pg-ws: Managing children with drug-resistant tuberculosis

Pharmacokinetic (PK) studies

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no conflicts of interest/disclosures

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- Stellenbosch Univ.: Anneke Hesseling, Simon Schaaf, Peter Donald & DTTC PK research team

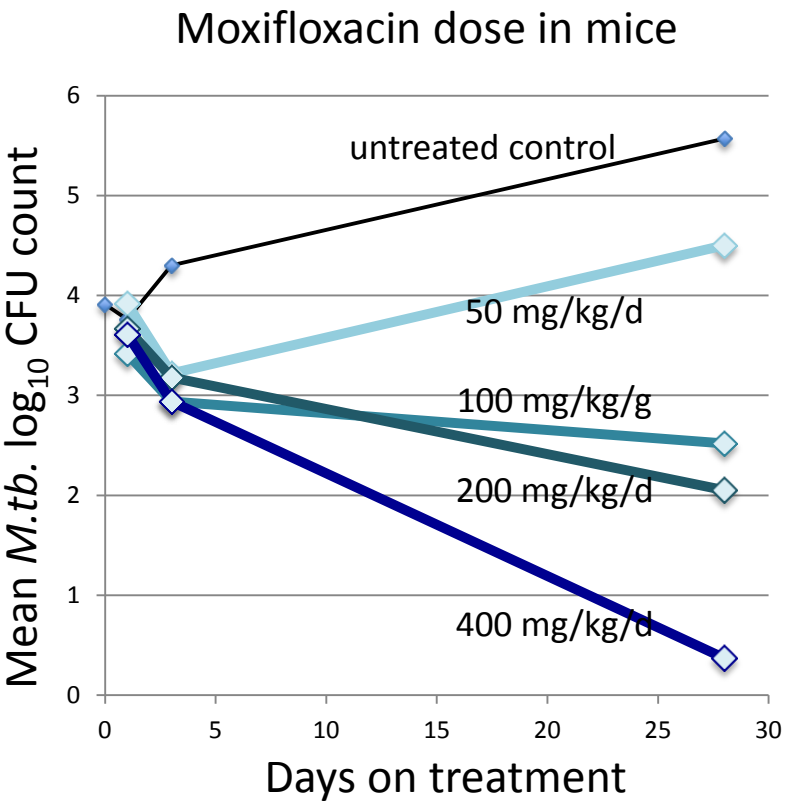
- Univ. Cape Town: Pete Smith, Lubbe Wiesner, Jen Norman, Sandy Meredith & Div. Pharmacology Laboratory team; Emmanuel Chigutsa, Simbarashe Zvada

- DP Marais Hospital staff, Rifaquin team

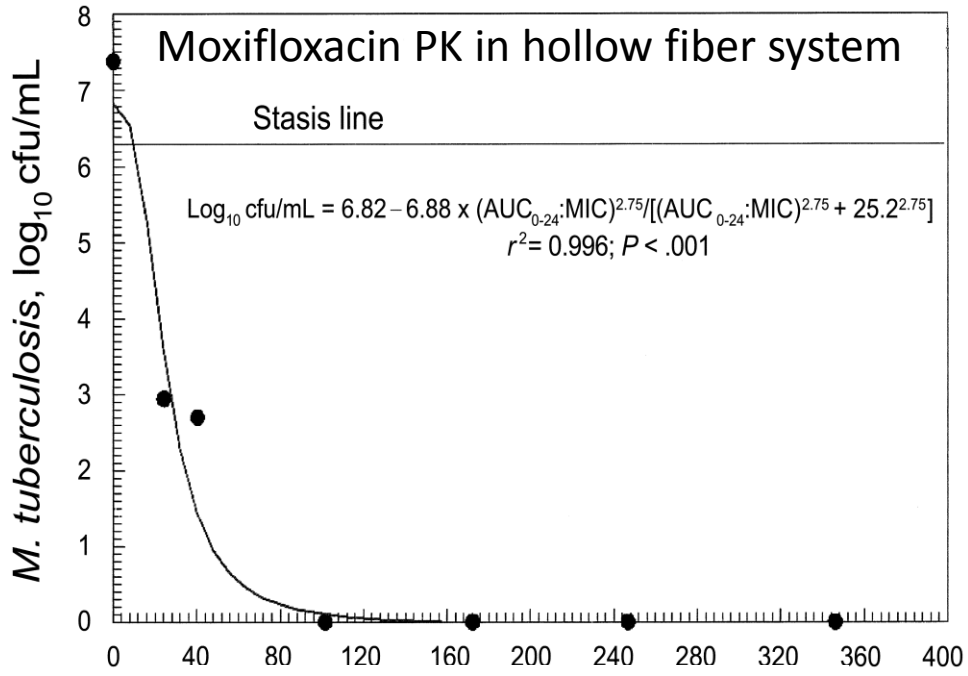
overview

- A few basic principles
- A little bit of data
- Role of PK studies in accelerating access to effective, safe treatment (± new drugs) in children with DR-TB

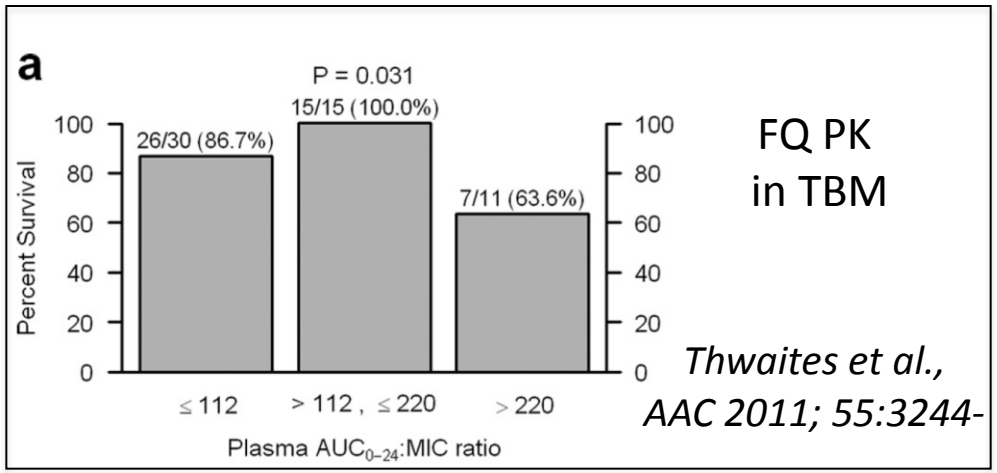
Drug exposure determines effect (PD)



