An easy-to-use Paediatric Dosing Tool - Because one mg/kg dose does NOT fit all.

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Background and Objectives

First strategy for paediatric dosing of anti-infectives is **to target exposures similar to** successfully treated **adults**. Scaling pharmacokinetics (PK) is a key first step.

- **Body size alone** explains most of the changes down to **2-3 years of age**.
- Allometric scaling [1] describes the **nonlinear** effect of body size on PK
- Other factors, including **maturation**, mostly in children <2 years old [2]

Same mg/kg dose in children and adults causes under-dosing (Figure 1).
Even with no info available, allometry is a better guess than constant mg/kg [4]

Paediatric dosing regimens still incorrectly use constant mg/kg dosing as first "best-guess", possibly because of the difficulty due to the non-linearity.

The objective of this work is to bridge this gap by proposing an intuitive and easy-to-use tool to assist researchers not conversant in PK modelling to design and evaluate paediatric dosing regimens.

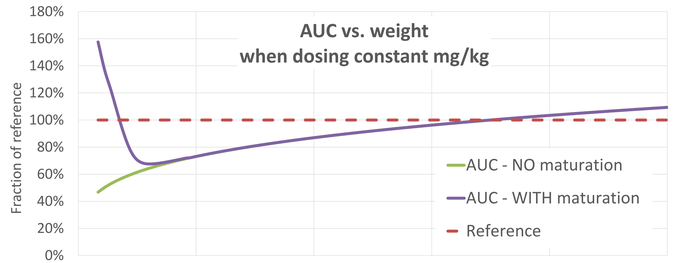


Figure 1. Exposure (area under the curve - AUC) achieved with constant mg/kg dosing VS. child weight

Methods

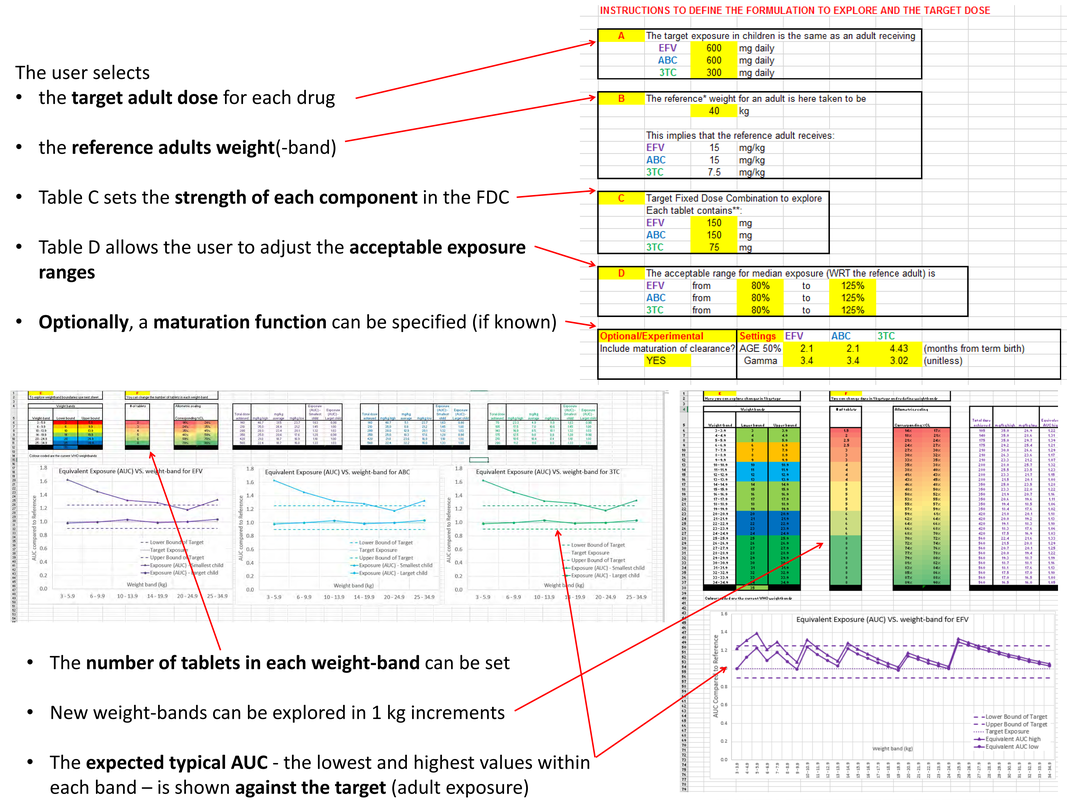
The tool was designed using Microsoft Excel,
- chosen for its ease of use and ubiquity
- familiarity amongst clinicians
- with easy steps to follow and
- results displayed in a graphical form in real-time

The tool uses **allometric scaling** to adjust for the **effect of body size** on clearance.
It targets the same exposure in terms of area under the time-concentration curve (AUC) as adults.
It shows the expected median exposure in the smallest and largest child in each weight-band.

