Of “clever” models and “dumb” spreadsheets: what is more effective to drive policy change?

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Partly presented at ACoP 10 on October 21st 2019, Orlando, FL

About me

Masters Degree in Computer Engineering,
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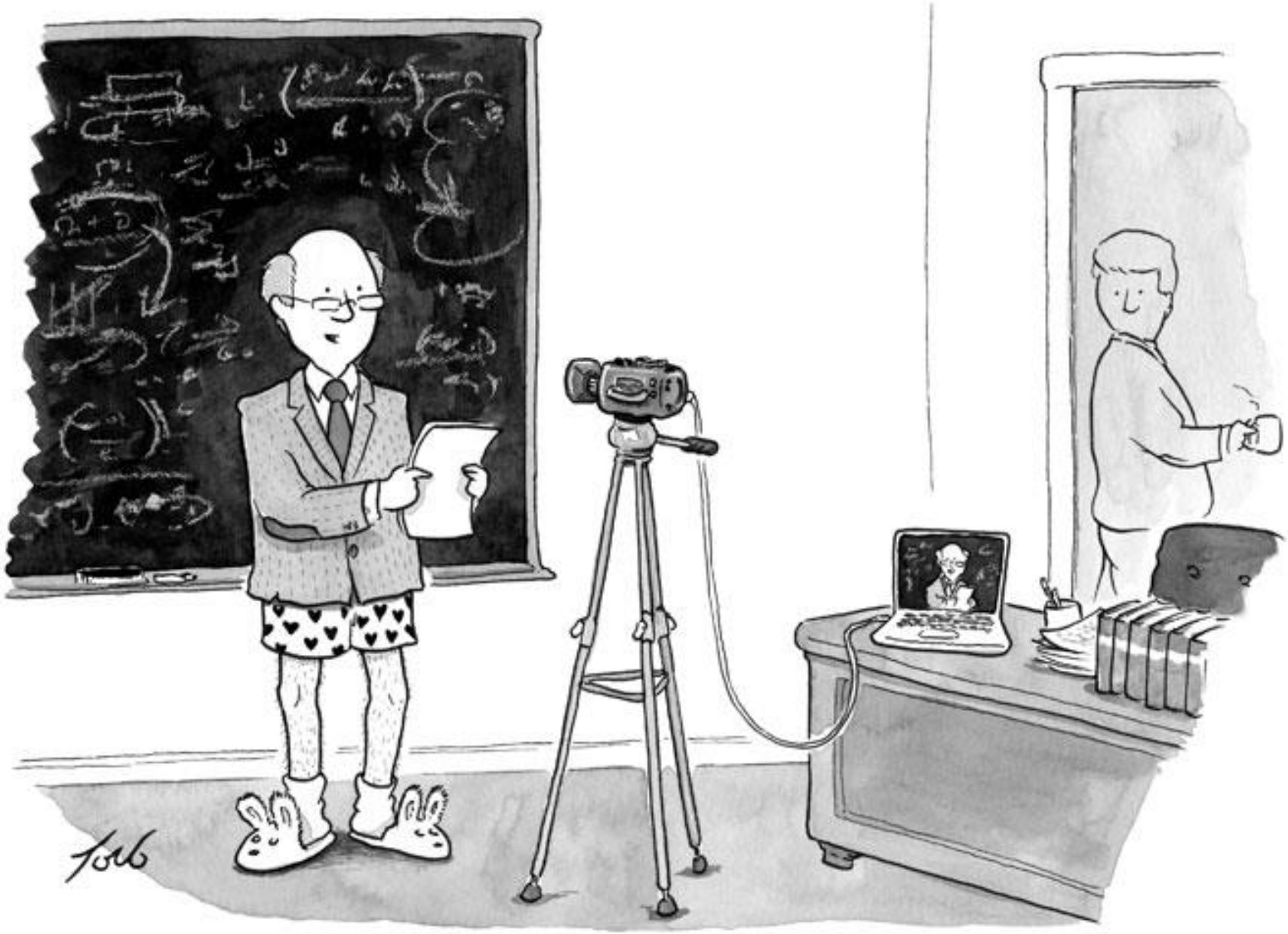


"I'm honored to share my research at your virtual academic conference."

This is me, lockdown version… ☺

Outline of the talk

- Principles of dosing in children
- The science: allometry and maturation
- Do the scientific results affect policy?
- WHO paediatric dosing tool
- (Obvious) limitations
- Shiny app

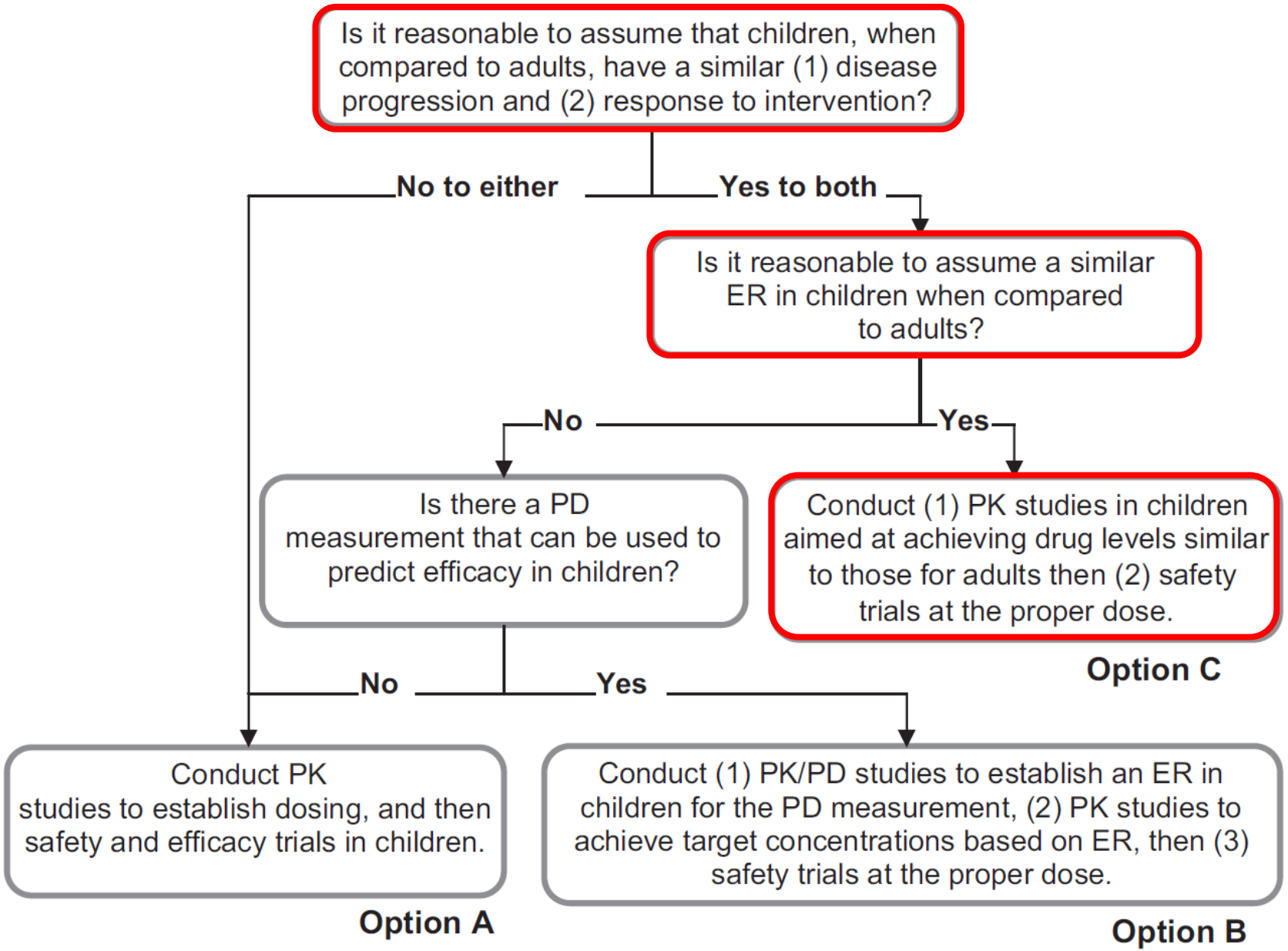
Dosing in children

What is the right dose in children?

Creation of child-friendly formulations.

https://www.tballiance.org/sites/default/files/child-resources/New_Pathways_for_Childhood_TB_Treatment.pdf

Dosing in children - FDA Paediatric study decision tree



Climbing the tree for anti-infectives…

1. Similar disease progression and response to intervention as in adults
2. Similar exposure/response relationship

Dunne J et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics (2011)

FDA Guidance for Industry Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications (2003)

For anti-infectives

Target **same exposure as** used for treatment in **adults**, monitor safety.

PK studies in children

What is the adult-equivalent dose in children?

How do physiological processes scale from adults to children?

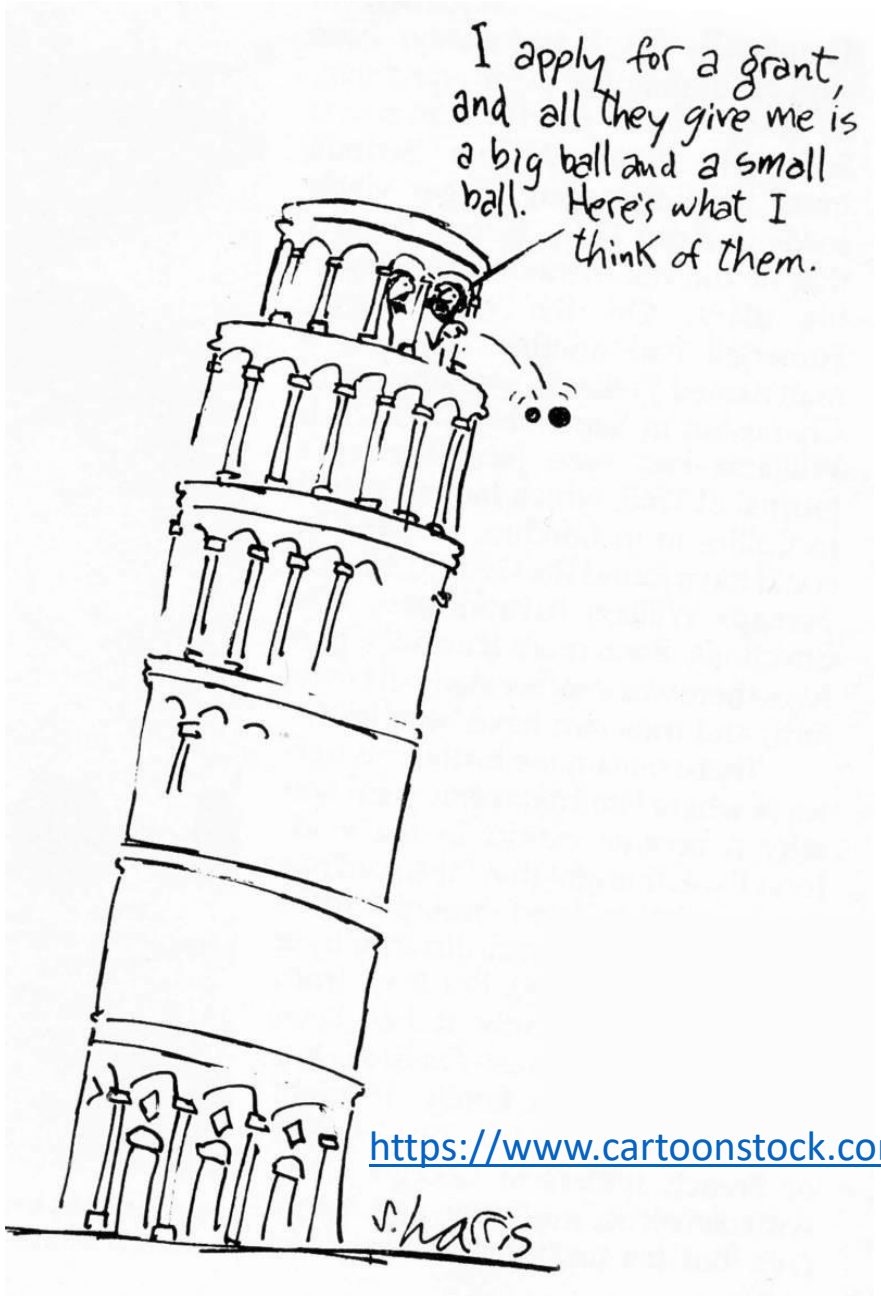
Why can't we just assume that everything is linear?
I.e., can't we give children the same mg/kg dose as adults?

Why linear scaling does **NOT** work!

