four. Only a per-dose interpretation is consistent with the observed range, and the variable was analysed accordingly (Supplementary Table 1).

2.6 Dose-accuracy classification

Tolerance rules were fixed before any error distribution was examined. Exact agreement was defined as a recorded dose equal to the rounded recommended dose. A $\pm 10\%$ band around the unrounded recommended dose was prespecified as the primary definition of a clinically acceptable artesunate dose: at the lightest weight in this cohort one 1 mg increment is about 4.5% of the recommended dose, so the band accommodates roughly two feasible increments while remaining well inside the difference between the two guideline rules. Doses outside the band were classified as below or above the recommendation by the sign of the error. Exact agreement, $\pm 5\%$, $\pm 15\%$ and one-increment rules were prespecified as sensitivity analyses. For artemether–lumefantrine, exact weight-band matching was the primary definition; tablet splitting was not assumed.

2.7 Data validation

Record counts, unique identifiers and facility counts were verified against the frozen dataset. Weight was compared with the original value in grams and screened for missing, zero, negative and implausible values; children within 0.1 kg and 0.5 kg of each relevant band cut-off were flagged for boundary sensitivity analysis, and extreme but plausible weights were retained. Doses were checked for numeric type, unit, the missing-value code 999 and impossible values, and consistency between the treatment-status indicator and the presence of a recorded dose was examined. Independently derived recommended doses were reconciled against the previously calculated expected-dose and variance fields carried in the source dataset, with all discrepancies documented (Supplementary Tables 4 and 5). Children evaluable and not evaluable for artesunate dosing were compared on age, sex, weight, weight-for-age Z-score, facility, admission haemoglobin, anaemia category and medicine availability, with standardised differences reported alongside P values.

2.8 Statistical analysis

Continuous measures are summarised as means with standard deviations and medians with interquartile ranges and ranges; proportions are reported with numerators and denominators throughout. Wilson 95% confidence intervals were used for binary proportions and exact binomial intervals where event counts were small²²; bootstrap percentile intervals with 10,000 resamples were used for skewed continuous measures. Facility was treated as an eight-level categorical variable and compared using Kruskal–Wallis and χ^2 tests, with estimates and confidence intervals emphasised over hypothesis tests. Weight bands of <10, 10 to <15, 15 to <20 and ≥ 20 kg were used for artesunate and the guideline bands for artemether–lumefantrine. Predictors were specified on clinical grounds; no stepwise selection was used. Where inaccurate-dose counts permitted, modified Poisson regression with robust variance estimated prevalence ratios²³; absolute percentage dose error was modelled by linear regression with HC3 robust standard errors and, as a distributional check, median regression with bootstrap intervals. Facility fixed effects were used in sensitivity analyses; facility random effects were not used as a primary model because only eight facilities were represented.



Prespecified sensitivity analyses addressed the alternative uniform 2.4 mg/kg rule, alternative tolerances, the broader recipient definition, weight-band boundary effects, the artemether–lumefantrine unit interpretation, selection from incomplete dose documentation, and facility adjustment. Two-sided α was 0.05. Analyses used Python 3.12 with NumPy, pandas and SciPy; the complete code is Supplementary File 2.

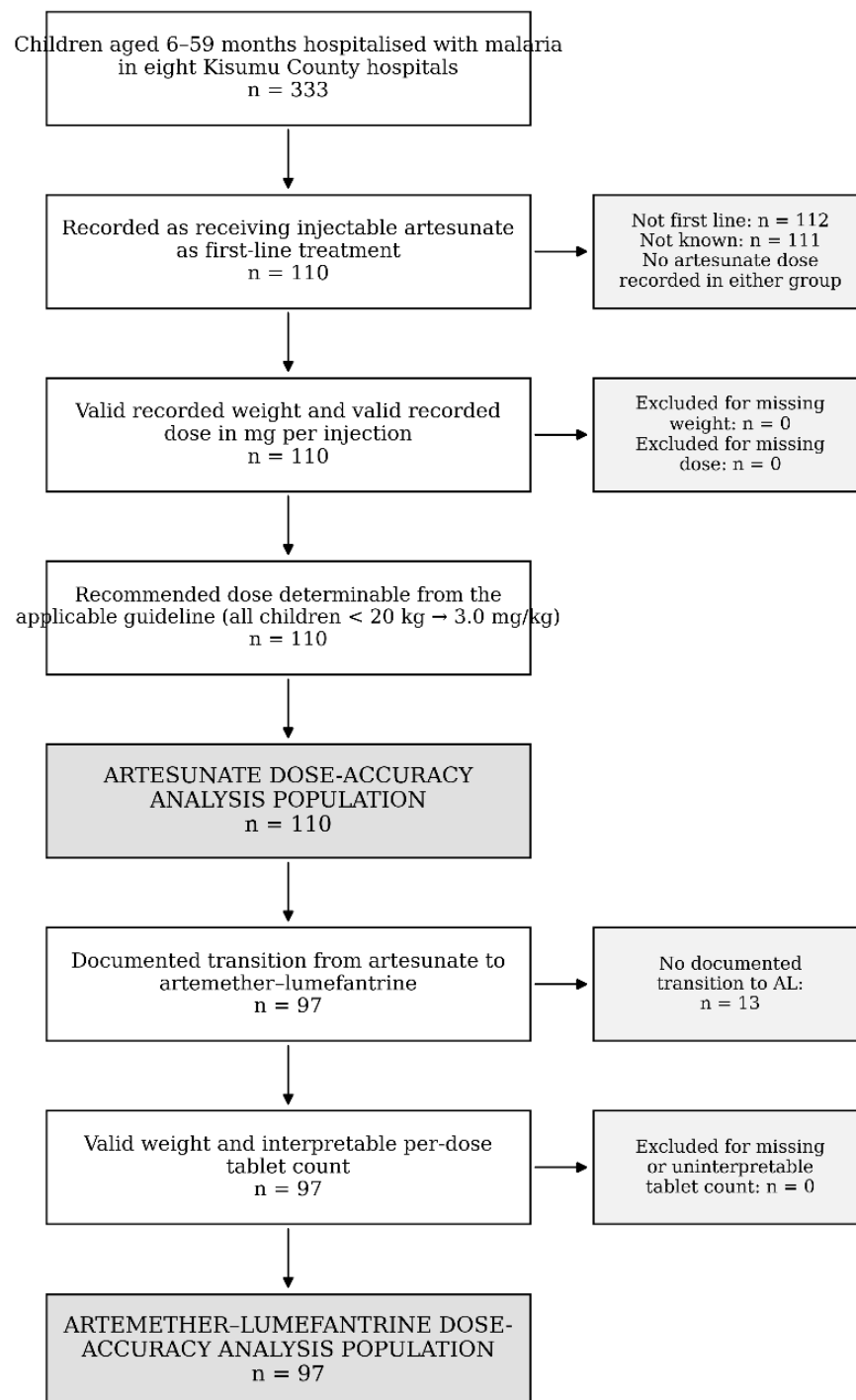
2.9 Ethical considerations

Masinde Muliro University of Science and Technology Institutional Scientific and Ethics Review Committee (MMUST-ISERC), approval number MMUST-ISERC/179/2023, approved 11 August 2023, valid 11 August 2023 to 11 August 2024; administrative reference MMU/COR: 403012 Vol 6 (01). National research licence NACOSTI/P/23/29045 issued 16 September 2023 by the National Commission for Science, Technology and Innovation, valid to 16 September 2024 (applicant reference 903302). Data-collection authorisation from the County Government of Kisumu, Department of Medical Services, Public Health and Sanitation, reference GN 133 VOL. XIV/(438), dated 25 September 2023.

III. FINDINGS

3.1 Participant flow

The parent cohort comprised 333 children with 333 unique identifiers across eight facilities. Injectable artesunate was recorded as first-line treatment for 110 children (33.0%); 112 (33.6%) were coded as not receiving it first line and 111 (33.3%) as not known. The dosing analysis was necessarily confined to children with artesunate documented as first-line treatment and a recorded dose; the remaining 223 had no dose entry against which accuracy could be judged and were not excluded for any data-quality reason. A recorded artesunate dose was present for exactly the 110 coded “yes” and for none of the others, so missing treatment status could not be reinterpreted as receipt and the prespecified dose-record-based sensitivity cohort was identical to the primary cohort. Weight was available for all 333 children and a valid dose for all 110 recipients, so none was excluded for missing weight, missing dose or an unresolved unit. Of the 110, 97 (88.2%) were documented as transitioning to artemether–lumefantrine and 13 (11.8%) were not, with none coded unknown; all 97 had a valid weight and an interpretable per-dose tablet count. No child received another antimalarial. The derivation is shown in Figure 1. Comparing the 110 children evaluable for artesunate dosing with the 223 who were not, there was no evidence of difference in age ($P=.19$), weight ($P=.33$), sex ($P=.65$), facility ($P=.20$), admission haemoglobin ($P=.57$), anaemia category ($P=.88$) or recorded medicine availability ($P=.81$). Weight-for-age Z-score was lower among evaluable children (mean -0.48 versus -0.23 ; $P=.004$), consistent with parenteral treatment being given to more unwell children. Standardised differences were correspondingly small for age (0.00), weight (-0.13), sex (-0.07) and medicine availability (-0.04), and were -0.30 for weight-for-age Z-score (Supplementary Table 3)



No child received artemether-lumefantrine without preceding artesunate ("another antimalarial used" = no for all 333 children).

Figure 1

Derivation of the artesunate and artemether-lumefantrine analytical cohorts.

No child was excluded for missing weight, missing dose or an unresolved dose unit.

3.2 Characteristics of the medication cohorts

Children in the artesunate cohort had a mean age of 31.8 months (SD 15.4) and a mean weight of 12.44 kg (SD 2.86); 57/110 (51.8%) were male. Twenty children weighed under 10 kg, 67 weighed 10 to under 15 kg and 23 weighed 15 to under 20 kg; no child in either cohort weighed 20 kg or more, the heaviest weighing 18.17 kg. Facility contributions ranged from 5 to 36 children for artesunate and from 5 to 29 for artemether-lumefantrine. Malaria was diagnosed by microscopy in 35/110, by rapid diagnostic test in 39/110 and clinically in 36/110, and diagnosed after admission in



43/110 (39.1%). Documented severity features were common, including pallor in 60/110, respiratory distress in 58/110 and impaired consciousness in 50/110. The prescribed antimalarial was recorded as available for 53/110 (48.2%) of artesunate recipients. Full characteristics are given in Table 1.

