

# Dose optimization of ivermectin to achieve equivalent exposure coverage in children and adults

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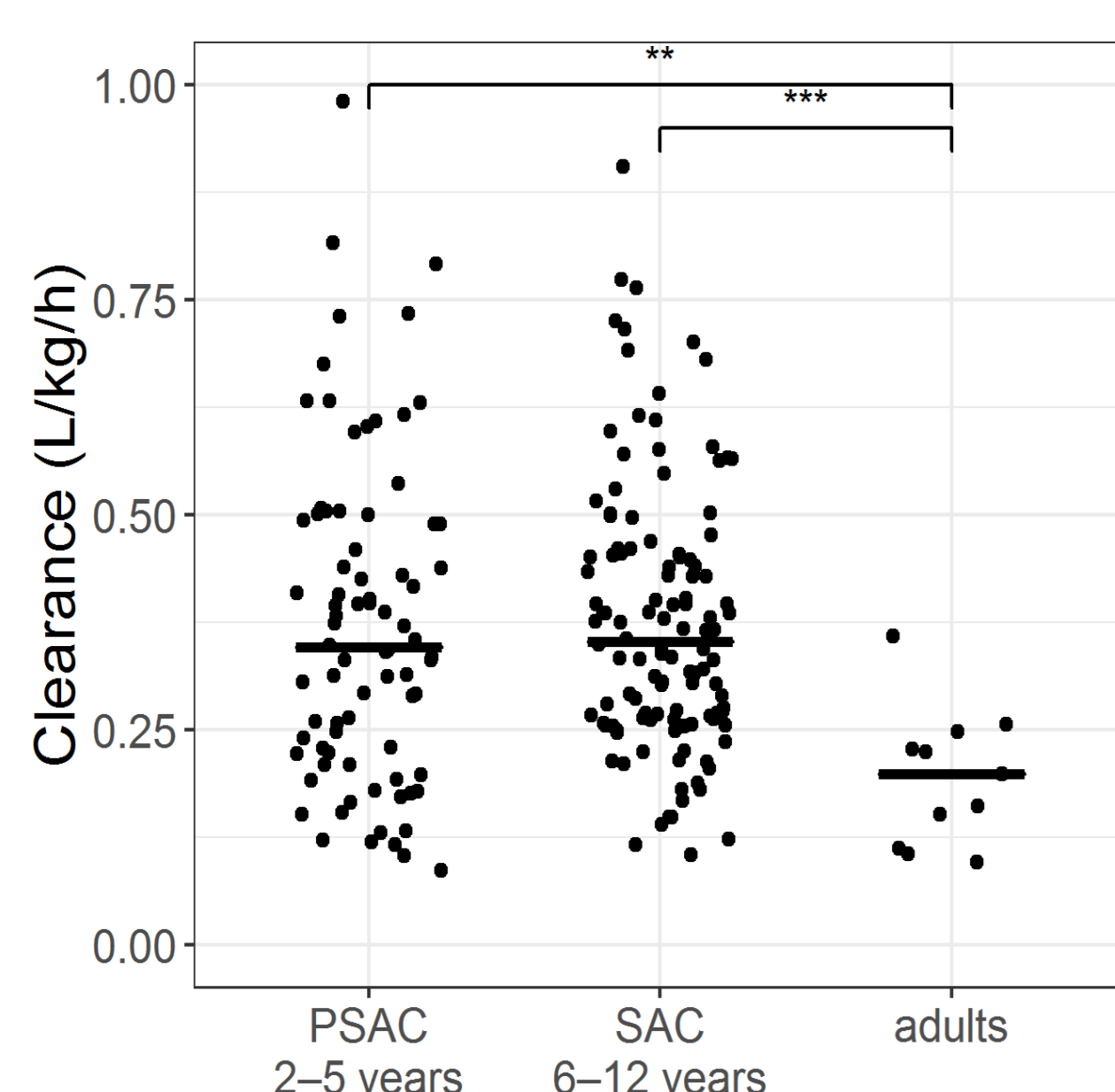
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## Background

- Soil-transmitted helminthiasis: neglected tropical disease.
- Approximately 1.5 billion people infected worldwide [1].
- Ivermectin: commonly-used broad-spectrum antiparasitic drug, but doses associated with consistent exposure in children 2–12 years of age and adults are unknown.

### Objectives:

- To develop a population PK model for ivermectin in children
- To identify a dosing strategy for both pre-school-aged children (2–5 years of age) and school-aged children (6–12 years of age) that is associated with equivalent exposure coverage in children and adults.