Why can’t we just scale everything **linearly**?
As done when in PK we assume constant mg/kg dose?

For the same reason a spider **THIS BIG** cannot exist in nature… ☺

This has been studied **for a while**…



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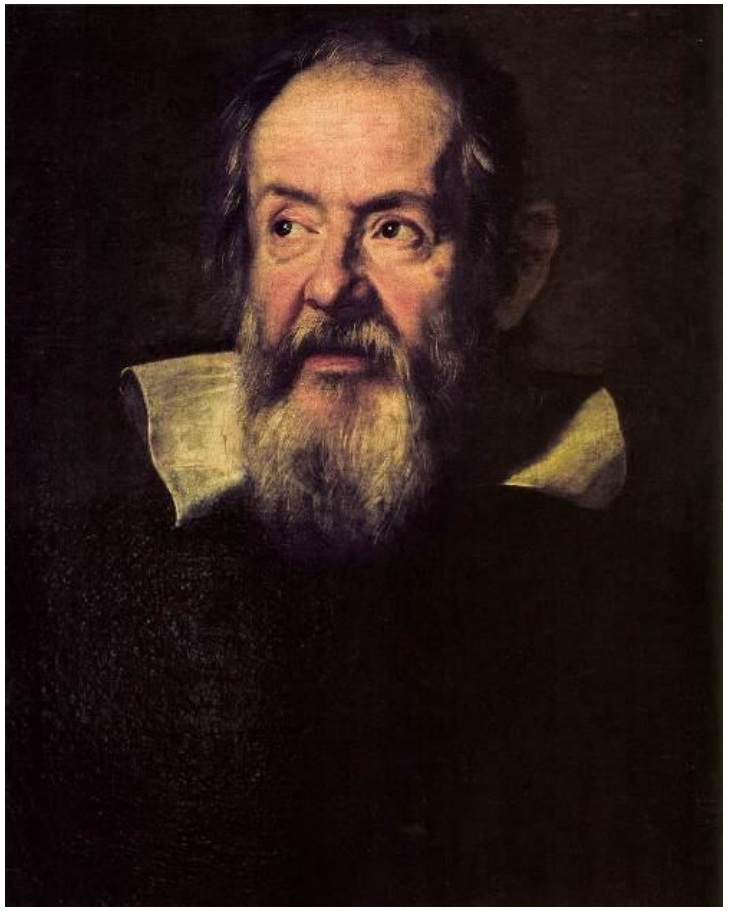


Galileo Galilei (1564 – 1642)

Allometry: effect of body size on morphology

Galileo's horrifying use of laboratory animals.

*"Who does not know that a **horse** falling from a height of three or four cubits will break his bones, while a **dog** falling from the same height or a **cat** from a height of eight or ten cubits will suffer no injury?"*

*"Do not **children** fall with impunity from heights which would cost their **elders** a broken leg or perhaps a fractured skull?"*

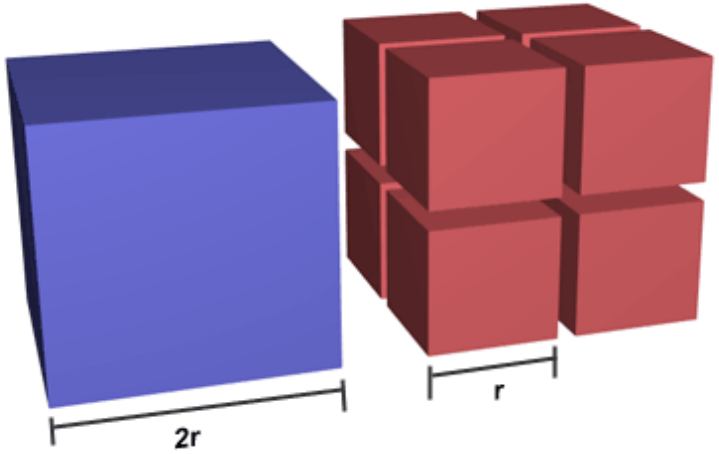
Galileo Galilei (**1638**), Discorsi e Dimostrazioni Matematiche Intorno a Due Nuove Scienze

Galileo already knew **nearly 400 years ago** that biology does not necessarily scale linearly with size.

Back to our giant spider…

Going back to our spider, if its **length** increased by 100 times,
its **volume** (and its weight) would increase 1’000’000 times,
but the section of its legs (a **surface**) would only increase 10’000 times.

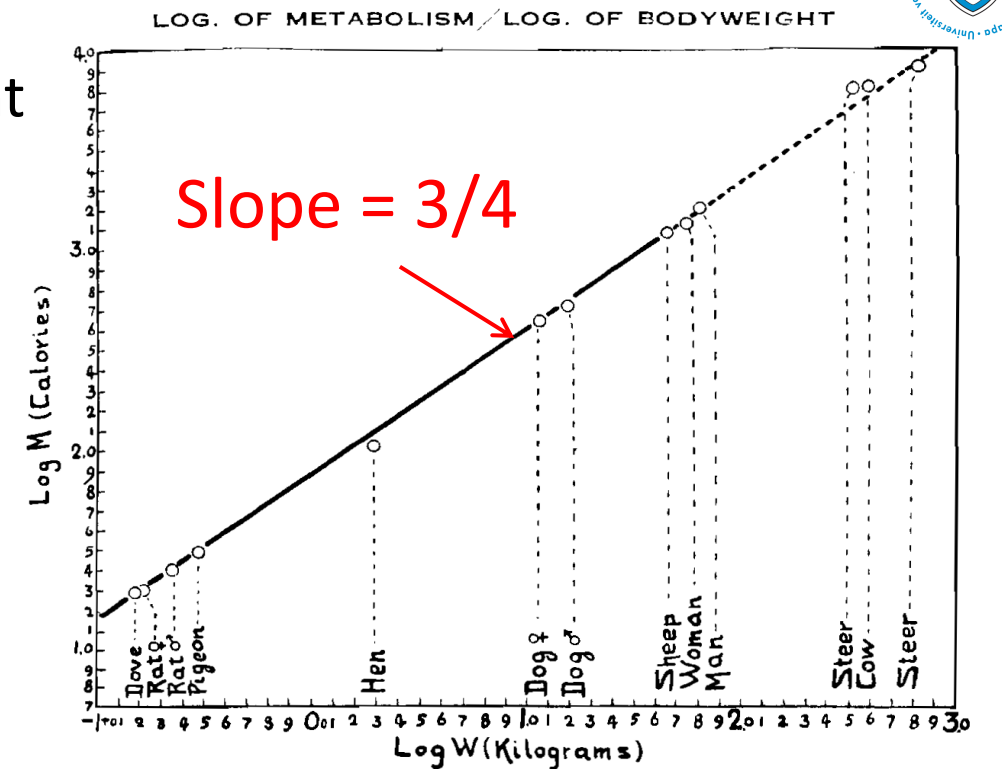
The same material of the legs would need to carry 100 times more weight per m^2. The giant spider would collapse under its own weight!



Scaling for pharmacokinetics parameters

Volume of distribution scales linearly with body weight if the body composition remains similar. Easy.

Clearance involves movement of molecules across membranes, so it relates to surfaces of contact between tissues and blood vessels.
This is the idea behind body surface area for scaling CL (which lead to an exponent of 2/3 with weight).



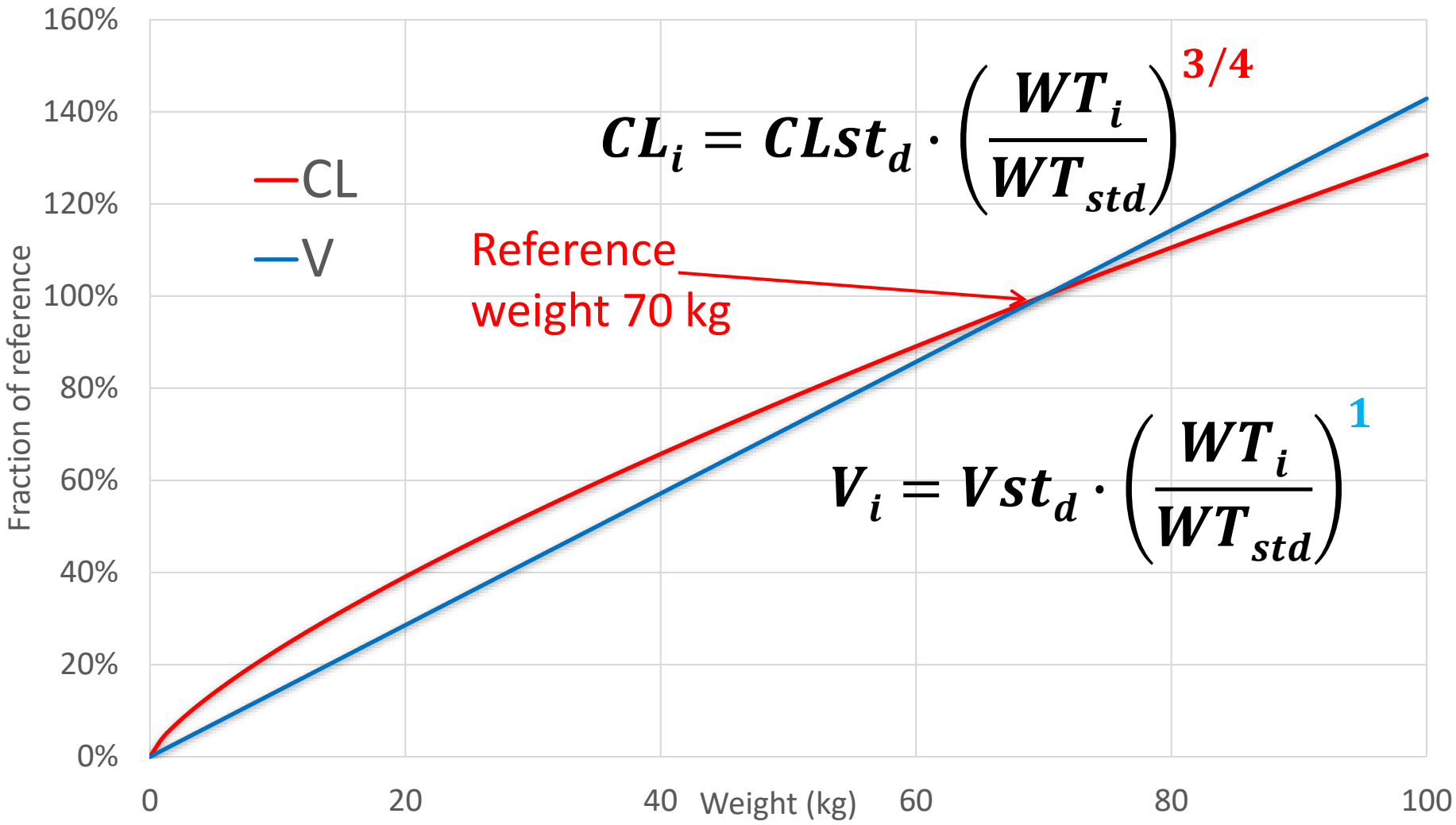
Kleiber, M. (1932). Body size and metabolism. *Hilgardia*

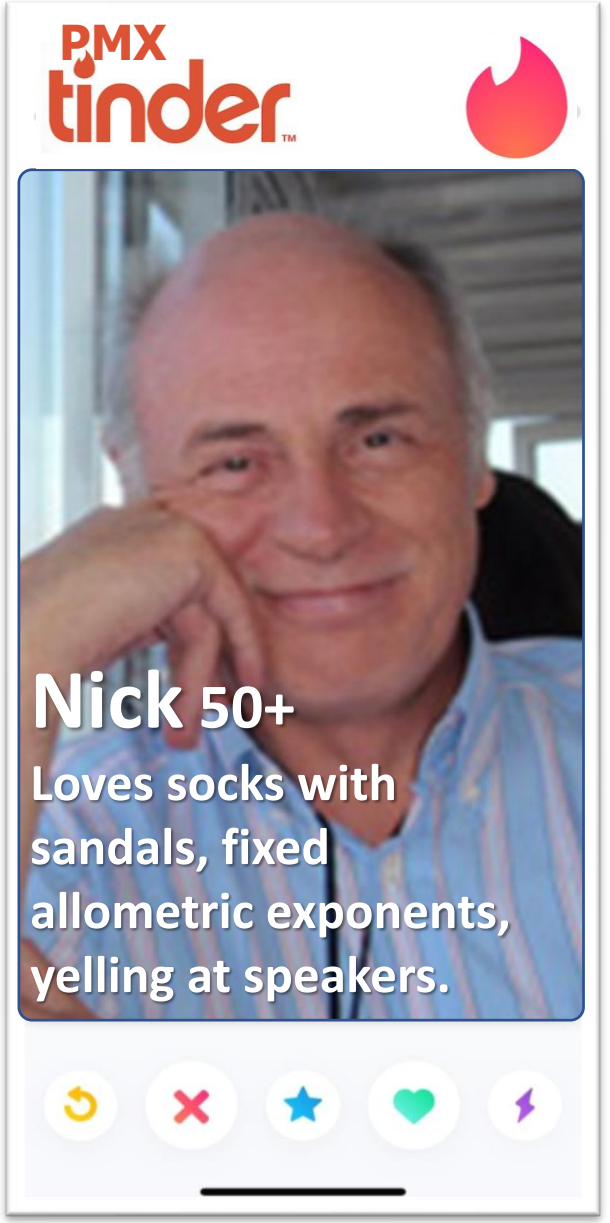

Fractal geometry in romanesco broccoli

Kleiber has shown as early as 1932 (!!!) that metabolism scales with exponent 3/4 between different species.