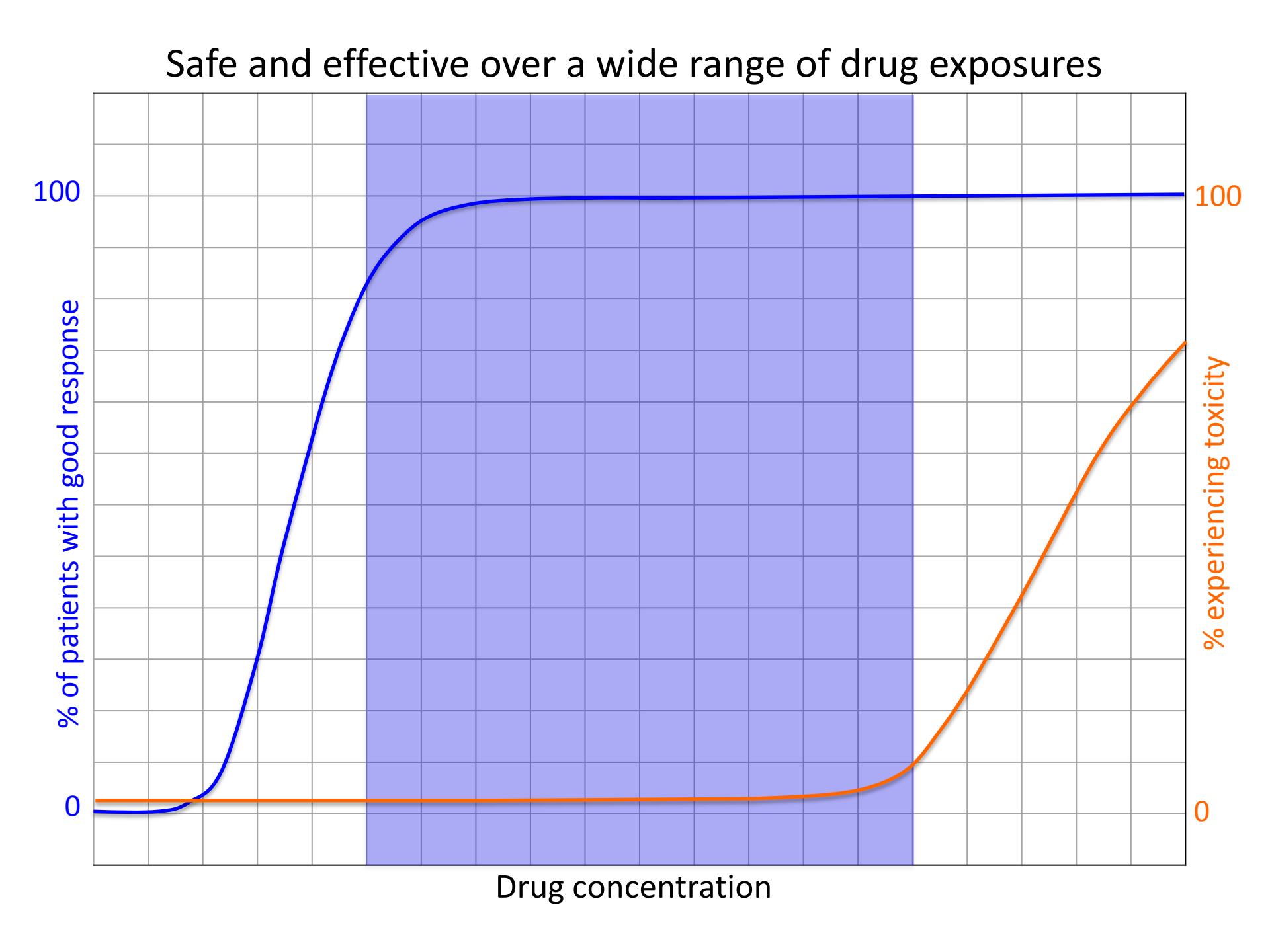
Yoshimatsu et al., AAC 2002; 46:1875-9

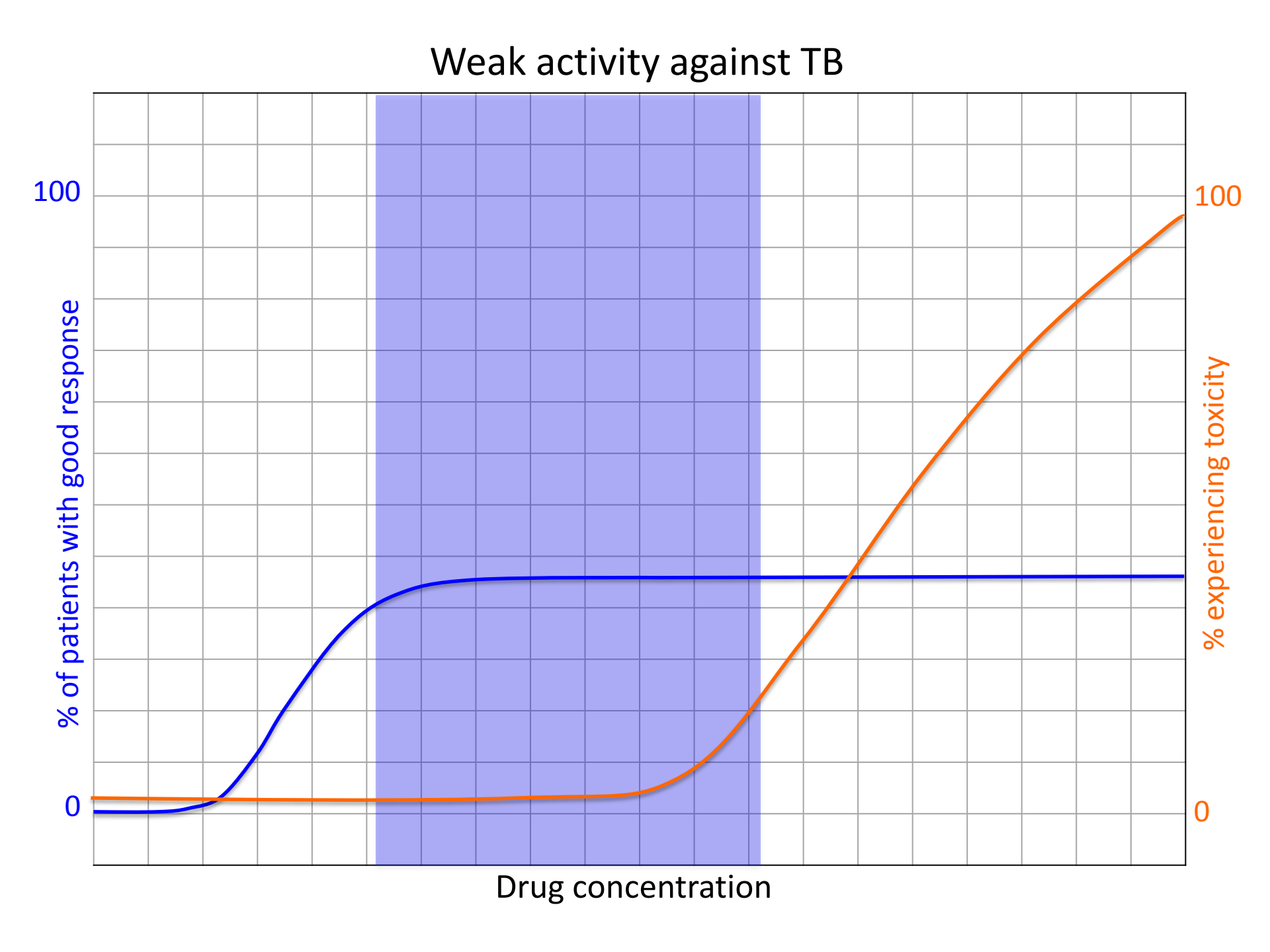


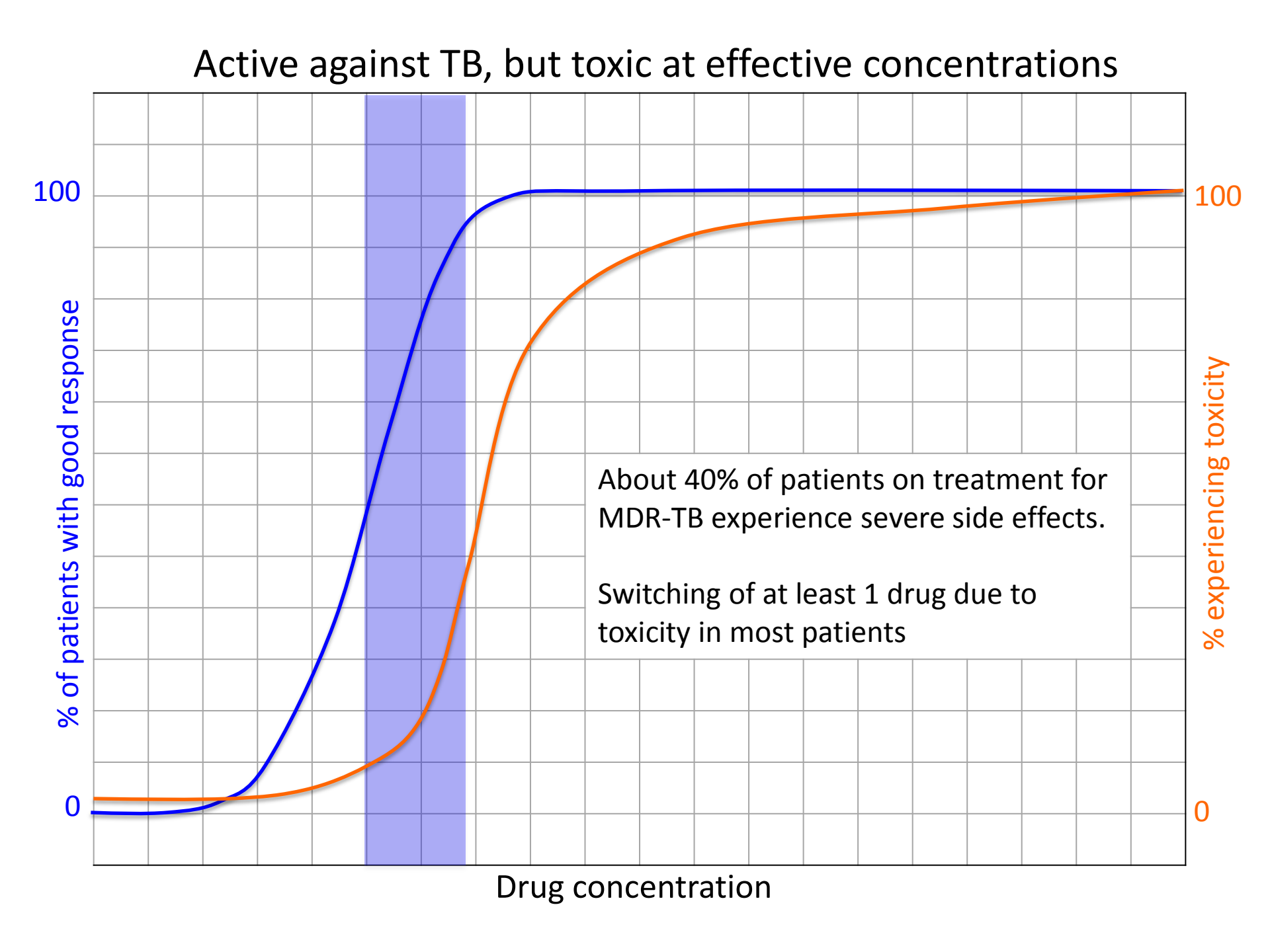
Gumbo et al., JID 2004;190:1642-51



Thwaites et al., AAC 2011; 55:3244-

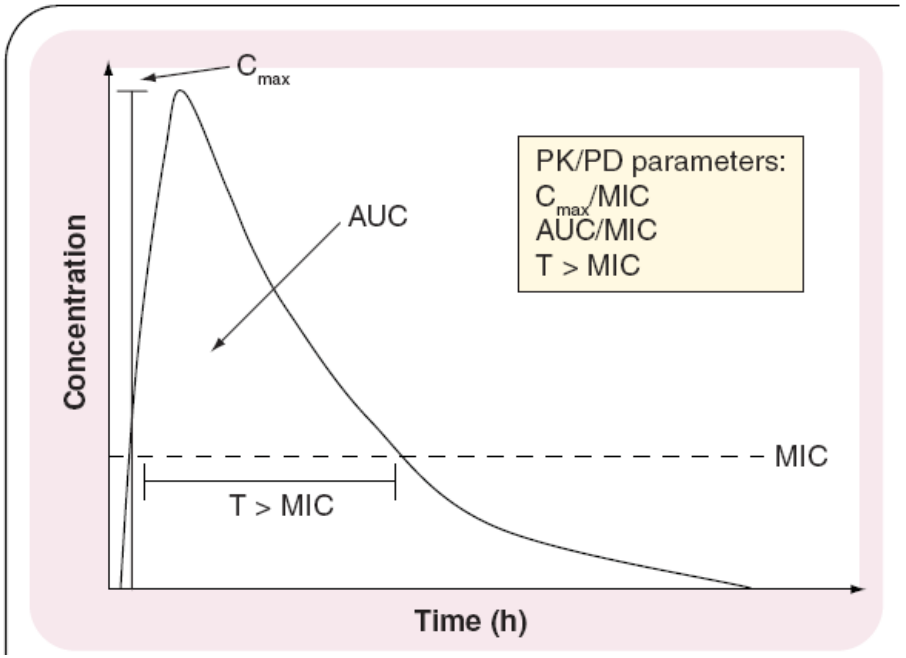

Safe and effective over a wide range of drug exposures
100
0
% of patients with good response
100
0
% experiencing toxicity
Drug concentration


Weak activity against TB
100
0
% of patients with good response
100
0
% experiencing toxicity
Drug concentration


Active against TB, but toxic at effective concentrations
100
0
% of patients with good response
100
0
% experiencing toxicity
About 40% of patients on treatment for MDR-TB experience severe side effects.
Switching of at least 1 drug due to toxicity in most patients
Drug concentration

PK targets in children

- PK-PD
  - *in vitro*
  - animals
  - adults



- 'Normal' adult exposures

"…it is highly likely that children will respond well to a new regimen if given a drug formulation and dose that achieves pharmacokinetic parameters comparable to those among adults." *(Burman et al., Plos Med 2008; 5(8): e176)*

one mg/kg dose for all…?