Table 1

Characteristics of children included in the artesunate and artemether–lumefantrine dosing analyses

Characteristic	Parent cohort (n=333)	Artesunate cohort (n=110)	AL cohort (n=97)
Age, months, mean (SD)	31.8 (15.2)	31.8 (15.4)	29.1 (14.2)
Age, months, median	31.0	29.5	27.0
6-11 months, n/N (%)	32/333 (9.6)	10/110 (9.1)	10/97 (10.3)
12-23 months, n/N (%)	90/333 (27.0)	33/110 (30.0)	33/97 (34.0)
24-35 months, n/N (%)	66/333 (19.8)	23/110 (20.9)	23/97 (23.7)
36-47 months, n/N (%)	80/333 (24.0)	22/110 (20.0)	18/97 (18.6)
48-59 months, n/N (%)	65/333 (19.5)	22/110 (20.0)	13/97 (13.4)
Male sex, n/N (%)	180/333 (54.1)	57/110 (51.8)	51/97 (52.6)
Weight, kg, mean (SD)	12.68 (2.83)	12.44 (2.86)	11.89 (2.55)
Weight, kg, median (IQR)	12.50 (10.50–15.00)	12.17 (10.54–14.42)	11.83 (10.17–13.50)
<10 kg, n/N (%)	59/333 (17.7)	20/110 (18.2)	20/97 (20.6)
10 to <15 kg, n/N (%)	187/333 (56.2)	67/110 (60.9)	66/97 (68.0)
15 to <20 kg, n/N (%)	87/333 (26.1)	23/110 (20.9)	11/97 (11.3)
≥20 kg, n/N (%)	0/333 (0.0)	0/110 (0.0)	0/97 (0.0)
WHO weight-for-age Z-score, mean (SD)	-0.31 (0.85)	-0.48 (0.86)	-0.53 (0.89)
Facility 1, n/N (%)	92/333 (27.6)	36/110 (32.7)	29/97 (29.9)
Facility 2, n/N (%)	58/333 (17.4)	20/110 (18.2)	19/97 (19.6)
Facility 3, n/N (%)	37/333 (11.1)	11/110 (10.0)	10/97 (10.3)
Facility 4, n/N (%)	24/333 (7.2)	5/110 (4.5)	5/97 (5.2)
Facility 5, n/N (%)	27/333 (8.1)	13/110 (11.8)	12/97 (12.4)
Facility 6, n/N (%)	31/333 (9.3)	9/110 (8.2)	9/97 (9.3)
Facility 7, n/N (%)	27/333 (8.1)	9/110 (8.2)	7/97 (7.2)
Facility 8, n/N (%)	37/333 (11.1)	7/110 (6.4)	6/97 (6.2)
Microscopy, n/N (%)	92/333 (27.6)	35/110 (31.8)	31/97 (32.0)
Rapid diagnostic test, n/N (%)	137/333 (41.1)	39/110 (35.5)	35/97 (36.1)
Clinical diagnosis only, n/N (%)	104/333 (31.2)	36/110 (32.7)	31/97 (32.0)
Malaria diagnosis made after admission, n/N (%)	124/333 (37.2)	43/110 (39.1)	43/97 (44.3)
Pallor documented, n/N (%)	170/333 (51.1)	60/110 (54.5)	51/97 (52.6)
Respiratory distress documented, n/N (%)	156/333 (46.8)	58/110 (52.7)	50/97 (51.5)
Seizures documented, n/N (%)	155/333 (46.5)	53/110 (48.2)	44/97 (45.4)
Shock documented, n/N (%)	164/333 (49.2)	52/110 (47.3)	48/97 (49.5)
Impaired consciousness documented, n/N (%)	160/333 (48.0)	50/110 (45.5)	41/97 (42.3)
Admission haemoglobin, g/dL, mean (n with valid value)	9.28 (295)	9.39 (98)	9.40 (87)
Prescribed antimalarial recorded as available, n/N (%)	165/333 (49.5)	53/110 (48.2)	48/97 (49.5)

AL, artemether–lumefantrine; IQR, interquartile range; SD, standard deviation; WHO, World Health Organization. Weight bands are those used for the artesunate analysis. “Clinical diagnosis only” denotes children admitted and treated for malaria on a clinician’s diagnosis where parasitological testing was not available. The artemether–lumefantrine cohort is a subset of the artesunate cohort. Facility codes are anonymised and are not ordered by hospital level, size or location. Artesunate dose concordance: Because every artesunate recipient weighed less than 20 kg, the applicable rule for all 110 children was 3.0 mg/kg per dose. Recorded doses had a mean of 29.55 mg (SD 6.97; range 15.0–47.0) against a mean recommended dose of 37.32 mg (SD 8.57). Expressed per kilogram, recorded doses had a median of 2.37 mg/kg (interquartile range 2.22–2.52; range 2.05–2.64), and 76/110 (69.1%, 95% CI 59.9–77.0) were below 2.5 mg/kg. No recorded dose reached 3.0 mg/kg.

The mean signed dose error was -7.77 mg (SD 2.86), with a median of -7.50 mg (interquartile range -9.87 to -5.50; 95% bootstrap CI for the median -8.49 to -6.50) and a range from -16.01 to -2.99 mg. Every signed error was negative. Mean percentage dose error was -20.8% (SD 5.8) and mean absolute percentage dose error was 20.8% (95% bootstrap CI 19.7–21.9), with a median of 20.9% (interquartile range 15.8–26.0; 95% bootstrap CI 18.1–22.8) and a range from 12.0% to 31.8%. No recorded dose matched the rounded recommended dose exactly (0/110; 95% CI 0–3.4)



and none fell within the prespecified $\pm 10\%$ tolerance (0/110; 95% CI 0–3.4). All 110 doses (100%, 95% CI 96.6–100) were below the recommended range and none was above it. Table 2 gives the full dose and error distributions, and Figure 2 shows recorded against recommended doses with the line of equality, the tolerance boundaries and the line corresponding to dosing at 2.4 mg/kg. The observations lie close to the 2.4 mg/kg line rather than scattering about equality. Figure 3 shows the distribution of percentage dose error, which is unimodal, entirely negative and centred near -21% .

Table 2

Recorded and recommended artesunate doses and dose-error measures (n=110)

Measure	Mean (SD)	Median (IQR)	Minimum, maximum
Recorded weight, kg	12.44 (2.86)	12.17 (10.54 to 14.42)	7.33, 18.17
Recorded dose, mg per injection	29.55 (6.97)	30.00 (24.25 to 34.75)	15.00, 47.00
Guideline-recommended dose, mg (3.0 mg/kg)	37.32 (8.57)	36.51 (31.63 to 43.25)	21.99, 54.51
Recorded dose, mg/kg	2.38 (0.17)	2.37 (2.22 to 2.52)	2.05, 2.64
Signed dose error, mg	-7.77 (2.86)	-7.50 (-9.87 to -5.50)	-16.01, -2.99
Absolute dose error, mg	7.77 (2.86)	7.50 (5.50 to 9.87)	2.99, 16.01
Percentage dose error, %	-20.8 (5.8)	-20.9 (-26.0 to -15.8)	-31.8, -12.0
Absolute percentage dose error, %	20.8 (5.8)	20.9 (15.8 to 26.0)	12.0, 31.8

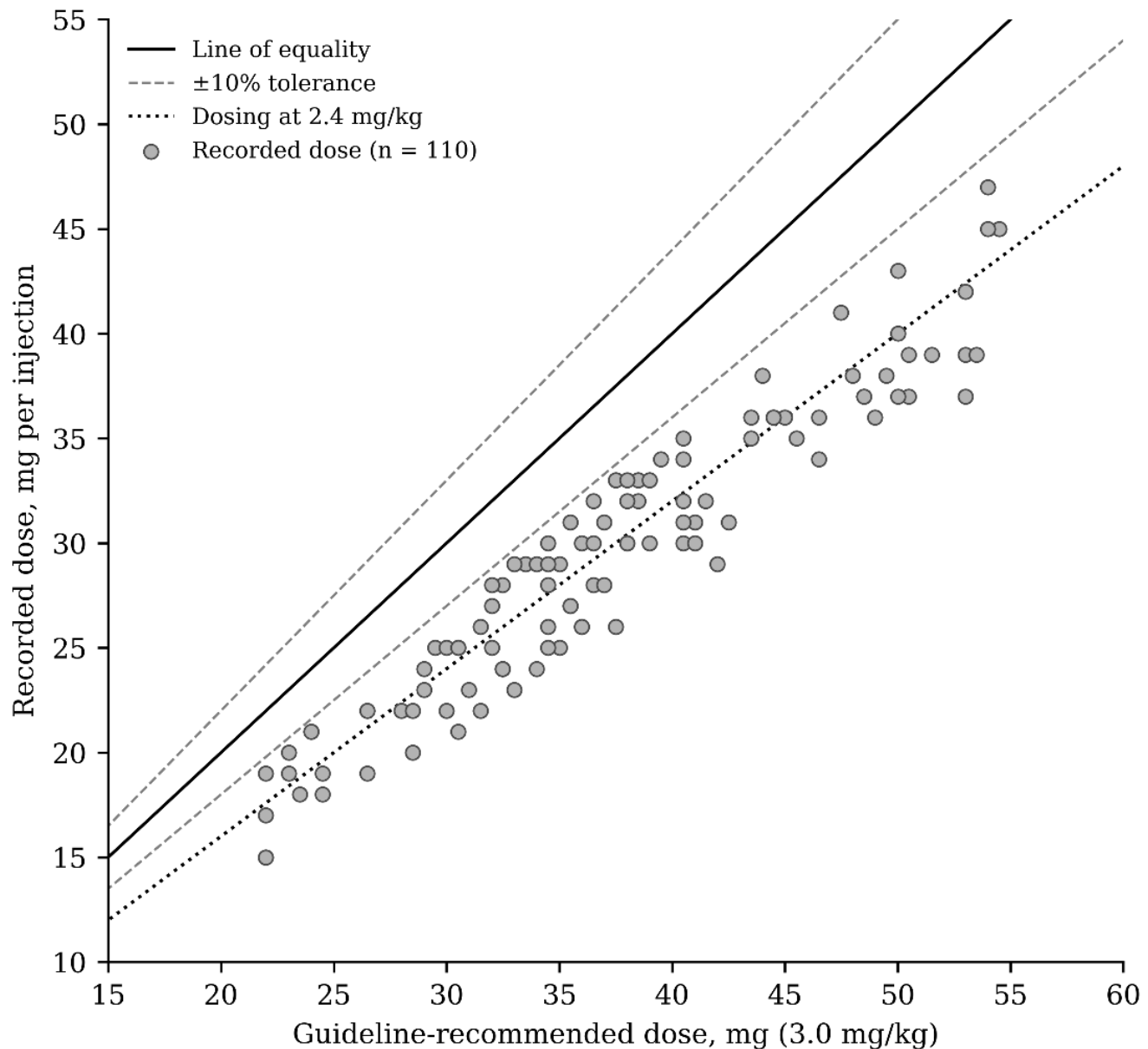
Mean absolute percentage dose error 20.8% (95% bootstrap CI 19.7–21.9); median absolute percentage dose error 20.9% (95% bootstrap CI 18.1–22.8); median signed dose error -7.50 mg (95% bootstrap CI -8.49 to -6.50). Signed error is the recorded dose minus the unrounded guideline-recommended dose; a negative value indicates a recorded dose below the recommendation.