Surfaces in our body are not entirely “conventional” and behave more like fractal geometry, loosely speaking very convoluted curves.

Effect of body size (allometric scaling) on PK





Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. (2008)

Is it THAT simple?

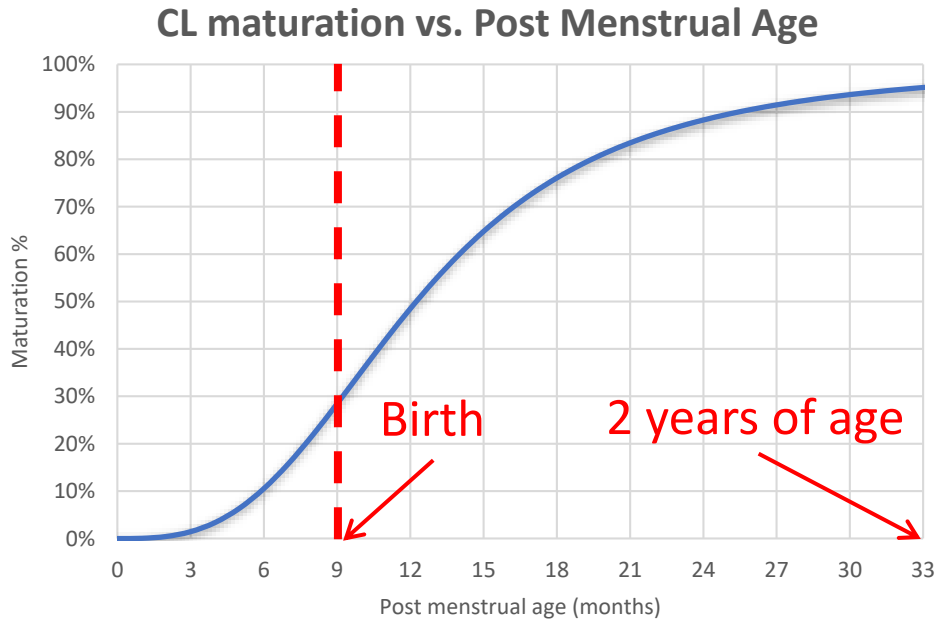
For children > 2 years of age, yes!

For **younger** children, age (maturation) **also matters, besides weight**.

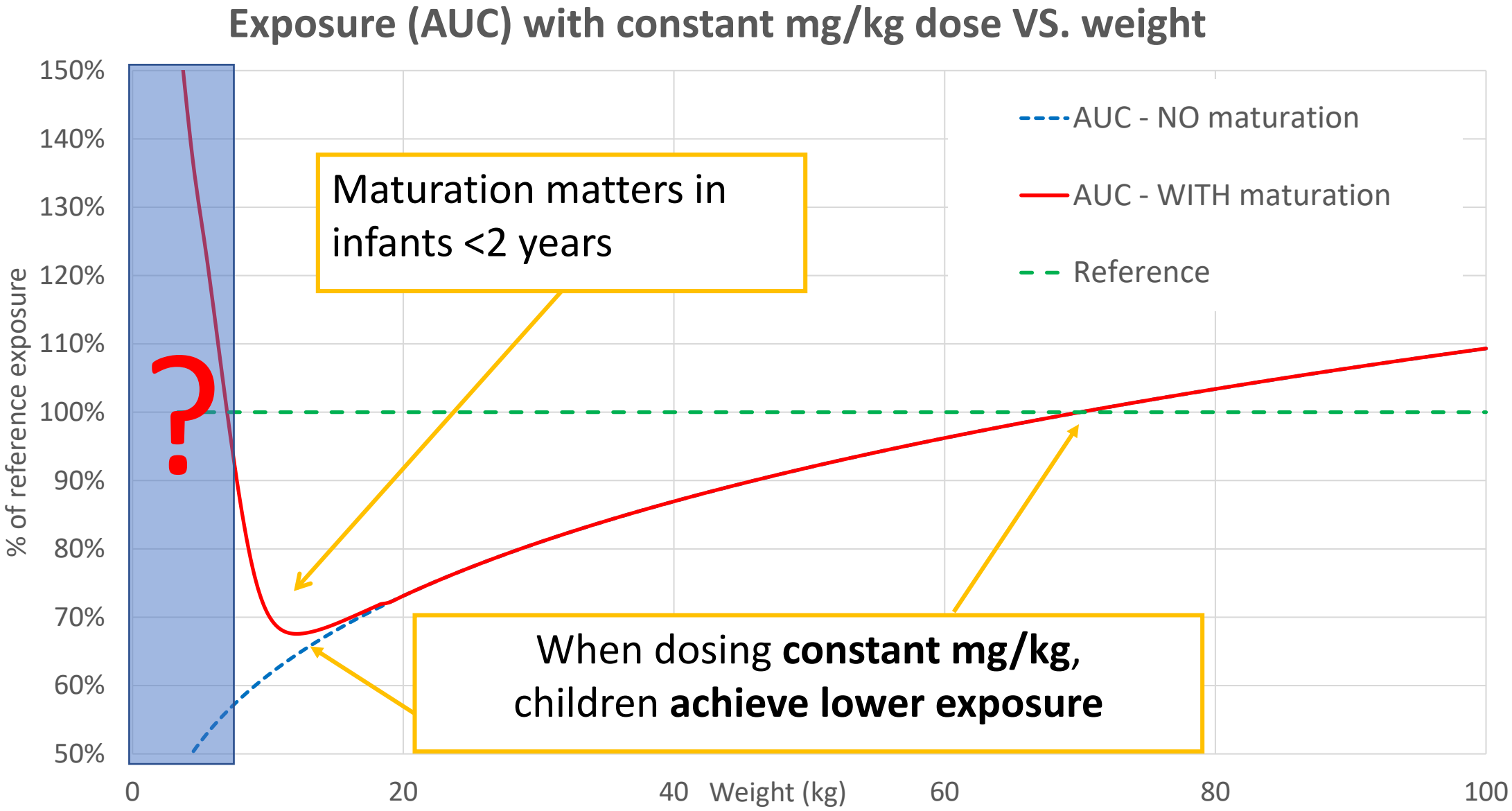
Metabolic pathways are generally not mature yet, so they are slower than what size alone would predict.

This is drug-specific, and depends on the elimination pathways of the drug

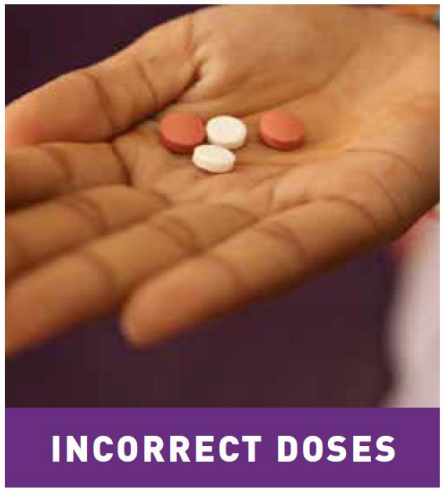
"Children are small adults, neonates are immature children" (Anderson & Holford)



Allometry predicts **higher** maintenance dose/kg in children

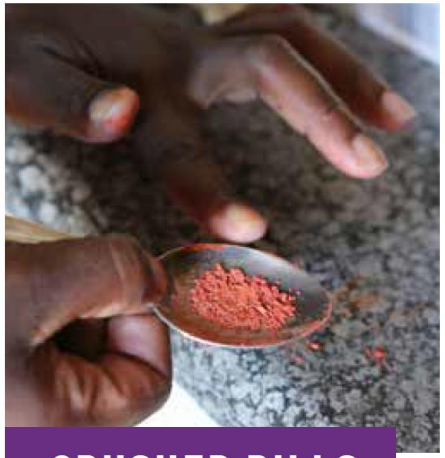


In very young children, it's a bit more complicated…

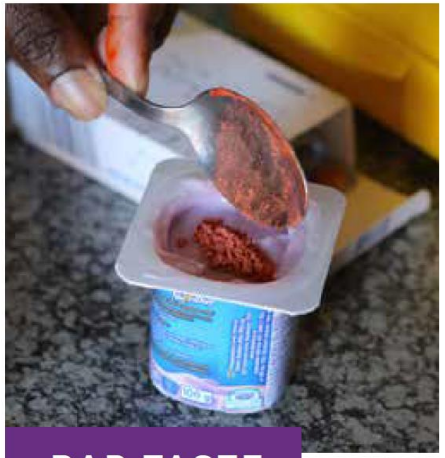


INCORRECT DOSES

BROKEN PILLS



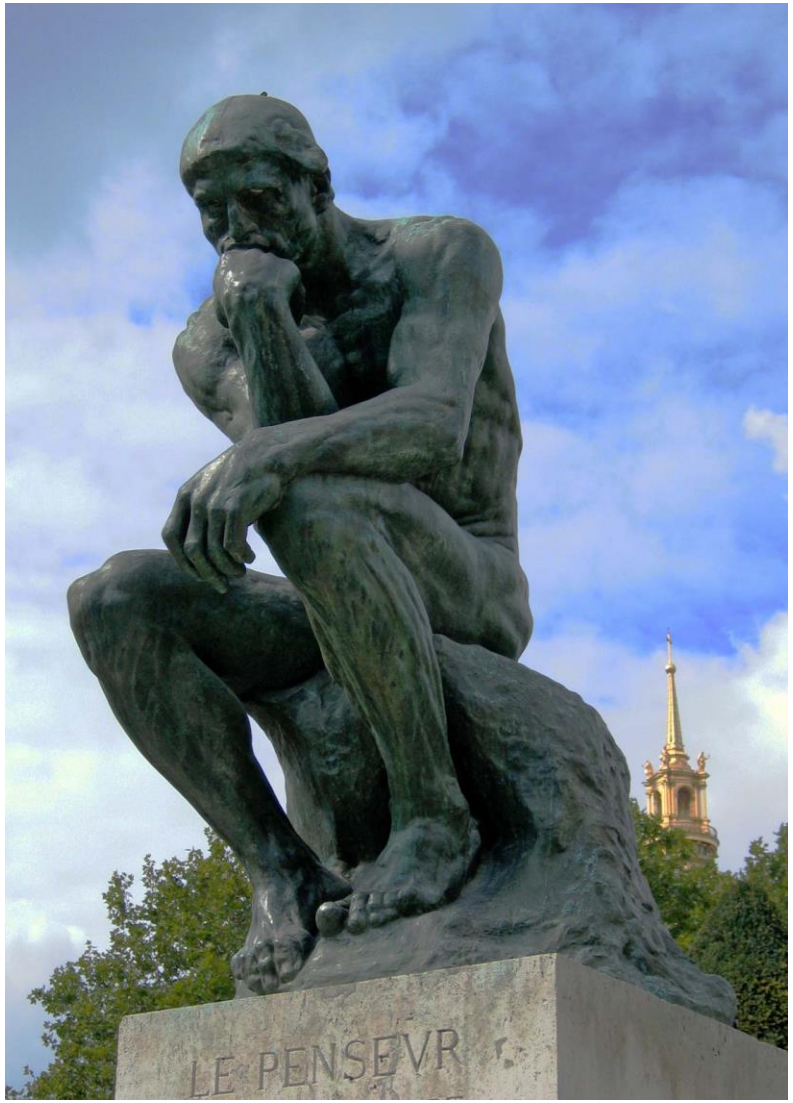
CRUSHED PILLS



BAD TASTE

https://www.tballiance.org/sites/default/files/child-resources/New_Pathways_for_Childhood_TB_Treatment.pdf

Summary of all these centuries of science…



Pharmacokinetics in children > 2 years of age, is pretty much **fully predictable** based on adult data. And children need larger mg/kg doses to achieve adult exposure for **ALL DRUGS.**

In infants (<2 years and even more so neonates) maturation plays a role, and is **drug-specific.**
One can use PBPK modelling and use some a priori assumptions, but predictions need confirmation

Is all this knowledge affecting policy on dosing in children?
At least for older children, for whom we can predict PK “a priori” very well?