Features
- analysis of multiple drugs in a **fixed-dose combination (FDC)**
- use of **standard dosing weight-bands** or **customised weight bands** can be explored
- possibility of including the effect of maturation (if known for the drug)

Results – WHO Paediatric Dosing Tool

The user selects
- the **target adult dose** for each drug
- the **reference adults weight**(-band)
- Table C sets the **strength of each component** in the FDC
- Table D allows the user to adjust the **acceptable exposure ranges**
- **Optionally**, a **maturation function** can be specified (if known)



- The **number of tablets in each weight-band** can be set
- New weight-bands can be explored in 1 kg increments
- The **expected typical AUC** - the lowest and highest values within each band – is shown **against the target** (adult exposure)

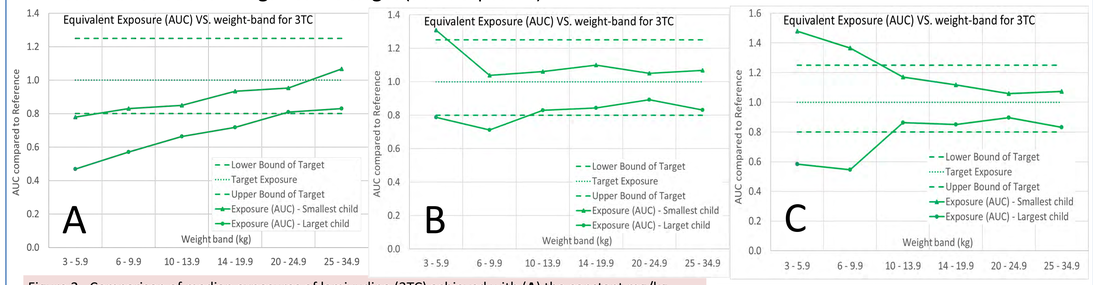


Figure 2. Comparison of median exposures of lamivudine (3TC) achieved with (**A**) the constant mg/kg dosing (left), (**B**) optimised dosing with allometric scaling but WITHOUT accounting for maturation (centre) and (**C**) optimised dosing using allometric scaling and maturation

Example – lamivudine:
Target exposure = equivalent to adult daily 300 mg daily
Visual output (Figure 3) and doses (Table 1) obtained using constant mg/kg, allometry (similar results to [3]) and maturation (with maturation parameters from [4])

	Constant mg/kg		Allometry		Allomery + Maturation	
Weight-band	Total dose	mg/kg dose	Total Dose	mg/kg dose	Total Dose	mg/kg dose
3 - 5.9	34	7.5	56	12.6	15	3.4
6 - 9.9	60	7.5	75	9.4	45	5.7
10 - 13.9	90	7.5	113	9.4	113	9.4
14 - 19.9	128	7.5	150	8.8	150	8.8
20 - 24.9	170	7.6	188	8.4	188	8.4
25 - 34.9	225	7.5	225	7.5	225	7.5

Table 1. Lamivudine (3TC) dosing using constant mg/kg (left) allometry (centre) and allometry+maturation (right)

Limitations

This tool is **ONLY meant to provide general guidelines**, mostly based on the theory of allometric scaling, accounting for the effect of body size on PK

Allometric scaling alone works well down to 2 years of age, but below that, **immature organ function** may cause clearance to be lower than body size alone would predict. This is explored in the tool but is **strongly drug-specific**

Other factors – not accounted for in the tool - **may have a large impact,** e.g.:
- lower protein binding in young children,
- differences in drug formulation,
- or poor absorption.

Additionally, **terminal half life is generally shorter in children**, so targeting the same AUC - as in this tool - may achieve higher C_{max} and lower C_{min}.
To avoid toxicity (high C_{max}) or poor efficacy (low C_{min}), it **may be necessary to switch from QD to BID dosing** in smaller children.

Only typical values are shown and no between subject variability is included here. Some drugs may be characterised by large variability

Discussion

The purpose of the tool is to **assist in the design of clinical trials** for dosing in paediatrics, and is meant as a first step, **not a substitute to confirmatory studies**.

The use of this tool (and thus allometric scaling) for study design would represent a significant step away from the constant mg/kg paradigm, possibly leading to improvements in the efficacy of paediatric dosing trials.

References

[1] B. J. Anderson and N. H. G. Holford, "Mechanism-based concepts of size and maturity in pharmacokinetics.," *Annu. Rev. Pharmacol. Toxicol.*, vol. 48, pp. 303–32, Jan. 2008.

[2] Liu T, Ghafoori P, Gobburu JVS. 2016. Allometry is a reasonable choice in pediatric drug development. J. Clin. Pharmacol. 1–20.

[3] 1. Bouazza N, Cressey TR, Foissac F, Bienczak A, Denti P, McIlleron H, Burger D, Penazzato M, Lallemant M, Capparelli E V., Treluyer J-M, Urien S. 2016. Optimization of the strength of the efavirenz/lamivudine/abacavir fixed-dose combination for paediatric patients. J. Antimicrob. Chemother.

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Link

Link on WHO website:
http://www.who.int/hiv/paediatric/generictool/en/

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