**Figure 1.** Clearance per kilogram body weight, stratified per age group. A nonparametric test of group differences was performed using the independent 2-group Wilcoxon-Mann-Whitney Test, with \*\*\* indicating a p-value <0.001 and \*\* for p <0.01.

**Table I.** Model parameters and bootstrap results

Parameter (unit)	Value (RSE %) [shrinkage]	Bootstrap median (90% CI)
CL/F (L/h)	5.94 (5%) × (WT/18) <sup>0.75</sup>	5.94 (5.38–6.46)
V <sub>c</sub> /F (L)	116 (6%) × (WT/18)	115 (104–128)
V <sub>p</sub> /F (L)	91.2 (14%) × (WT/18)	90.6 (75.5–130)
Q/F (L/h)	5.86 (15%) × (WT/18) <sup>0.75</sup>	5.83 (4.66–7.83)
k <sub>a</sub> , k <sub>tr</sub> (h <sup>-1</sup> ) <sup>#</sup>	0.907 (4%) +44% (8%) in adults*	0.904 (0.846–0.967) +44% (25.1–65.5)
IIV CL/F (CV%)	28.6 (7%) [10%]	28.8 (22.4–38.3)
IIV V <sub>c</sub> /F (CV%)	37.9 (9%) [9%]	37.1 (25.2–51.4)
IIV V <sub>p</sub> /F (CV%)	58.4 (28%) [49%]	58.4 (17.5–165)
IIV k <sub>a</sub> (CV%)	26.2 (7%) [10%]	26.0 (19.8–33.4)
Prop. error	0.051 (12%) [16%]	0.051 (0.040–0.065)
Add. error	1.54 (24%) [16%]	1.53 (0.74–2.36)

CL: clearance, F: bioavailability, V<sub>c</sub> and V<sub>p</sub>: volume of distribution in central and peripheral compartment, Q: inter-compartmental clearance, k<sub>a</sub>: absorption rate constant, IIV: inter-individual variability, reported as coefficient of variation (CV%). RSE: relative standard error. 90%CI: 5<sup>th</sup>–95<sup>th</sup> percentile representing the 90% confidence interval. Proportional and additive errors are reported as variance estimates (σ<sup>2</sup>). Bootstrap results are reported based on 91.4% successful runs.

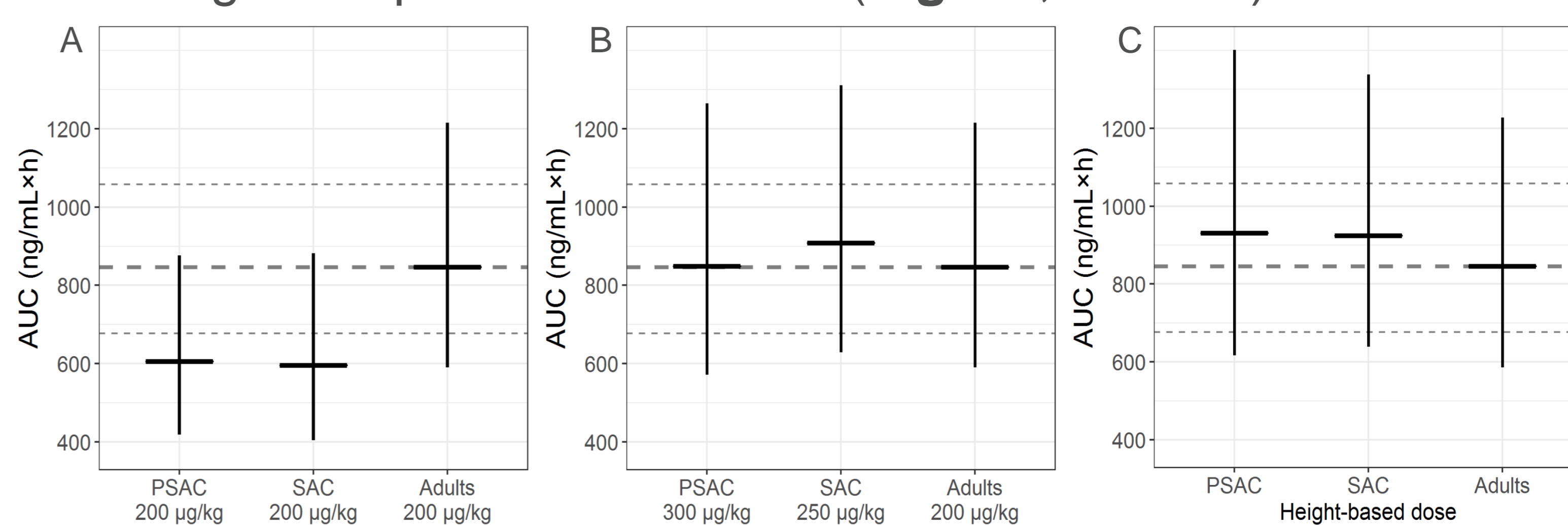
<sup>#</sup>The model included 2 transit compartments with k<sub>tr</sub> = k<sub>a</sub>, leading to a mean transit time (MTT) of 3.14 h (median, 90%CI 1.61–6.43 h) in the whole population. \*The absorption in adults was 44% faster than in children with a typical k<sub>a</sub> and k<sub>tr</sub> value of 1.31 h<sup>-1</sup>.