Is this knowledge getting to clinical practice?

Antibiotic Dosing for Children: Expert Recommendations

For Children Ages 2 months to 12 years

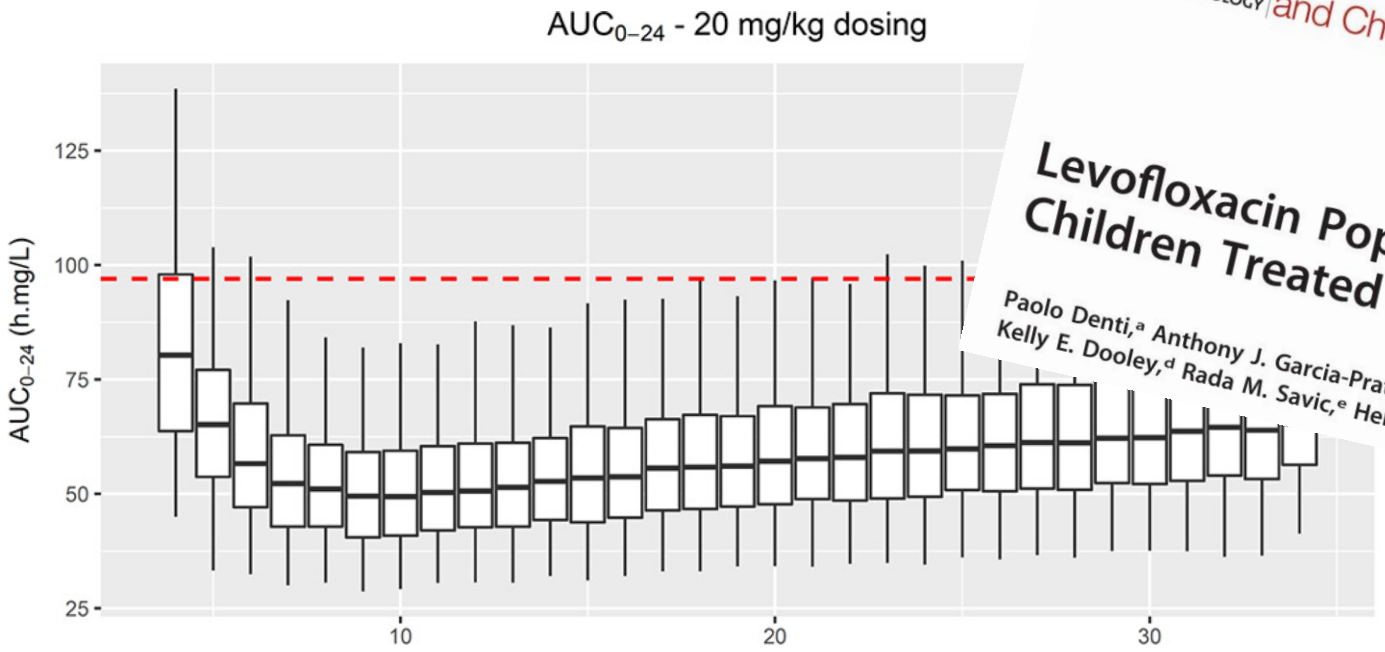
The official WHO guidelines for most drugs, still advise constant mg/kg!

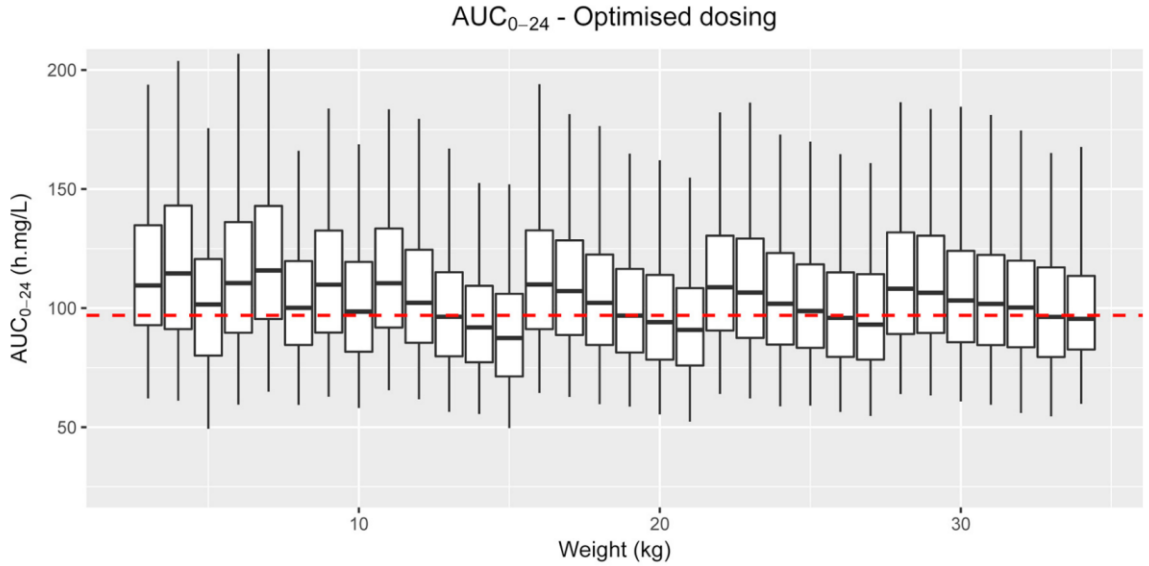
Imipenem	60 mg/kg/day divided in 3 or 4 doses
Levofloxacin	20 mg/kg/day PO divided in 2 doses
Linezolid	30 mg/kg/day PO or IV divided in 2 or 3 doses

Benzylpenicillin	100 mg/kg/day IV divided in 2 or 4 doses 200 mg/kg/day IV divided in 2 or 4 doses (in severe infection)
Cefalexin	50 mg/kg/day PO divided in 2 or 4 doses
Cefazolin	50 mg/kg/day IV divided in 2 or 3 doses
Cefotaxime	150 mg/kg/day IV divided in 3 doses
Ceftazidime	150 mg/kg/day IV divided in 3 doses
Ceftriaxone	80 mg/kg/day IV given once daily
Cefuroxime	30 mg/kg/day PO or 100 mg/kg/day IV divided in 2 doses
Chloramphenicol	50 mg/kg/day IV divided in 2 or 4 doses
Ciprofloxacin	30 mg/kg/day PO or IV divided in 2 doses
Clarithromycin	15 mg/kg/day PO or IV divided in 2 doses
Clindamycin	20 mg/kg/day PO or IV divided in 3 or 4 doses
Linezolid	30 mg/kg/day PO or IV divided in 2 or 3 doses
Meropenem	60 mg/kg/day IV divided in 3 doses 120 mg/kg/day IV divided in 3 doses (in severe infection)
Metronidazole	20 mg/kg/day PO or IV divided in 2 or 3 doses
Moxifloxacin	10 mg/kg/day PO given once daily
Nitrofurantoin	4 mg/kg/day PO divided in 2 or 4 doses
Phenoxymethylpenicillin	100 mg/kg/day PO divided in 2 or 4 doses 200 mg/kg/day PO divided in 2 or 4 doses in severe infection
Piperacillin-tazobactam	300 mg/kg/day IV divided in 3 or 4 doses
Trimethoprim	8 mg/kg/day PO divided in 2 doses
Trimethoprim / sulfamethoxazole	50 mg/kg/day PO divided in 2 doses
Vancomycin	50 mg/kg/day IV divided in 2 or 3 or 4 doses

https://www.who.int/selection_medicines/committees/expert/21/applications/s6_ab_paed_dosing_rev.pdf

Levofloxacin





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Levofloxacin Population Pharmacokinetics in South African Children Treated for Multidrug-Resistant Tuberculosis

Paolo Denti,[a] Anthony J. Garcia-Prats,[b] Heather R. Draper,[b] Lubbe Wiesner,[a] Jana Winckler,[b] Stephanie Thee,[c] Kelly E. Dooley,[d] Rada M. Savic,[e] Helen M. McIlleron,[a] H. Simon Schaaf,[b] Anneke C. Hesseling[b]

PHARMACOLOGY

TABLE 3 Weight-banded dosing of levofloxacin 100-mg scored dispersible tablets required to approximate exposures in adults with a 750-mg dose

Weight band (kg)	No. of 100-mg tablets/dose	Daily dose (mg)	Median (range) daily dose (mg/kg)
3 to <4	0.5	50	14.3 (12.5–16.7)
4 to <5	0.75	75	16.7 (15–18.8)
5 to <6	1	100	18.2 (16.7–20)
6 to <7	1.5	150	23.1 (21.4–25)
7 to <9	2	200	25 (22.2–28.6)
9 to <11	2.5	250	25 (22.7–27.8)
11 to <16	3	300	22.2 (18.8–27.3)
16 to <22	4	400	21.1 (18.2–25)
22 to <28	5	500	20.0 (17.9–22.7)
28 to <35	6	600	19.1 (17.2–21.4)

Why isn't this knowledge being used?!? ☹

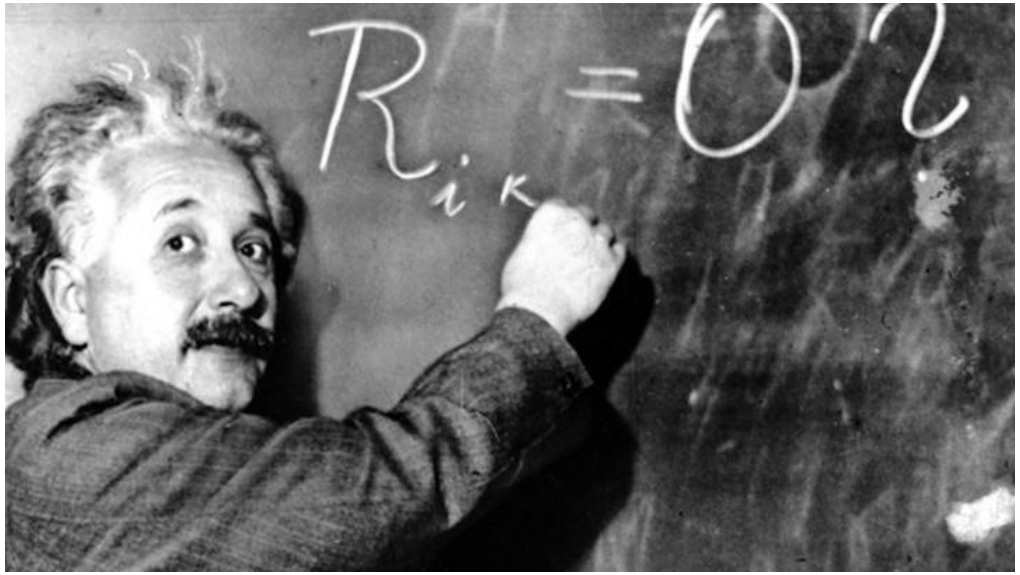
Probably because non-linear = non-intuitive

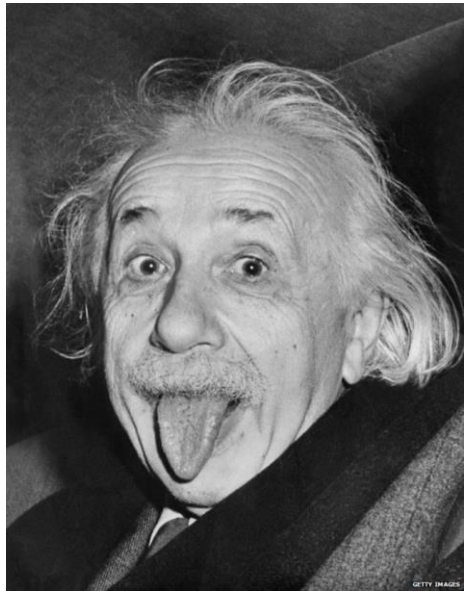
The therapeutic range of these drugs is not always that narrow?

Effect small enough to think it is negligible…

What can we do if our **clever models** don't have an impact?

