

*7th International Workshop on Clinical Pharmacology of TB drugs
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Pharmacokinetics of rifampicin, isoniazid and pyrazinamide in children on 2010 WHO/IUATLD guideline doses



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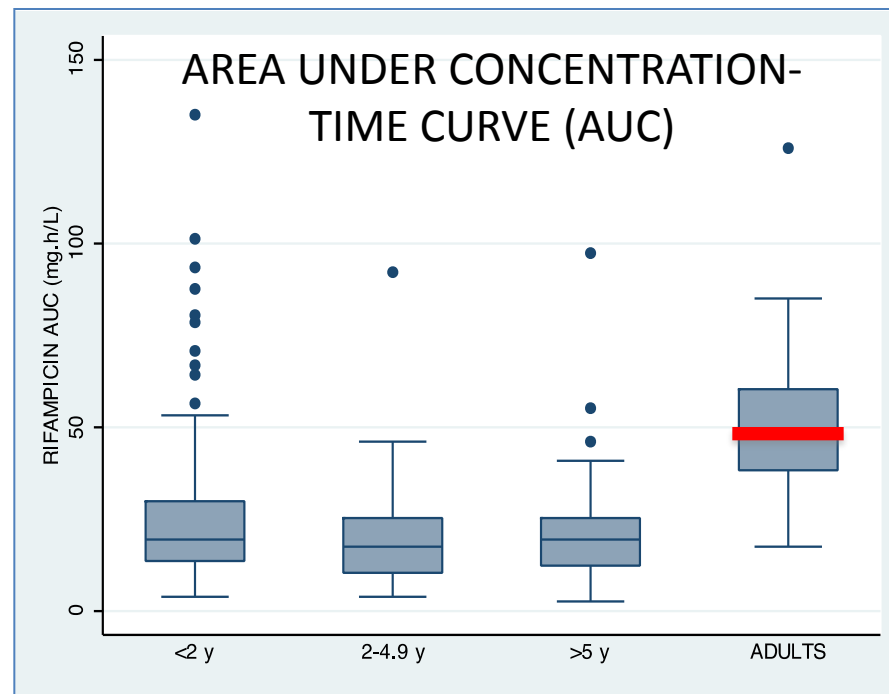
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NIH/NICHD R01HD069175 (DATiC study)

“Controlling TB in adults has been considered enough to control TB in children, but it isn't.”