TABLE 9.1 **Paediatric dosing of second-line antituberculosis drugs (*4*, *10*)**

DRUG	DAILY DOSE (MG/KG)	FREQUENCY	MAXIMUM DAILY DOSE
streptomycin	20–40	Once daily	1 g
kanamycin	15–30	Once daily	1 g
amikacin	15–22.5	Once daily	1 g
capreomycin	15–30	Once daily	1 g
ofloxacin	15–20	Twice daily	800 mg
levofloxacin	7.5–10	Once daily	750 mg
moxifloxacin	7.5–10	Once daily	400 mg
ethionamide	15–20	Twice daily	1 g
protionamide	15–20	Twice daily	1 g
cycloserine	10–20	Once or twice daily	1 g
p-aminosalicylic acid	150	Twice or thrice daily	12 g

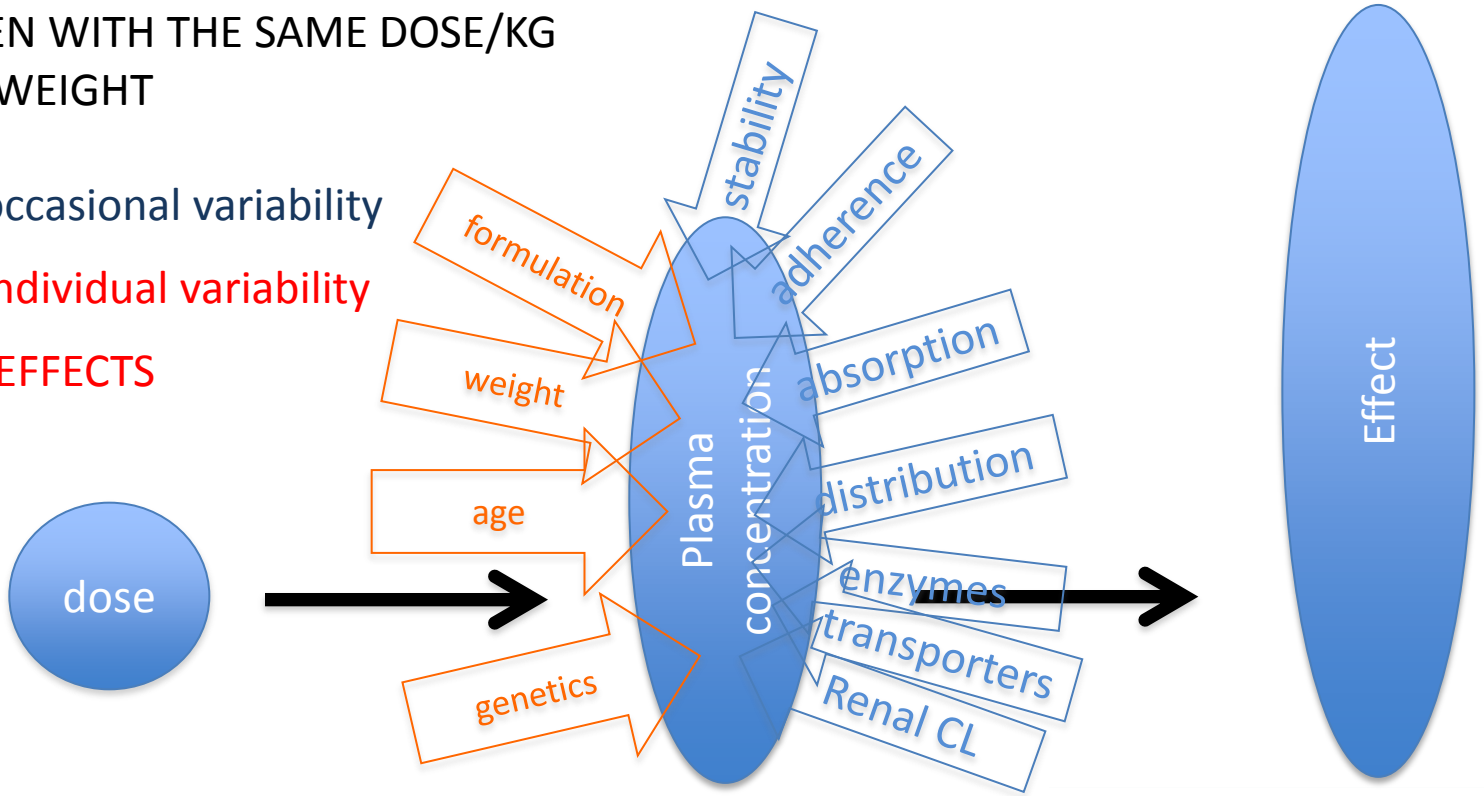
WHO, Emergency Update, 2008

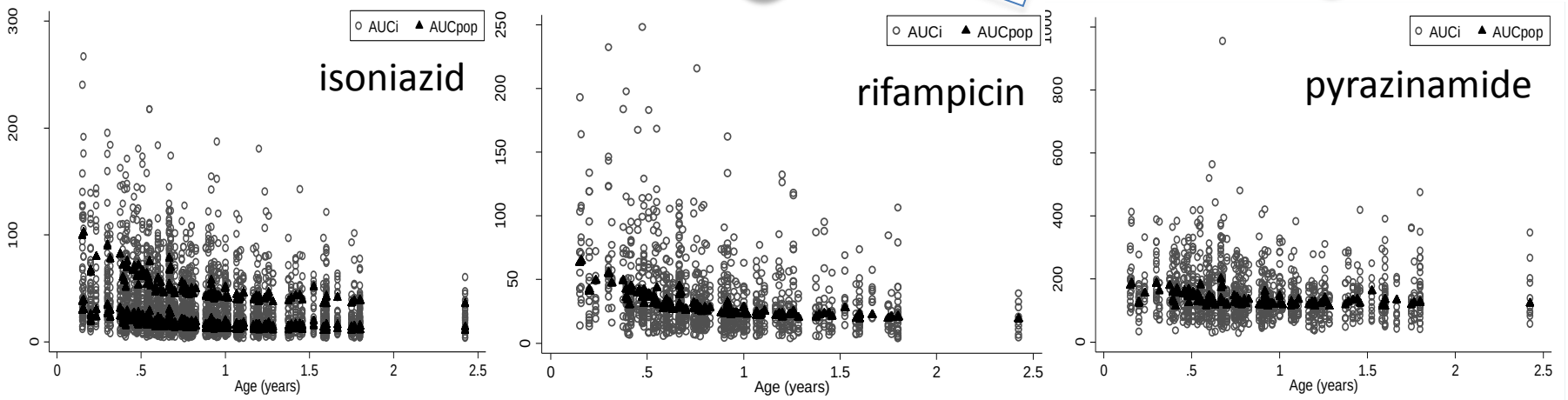
THERE IS A LOT OF VARIABILITY IN PK EVEN WITH THE SAME DOSE/KG BODY WEIGHT

Inter-occasional variability

Inter-individual variability

FIXED EFFECTS





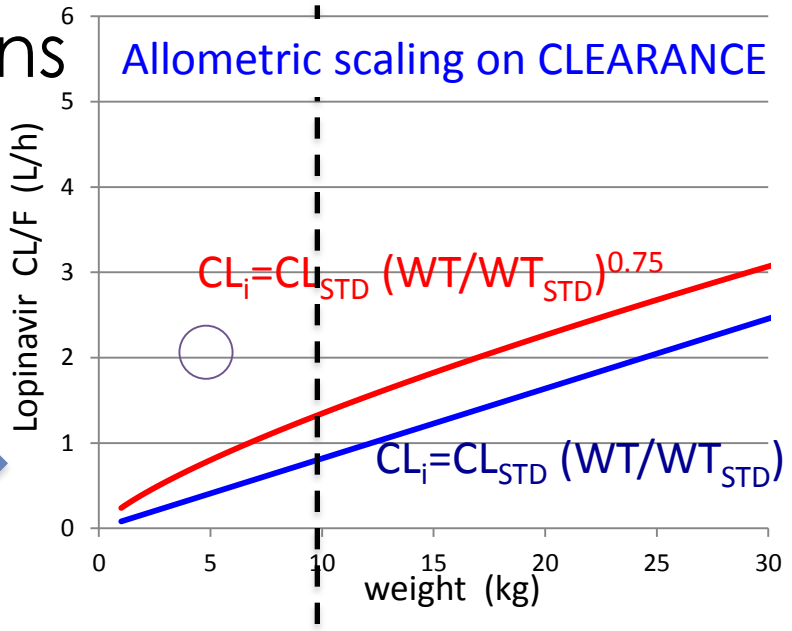
S Zvada., 2013

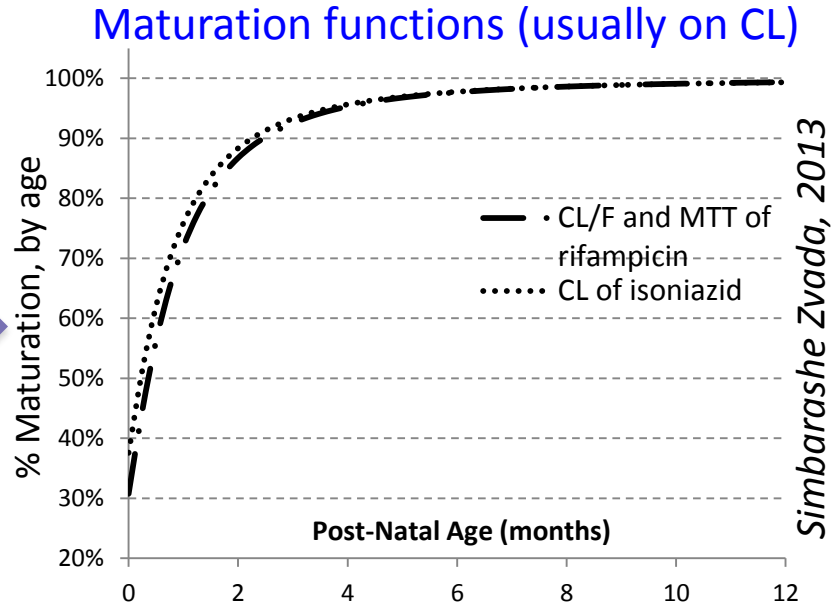
Paediatric PK considerations

enteric pH gastric motility intestinal transit time intestinal metabolism & transporter activity	**A**
body composition plasma protein binding	**D**
enzyme & transporter maturation	**M**
tubular secretion GFR	**E**