Let's **dumb** things down… ☺





NONMEM7™
The program for Nonlinear Mixed Effects Modeling

LIXOFT

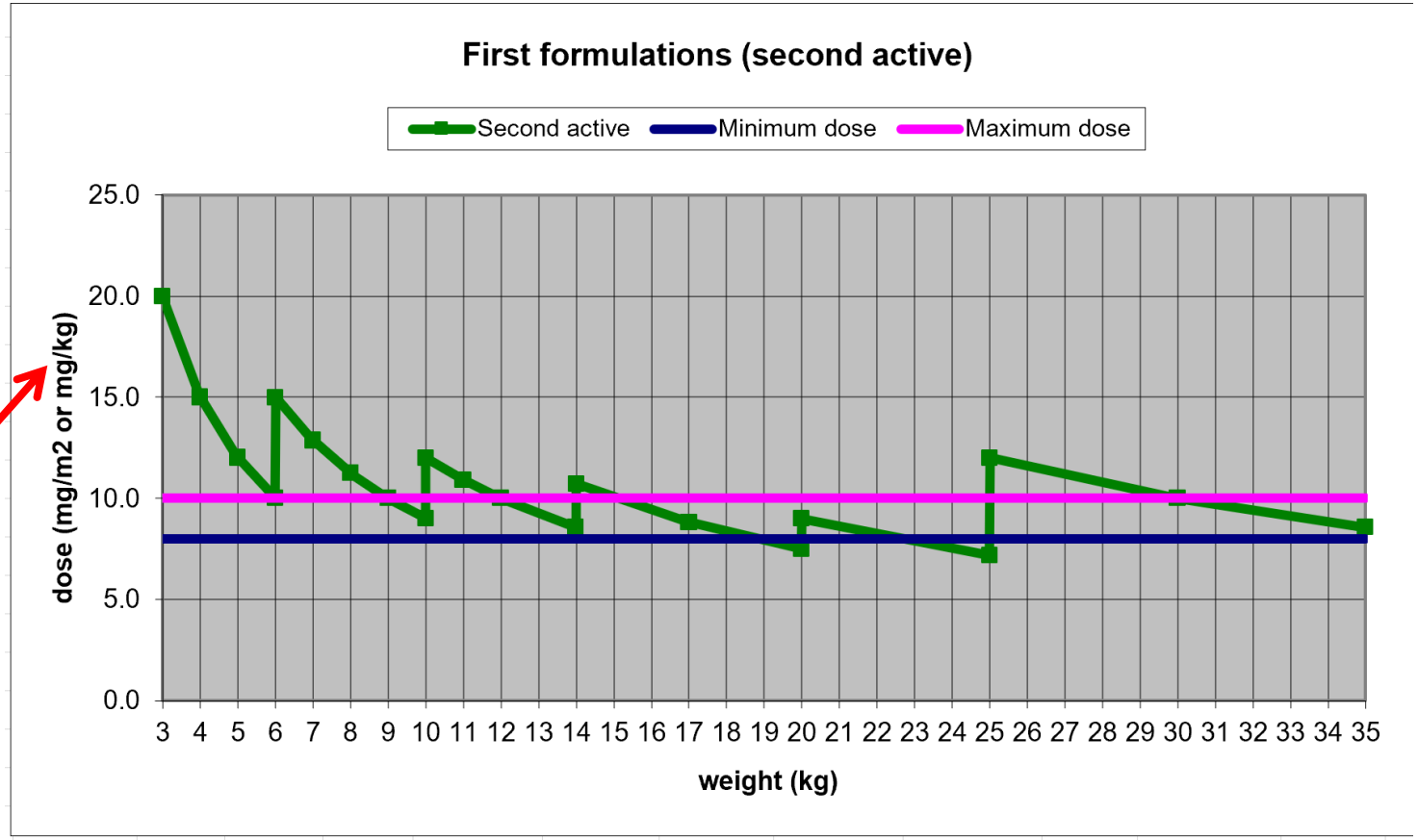
Excel

The WHO paediatric dosing tool

The WHO Paediatric Anti-retroviral Working Group (PAWG) devised a tool to visually assesses the dosing recommendations for HIV treatment in children across weight-bands.

The OLD version of tool allowed the evaluation of the mg/kg dose across the weight-bands.

It targeted same mg/kg as adults.



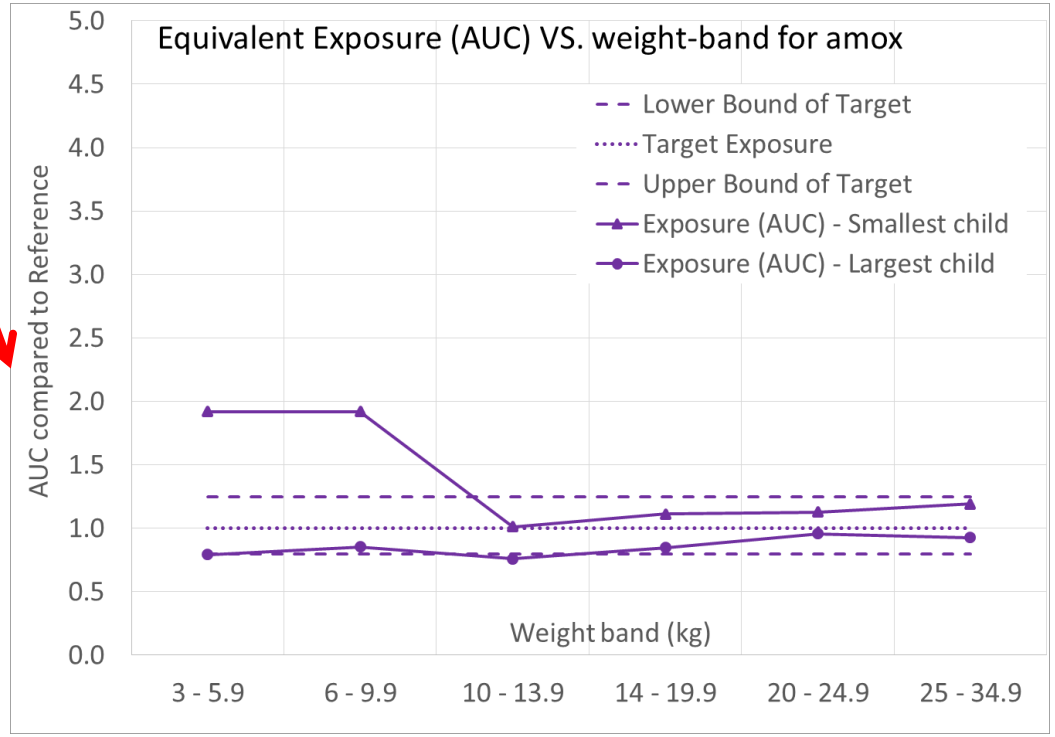
https://www.who.int/hiv/paediatric/generictool/en/

The NEW version of the dosing tool

Targets constant drug exposure (AUC) relative to a reference adult (NOT same mg/kg dose) and it **accounts for allometric scaling**

It calculates **typical exposure** for different weights and displays relative exposure for largest and smallest child in each weight-band

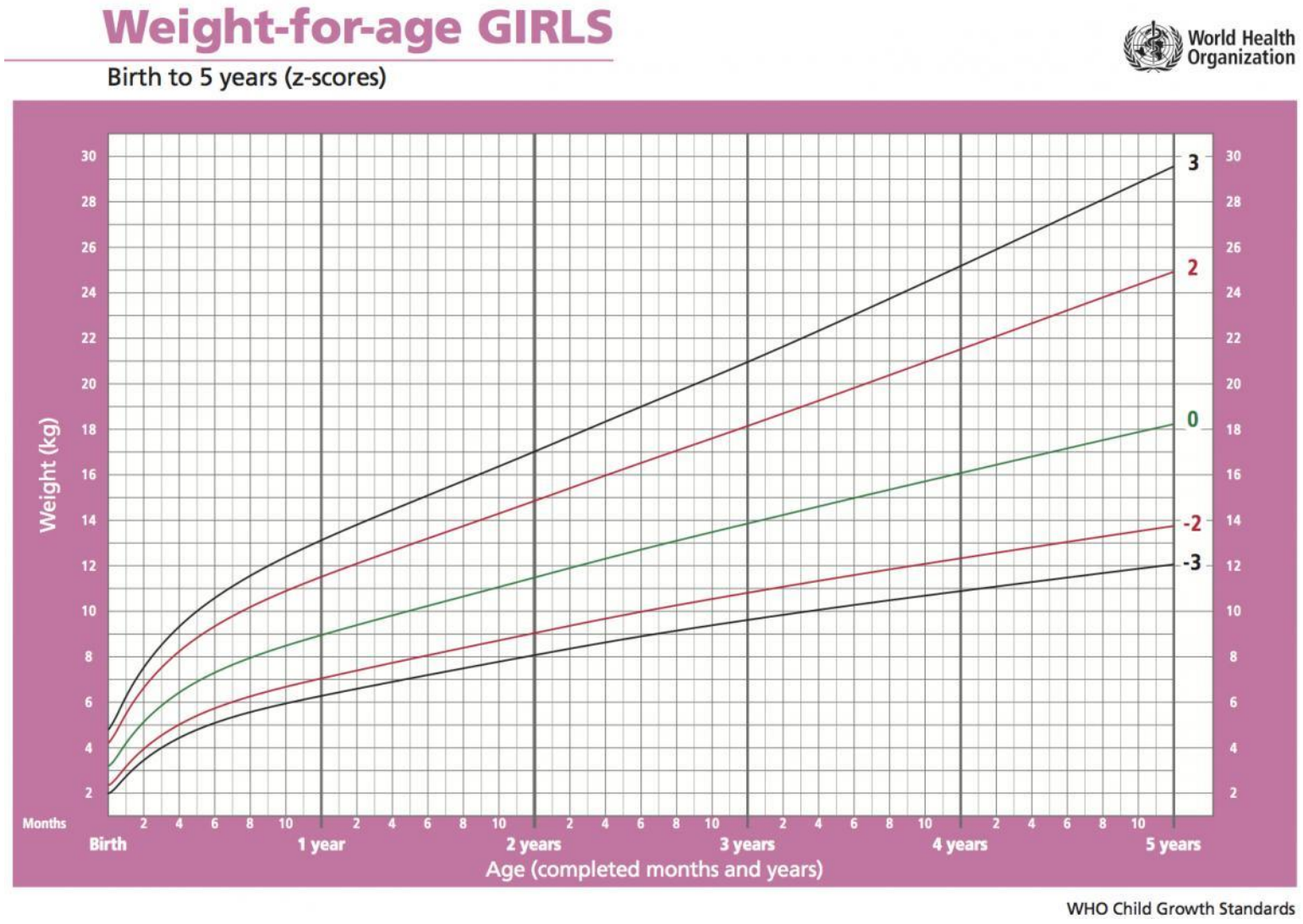
The user can try a different number of tablets to get acceptable exposure for each weight band



Maturation

If maturation is known for the drugs under investigation it can be included.

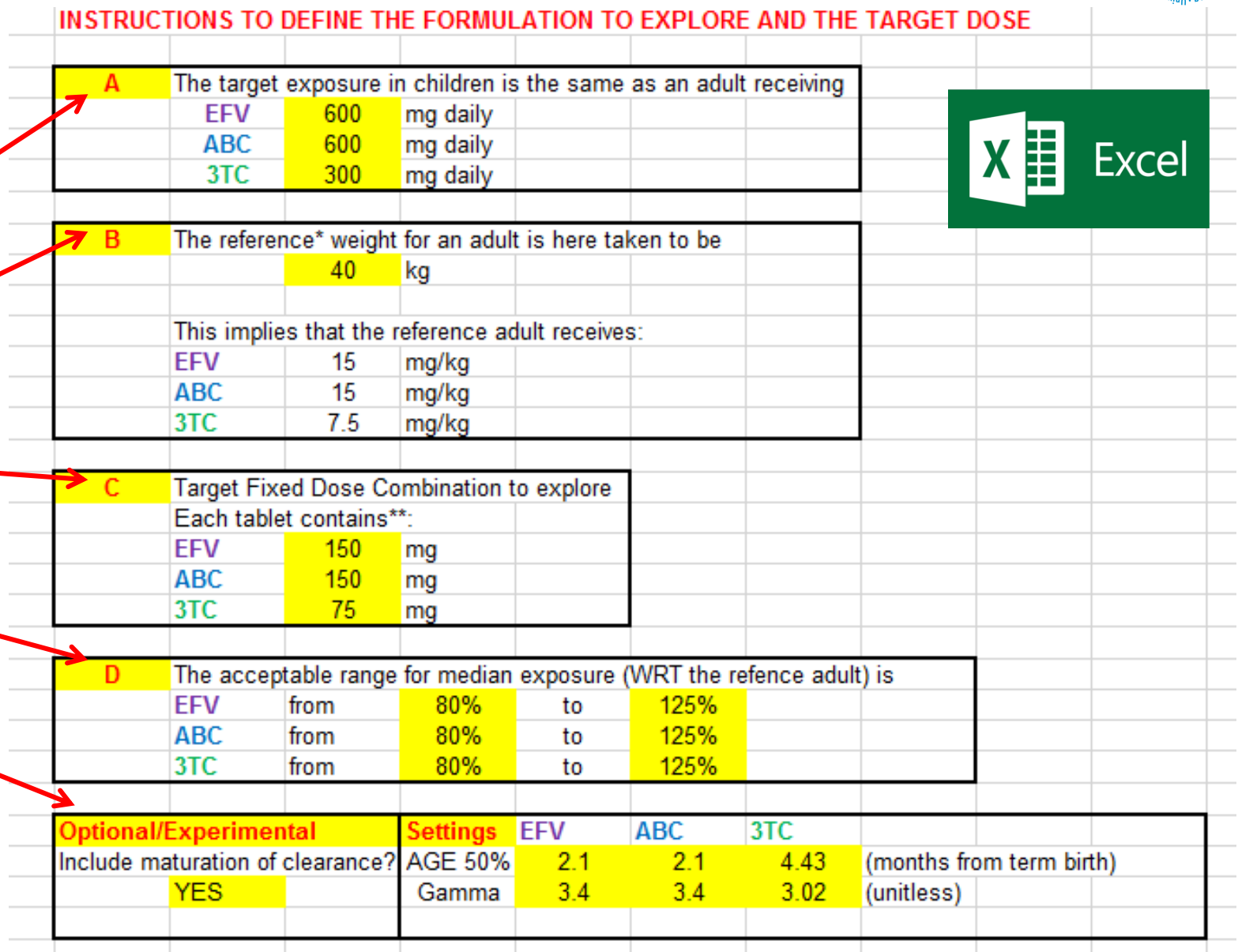
The tool uses **WHO weight-for-age growth charts** to deduce a reasonable age range, given the weight.