Table 3

Dose-accuracy classification

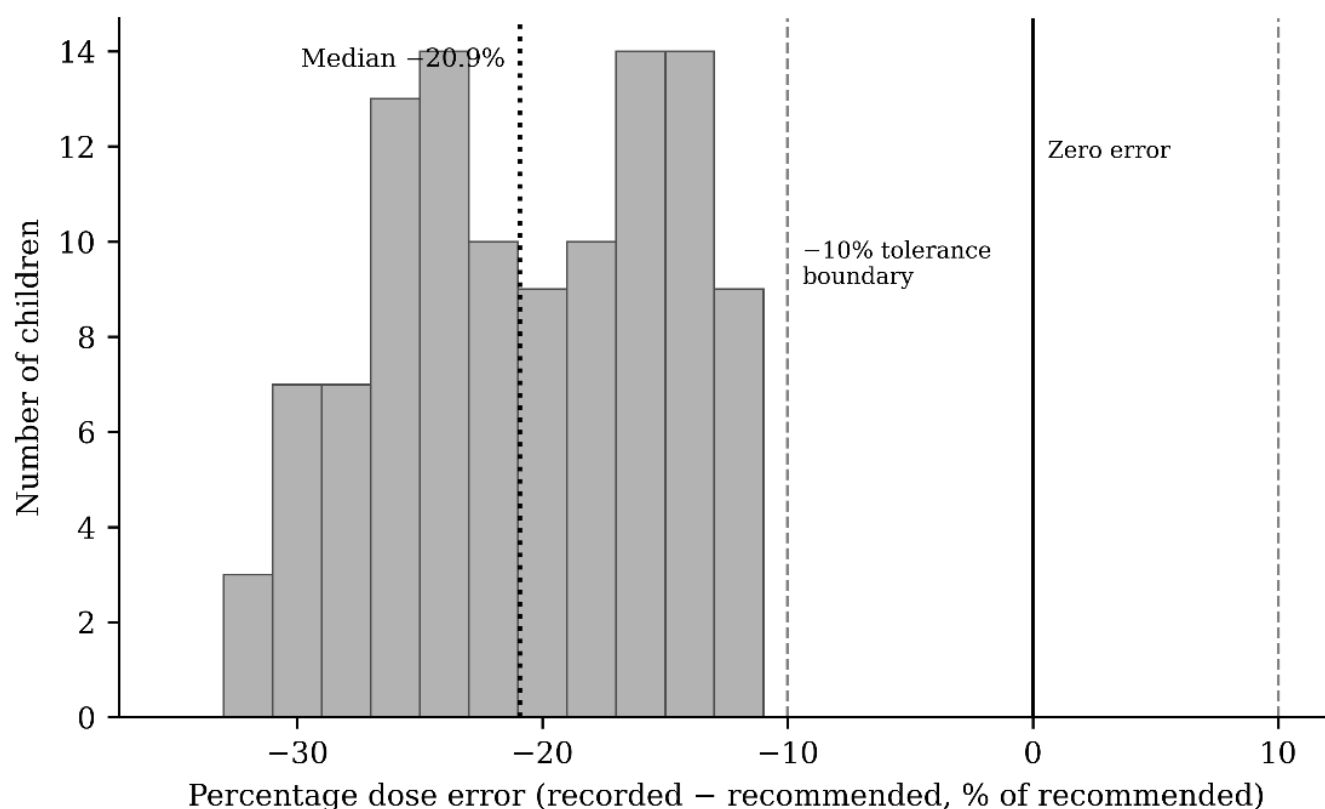
Classification	n/N	% (95% CI)
Exact match with the rounded recommended dose	0/110	0.0 (0.0–3.4)
Within the prespecified $\pm 10\%$ tolerance (accurate)	0/110	0.0 (0.0–3.4)
Recorded dose below the recommended range (underdose)	110/110	100.0 (96.6–100.0)
Recorded dose above the recommended range (overdose)	0/110	0.0 (0.0–3.4)
Recorded dose < 2.5 mg/kg	76/110	69.1 (59.9–77.0)

CI, confidence interval. Proportions use Wilson 95% confidence intervals. The applicable dosing rule for every child in this cohort was 3.0 mg/kg per dose, because all 110 children weighed less than 20 kg (range 7.33–18.17 kg).

**Figure 2**

Recorded versus guideline-recommended artesunate dose (n=110).

The solid diagonal is the line of equality and the dashed lines mark the prespecified $\pm 10\%$ tolerance. The dotted line shows the dose that would result from applying 2.4 mg/kg, the rule for patients weighing 20 kg or more. Every observation lies below the tolerance band.

**Figure 3**

Distribution of artesunate percentage dose error (n=110).

Zero error and the $\pm 10\%$ tolerance boundaries are marked; the dotted vertical line is the median (-20.9%). The distribution is unimodal and entirely negative. Artemether–lumefantrine dose concordance among the 97 evaluable children, 86 fell in the 5 to <15 kg band, requiring one tablet per dose, and 11 fell in the 15 to <25 kg band, requiring two. Recorded tablet counts were one tablet for 46 children, two for 47 and three for 4. Forty-seven of 97 (48.5%, 95% CI 38.8–58.3) matched the recommended count exactly, 47/97 (48.5%, 95% CI 38.8–58.3) exceeded it and 3/97 (3.1%, 95% CI 1.1–8.7) fell below it. Every discordant record differed from the recommendation by exactly one tablet per dose; the mean signed tablet error was $+0.45$ (SD 0.56). The pattern differed by band. In the 5 to <15 kg band, 43/86 (50.0%, 95% CI 39.0–61.0) matched, and the remaining 43 children all received two tablets where one was recommended — a doubling of the intended per-dose amount. In the 15 to <25 kg band, 4/11 matched, 4 received three tablets and 3 received one. There was no evidence that the overall error proportion differed between bands ($P=.53$). Table 3 and Supplementary Figure 2 present these results.

Table 3

Artemether–lumefantrine dose concordance by weight band (n=97)

Weight band	Recommended tablets per dose	Children, n	Exact match, n/N (% [95% CI])	Underdose, n	Overdose, n
5 to <15 kg	1	86	43/86 (50.0 [39.0–61.0])	0	43
15 to <25 kg	2	11	4/11 (36.4 [10.9–69.2])	3	4
All children	—	97	47/97 (48.5 [38.8–58.3])	3	47

CI, confidence interval. Exact binomial confidence intervals are used within weight bands because of small event counts; the overall estimate uses a Wilson interval. No child weighed 25 kg or more. Every discordant record differed from the recommendation by exactly one tablet per dose. Recommended tablets per dose follow the Kenya national malaria treatment guideline schedule for artemether 20 mg/lumefantrine 120 mg tablets. Distribution of recorded tablets per dose: 1 tablet, 46 children; 2 tablets, 47 children; 3 tablets, 4 children. Distribution of recommended tablets per dose: 1 tablet, 86 children; 2 tablets, 11 children.

Facility and weight-band variation: No facility achieved any artesunate dose within the $\pm 10\%$ tolerance, so the accurate proportion was 0% at all eight sites and no comparative test of that proportion is informative. The magnitude of the shortfall varied modestly: median absolute percentage dose error ranged from 14.3% to 24.3% and median



recorded dose from 2.27 to 2.57 mg/kg (Kruskal–Wallis $P=.058$); the two facilities with the smallest shortfall contributed 5 and 9 children, so their estimates are imprecise and should not be read as superior performance. Across weight bands, median absolute percentage error was 21.1% below 10 kg, 19.1% at 10 to under 15 kg and 23.1% at 15 to under 20 kg ($P=.39$). For artemether–lumefantrine, the exact-match proportion ranged from 22.2% to 80.0% with wide, overlapping confidence intervals and no evidence of between-facility variation ($P=.57$). Table 4 and Figure 4 summarise these comparisons; Supplementary Figure 1 shows recorded mg/kg doses by facility against both guideline rules.

Table 4

Artesunate and artemether–lumefantrine dose accuracy across eight anonymised facilities

Facility	Artesunate, evaluable n	Artesunate within $\pm 10\%$, n/N (%)	Artesunate median absolute error (IQR) %	Artesunate median recorded mg/kg (IQR)	AL, evaluable n	AL exact match, n/N (%) [95% CI]
Facility 1	36	0/36 (0.0)	21.1 (16.0–26.1)	2.37 (2.22–2.52)	29	15/29 (51.7 [32.5–70.6])
Facility 2	20	0/20 (0.0)	22.8 (17.0–26.3)	2.31 (2.21–2.49)	19	10/19 (52.6 [28.9–75.6])
Facility 3	11	0/11 (0.0)	22.7 (16.9–26.3)	2.32 (2.21–2.49)	10	5/10 (50.0 [18.7–81.3])
Facility 4	5	0/5 (0.0)	14.3 (13.0–17.5)	2.57 (2.48–2.61)	5	4/5 (80.0 [28.4–99.5])
Facility 5	13	0/13 (0.0)	22.5 (17.8–26.5)	2.33 (2.20–2.47)	12	5/12 (41.7 [15.2–72.3])
Facility 6	9	0/9 (0.0)	15.8 (13.2–17.3)	2.53 (2.48–2.60)	9	2/9 (22.2 [2.8–60.0])
Facility 7	9	0/9 (0.0)	19.5 (17.4–23.3)	2.41 (2.30–2.48)	7	4/7 (57.1 [18.4–90.1])
Facility 8	7	0/7 (0.0)	24.3 (20.6–26.4)	2.27 (2.21–2.38)	6	2/6 (33.3 [4.3–77.7])
All facilities	110	0/110 (0.0)	20.9 (15.8–26.0)	2.37 (2.22–2.52)	97	47/97 (48.5 [38.8–58.3])

AL, artemether–lumefantrine; CI, confidence interval; IQR, interquartile range. Facility codes are anonymised, are not ordered by hospital level and are not intended to permit identification or ranking of individual hospitals. Kruskal–Wallis test for between-facility variation in artesunate absolute percentage dose error, $P=.058$; χ^2 test for between-facility variation in artemether–lumefantrine exact-match proportion, $P=.573$. No facility achieved any artesunate dose within the $\pm 10\%$ tolerance, so no comparative test of that proportion is informative.