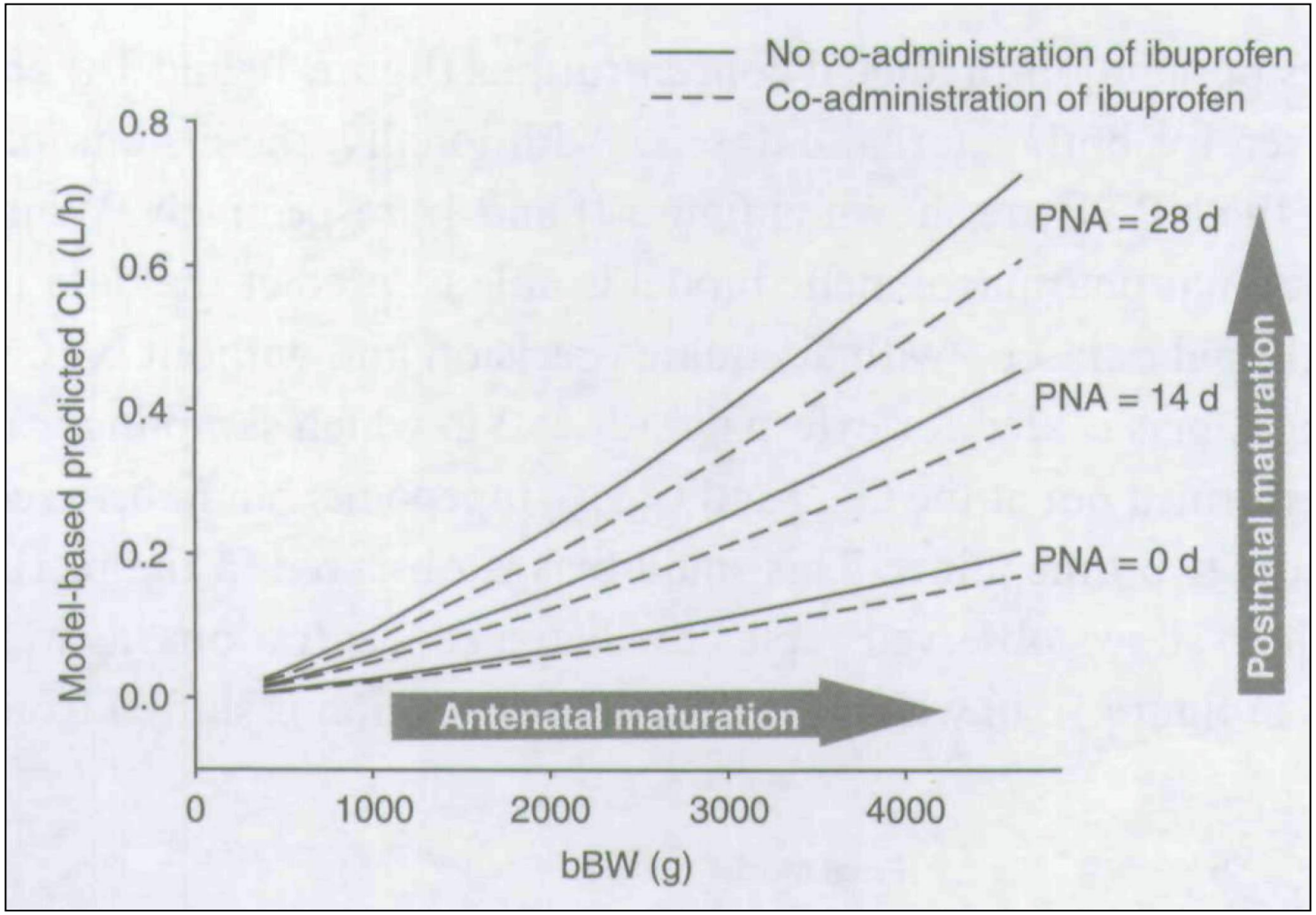
growth/size/weight

development/maturation





amikacin CL: age and weight dependent



De Cock et al., Clin Pharmacokinet 2012; 51 (2): 105.117

amikacin 20 mg/kg/d, i.m.

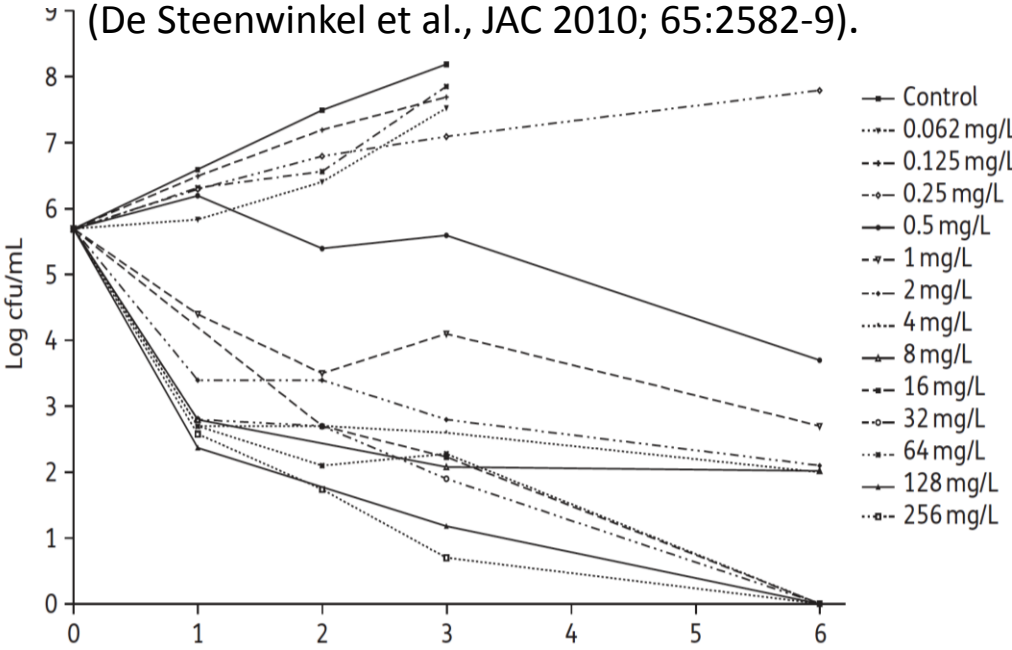
	C_{max} (µg/ml)			T_{max} (h)			AUC_{0-8} (µg·h/ml)		
	N	Median (IQR)	p-value	N	Mean (SD)	p-value	N	Median (IQR)	p-value
Age group									
0-2 years	6	43.65 (42.20 - 49.20)		6	1.00 (0.00)		6	103.85 (96.80 - 119.10)	
2-5 years	7	49.10 (40.70 - 59.20)		7	1.14 (0.38)		7	124.15 (97.75 - 162.05)	
6-15 years	15	49.60 (40.30 - 56.40)	0,845	15	1.13 (0.35)	0,593	14	159.25 (124.20 - 179.48)	0,016
HIV status									
HIV-infected	10	47.05 (42.20 - 54.40)		10	1.10 (0.31)		9	151.00 (109.40 - 162.05)	
HIV-uninfected	18	46.85 (40.70 - 53.00)	0,719	18	1.11 (0.32)	0,931	18	128.65 (112.50 - 174.95)	0,918

Hesseling et al., IUATLD meeting , KL, 2012

Typical C_{max} in adults on 15 mg/kg daily: 35-45 µg/ml
(Peloquin. Drugs 2002; 62: 2169-83)

In vitro bactericidal effect of amikacin at different concentrations over time

(De Steenwinkel et al., JAC 2010; 65:2582-9).



Narrow therapeutic range:

- bactericidal activity

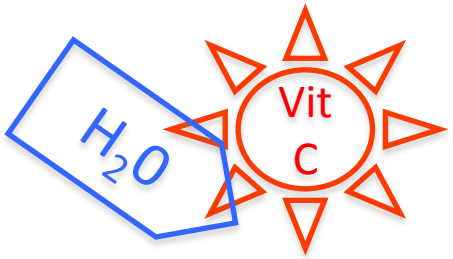
  -PK (? C_{max})
- Hearing loss
  - cumulative exposure (? C_{min})
  - genetic predisposition

‘unfriendly’ adult formulations for children

image: Damien Schumann, from Seddon et al., Tuberculosis 2012, 92:9-17

Formulation & administration concerns with 1st-line TB drugs

•RIF degradation



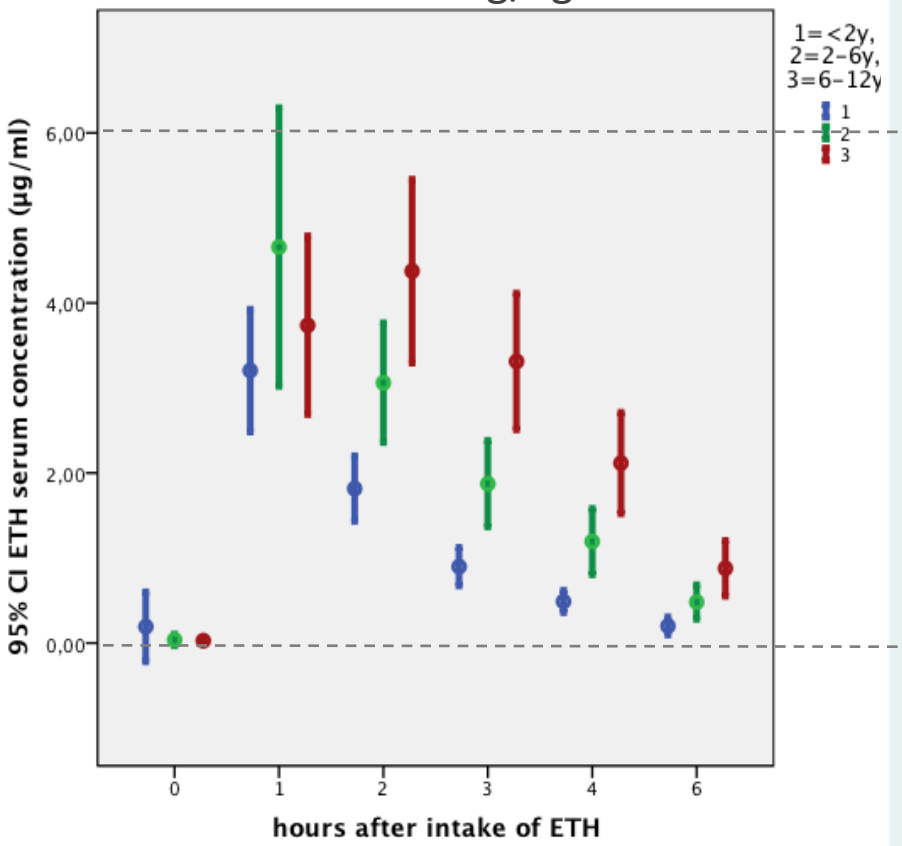
RIF-INH

•RIF binds to polypropylene, plastics. Poorly soluble
•INH interacts with lactose, other sugars
•EMB hygroscopic chelates di- & tri-valent cations