Using the generic paediatric dosing tool (1)

The user selects:

- the **target adult dose** for each drug
- the **reference adult weight**(-band)
- the **strength of each component** in the paediatric FDC
- the **acceptable exposure ranges.**
- **Optionally**, a **maturation function** can be specified (if known)

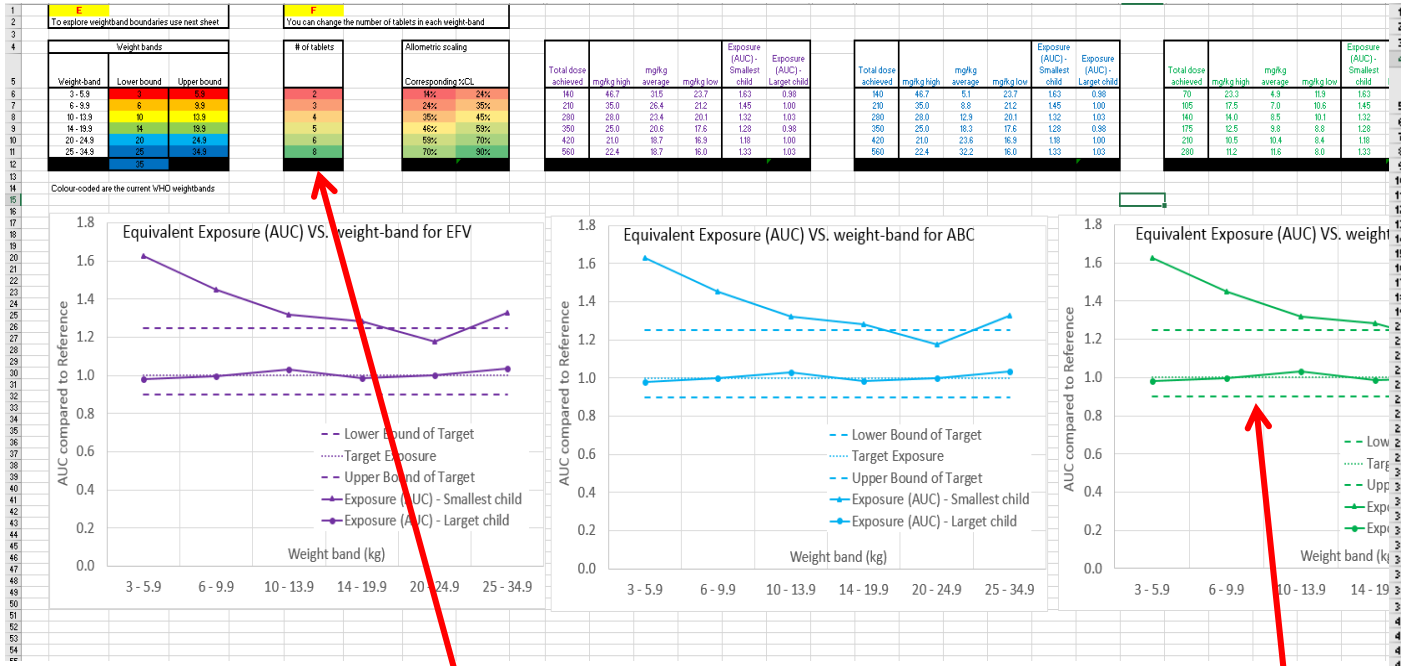


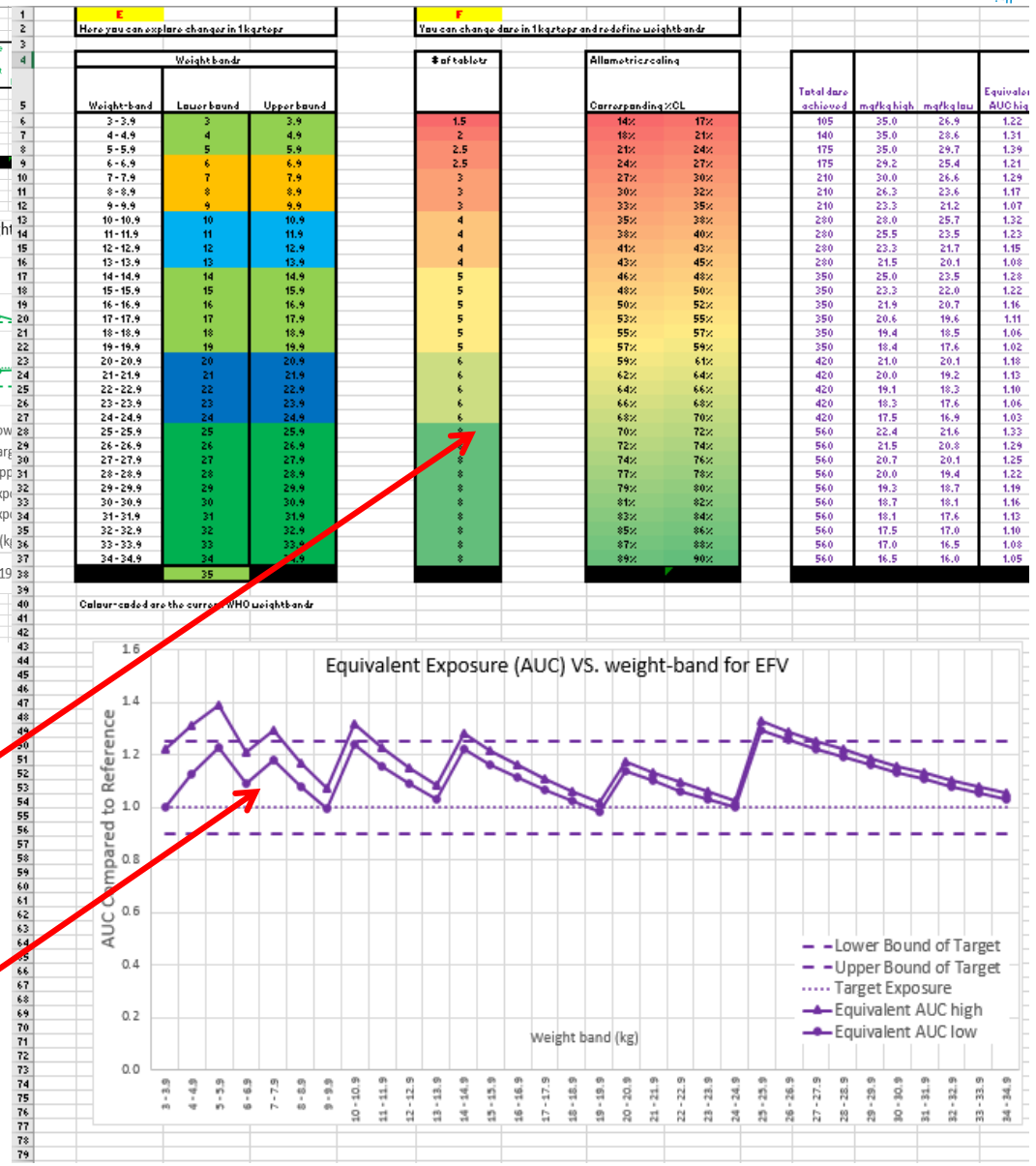
INSTRUCTIONS TO DEFINE THE FORMULATION TO EXPLORE AND THE TARGET DOSE

A	The target exposure in children is the same as an adult receiving					
	EFV	600	mg daily			
	ABC	600	mg daily			
	3TC	300	mg daily			
B	The reference* weight for an adult is here taken to be					
		40	kg			
	This implies that the reference adult receives:					
	EFV	15	mg/kg			
	ABC	15	mg/kg			
	3TC	7.5	mg/kg			
C	Target Fixed Dose Combination to explore					
	Each tablet contains**:					
	EFV	150	mg			
	ABC	150	mg			
	3TC	75	mg			
D	The acceptable range for median exposure (WRT the refence adult) is					
	EFV	from	80%	to	125%	
	ABC	from	80%	to	125%	
	3TC	from	80%	to	125%	

Optional/Experimental	Settings	EFV	ABC	3TC	
Include maturation of clearance?	AGE 50%	2.1	2.1	4.43	(months from term birth)
YES	Gamma	3.4	3.4	3.02	(unitless)

Using the generic paediatric dosing tool (2)





- 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)

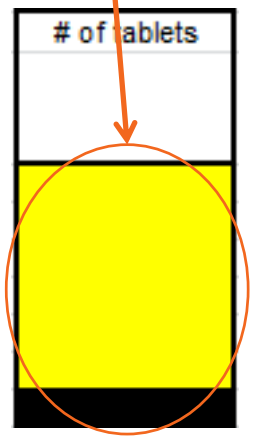
Example – Amoxicillin (1)

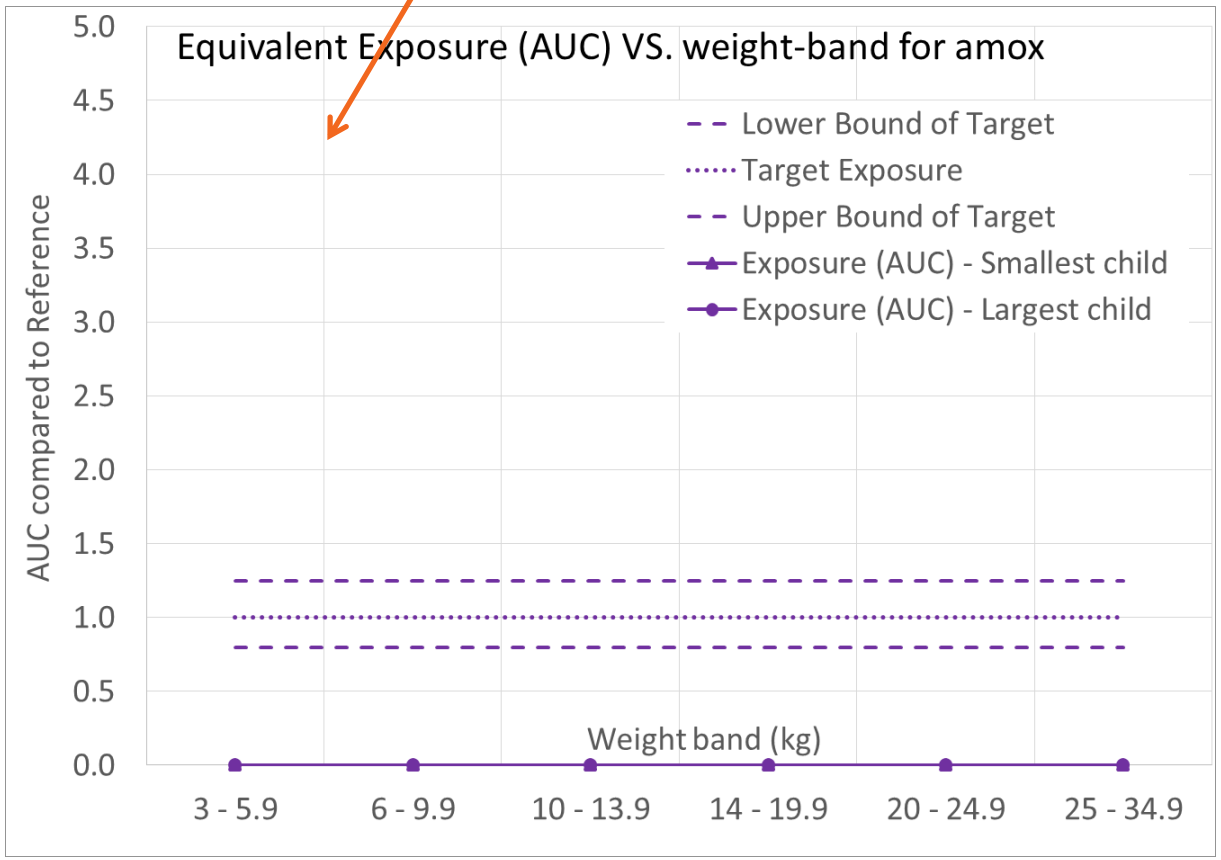
Weight bands

tablets (alter this)

