I-080

Simulation-based guideline implementation of weight-banded dosing strategies for childhood leprosy

Jennie van Dyk[1], Tiziana Masini[2], Saba M. Lambert[3], Joydeepa Darlong[4], Patricia D. Deps[5], Mauricio L. Nobre[6], Wim van Brakel[7], Becks Hill[8], Parul Malik[9], Vivek Lal[9], Roeland E. Wasmann[1]

[1] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa, [2] Global Accelerator for Paediatric Formulations, Science for Health Department, World Health Geneva, Switzerland, [3] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK, [4] The Mission Trust India, New Delhi, India, [5] Tropical Disease Institute, Health Organization, Geneva, Switzerland, [3] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK, [4] The Mission Trust India, New Delhi, India, 5 Faculty of Medicine, Department of Public Health, Postgraduate Program of Infectious Diseases, Federal University of Espirito Santo, Vitoria-ES, Brazil, 6 Tropical Disease Institute, Federal University of Rio Grande do Norte, Brazil, 7 International Leprosy Association, Brentford, London, UK, 8 Director of Programmes and Advocacy, Lepra, Colchester, UK, 9 Global Leprosy Programme, World Health Organization, New Delhi, India
Federal University of Rio Grande do Norte, Brazil, [6]

Email: vdyjen001@myuct.ac.za

UCT Pharmacometrics

Background

Leprosy is a neglected tropical disease causing lifelong disability if inadequately treated. Each year, ~10,000 new leprosy cases are reported in children globally.

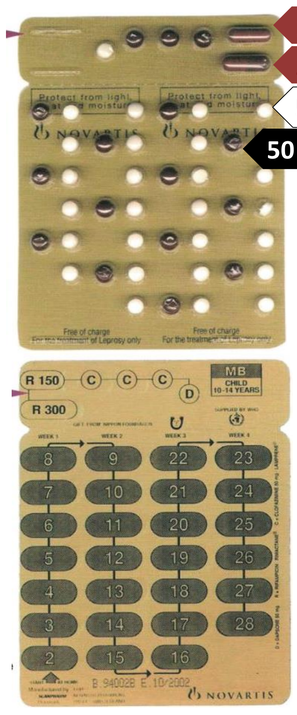

Figure 1: Child blister pack (age 10-14 years)

Multidrug therapy (MDT) is effective and distributed as **free-of-charge blister packs** using **age-based dosing** for adults and 10-14 year old children **(Fig 1)** [1]:

Adult (> 14 years)

600 mg rifampicin + 300 mg clofazimine monthly
100 mg dapsone + 50 mg clofazimine daily

Children 10-14 years old

450 mg rifampicin + 150 mg clofazimine monthly
50 mg dapsone daily + 50 mg clofazimine alternate day

For younger children, treatment is **operationally difficult** [2] and no blister pack is available :

Children <10 years *current recommendations*

10 mg/kg rifampicin + 100 mg clofazimine monthly
2 mg/kg dapsone daily + 50 mg clofazimine twice weekly

- Complex mg/kg dose calculations
- Incompatible with available formulation
- Underexposure at smaller weights

After early infancy, **body size** is the best predictor of drug exposure and **weight-based dosing** is standard practice [3].

Objectives

1. Use modelling and simulation informed by allometry and maturation to transition from **age-based to weight-banded MDT dosing** in young children
2. Evaluate dose delivery using **existing MDT blister packs**

Methods

Model selection: Adult exposure matching

The **WHO Paediatric Dosing Tool** [3] was used to evaluate doses ($Dose_{child}$) across harmonized paediatric weight bands (6–<40 kg) [4].

$Dose_{child}$ was selected to achieve **80–125% adult-equivalent steady-state exposure** $\left(\frac{AUC_{child}}{AUC_{adult}}\right)$.

- $\boldsymbol{AUC_{adult}}$ based on standard MDT ($Dose_{adult}$) in a 60 kg adult [2].
- $\boldsymbol{AUC_{child}}$ predicted using Eq. 1:

$$\frac{AUC_{child}}{AUC_{adult}} = \frac{Dose_{child} \cdot F_{child}}{\cancel{CL} \cdot \left(\frac{Weight_{child}}{60}\right)^{0.75} \cdot MAT_{CL,child}} \Big/ \frac{Dose_{adult} \cdot F_{adult}}{\cancel{CL}} \quad [Eq.1]$$

Assumptions:

- Equivalent oral bioavailability ($\boldsymbol{F_{child} = F_{adult}}$)
- Allometric scaling with body weight
- **Full maturation** of clearance pathways in children ≥2 years $\left(\boldsymbol{MAT_{CL,child} = 1}\right)$
- **Children <2 years excluded due to very low incidence of leprosy [5]**

Safety benchmark

Doses from other pediatric indications simulated for comparison as reference standards

- WHO paediatric tuberculosis dosing guidelines for **rifampicin** and **clofazimine** [6]
- **Dapsone** dosing in current leprosy protocols

Implementation

Use of child blister packs for dose delivery was explored, acknowledging potential acceptability and feasibility limitations.

Expert consultation

Several weight banded dosing options were derived from our simulations and options were given for discussion to the WHO Technical Working Group on Leprosy in Children.