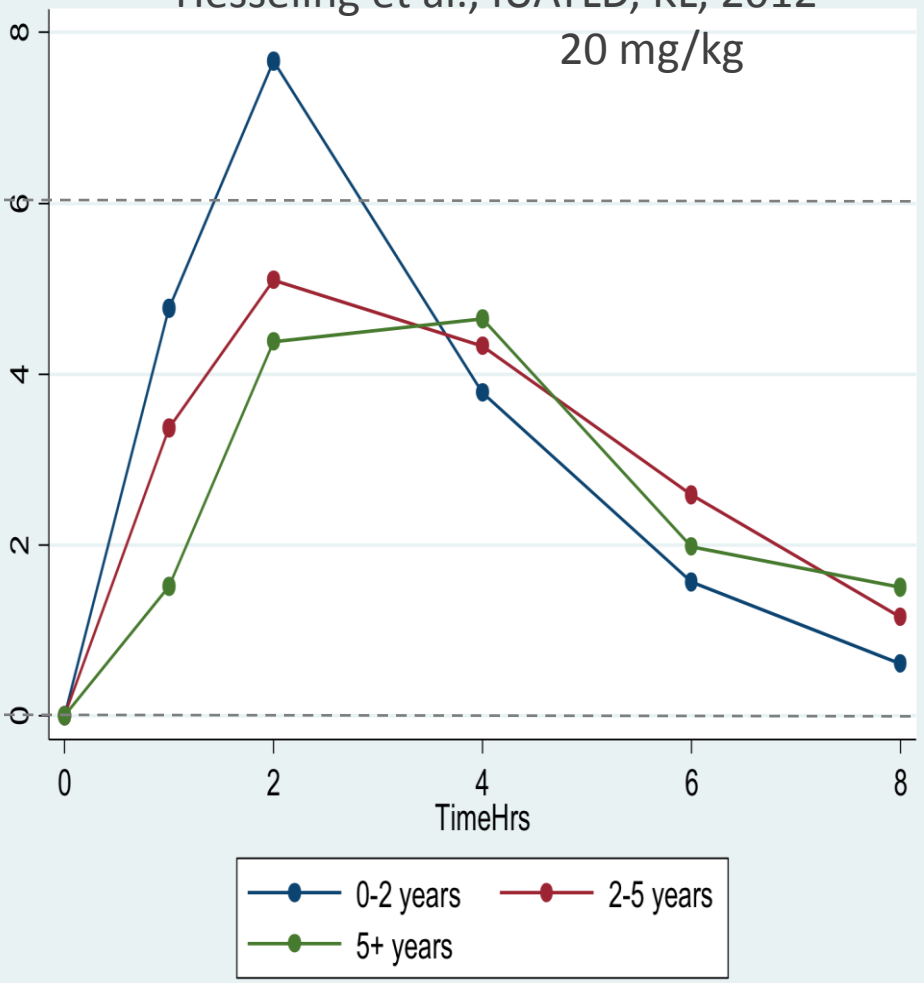
…in practice TB drugs crushed and mixed with:-
Multi-vit. syrup, fruit juice, jam, peanut butter, milk, etc.

Ethionamide PK in children, by age

Thee et al., AAC 2011; 55:4594-600
15-20 mg/kg



Hesseling et al., IUATLD, KL, 2012
20 mg/kg



Limited PK data in adult patients on currently recommended doses (15-20 mg/kg)

Ofloxacin, 20 mg/kg, oral*

	C_{max} (µg/ml)			T_{max} (h)			AUC_{0-8} (µg·h/ml)		
	N	Median (IQR)	p-value	N	Mean (SD)	p-value	N	Median (IQR)	p-value
Study group									
MDR disease	32	7.86 (6.83 - 9.54)		32	2.00 (0.98)		32	40.70 (35.47 - 47.02)	
MDR prophylaxis	11	9.82 (7.44 - 11.40)	0,148	11	1.27 (0.47)	0,003	11	42.43 (39.33 - 50.83)	0,404
Age group									
0-2 years	12	9.54 (8.57 - 10.60)		12	1.42 (0.52)		12	45.11 (38.34 - 47.92)	
2-5 years	21	8.79 (6.98 - 9.99)		21	1.67 (0.73)		21	42.43 (35.62 - 50.83)	
6-15 years	10	7.16 (5.84 - 7.66)	0,407	10	2.60 (1.27)	0,039	10	39.19 (32.09 - 42.33)	0,220
HIV status									
HIV-infected	7	8.90 (7.51 - 9.37)		7	1.71 (1.11)		7	41.37 (35.91 - 46.43)	
HIV-uninfected	36	8.57 (6.83 - 10.21)	0,818	36	1.83 (0.91)	0,761	36	42.17 (35.88 - 48.21)	0,844

Symposium, Friday 1 Nov: MDR-TB IN CHILDREN AND ADOLESCENT TUBERCULOSIS ISSUES; Tony Garcia-Prats

Session 14: Saturday 2 Nov, 12:45-14:15, Room 241

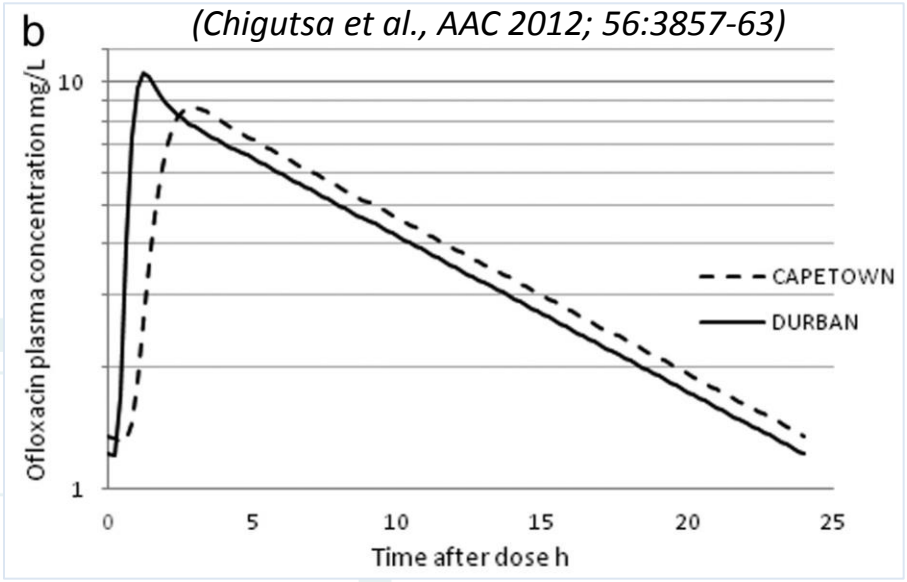
OP-212-02; Stefanie Thee; PK of ofloxacin and levofloxacin in children with MDR-TB

*tablets crushed and mixed with water in children unable to swallow tablets

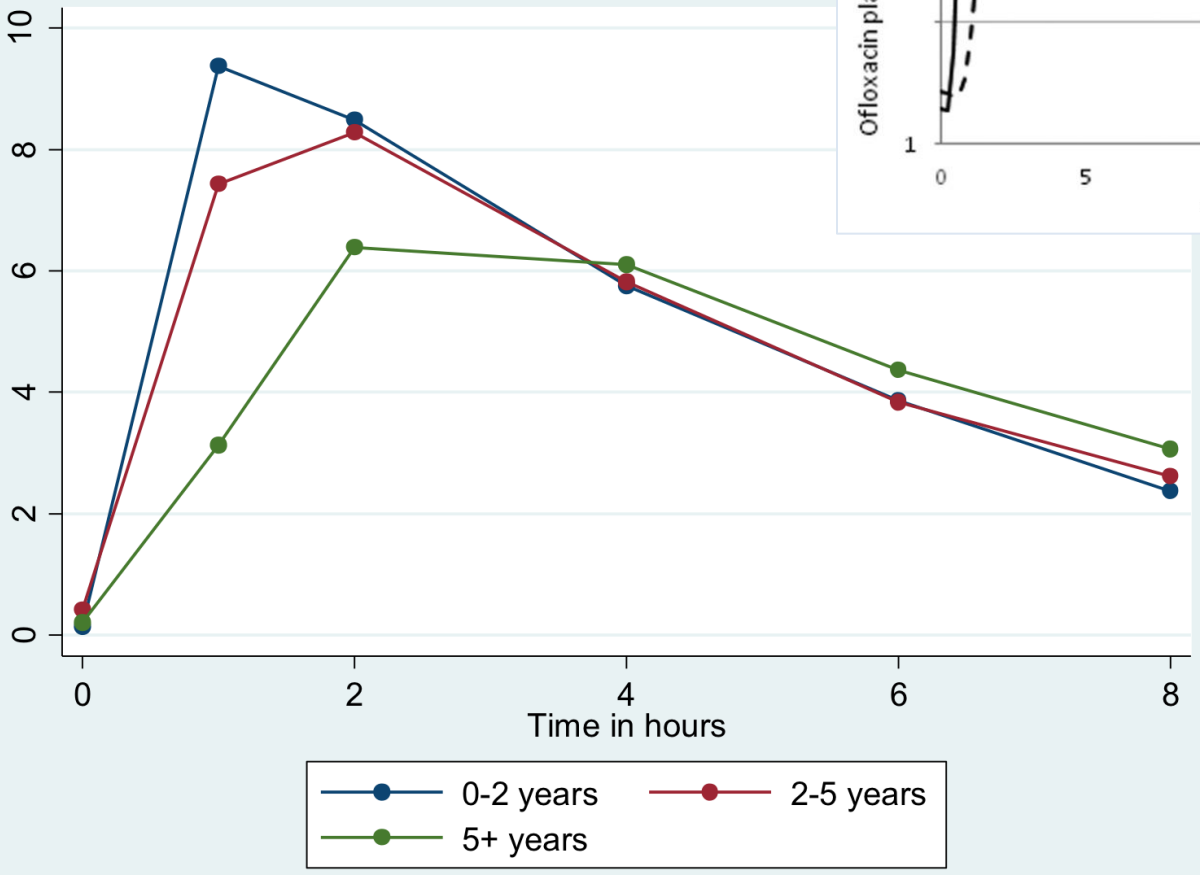
Hesseling et al., IUATLD, KL, 2012

Adults with PTB on 15 mg/kg/d

(Chigutsa et al., AAC 2012; 56:3857-63)