Min and max AUC in each weight band (ref dose = 1)

Weight bands		
Weight-band	Lower bound	Upper bound
3 - 5.9	3	5.9
6 - 9.9	6	9.9
10 - 13.9	10	13.9
14 - 19.9	14	19.9
20 - 24.9	20	24.9
25 - 34.9	25	34.9
	35	





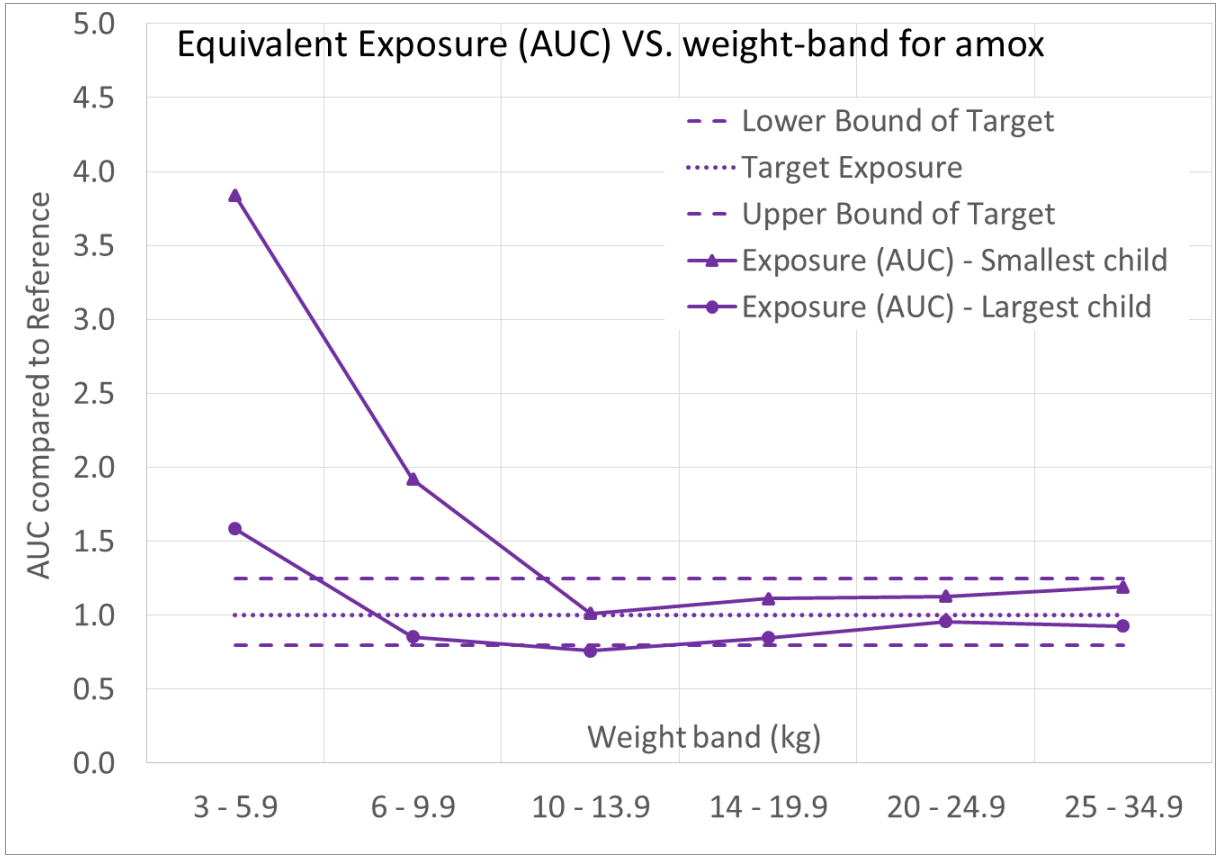
Try different number of tablets in each weight band to get most acceptable AUC

Slide courtesy of Michelle Clements, University College London

Example – Amoxicillin (2)

Weight bands		
Weight-band	Lower bound	Upper bound
3 - 5.9	3	5.9
6 - 9.9	6	9.9
10 - 13.9	10	13.9
14 - 19.9	14	19.9
20 - 24.9	20	24.9
25 - 34.9	25	34.9
	35	

of tablets
2
3
4
6
8
10



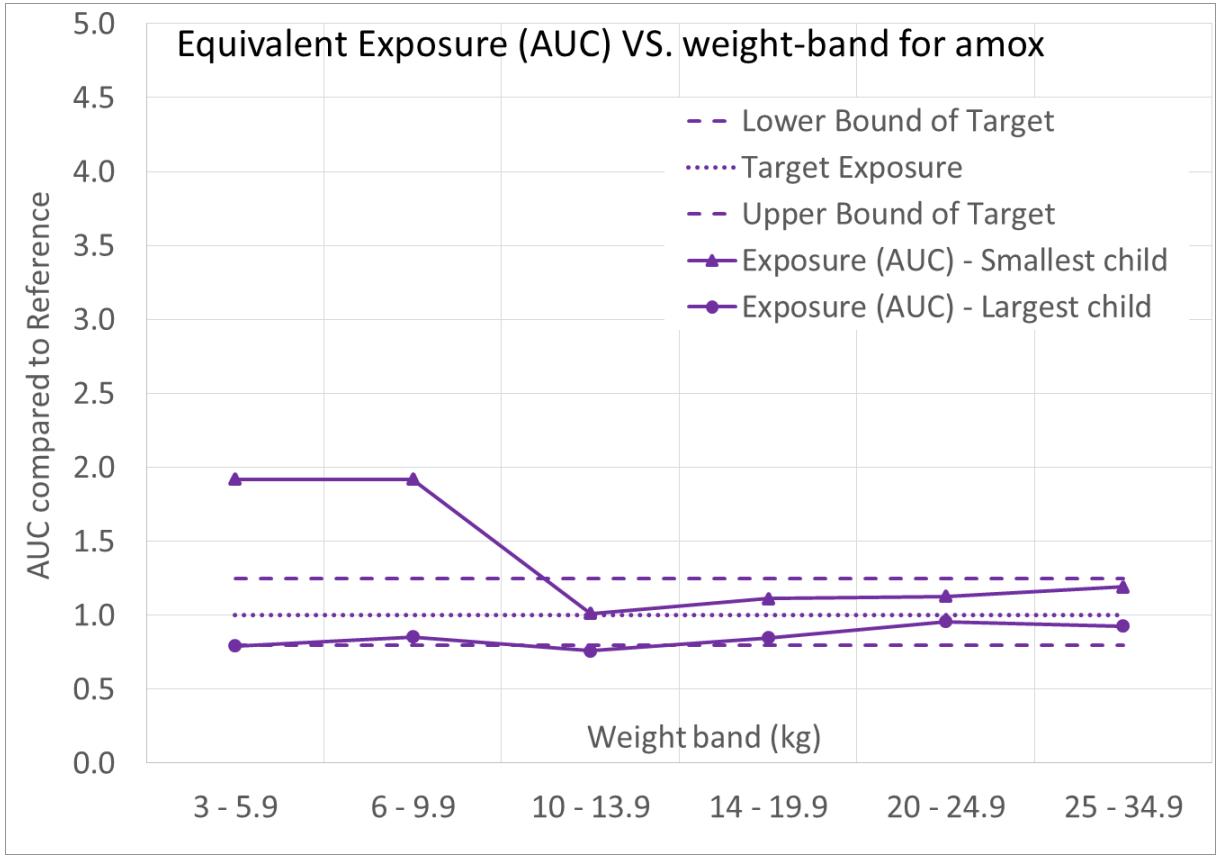
Try different number of tablets in each weight band to get most acceptable AUC

Slide courtesy of Michelle Clements, University College London

Example – Amoxicillin (3)

Weight bands		
Weight-band	Lower bound	Upper bound
3 - 5.9	3	5.9
6 - 9.9	6	9.9
10 - 13.9	10	13.9
14 - 19.9	14	19.9
20 - 24.9	20	24.9
25 - 34.9	25	34.9
	35	

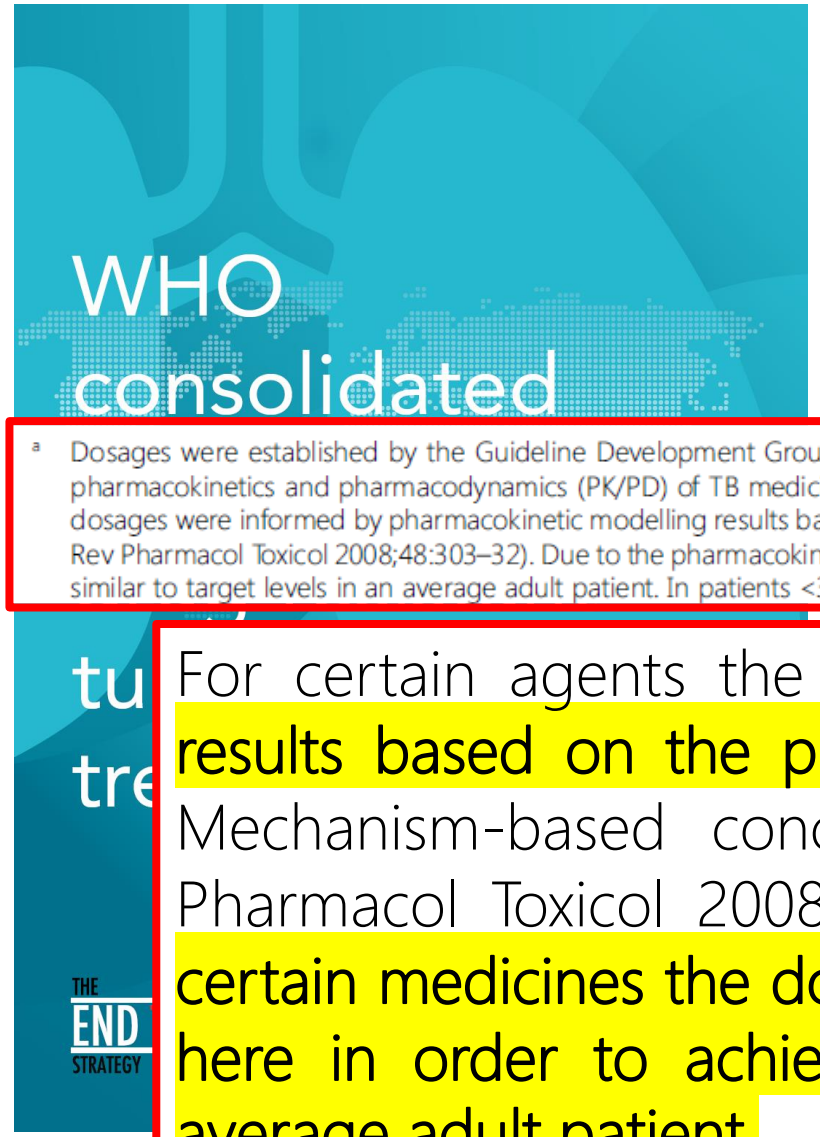
of tablets
1
3
4
6
8
10



Try different number of tablets in each weight band to get most acceptable AUC

Slide courtesy of Michelle Clements, University College London

New WHO guidelines for MDR-TB



Annex 2: Dosage by weight band for medicines used in MDR-TB regimens, adults and children

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years[a]

Group	Medicine	Weight-based daily dose[b]	Formulation	Weight bands among patients not yet 15 years old[a] 5–6 kg	7–9 kg	10–15 kg	16–23 kg	24–30 kg	31–34 kg	>34 kg	Usual upper daily dose[b]	Comments
A	*Fluoroquinolones*											
	Levofloxacin	15–20 mg/kg	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	(>14 y)	1.5 g	

[a] Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower

For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient.