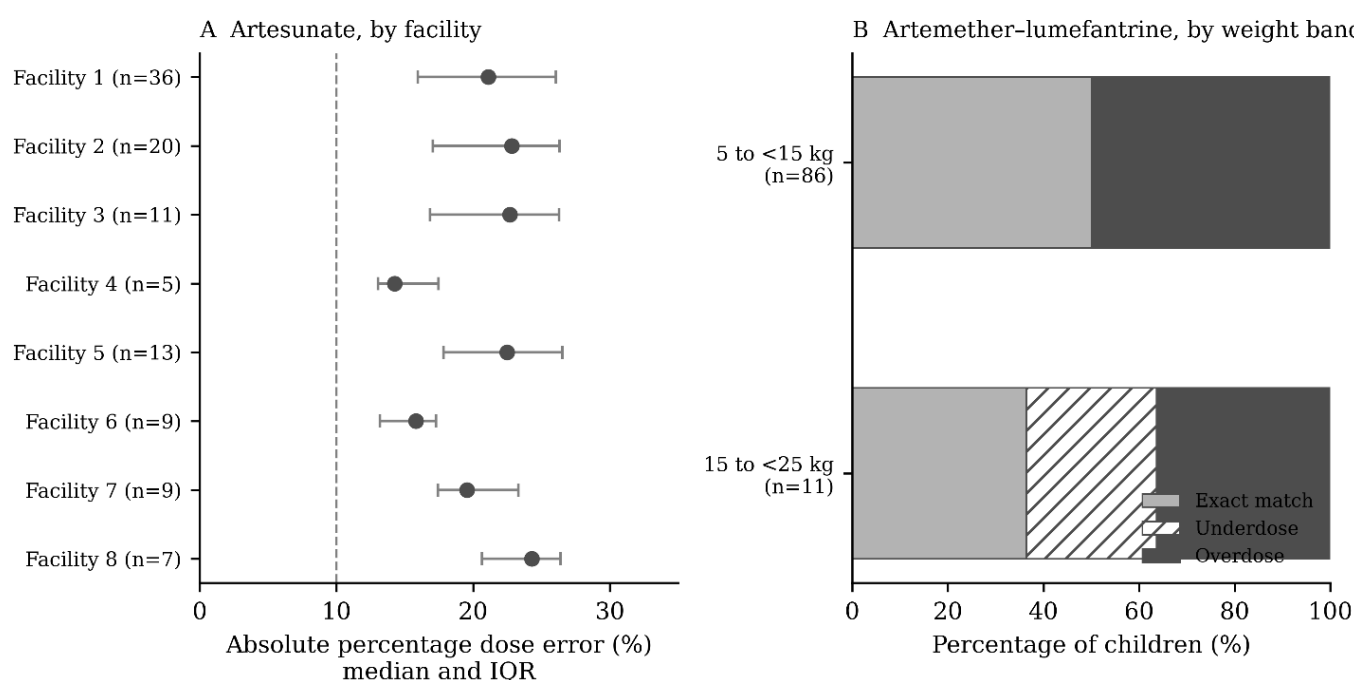


Figure 4

Dose accuracy by facility and weight band.



Panel A shows the median and interquartile range of artesunate absolute percentage dose error for each anonymised facility, with the $\pm 10\%$ tolerance marked. Panel B shows artemether–lumefantrine per-dose concordance by weight band. Facility codes are anonymised and are not ordered by hospital level. Factors associated with inaccurate dosing: Multivariable modelling of the primary artesunate categorical outcome was not performed: every evaluable record was classified as inaccurate, so the binary outcome had no variance and no prevalence-ratio model was estimable, a situation in which the statistical analysis plan permits descriptive stratified reporting. Modelling the continuous absolute percentage dose error instead, neither weight (β 0.06 percentage points per kg, 95% CI -0.34 to 0.46 ; $P=.76$) nor recorded medicine availability (β 2.01, 95% CI -0.17 to 4.18 ; $P=.070$) was associated with the magnitude of the shortfall; median regression, a model adding age and sex, and a facility fixed-effect model all agreed. Age and weight were collinear ($r=0.92$) and were not entered together.

For artemether–lumefantrine, 50 dose errors among 97 children permitted a modified Poisson model. Neither weight (prevalence ratio 1.06 per kg, 95% CI 0.99–1.13; $P=.121$) nor recorded medicine availability (prevalence ratio 0.84, 95% CI 0.57–1.24; $P=.383$) was associated with any dose error. Adding facility fixed effects did not materially change these estimates (Supplementary Table 9). Table 5 presents both panels. Multivariable modelling of the primary artesunate categorical outcome was not performed. Every evaluable artesunate record (110/110) was classified as inaccurate, so the binary outcome had no variance and no prevalence-ratio model was estimable. The prespecified statistical analysis plan permits descriptive stratified reporting in this situation. Panel A therefore reports stratified descriptive estimates for artesunate, together with a robust linear model of the continuous absolute percentage dose error. Panel B reports a modified Poisson model for any artemether–lumefantrine dose error, for which 50 events were available. Factors examined in relation to inaccurate antimalarial dosing

Table 5a

Panel A. Artesunate absolute percentage dose error (n=110)

Stratum or term	n	Median absolute % error (IQR) or β (95% CI)	P value
<10 kg	20	21.1 (16.5–24.2)	
10 to <15 kg	67	19.1 (15.4–25.9)	
15 to <20 kg	23	23.1 (20.0–26.2)	
Weight band, Kruskal–Wallis	110		.389
Medicine recorded as available	53	22.9	
Medicine not recorded as available	57	19.1	
Facility, Kruskal–Wallis	110		.058
Robust linear model: weight, per kg	110	0.06 (-0.34 to 0.46)	0.758
Robust linear model: medicine available	110	2.01 (-0.17 to 4.18)	0.070

Table 5b

Panel B. Any artemether–lumefantrine dose error, modified Poisson regression with robust variance (n=97, 50 events)

Term	Prevalence ratio (95% CI)	P value
Weight, per kg	1.06 (0.99–1.13)	0.121
Prescribed medicine recorded as available	0.84 (0.57–1.24)	0.383

CI, confidence interval; IQR, interquartile range. β coefficients are percentage points of absolute dose error; the robust linear model uses HC3 heteroscedasticity-consistent standard errors. Reference categories: medicine not recorded as available. Facility fixed-effect versions of both models are reported in Supplementary Table 9 and did not materially change the estimates. P values are two-sided.

3.2.1 Treatment sequence and medicine availability

Of 110 artesunate recipients, 97 (88.2%, 95% CI 80.8–93.0) were documented as transitioning to artemether–lumefantrine and 13 (11.8%) were not. Because eligibility for oral transition — ability to tolerate oral medicine, clinical improvement and discharge status — could not be reconstructed from the abstracted record, non-transition is reported descriptively and is not classified as non-adherence. Antimalarials were recorded as available for 53/110 (48.2%) of artesunate recipients and 48/97 (49.5%) of artemether–lumefantrine recipients. Dose accuracy did not differ by availability status for either medicine, but this variable reflects a record-abstracted statement rather than a verified facility stock audit, and no causal interpretation is offered.

3.3 Sensitivity analyses



The alternative-guideline analysis is the most informative. Applying the uniform 2.4 mg/kg rule embedded in the source dataset — the rule for patients weighing 20 kg or more — instead of the applicable paediatric rule, 98/110 doses (89.1%, 95% CI 81.9–93.6) would have fallen within $\pm 10\%$, the mean signed error would be -0.31 mg (95% CI -0.70 to $+0.08$), and the mean absolute percentage error would fall from 20.8% to 6.3%. The distribution of recorded doses is therefore closely centred on 2.4 mg/kg and not on 3.0 mg/kg.

Varying the tolerance did not alter the primary conclusion: no dose was accurate under exact agreement, $\pm 5\%$ or a one-increment rule, and 23/110 (20.9%) fell within a $\pm 15\%$ band, all remaining discordant records being below the recommendation. Because a recorded dose was present for exactly the 110 children coded as receiving first-line artesunate, the broader recipient-definition analysis reproduced the primary cohort. Twenty-two children lay within 0.5 kg of an artesunate band cut-off and three within 0.1 kg, but as no child approached 20 kg, no plausible measurement error would have changed the applicable milligram-per-kilogram rule. A total-course interpretation of the artemether–lumefantrine tablet variable was not tenable, the maximum recorded value being three tablets against a smallest course total of six. No confirmed data-entry error, impossible dose or unresolvable unit error was identified, and no record was excluded as an outlier.

Reconciliation with the previously derived variables is reported in full in Supplementary Tables 4 and 5. In brief, the expected artesunate dose carried in the source dataset was exactly 2.4 times the recorded weight for all 110 children, so that all 110 accuracy classifications change under the applicable guideline; and the expected artemether–lumefantrine tablet count had been derived from an age- and sex-based reference weight rather than the measured weight, which reclassifies 8 children.

IV. DISCUSSION

Among 333 children hospitalised with malaria in eight Kisumu County hospitals, 110 had an evaluable artesunate dose and 97 an evaluable artemether–lumefantrine tablet count. Every artesunate recipient weighed less than 20 kg and therefore required 3.0 mg/kg under the guideline in force; none received it. All 110 recorded doses fell below the recommendation, by a median of 20.9% and 7.50 mg, clustering tightly at a median of 2.37 mg/kg — the rule for patients weighing 20 kg or more, under which 89.1% of the same doses would have been within $\pm 10\%$ with a mean signed error close to zero. Just under half of artemether–lumefantrine records matched the recommended per-dose tablet count, with half the children in the lightest band receiving two tablets where one was indicated. Neither weight, age, sex, facility nor recorded availability explained the magnitude of the artesunate shortfall.