## Methods

- Ivermectin PK data collected in 211 patients with *Trichuris trichiura* infections in Côte d'Ivoire, including:
  - 80 pre-school-aged children (PSAC, 2–5 years) [2],
  - 120 school-aged children (SAC, 6–12 years) [2]
  - 11 adults [3]
- DBS densely sampled (8–11 samples/participant)
- Dose administered: PSAC 100 or 200 µg/kg, SAC 200, 400, or 600 µg/kg, and adults 200 µg/kg.
- A population PK model was developed using NONMEM 7.4.
- Model-based simulations of different dosing scenarios:
  - current dose of 200 µg/kg,
  - an increased weight-based dose,
  - an increased dose based on height,
 all rounded to whole 3-mg tablets. Target exposure was defined as within the 80–125% range of the median adult exposure observed with a 200 µg/kg ivermectin dose.

## Results

- Parameter estimates of the two-compartmental PK model with two transit compartments are listed in **Table I**.
- Clearance/kg bodyweight in PSAC and SAC were similar (0.346 (0.12–0.73) L/h/kg and 0.352 (0.17–0.69) L/h/kg), but higher than in adults (0.20 (0.10–0.31) L/h/kg) (**Fig. 1**).
- Consequently, a 200 µg/kg dose in children is associated with lower exposure in children than in adults (**Fig. 2a**).
- Simulations indicate that an increased dose of 300 and 250 µg/kg would be needed in PSAC and SAC, respectively (**Table II**), to achieve equivalent exposure coverage in children and adults (**Fig. 2b**).
- Alternatively, we also provide a height-based dosing schedule, as height is easier to measure than body weight in settings with poor infrastructure (**Fig. 2c, Table II**).



**Figure 2.** Simulated ivermectin exposure (AUC) following (A) a dose of 200 µg/kg in all populations, rounded to whole 3-mg tablets; (B) a dose based on body weight, with a stepwise increase in dose with increasing body weight as shown in Table II, corresponding to approximately 300 µg/kg in PSAC and 250 µg/kg in SAC; (C) a dose based on height, with increasing dose with increasing height (Table II). Horizontal black lines: median value in the population, vertical black lines: inter-quartile range. Grey dashed lines indicate the median (80–125%) exposure in adults following a 200 µg/kg dose.

## Conclusion

Using a model-based approach, we report the first dosing strategy for ivermectin that is associated with equivalent exposure coverage in children and adults.

**Table II.** Model-based dose recommendations, to reach an exposure coverage equivalent to a 200 µg/kg dose in adults, in pre-school-aged children (PSAC, 2–5 years of age) and school-aged children (SAC, 6–12 years of age), when ivermectin is administered as whole 3-mg tablets.

Number of 3-mg tablets advised	200 µg/kg dose (Current dose) <sup>#</sup>	Proposed pediatric dose based on body weight	Proposed pediatric dose based on height
1 tablet	15–24 kg	10–14 kg	78–90 cm
2 tablets	25–35 kg	15–29 kg	90–130 cm
3 tablets	36–50 kg	30–41 kg	130–150 cm
4 tablets	51–65 kg	42–50 kg	150–165 cm
5 tablets	66–79 kg	-	165–175 cm

<sup>#</sup>No safe dose for patients with a weight <15 kg had been established yet.

## References

- [1] WHO, 2018, Factsheet on Soil-Transmitted Helminthiasis. Available from <https://www.who.int/en/news-room/factsheets/detail/soil-transmitted-helminth-infections>
- [2] Wimmersberger D, et al. Clin Infect Dis. 2018; 67(8):1247-55
- [3] Schulz JD, et al. Anal. Methods, 2018, 10, 2901-9

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