Children on 20 mg/kg/d



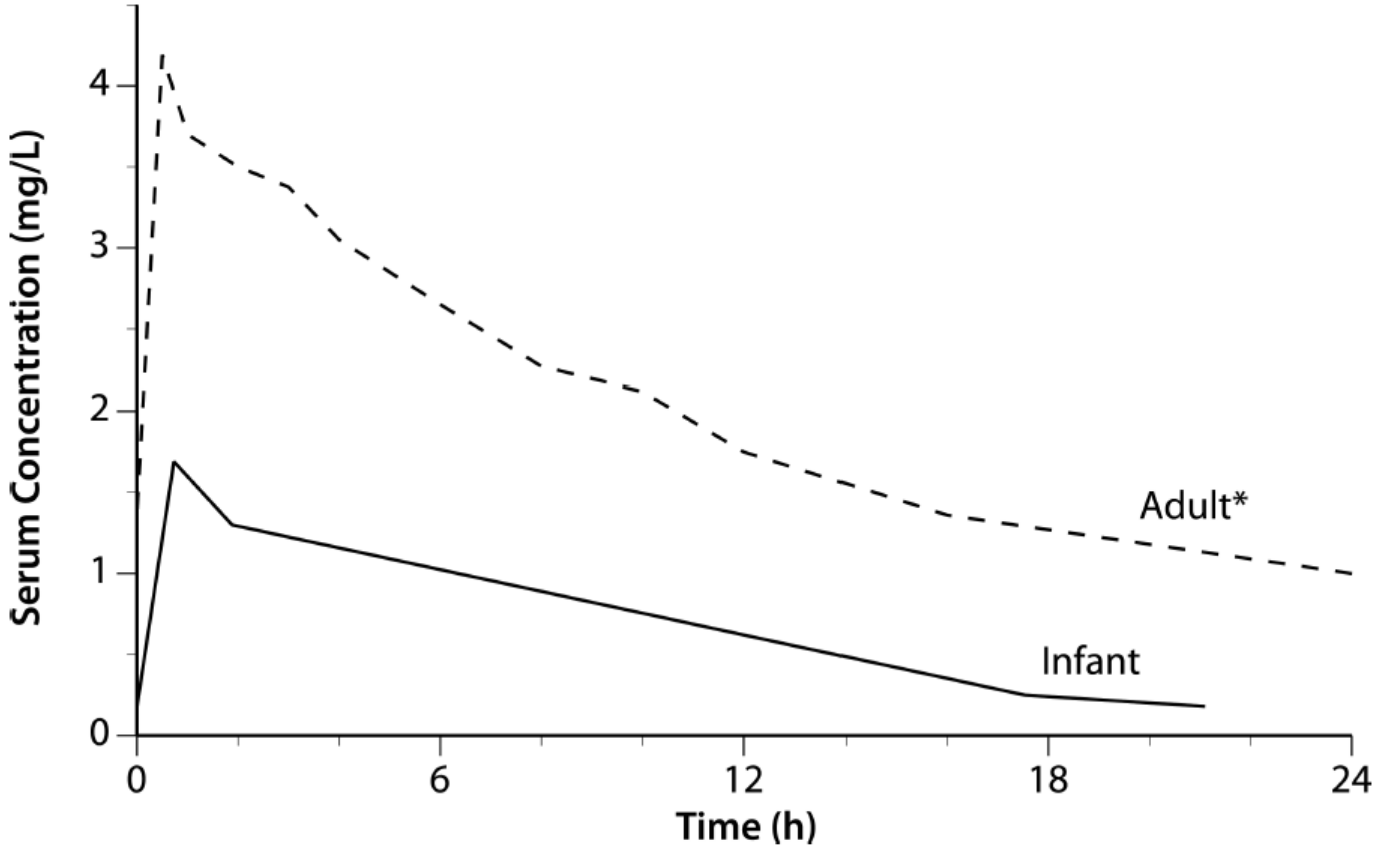
Hesseling et al., IUATLD, KL, 2012

PK studies need to confirm appropriate dosing in children

- Growth and maturation
- Understand and address inter-individual variability in PK
  - weight, age, genotype, etc.
  - formulation & formulation preparation
  - co-morbidity, co-medication

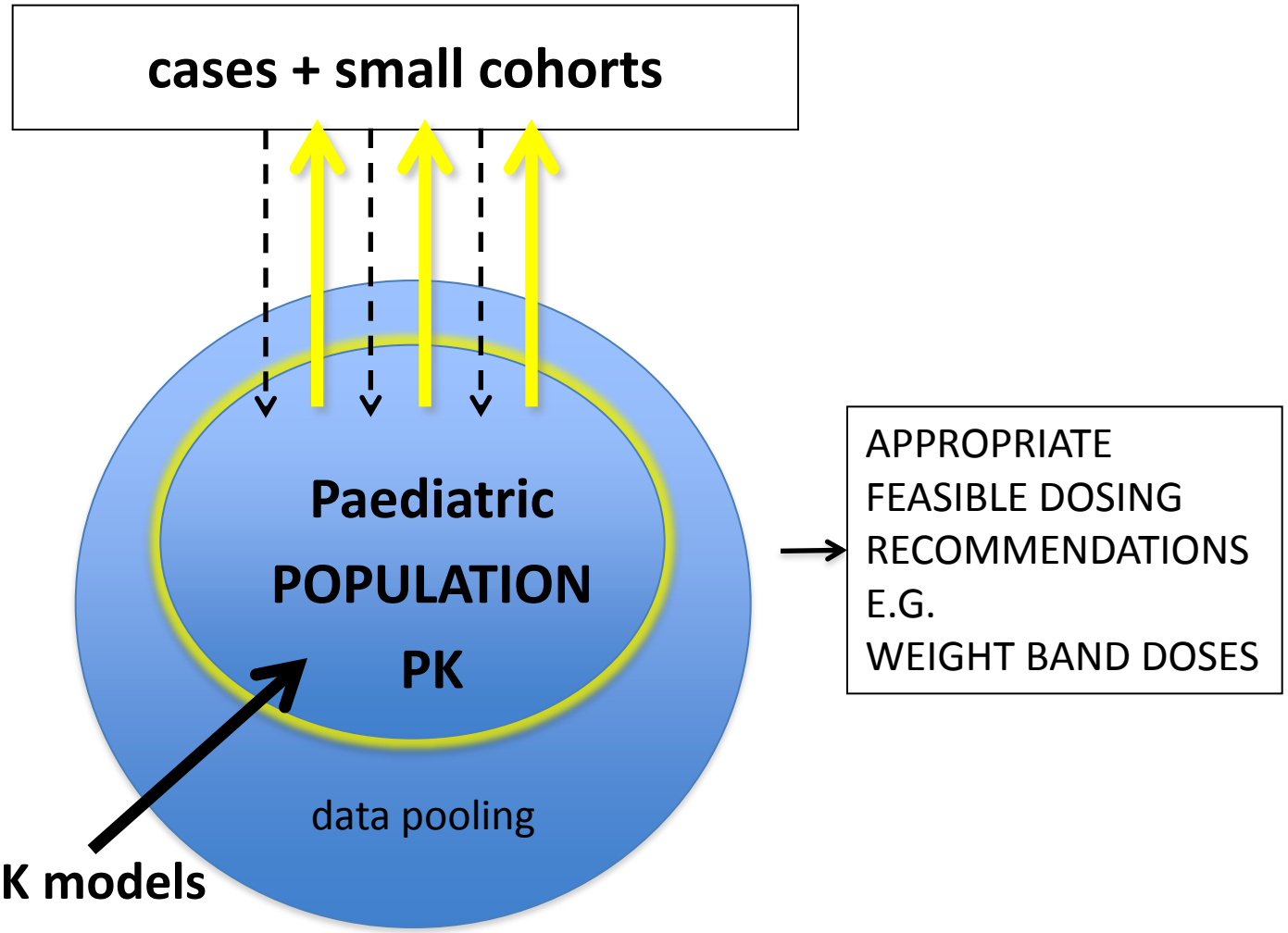
  THE MAGNITUDE OF DDIs MAY BE DIFFERENT IN CHILDREN

PK moxi in prem. baby (5 mg/kg IV)



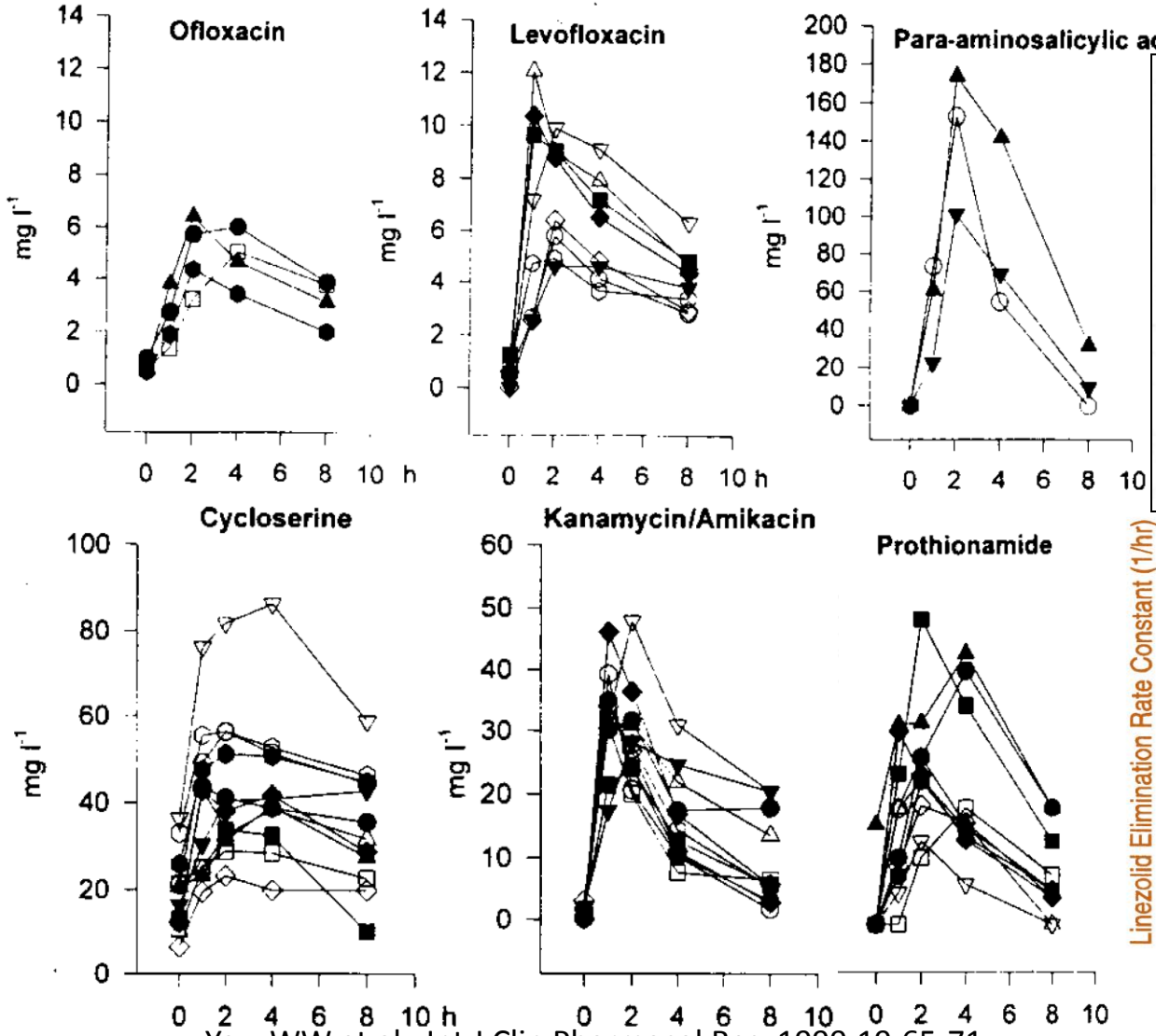
Watt et al., PIDJ 2012; 31: 197-9.