The shape of these findings matters more than their magnitude. A distribution of dose errors centred on zero with scatter in both directions would indicate calculation and measurement error. What was observed instead is a distribution centred on a different, internally consistent rule, with no overdoses at all. That signature points to a guideline that has not been translated into practice rather than to arithmetic failure by individual clinicians, and the distinction changes what should be done about it.

The finding is consistent in direction with, but more extreme than, previous Kenyan work. National surveys of all 47 county referral hospitals in 2016 found that recommended artesunate dosing among weighed patients rose from 57.3% to 70.0% within a year, that under-dosing was substantially more common below 20 kg than in heavier patients, and that fewer than two-thirds of inpatient health workers could state the correct dose for children under 20 kg — a gap attributed to the recency of the 2015 change from 2.4 to 3 mg/kg.^{7,20} The present study, conducted seven years later in level-four and level-six hospitals, found no correctly dosed child at all. The earlier surveys assessed a mixed adult and paediatric population, applied their own correctness definition, and covered facilities receiving artesunate-specific training and job aids under a national monitoring programme; the present cohort is exclusively young children, for whom the higher dose applies universally and for whom that work already showed the widest knowledge gap.

Broader work on paediatric inpatient care in Kenya and Uganda has repeatedly documented incomplete guideline uptake, weak documentation of weight and over-use of injectable antimalarials^{8,12,13,14,15,16}, and studies of neonatal prescribing in Kenya have shown that weight-based dose errors persist after guideline dissemination where the calculation is non-trivial.¹⁷ The closest methodological comparator outside Kenya is a survey of 503 patients prescribed artemether–lumefantrine in rural Tanzania, in which 85.7% were dosed correctly by weight and 78.5% by age; patients in the middle dosing bands had significantly lower odds of correct dosing than the lightest patients, and neither health-worker training nor supervisory visits improved those odds.²⁴ That study assessed outpatients of all ages and treated age-based dosing as an acceptable alternative, so its higher accuracy is not directly comparable, but its central signal — error concentrated where weight bands adjoin, and unresponsive to training alone — recurs in the present cohort.

Interpretation of the artesunate findings: Three explanations deserve consideration. The first, which the data most support, is that the 2.4 mg/kg figure remains the operative rule in these wards. It was the recommendation for all ages before 2015, including in the third edition of the Kenyan guideline (2010),²⁷ it remains the rule for patients of 20 kg and above, and a single rule is easier to apply than one conditioned on a weight threshold. Consistent with this, the



recommended-dose field carried in the parent dataset itself applied 2.4 mg/kg uniformly to every child, indicating that the assumption was embedded in the study instrument as well as in practice. The second is measurement and preparation: artesunate must be reconstituted, and the volume corresponding to 3.0 mg/kg differs from that for 2.4 mg/kg by a quarter, so anchoring to a familiar volume or vial fraction produces a systematic shortfall — and the complete absence of overdoses is consistent with a downward-anchored process. The third is documentation, since a prescribed value copied forward would not reveal what was drawn up and given. None can be distinguished with clinical-record data alone, and the study was not designed to attribute error to any step or any individual.

The clinical significance of a 21% shortfall cannot be established from this study, which measured no treatment outcome. It is, however, the deviation that the 2015 guideline change was designed to prevent. Population pharmacokinetic modelling in African children showed that smaller children achieve lower artesunate and dihydroartemisinin exposure at a uniform milligram-per-kilogram dose⁵, and recent modelling of children given 2.4 mg/kg concluded that most younger children do not reach the exposure achieved by children above 20 kg, supporting the higher paediatric dose and noting the potential for harm from under-dosing in a rapidly lethal infection.⁶ It should be recorded that this position is not universally held: the United States Food and Drug Administration, reasoning from a simulated paediatric population, concluded that children below 20 kg given 2.4 mg/kg would attain comparable or greater dihydroartemisinin exposure than heavier patients, and approved a uniform dose partly on the argument that one rule for all weights simplifies care and avoids the administration errors that multiple weight-specific recommendations invite.²⁵ The present findings speak to that second, procedural argument more directly than to the first: a two-tier rule was indeed not reliably applied. They do not, however, support resolving the difficulty by lowering the dose, since the case for the higher paediatric dose rests on measured drug concentrations in African children rather than on simulation alone.^{5,6} The disagreement is about which dose is optimal, not about which dose was required in Kenya during the study period, and it does not soften the finding that the applicable national recommendation was not met.

Interpretation of the artemether–lumefantrine findings: The artemether–lumefantrine picture differs in kind. Almost all errors were a single extra tablet, and half the children in the 5 to <15 kg band received two tablets where one was recommended, doubling the intended per-dose amount. Because tablets are discrete and the 15 kg boundary falls near the middle of this cohort's weight distribution, an approximated weight translates directly into a whole-tablet error. This is the same vulnerability that dominated artemether–lumefantrine accuracy in rural Tanzania, where correctness was lowest in the middle weight and age bands rather than at the extremes of the distribution.²⁴ The reconciliation is instructive here: the expected tablet count carried in the source dataset had itself been derived from an age-based reference weight rather than the measured weight, misclassifying eight children. The same substitution in practice would produce exactly the observed pattern, since reference weights exceeded measured weights for most children.

The ambiguity of the recorded unit tempers this. A per-dose interpretation is the only one consistent with the observed value range, but the record does not establish that six doses were completed, that tablets were given with fat-containing food as lumefantrine absorption requires, or that the course was finished after discharge; the analysis should be read as concordance of a documented per-dose tablet count, not as a verified account of the treatment course.

Direction of error matters for interpretation, and here the present findings diverge from the pharmacokinetic literature. Simulation across 372,363 children under five in 25 high-burden countries indicates that young children are, if anything, prone to sub-therapeutic day-7 lumefantrine concentrations on standard weight-band dosing, and one of the corrective regimens formally evaluated was an additional 120 mg tablet at each dose.²⁶ An extra tablet in a child of 5 to <15 kg is therefore a departure from the national schedule rather than a presumptive toxicity. That is not an argument for tolerating it: the underlying error is undirected, and the same weight approximation that adds a tablet above the boundary removes one below it, where the exposure margin is narrowest.

Facility variation: Between-facility differences were modest and should be interpreted cautiously: every facility recorded a shortfall in every artesunate dose, so the variation concerns magnitude, not presence, and the two facilities with the smallest median error contributed five and nine children. Differences of this size are compatible with variation in prescribing systems, availability of job aids, pharmacy review, documentation practice or case mix. No staff-level linkage exists in these data, so attributing variation to staff competence would not be supportable, and no ranking of facilities is offered or intended.

Clinical implications: The remedies suggested by these findings are inexpensive and specific. The first is dissemination of the weight-threshold rule itself: 3.0 mg/kg for children under 20 kg is a single fact that was not in use at any of the eight sites, and correcting it requires no new equipment or medicines. The second is weight-band dosing charts and administration job aids displayed at the point of care, converting weight directly to milligrams and to a reconstituted volume so that no arithmetic is needed at the bedside; national artesunate job aids already exist, though their display has been shown to require repeated engagement. The third is accurate weighing on admission, with the measured value recorded before the dose is calculated and explicit prohibition of dosing from an age-based reference weight — a substitution this study found embedded even in the derived data. The remaining measures are independent double-checking of paediatric antimalarial doses by a second clinician or by pharmacy, targeted at children near band



boundaries; standardised reconstitution with separate documentation of the amount prepared and the amount given; and periodic audit and feedback on dose accuracy, which this study shows is feasible from routine records wherever weight and dose are documented.

V. CONCLUSION & RECOMMENDATIONS

5.1 Conclusion

Among children aged 6–59 months hospitalised with malaria in eight Kisumu County hospitals, no recorded injectable artesunate dose met the weight-based recommendation applicable during the study period; all 110 evaluable doses fell below it by a median of about a fifth, in a pattern closely consistent with the 2.4 mg/kg rule for patients of 20 kg or more being applied to children who all weighed less. Just under half of recorded artemether–lumefantrine per-dose tablet counts matched the weight-band recommendation, most discordance being a single additional tablet given to children in the lightest band, and deviations were of similar magnitude across facilities and weight bands. These findings describe a dosing rule that has not been implemented rather than error in its application, and point to correctable system-level gaps in guideline dissemination, weighing, dose verification and documentation. No inference about clinical harm can be drawn from these data.

5.2 Recommendations

County health management teams and hospital administrations in Kisumu County should prioritise dissemination of the current weight-threshold rule for injectable artesunate (3.0 mg/kg per dose for children weighing under 20 kg) and withdraw any job aids, wall charts or prescribing references still based on the superseded 2010 guideline. Paediatric wards should display weight-band dosing charts at the point of care that convert measured weight directly to milligrams and reconstituted volume of artesunate, and to tablets per dose of artemether–lumefantrine. Every child should be weighed on admission and the measured weight recorded before any dose is calculated; age-based or estimated weights should not be used for dosing. Hospitals should introduce independent double-checking of paediatric antimalarial doses by a second clinician or pharmacist, particularly for children near weight-band boundaries, and treatment sheets should record the amount prescribed and the amount given as separate entries. Audit and feedback on dose accuracy should be built into existing quality-of-care reviews.

Future research should use prospective observation of dose preparation and administration, and link recorded doses to parasitological and clinical outcomes, to establish where in the treatment chain errors arise and how they affect outcomes.