Results

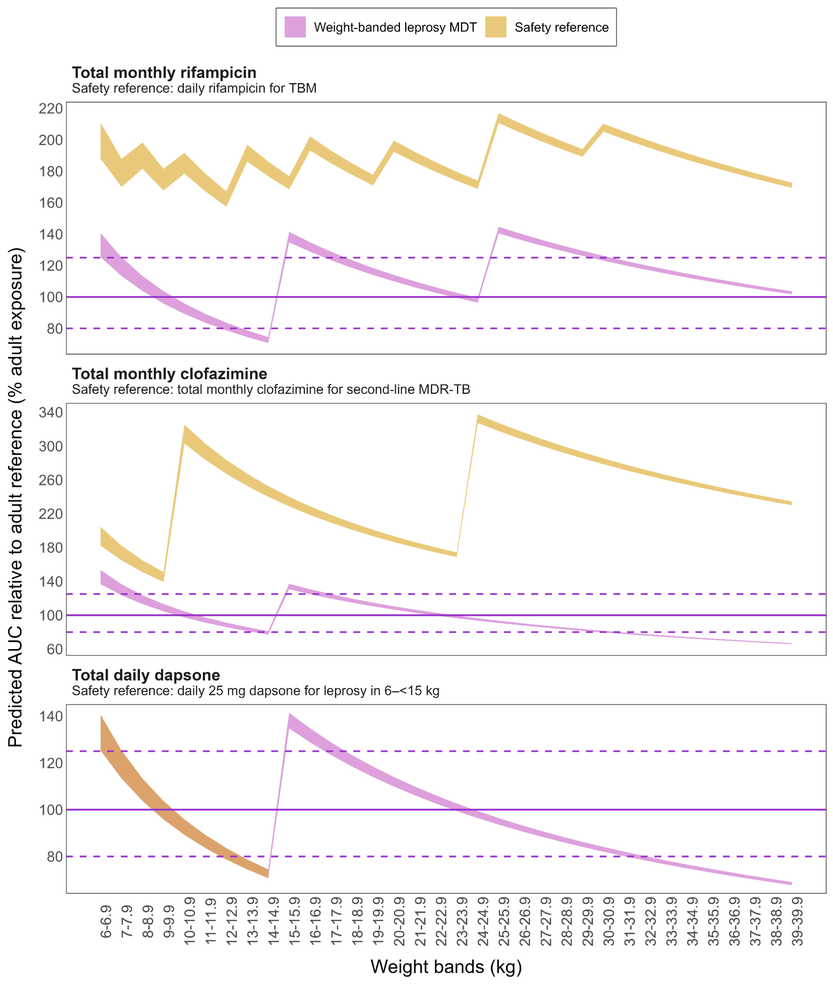

Figure 2: Simulated MDT exposures

Predicted adult-equivalent exposures (shaded area) by weight band for children receiving weight-banded MDT regimens (purple) and safety reference standard therapies (orange). Dapsone exposures equivalent to safety reference with overlapping distributions. Solid and dashed lines indicate 100% and 80–125% adult-equivalent exposure, respectively.

Children <10 years *updated recommendations*

Weight band	6-9.9 kg	10-14.9 kg	15-19.9 kg	20-24.9 kg	25-29.9 kg	30-39.9 kg
Rifampicin (mg)	**150 monthly**	**150 monthly**	**300 monthly**	**300 monthly**	**450 monthly**	**450 monthly**
Clofazimine (mg)	**100 monthly** 50 twice-weekly	**100 monthly** 50 twice-weekly	**150 monthly** 50 alternate day	**150 monthly** 50 alternate day	**150 monthly** 50 alternate day	**150 monthly** 50 alternate day
Dapsone (mg)	50 alternate day	50 alternate day	50 daily	50 daily	50 daily	50 daily

Figure 3: Weight-banded dosing

(Top) Weight-banded MDT dosing table in children aged 2 to <10 years old and/or weighing 6–39.9 kg. Includes monthly and daily doses of rifampicin, clofazimine, and dapsone.
(Bottom) Updated MDT regimen using modified pediatric blister packs for each weight band. Crosses (×) indicate tablets that clinicians should remove. Children weighing 25–39.9 kg do not require blister pack modifications.

Conclusion

We adapted age-based to weight-based dosing in young children which achieved:

- Balanced exposure across weight bands
- Within adult range and below other pediatric indication exposure

Weight-banded dosing is more consistent with pharmacokinetic principles and aligns with current practice in pediatric antimicrobial treatment [4]

Implementable in children <10 years using existing MDT blister packs

- Acceptability may be limited in younger children
- A WHO Paediatric Drug Optimization (PADO) meeting for leprosy is planned to discuss child-friendly formulations that are available for children with leprosy [7]

This work highlights the value of model-informed dose optimization in neglected pediatric populations with limited pharmacokinetic and pharmacodynamic data

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Acknowledgements

We thank the members of the WHO Technical Working Group on Leprosy among Children for their expert guidance, clinical insights, and support throughout this work.

This project is funded by the National Research Foundation (PMDS23042597212).

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