Figure 1.
Moxifloxacin serum concentrations in an infant compared with adults * Adult data adapted from Avelox® Label (Bayer Pharmaceuticals Corporation, Leverkusen, Germany).[6]

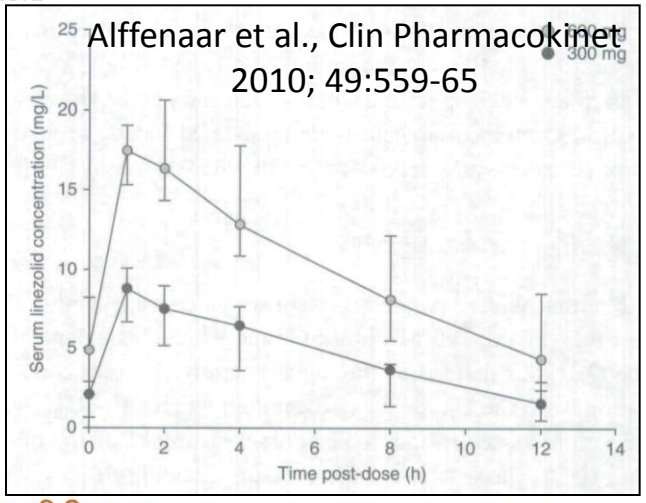


- allometric scaling
- maturation function

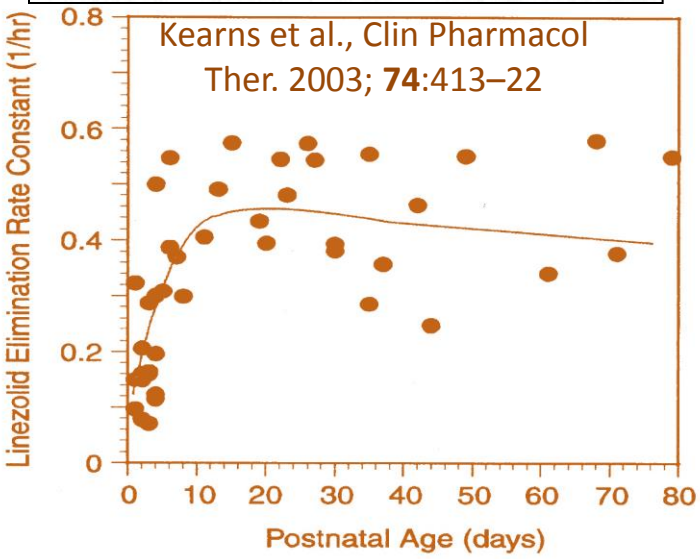
PK (&PD) characterization of 2nd-line drugs in TB patients is insufficient, more so in children



Yew WW et al., Int J Clin Pharmacol Res. 1999;19:65-71



Alffenaar et al., Clin Pharmacokinet 2010; 49:559-65

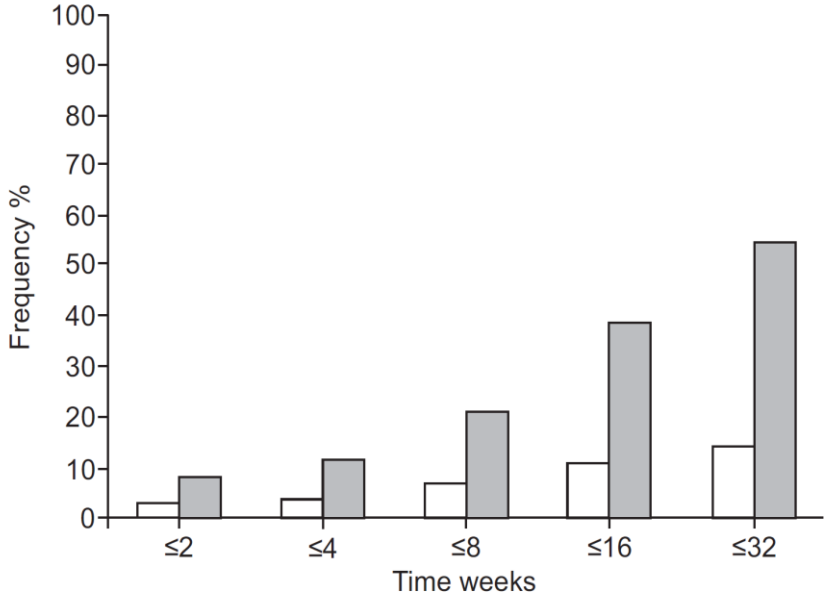


Kearns et al., Clin Pharmacol Ther. 2003; **74**:413–22

Clofazimine, linezolid, cycloserine/terizidone, capreomycin…

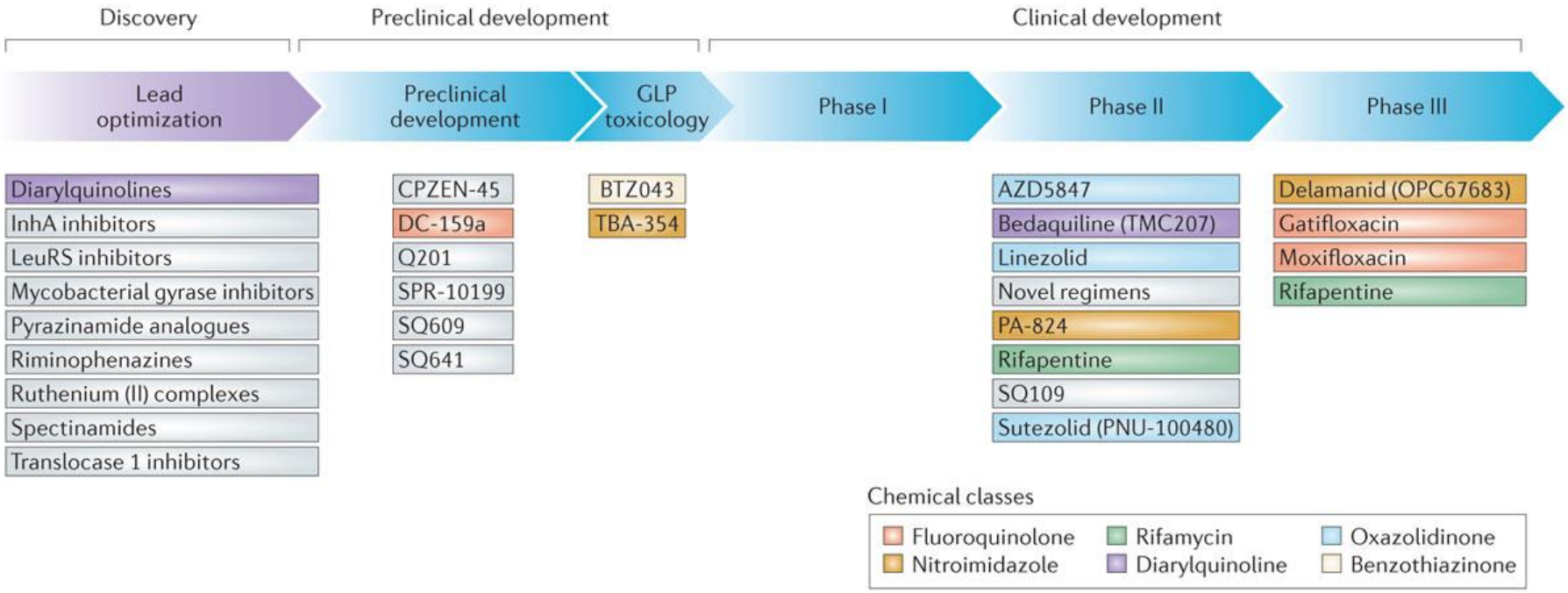
- Increasing use in children with DR-TB
- Dose-related toxicity
- Urgent need to evaluate exposure-efficacy & toxicity relationships

Frequency of AEs in patients treated with linezolid – relation to dose & time on treatment
600 mg/d vs. 1200 mg/d