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Supplementary material

Supplementary material

Accuracy of weight-based artesunate and artemether–lumefantrine dosing among children hospitalised with malaria in Kisumu County, Kenya: a multicentre clinical-record study

Table 6

Supplementary File 1. STROBE checklist for cross-sectional studies

Item	Recommendation	Location in manuscript
1a	Indicate the study design with a commonly used term in the title or abstract	Title; Abstract, Methods
1b	Provide in the abstract an informative and balanced summary	Abstract
2	Explain the scientific background and rationale	Introduction, paragraphs 1–5
3	State specific objectives, including any prespecified hypotheses	Introduction, final paragraph
4	Present key elements of study design early in the paper	Methods, Study design
5	Describe the setting, locations and relevant dates	Methods, Study setting; Dosing guideline verification (dates); Limitations (exact dates undocumented)
6a	Give the eligibility criteria and the sources and methods of selection	Methods, Study population; Medication-analysis populations
7	Clearly define all outcomes, exposures, predictors, potential confounders and effect modifiers	Methods, Dose recalculation; Dose-accuracy classification; Supplementary Tables 1 and 2
8	For each variable, give sources of data and details of methods of assessment	Methods, Data sources; Data validation
9	Describe any efforts to address potential sources of bias	Methods, Data validation; Results, Participant flow (evaluable vs non-evaluable comparison); Supplementary Table 3
10	Explain how the study size was arrived at	Methods, Study population; Results, Participant flow. The analysis was restricted to all available evaluable records; no separate sample-size calculation was performed for this secondary analysis
11	Explain how quantitative variables were handled in the analyses	Methods, Dose recalculation; Statistical analysis
12a	Describe all statistical methods, including those used to control for confounding	Methods, Statistical analysis
12b	Describe any methods used to examine subgroups and interactions	Methods, Statistical analysis; Results, Facility and weight-band variation
12c	Explain how missing data were addressed	Methods, Data validation; Statistical analysis. No imputation was performed
12d	If applicable, describe analytical methods taking account of sampling strategy	Methods, Statistical analysis (facility fixed effects)
12e	Describe any sensitivity analyses	Methods, Statistical analysis; Results, Sensitivity analyses; Supplementary Tables 6–9
13a–c	Report numbers of individuals at each stage and reasons for non-participation; consider a flow diagram	Results, Participant flow; Figure 1
14a–b	Give characteristics of study participants and indicate numbers with missing data	Results, Characteristics of the medication cohorts; Table 1
15	Report numbers of outcome events or summary measures	Results, Artesunate dose concordance; Artemether–lumefantrine dose concordance; Tables 2–3
16a	Give unadjusted and, where applicable, confounder-adjusted estimates and their precision	Results, Factors associated with inaccurate dosing; Table 5
16b	Report category boundaries when continuous variables were categorised	Methods, Statistical analysis; Tables 3–4
16c	If relevant, consider translating estimates of relative risk into absolute risk	Results, Artesunate dose concordance (absolute proportions and n/N throughout)
17	Report other analyses done	Results, Treatment sequence and medicine availability; Sensitivity analyses



18	Summarise key results with reference to study objectives	Discussion, Principal findings
19	Discuss limitations, taking into account sources of potential bias or imprecision	Discussion, Limitations
20	Give a cautious overall interpretation of results	Discussion, Interpretation sections; Conclusion
21	Discuss the generalisability of the study results	Discussion, Limitations
22	Give the source of funding and the role of the funders	Declarations, Funding (to be confirmed by the authors)

Table 7*Supplementary Table 1. Medication Dosing Rule Matrix*

Field	Artesunate	Artemether–lumefantrine
Guideline title	Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya, 6th edition (revised 2020); WHO Guidelines for Malaria, 14 March 2023	Guidelines for the Diagnosis, Treatment and Prevention of Malaria in Kenya, 6th edition (revised 2020); WHO Guidelines for Malaria, 14 March 2023
Issuing body	Ministry of Health, Kenya (Division of National Malaria Programme); World Health Organization	Ministry of Health, Kenya (Division of National Malaria Programme); World Health Organization
Version / year	6th ed., revised 2020; WHO consolidated guidance as updated 14 March 2023 (WHO/UCN/GMP/2023.01)	As for artesunate
Applicable study period	Data-collection authorisation from 25 September 2023; ethical approval 11 August 2023 to 11 August 2024; national licence to 16 September 2024. Both documents were in force throughout	As for artesunate
Formulation	Injectable artesunate for intravenous or intramuscular use. Exact product, vial strength and reconstituted concentration not documented in the source records; all recorded doses were whole milligrams, consistent with a 10 mg/mL reconstitution	Artemether 20 mg / lumefantrine 120 mg tablets assumed; tablet strength not documented in the source records
Dose basis	mg/kg body weight, with a weight threshold	Weight band, tablets per dose
Weight categories	<20 kg and ≥20 kg	5 to <15 kg; 15 to <25 kg; 25 to <35 kg; ≥35 kg
Recommended dose	3.0 mg/kg per dose for <20 kg; 2.4 mg/kg per dose for ≥20 kg	1, 2, 3 and 4 tablets per dose respectively
Administration frequency	0, 12 and 24 hours, then daily until oral therapy is tolerated; minimum 24 hours of parenteral treatment	Twice daily for three days (six doses)
Recorded dataset unit	Milligrams per injection (integer values 15–47)	Number of tablets. Resolved as tablets per dose: recorded values 1–3 and expected values 1–2 are incompatible with a six-dose course total (6 or 12) or a daily total (2 or 4)
Rounding rule	Recommended dose retained unrounded for all error calculations; rounded to the nearest 1 mg for the exact-match classification (smallest reliably measurable increment at 10 mg/mL with a 1 mL syringe graduated at 0.1 mL)	Not applicable; tablets are discrete and splitting was not assumed
Tolerance rule	Primary: ±10% of the unrounded recommended dose, fixed before inspection of results. Sensitivity: exact rounded agreement, ±5%, ±15%, and one 1 mg administration increment	Primary: exact weight-band match
Source section	Kenya 6th ed., severe malaria treatment section; WHO 2023, treatment of severe malaria — parenteral artesunate dosing recommendation for children weighing <20 kg	Kenya 6th ed., uncomplicated malaria treatment section, artemether–lumefantrine dosing schedule; WHO 2023, ACT dosing
Interpretation limitation	Recorded value may be prescribed rather than administered dose; not established whether it is a single dose, the first dose or an average	Per-dose interpretation inferred from the value range rather than confirmed against the original Kobo form or codebook; completion of all six doses not verifiable



Exact page and section references for the Kenyan 6th edition could not be inserted because a paginated copy of that document was not among the source materials supplied; the authors should insert page and section numbers from their own copy before submission. This is listed under items requiring author verification.

Table 8

Supplementary Table 2. Variable dictionary for the dosing analysis

Variable	Source or derivation	Values
weight_kg	case_childs_weight_in_grams ÷ 1000	Continuous, 7.00–18.83 kg (parent cohort)
case_artesunate_injection_was_the_first_line	Clinical-record checklist	1 = yes (n=110); 2 = no (n=112); 3 = not known (n=111)
case_dosage_for_artesunate_mg_per_injection	Clinical-record checklist	Integer mg; 999 = missing (n=223)
artesunate_rec_mgkg	Derived: 3.0 if weight <20 kg else 2.4	3.0 for all 110 evaluable children
artesunate_recommended_mg_unrounded	Derived: rec_mgkg × weight_kg	Continuous, 21.99–54.51 mg
artesunate_recommended_mg_rounded	Derived: unrounded rounded to nearest 1 mg	Integer, 22–55 mg
artesunate_signed_error_mg	Derived: recorded – unrounded recommended	Continuous, –16.01 to –2.99 mg
artesunate_absolute_error_mg	Derived: signed error	Continuous, 2.99–16.01 mg
artesunate_percentage_error	Derived: signed error ÷ recommended × 100	Continuous, –31.79 to –12.00%
artesunate_absolute_percentage_error	Derived: percentage error	Continuous, 12.00–31.79%
artesunate_recorded_mg_per_kg	Derived: recorded dose ÷ weight_kg	Continuous, 2.05–2.64 mg/kg
artesunate_accuracy_category	Derived from the ±10% tolerance and the sign of the error	Accurate (0); Underdose (110); Overdose (0)
case_artesunate_followed_by_al	Clinical-record checklist	1 = yes (n=97); 2 = no (n=13); 999 = not applicable (n=223)
case_dosage_for_al_no_of_tablets	Clinical-record checklist	1 (n=46); 2 (n=47); 3 (n=4); 999 = missing (n=236)
al_recommended_tablets	Derived from actual weight_kg and the guideline weight bands	1 (n=86); 2 (n=11)
al_signed_error_tablets	Derived: recorded – recommended	–1 (n=3); 0 (n=47); +1 (n=47)



al_accuracy_category	Derived from the signed tablet error	Exact match (47); Underdose (3); Overdose (47)
facility_code	Anonymised facility identifier	1–8
case_antimalarials_prescribed_are_available_in_hospital	Clinical-record checklist	1 = yes (n=165); 2 = no (n=168)
who_waz	Recalculated WHO weight-for-age Z-score (LMS method)	Continuous; used as a descriptive covariate only

Table 9

Supplementary Table 3. Participant exclusions, missing dose documentation, and comparison of evaluable and non-evaluable children

Stage	Artesunate	Artemether–lumefantrine
Parent cohort	333	333
Documented recipient	110	97
Valid recorded weight	110	97
Valid recorded dose	110	97
Guideline-determinable recommendation	110	97
Included in the primary analysis	110	97
Excluded, weight missing	0	0
Excluded, dose missing	0	0
Excluded, unit or formulation unresolved	0	0
Excluded, other documented reason	0	0

Table 10

Comparison of the 110 children evaluable for artesunate dosing with the 223 who were not

Characteristic	Evaluable (n=110)	Not evaluable (n=223)	P value
Age, months, mean	31.8	31.8	0.974
Weight, kg, mean	12.44	12.80	0.328
WHO weight-for-age Z-score, mean	-0.48	-0.23	0.004
Admission haemoglobin, g/dL, mean	9.39	9.23	0.574
Sex	—	—	0.647
Facility	—	—	0.204
Recorded medicine availability	—	—	0.815
Anaemia category	—	—	0.880

Mann–Whitney U tests for continuous measures and χ^2 tests for categorical measures; two-sided P values. Weight-for-age Z-score was lower among evaluable children, consistent with parenteral treatment being given to more unwell children. No other characteristic differed materially.