World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019.

I am ready for the rotten tomatoes… ☺

Known limitations

The tool includes scaling only for clearance, so it targets overall AUC. For some drugs, Cmin and Cmax may be more relevant.

Terminal half-life is shorter in children, may be necessary to split dosing frequency

Target population not necessarily the standard WHO growth chart. Malnutrition?

The best descriptor for scaling may not be total body weight, but fat-free mass.

The current version only displays typical values, no between-subject variability

Other factors may matter for infants besides allometry and maturation, such as different formulations, higher pH in the stomach, lower plasma albumin levels, absorption.

Other limitations (Excel can be dangerous)…

Coronavirus caveat: Beware easy predictions

Most forecasts will be wrong. What really separates the good ones from the bad ones is why they're wrong.

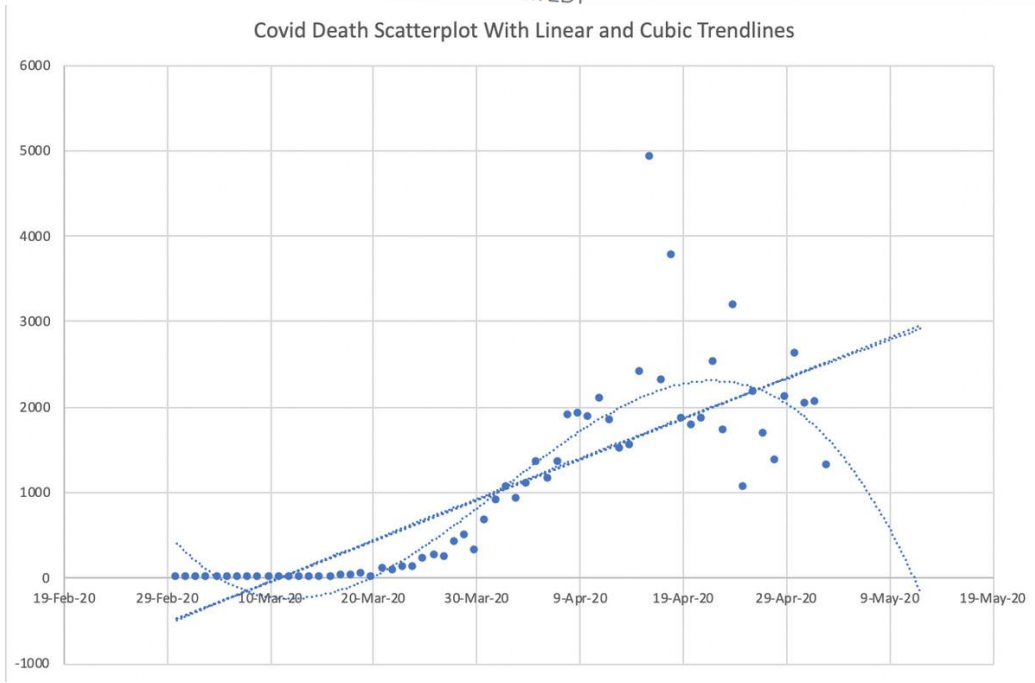
By Aubrey Clayton Updated May 11, 2020, 3:00 p.m.

The Trump administration's "cubic model" of coronavirus deaths, explained

An extremely foolish way to forecast the pandemic.

By Matthew Yglesias | @mattyglesias | matt@vox.com | May 8, 2020, 11:00am EDT

[…] a model prepared by Kevin Hassett, former chair of the Council of Economic Advisers. Since dubbed the "cubic model," it is by all accounts a travesty of data science, a naive forecast based on extending an existing trend line, the kind of analysis that would get a failing grade in a high school statistics class.



https://www.bostonglobe.com/2020/05/11/opinion/coronavirus-caveat-beware-easy-predictions/
https://www.vox.com/2020/5/8/21250641/kevin-hassett-cubic-model-smoothing

Shiny app (work in progress by Tjokosela Tikiso)

Prototype kindly hosted by Prof Marc Lavielle on his shiny server (thanks Marc! ☺)

http://shiny.webpopix.org/host/test_tool/

Same features as the Excel version, in a nicer, more intuitive interface

Extra features (work in progress)
Possibility of customising the children population of interest

Drug-specific section of the tool

- Library of models for specific drugs (written in Monolix)
- Possibility of simulating the entire PK curve (AUC, Cmin, Cmax)
- Inclusion of between-subject and –occasion variability
- Inclusion of other covariates effect

Shiny app (work in progress by Tjokosela Tikiso)

Paediatric Dosing Tool

help 3

GENERIC TOOL - SINGLE DRUG | GENERIC TOOL - FIXED DOSE COMBINATION (FDC) | GENERIC TOOL - CUSTOM WEIGHT-BANDS | MODEL SIMULATED INDIVIDUAL PROFILE | MODEL SIMULATION

PLOTS PER WEIGHT BAND | TABLES PER WEIGHT BAND | MATURATION PLOTS

Drug 1 strength (mg): 150
Drug 2 strength (mg): 150
Drug 3 strength (mg): 75

Adult 1 daily dose (mg): 600
Adult 2 daily dose (mg): 600
Adult 3 daily dose (mg): 300

Target adult weight (kg): 40

Maturation / No maturation — Plot

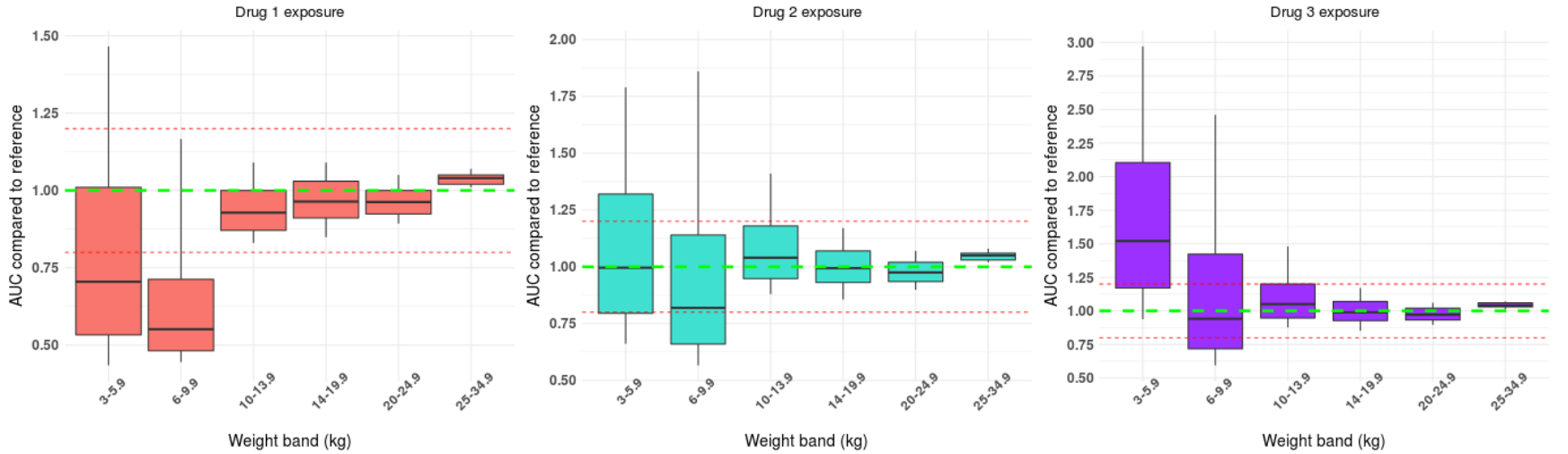
Drug 1: Maturation half-time (PMA) months: 12
Gamma: 4.47

Drug 2: Maturation half-time (PMA) months: 16
Gamma: 2.61

Drug 3: Maturation half-time (PMA) months: 18
Gamma: 3.02

Update Chart

Weight-band (Kg)	Number of tablets
3-5.9	0.2
6-9.9	0.6
10-13.9	1.5
14-19.9	2
20-24.9	2.5
25-34.9	3



Expected typical exposure of a child per weight-band(WITH MATURATION):The box indicates the inter-quartile range, while the whiskers denote the 2.5th and the 97.5th percentiles. The green horizontal dashed line represents the target exposure while the red dashed lines represent the upper and lower bound of exposure

Lower bound exposure: 0.8
Upper bound exposure: 1.2

Select data: Malnutrition | Custom | WHO growth standards

Generate report

Shiny app (work in progress by Tjokosela Tikiso)

Paediatric Dosing Tool

help 3

GENERIC TOOL - SINGLE DRUG | GENERIC TOOL - FIXED DOSE COMBINATION (FDC) | GENERIC TOOL - CUSTOM WEIGHT-BANDS | MODEL SIMULATED INDIVIDUAL PROFILE | MODEL SIMULATION

Select Drug: PZA

Select weight-band (Kg): 6-7.9

Tablet strength (mg): 500

Number of previous doses: 5

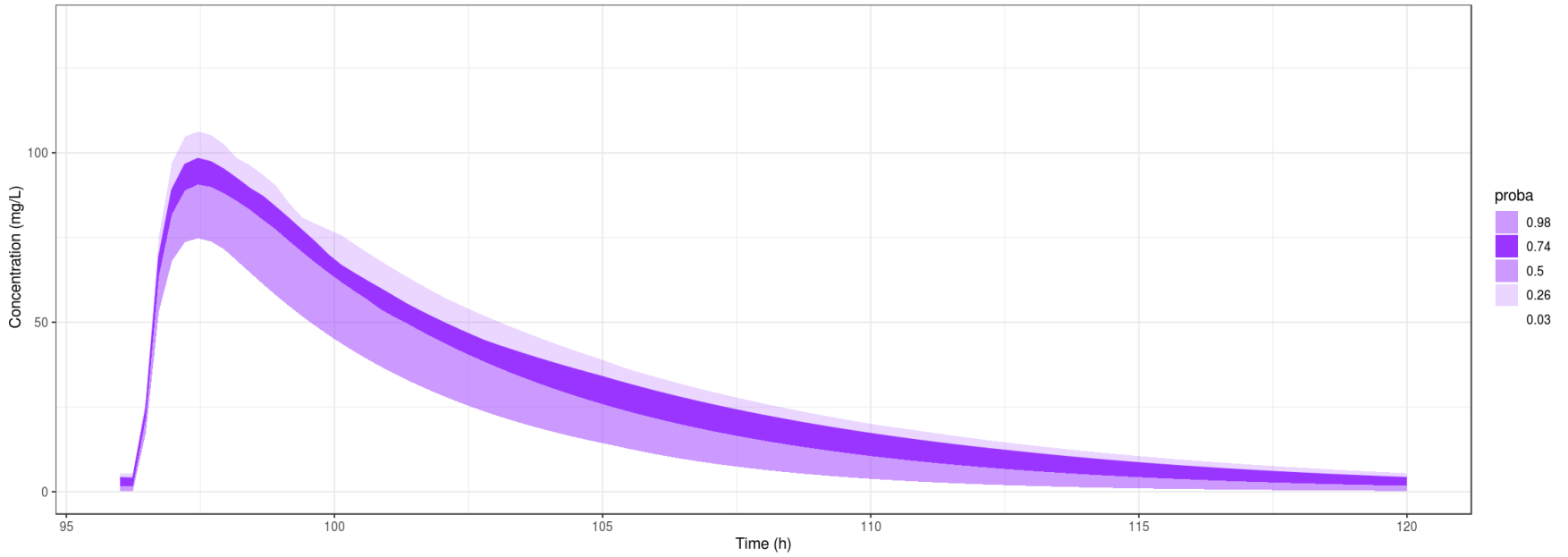
number of tablets: 1

Dosing interval (hr): 24

Select data

Malnutrition | Own | WHO growth standards

PLOT



Predicted concentrations for a typical child in the selected weight-band. The purple shaded area is the 95% confidence intervals, the solid purple line represents the median.

Normal scale | Log scale

Take home message

Good science may sadly remain in the Ivory Tower (even if in nice scientific papers with lots of citations ☺) unless it is made easy to use.

Way forward…

Publish the excel **dosing tool** on the website of the Global Accelerator For Pediatric Formulations (GAP-f)
http://gap-f.org/
along with **clear** limitations

Work on the **shiny app** with the intention of having a platform model-based simulations of drug regimens.

Acknowledgements

Clinical Pharmacology at the University of Cape Town
Jose Francis
Tjokosela Tikiso
Helen McIlleron

WHO Paediatric Antiretroviral Working Group
Nandita Sugandhi
Tim R. Cressey
Mark Mirochnick
Edmund V. Capparelli
Martina Penazzato