MIGLIORI et al. Eur Respir J 2009; 34:387-

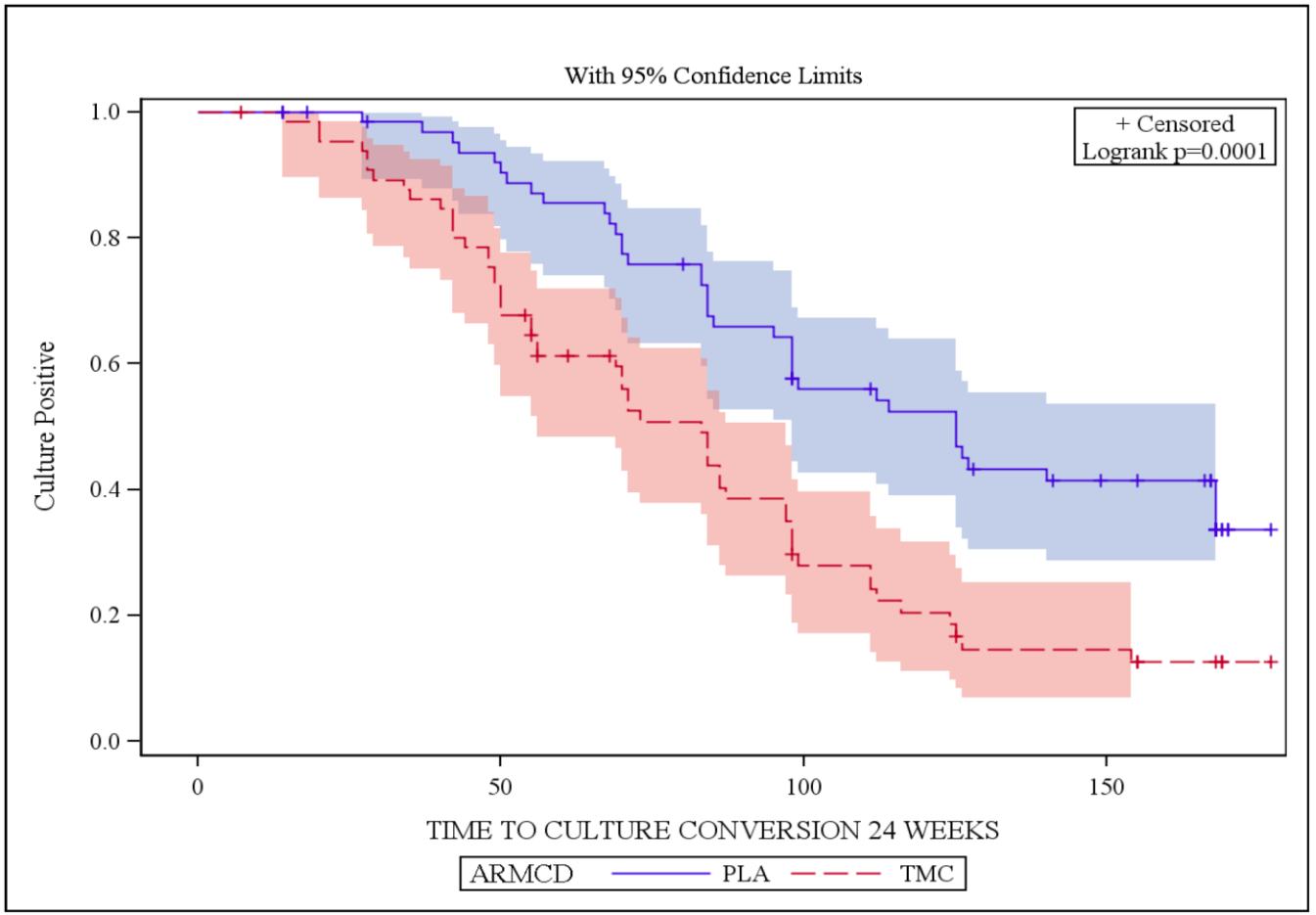
TB drug pipeline



Zumla et al., Nature Reviews Drug Discovery 2013; **12:**388–404

Bedaqualine

- C208, stage 2; culture conversion



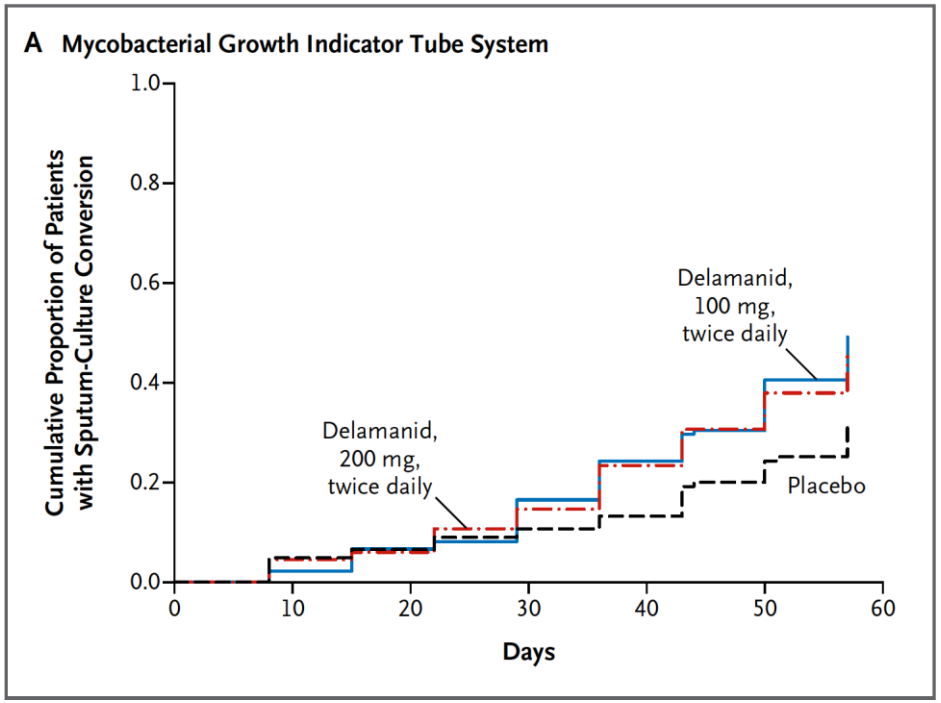
www.fda.gov

- Concerns:
  - Unexplained excess mortality in study C208
  - Optimal dose may be safety limited

    QT prolongation (especially in combination with delamanid, fluoroquinolones, clofazimine)
  - Long half-life and potential for resistance development
  - DDIs with ART: 1st dose > steady state > end BDQ

P1108: PK, safety and tolerability of TMC207 in children, in combination with a standard regimen for MDR-TB; <12 years on PAEDIATRIC FORMULATION (in development….)

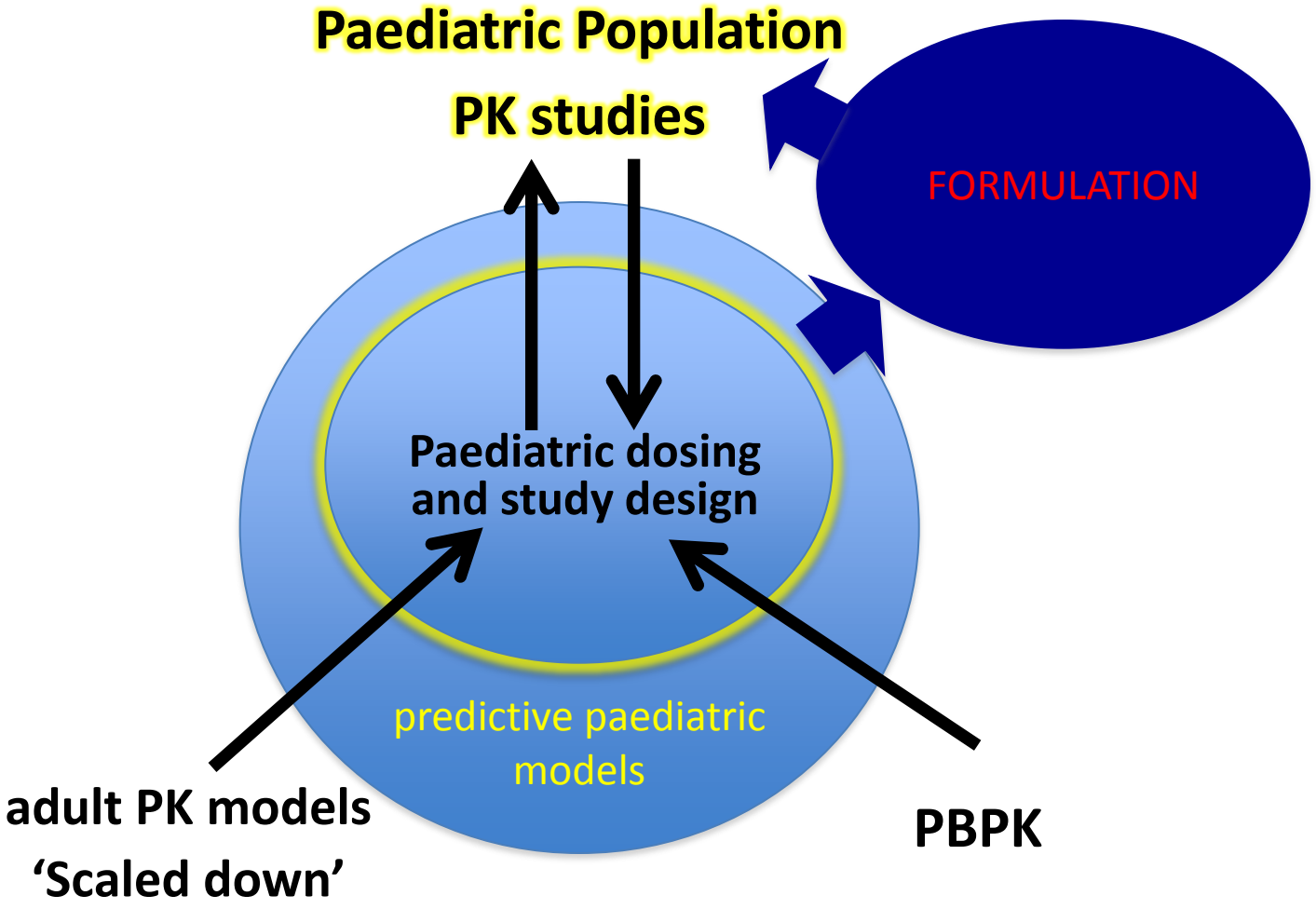
Delamanid



Gler et al., NEJM 2012; 366:2151-60

- DDIs:
  - efavirenz; NS
  - Tenofovir; NS
  - lopinavir/ritonavir; modest ↑ delamanid
- Paediatric formulation: small, dissolvable tablets
- Paediatric study: 12-17 y, 100 mg bd*10d (n=6)
  6-11 y, 50 mg bd*10d (n=6)

Paediatric formulation availability is a key step in characterizing PK Data pooling, and M&S facilitate efficient PKPD knowledge



- allometric scaling
- maturation function

concluding points

- Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)–

"Groups that are underrepresented in medical research should be provided appropriate access to participation in research."

- Regulatory legislation in both the US and Europe contains requirements as well as incentives for inclusion of children as part of product development plan.

- OLD drugs have not been adequately optimized in children

- PK information to support NEW drugs in children is needed urgently

- PK studies have a key role in getting the formulation & dose right, efficiently.