Table 11

Standardised differences between the 110 evaluable and 223 non-evaluable children

Characteristic	Evaluable (n=110)	Not evaluable (n=223)	Standardised difference
Age, months, mean (SD)	31.8 (15.4)	31.8 (15.1)	0.00
Weight, kg, mean (SD)	12.44 (2.86)	12.80 (2.81)	-0.13
WHO weight-for-age Z-score, mean (SD)	-0.48 (0.86)	-0.23 (0.83)	-0.30
Male sex, n (%)	57 (51.8)	123 (55.2)	-0.07
Microscopy, n (%)	35 (31.8)	57 (25.6)	0.14
Rapid diagnostic test, n (%)	39 (35.5)	98 (43.9)	-0.17
Clinical diagnosis only, n (%)	36 (32.7)	68 (30.5)	0.05
Diagnosis made after admission, n (%)	43 (39.1)	81 (36.3)	0.06
Medicine recorded as available, n (%)	53 (48.2)	112 (50.2)	-0.04



Standardised differences are the difference in means divided by the pooled standard deviation, or the difference in proportions divided by the pooled binomial standard deviation, derived from the summary data in Table 1; absolute values below 0.1 are conventionally negligible and values near 0.2 to 0.3 small. A standardised difference for admission haemoglobin was not derived.

Table 12

Supplementary Table 4. Reconciliation of previously derived and recalculated artesunate dose variables

Item	Previously derived (source dataset and thesis)	Recalculated in this analysis
Dosing rule applied	Uniform 2.4 mg/kg for every child (verified: the expected-dose field equals $2.4 \times$ recorded weight for all 110 children, maximum absolute deviation 0.002 mg)	3.0 mg/kg for all 110 children, all of whom weighed <20 kg, per the guideline in force during data collection
Mean expected dose	29.86 mg	37.32 mg
Mean difference (recalculated – previous)	—	+7.46 mg (median +7.30 mg)
Variance field definition	Recorded dose minus the previously expected dose (verified to hold for all 110 records)	Signed error = recorded dose minus the unrounded guideline-recommended dose
Mean signed error	–0.31 mg	–7.77 mg
Accuracy thresholds	Three categories reproduced as $\pm 5\%$ and $\pm 10\%$ bands around the uniform 2.4 mg/kg dose	Primary $\pm 10\%$ band around the guideline-recommended dose
Category counts, previously reported (thesis Table 4.4)	Negligible 47; clinically acceptable 48; clinically unacceptable 15	—
Category counts, reproduced under the identified thresholds	Within $\pm 5\%$: 47 (exact reproduction). Within 5–10%: 51. Beyond $\pm 10\%$: 12	—
Category counts under the applicable guideline	—	Accurate 0; underdose 110; overdose 0
Records whose classification changed	—	All 110

The three-record discrepancy between the previously reported counts (48 and 15) and the reproduced counts (51 and 12) arises at the 10% boundary and could not be resolved from the frozen dataset; the narrowest band reproduces exactly. The previously derived “clinically unacceptable” label was not used as an authoritative outcome in this manuscript.

Table 13

Supplementary Table 5. Reconciliation of previously derived and recalculated artemether–lumefantrine variables

Item	Previously derived	Recalculated in this analysis
Weight used for banding	Age- and sex-based reference weight (case_recommended_weight). The previously expected tablet count matches a reference-weight banding for all 97 children	Child’s actual recorded weight
Children in the 1-tablet band	78	86
Children in the 2-tablet band	19	11
Records discordant between the two derivations	—	8 children banded at 2 tablets on reference weight but at 1 tablet on measured weight
Exact match	51	47
One tablet below the recommendation	5	3
One tablet above the recommendation	41	47

Using an age-based reference weight rather than the measured weight systematically shifts children upward into the 2-tablet band, because reference weights exceeded measured weights for most children in this cohort. The recalculated figures use the measured weight, as required for a weight-based dosing assessment.

Table 14



Supplementary Table 6. Alternative artesunate tolerance definitions (n=110)

Tolerance rule	Accurate, n/N (% [95% CI])	Below recommendation, n	Above recommendation, n
Exact rounded match	0/110 (0.0 [0.0–3.4])	110	0
+/-5%	0/110 (0.0 [0.0–3.4])	110	0
+/-10% (primary)	0/110 (0.0 [0.0–3.4])	110	0
+/-15%	23/110 (20.9 [14.4–29.4])	87	0
+/-1 mg increment	0/110 (0.0 [0.0–3.4])	110	0

All tolerance rules were fixed before inspection of the error distribution. No tolerance is presented as equally primary with the prespecified $\pm 10\%$ rule. Even a $\pm 15\%$ band, which is wider than any conventional paediatric dose-accuracy tolerance, leaves 87 of 110 recorded doses below the recommendation.

Table 15

Supplementary Table 7. Alternative guideline-rule sensitivity analysis (n=110)

Measure	Study-period rule: 3.0 mg/kg (primary)	Uniform 2.4 mg/kg rule (source-dataset assumption)
Mean signed dose error, mg (95% CI)	-7.77 (-8.31 to -7.24)	-0.31 (-0.70 to 0.08)
Median signed dose error, mg	-7.50	-0.40
Mean absolute percentage error, % (95% CI)	20.8 (19.7–21.9)	6.3 (5.7–7.0)
Median absolute percentage error (IQR), %	20.9 (15.8–26.0)	5.8 (3.6–8.6)
Within $\pm 10\%$, n/N (% [95% CI])	0/110 (0.0 [0.0–3.4])	98/110 (89.1 [81.9–93.6])
Below recommendation, n/N (%)	110/110 (100.0)	12/110 (10.9)
Above recommendation, n/N (%)	0/110 (0.0)	0/110 (0.0)

The study-period rule remains the primary analysis. The uniform 2.4 mg/kg comparison is presented because it is the rule embedded in the source dataset and because the near-zero mean signed error under that rule characterises the pattern of recorded dosing. The current World Health Organization guidance does not differ from the study-period rule for either medicine in the respects relevant here, so no separate current-guidance analysis is presented.

Table 16

Supplementary Table 8. Weight-boundary sensitivity analysis

Boundary examined	Children within 0.1 kg	Children within 0.5 kg	Children whose applicable rule or band would change
Artesunate weight bands (10, 15, 20 kg)	3	22	0
Artesunate dosing threshold (20 kg)	0	0	0 (heaviest child 18.17 kg)
Artemether–lumefantrine band boundary (15 kg)	0	5	5 would move between the 1- and 2-tablet recommendation under a ± 0.5 kg weight perturbation

The primary weight was not altered in any analysis. No plausible measurement or rounding error would change the applicable artesunate milligram-per-kilogram rule for any child, because no child approached 20 kg. The artemether–lumefantrine classification is more sensitive to weight measurement, since a whole-tablet difference turns on which side of 15 kg a child falls; this is discussed in the Limitations.

Table 17

Supplementary Table 9. Facility-specific full results and facility fixed-effect models

Facility	Artesunate n	Median signed error, mg	Median absolute error (IQR) %	Median recorded mg/kg (IQR)	Accurate n/N (% [95% CI])	Below, n	Above, n
Facility 1	36	-7.50	21.1 (16.0–26.1)	2.37 (2.22–2.52)	0/36 (0.0 [0.0–9.7])	36	0
Facility 2	20	-7.49	22.8 (17.0–26.3)	2.31 (2.21–2.49)	0/20 (0.0 [0.0–16.8])	20	0
Facility 3	11	-6.51	22.7 (16.9–26.3)	2.32 (2.21–2.49)	0/11 (0.0 [0.0–28.5])	11	0
Facility 4	5	-5.49	14.3 (13.0–17.5)	2.57 (2.48–2.61)	0/5 (0.0 [0.0–52.2])	5	0



Facility 5	13	-8.50	22.5 (17.8–26.5)	2.33 (2.20–2.47)	0/13 (0.0 [0.0–24.7])	13	0
Facility 6	9	-6.00	15.8 (13.2–17.3)	2.53 (2.48–2.60)	0/9 (0.0 [0.0–33.6])	9	0
Facility 7	9	-8.50	19.5 (17.4–23.3)	2.41 (2.30–2.48)	0/9 (0.0 [0.0–33.6])	9	0
Facility 8	7	-8.49	24.3 (20.6–26.4)	2.27 (2.21–2.38)	0/7 (0.0 [0.0–41.0])	7	0

Table 18

Facility fixed-effect model of artesunate absolute percentage dose error (HC3 robust standard errors)

Term	β , percentage points (95% CI)	P value
Weight, per kg	0.10 (-0.28 to 0.49)	0.594
Prescribed medicine recorded as available	1.71 (-0.48 to 3.89)	0.126
Facility 2 (reference Facility 1)	0.97 (-2.44 to 4.38)	0.577
Facility 3 (reference Facility 1)	1.18 (-3.04 to 5.40)	0.583
Facility 4 (reference Facility 1)	-4.24 (-8.93 to 0.46)	0.077
Facility 5 (reference Facility 1)	1.33 (-2.44 to 5.10)	0.488
Facility 6 (reference Facility 1)	-5.33 (-7.79 to -2.87)	<.001
Facility 7 (reference Facility 1)	-0.80 (-4.78 to 3.18)	0.693
Facility 8 (reference Facility 1)	2.32 (-2.41 to 7.06)	0.336

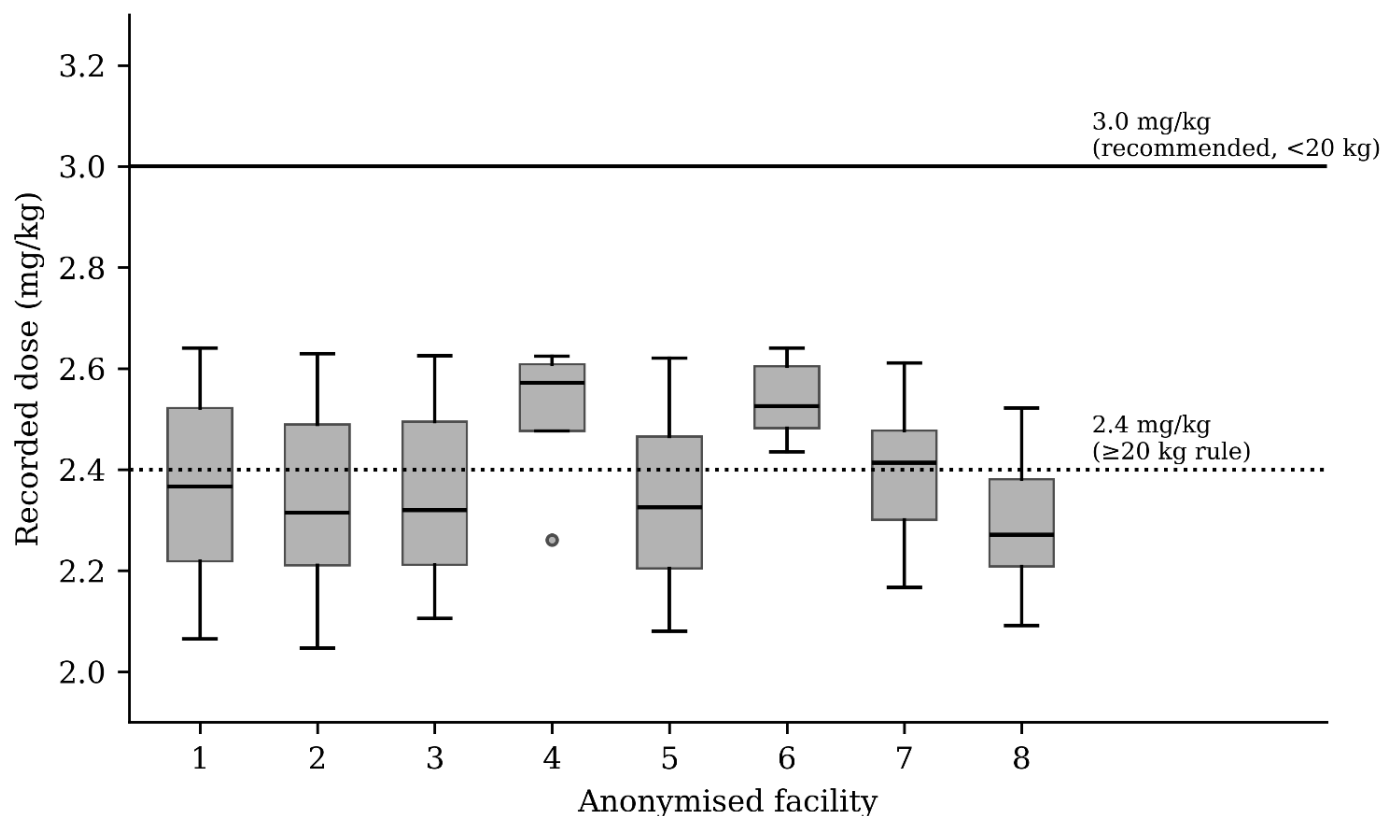
Table 19

Facility fixed-effect model of any artemether–lumefantrine dose error (modified Poisson with robust variance)

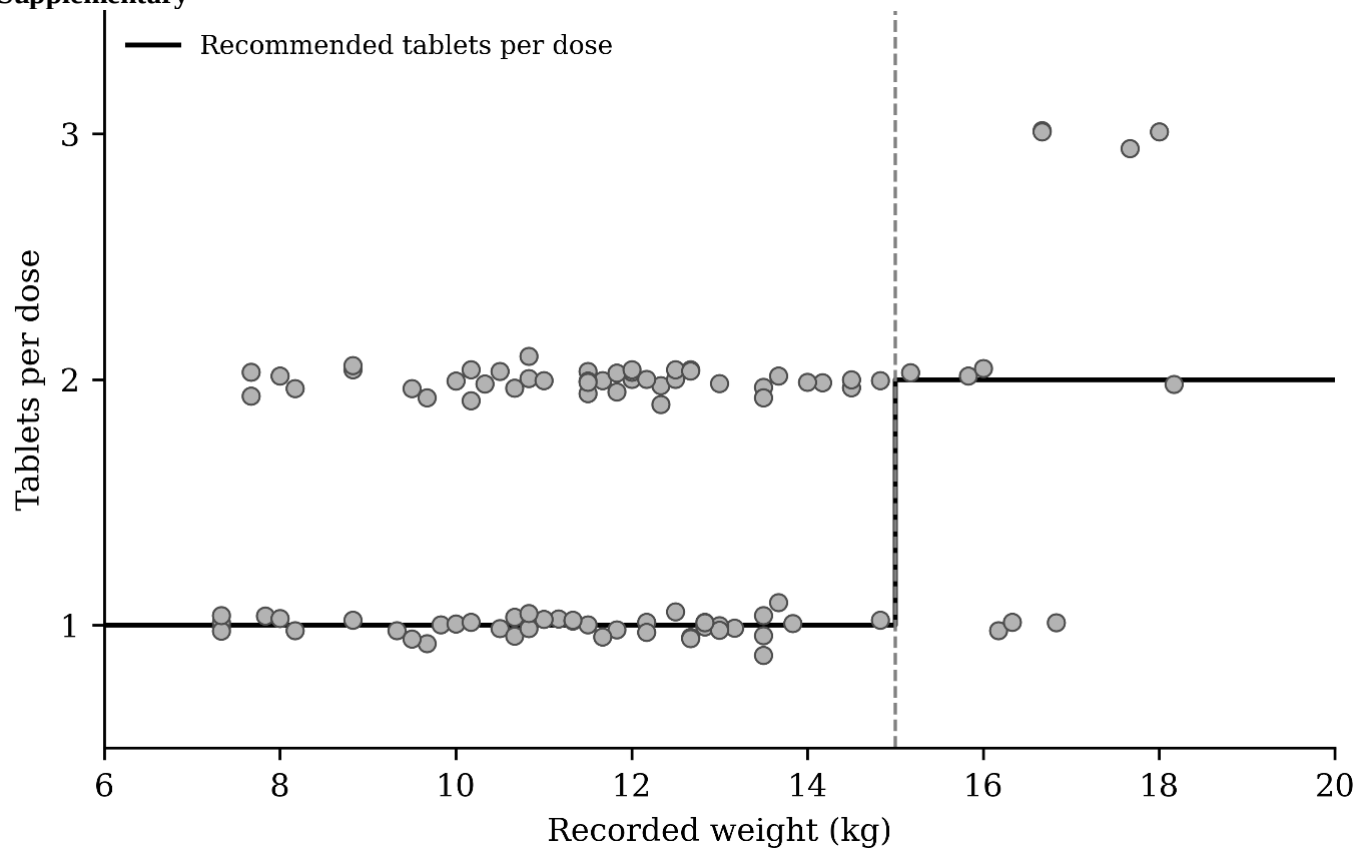
Term	Prevalence ratio (95% CI)	P value
Weight, per kg	1.05 (0.98–1.13)	0.171
Prescribed medicine recorded as available	0.83 (0.57–1.22)	0.353
Facility 2 (reference Facility 1)	1.02 (0.56–1.88)	0.944
Facility 3 (reference Facility 1)	1.12 (0.54–2.29)	0.763
Facility 4 (reference Facility 1)	0.42 (0.07–2.47)	0.340
Facility 5 (reference Facility 1)	1.17 (0.65–2.12)	0.600
Facility 6 (reference Facility 1)	1.53 (0.90–2.59)	0.117
Facility 7 (reference Facility 1)	0.87 (0.33–2.26)	0.773
Facility 8 (reference Facility 1)	1.52 (0.80–2.90)	0.206

Facility fixed effects were used in preference to facility random effects because only eight facilities are represented. Cluster-robust standard errors at facility level were not relied upon for the same reason. Adding facility fixed effects did not materially change the weight or availability estimates in either model. Individual facility coefficients are imprecise and are reported for completeness rather than for interpretation; they must not be read as a ranking of hospitals.

Supplementary

**Figure 1**

Recorded artesunate dose in mg/kg by anonymised facility, against both guideline dose rules.

Supplementary**Figure 2**

Recorded artemether–lumefantrine tablets per dose against recorded weight, with the recommended weight-band step function.

**Table 20***Supplementary File 4. Analysis log*

Item	Detail
Input file	01_Nabuwanga_Authoritative_Master_Dataset.xlsx, sheet Master_Clean_333 (333 rows × 169 columns, header on row 3)
Input file SHA-256	cf21589050394e22d07c910f7f91c6914a0e56659d03de06b3598e1e4ba23026
File handling	Opened read-only; all recoding and derivation performed by script on a working copy; no manual edits
Governing analysis plan	08_Nabuwanga_Statistical_Analysis_Plans_6_Papers.xlsx, sheets Common_Analysis_Rules and P6_EASci
Software	Python 3.12; NumPy 2.4.4; pandas 3.0.2; SciPy 1.17.1; Matplotlib 3.10.8
Random seed	20260802 (bootstrap resampling and quantile-regression bootstrap)
Bootstrap resamples	10,000 for descriptive intervals; 1,000 for quantile-regression intervals
Estimators implemented directly	Wilson and exact binomial intervals; modified Poisson regression with sandwich variance; HC3 robust linear regression; median regression by iteratively reweighted least squares. No general-purpose regression library was available in the analysis environment; the complete implementation is supplied as Supplementary File 2

Table 21*SAP amendments*

No.	Original specification	Change and rationale	Made seeing results? before model
1	P6_EASci: “The existing right artesunate dose appears to apply 2.4 mg/kg uniformly”; required action to verify the operative guideline	Guideline verified as Kenya 6th edition (revised 2020) and WHO 2023, both specifying 3.0 mg/kg for children <20 kg. The 3.0 mg/kg rule was adopted as primary and the uniform 2.4 mg/kg rule retained as a prespecified sensitivity analysis. This is implementation of the SAP’s required action, not a deviation	Yes
2	P6_EASci: “Modified Poisson for unacceptable error using weight, age, facility and availability”	Not estimable for artesunate: the binary outcome had no variance (110/110 inaccurate). Descriptive stratified reporting was used instead, as the SAP permits for sparse or degenerate outcomes, together with robust linear and median models of the continuous error. The model was fitted as specified for artemether–lumefantrine	Yes
3	P6_EASci: tolerance rule to be frozen before classification	Primary tolerance fixed at $\pm 10\%$ of the unrounded recommended dose, justified by the 1 mg administration increment; exact, $\pm 5\%$, $\pm 15\%$ and one-increment rules prespecified as sensitivity analyses	Yes
4	P6_EASci: resolve the artemether–lumefantrine tablet unit before classification	Resolved as tablets per dose on the basis of the observed value range (1–3 recorded, 1–2 expected), which is incompatible with a course or daily total. Documented as an inference rather than a confirmation against the original instrument	Yes

Supplementary Files 2, 3 and 5

Supplementary File 2 (complete statistical analysis code) is supplied as the accompanying Python source files. Supplementary File 3 (data dictionary) is given as Supplementary Table 2 above and in the accompanying machine-readable file. Supplementary File 5 (minimal de-identified dataset) is supplied as the accompanying comma-separated value file containing the participant-level weight, dose, recalculated recommended dose, error and classification variables together with anonymised facility codes; it also constitutes the underlying data for Figures 2, 3 and 4.