www.childhoodtb.org

15-20% of TB in low/middle-income settings



WHO/IUATLD dosing guidelines for children <12 years of age

Rifampicin (R) 15 (10-20) mg/kg ↑ 50%

Isoniazid (H) 10 (7-15) mg/kg ↑ 100%

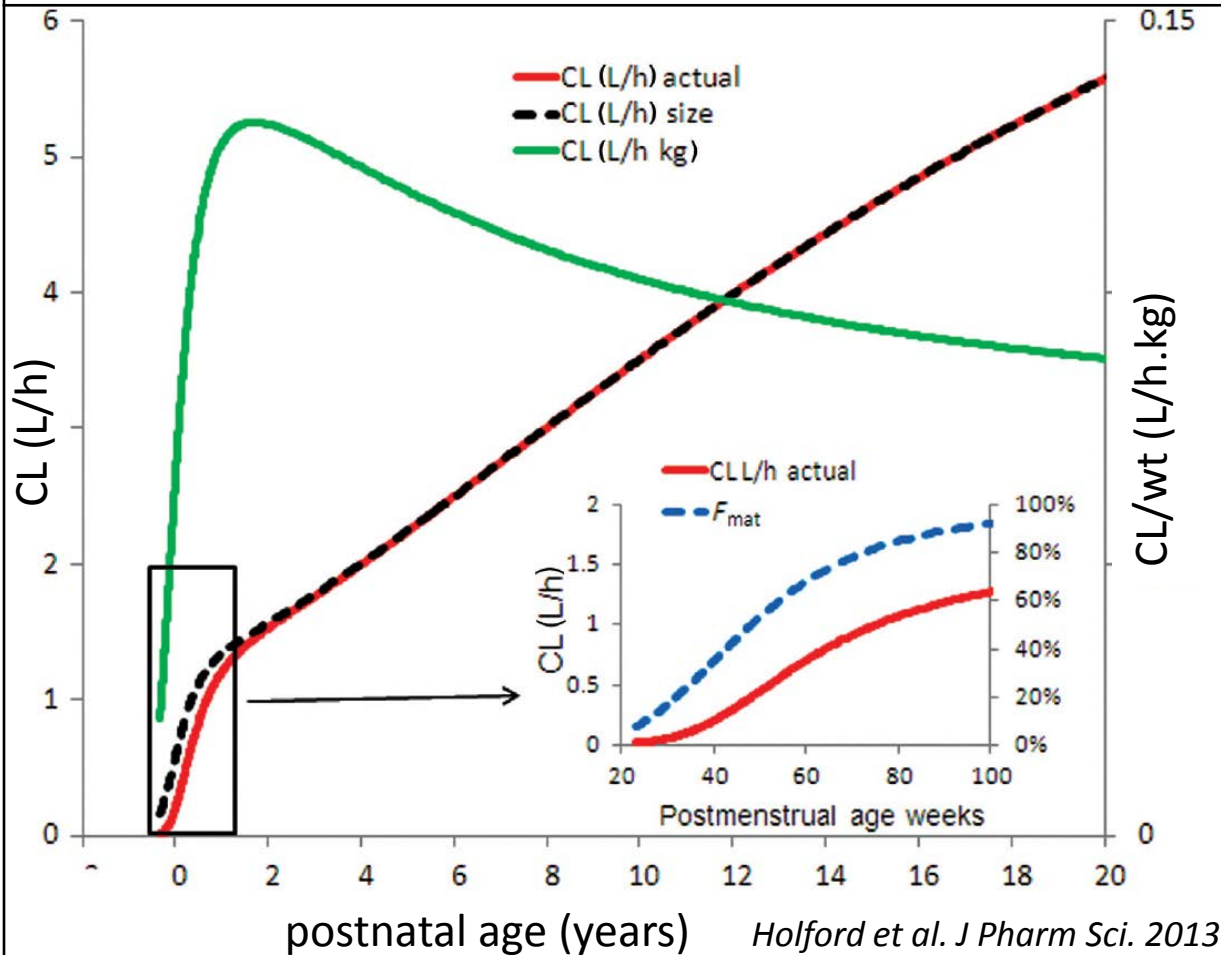
Pyrazinamide 35 (Z) (30-40) mg/kg ↑ 40%

Evidence needed to support MINIMUM requirement -
drug **formulations** and **doses** that achieve
comparable PK to adults

variability in mg/kg dose requirement

Size, maturity

Other factors



HIV infection
nutritional status
disease severity
sex

drug interactions

formulation
dose preparation

DATiC study: Steady-state pharmacokinetics (PK) of 1st-line TB drugs in 240 South African and Malawian children 0-12 years old

support optimal pragmatic dosing guidelines, and efficient combination for FDCs- taking into account weight, maturation, HIV, nutrition

- PK for R, H and Z in 47 children enrolled in South Africa
- Stringent regulator- or WHO GDF- approved formulations in the 'new/revised' doses
 - R-granulate for oral suspension (10-20 mg/kg)
 - H-50 mg tablet (7-15 mg/kg)
 - Z-150 mg tablet (30-40 mg/kg)
- 0.6 mL blood samples for over 8-10 hours during the 2nd month of treatment
 - Pre-dose and 1, 2, 4, 6, 10 h after dose (n=20)
 - Pre-dose and 2, 4, 6, 8 h after dose (n=27)

Methods, cont...

LC-MS/MS

- LLQ: R-0.117; H-0.05 mg/L; Z-0.2 mg/L

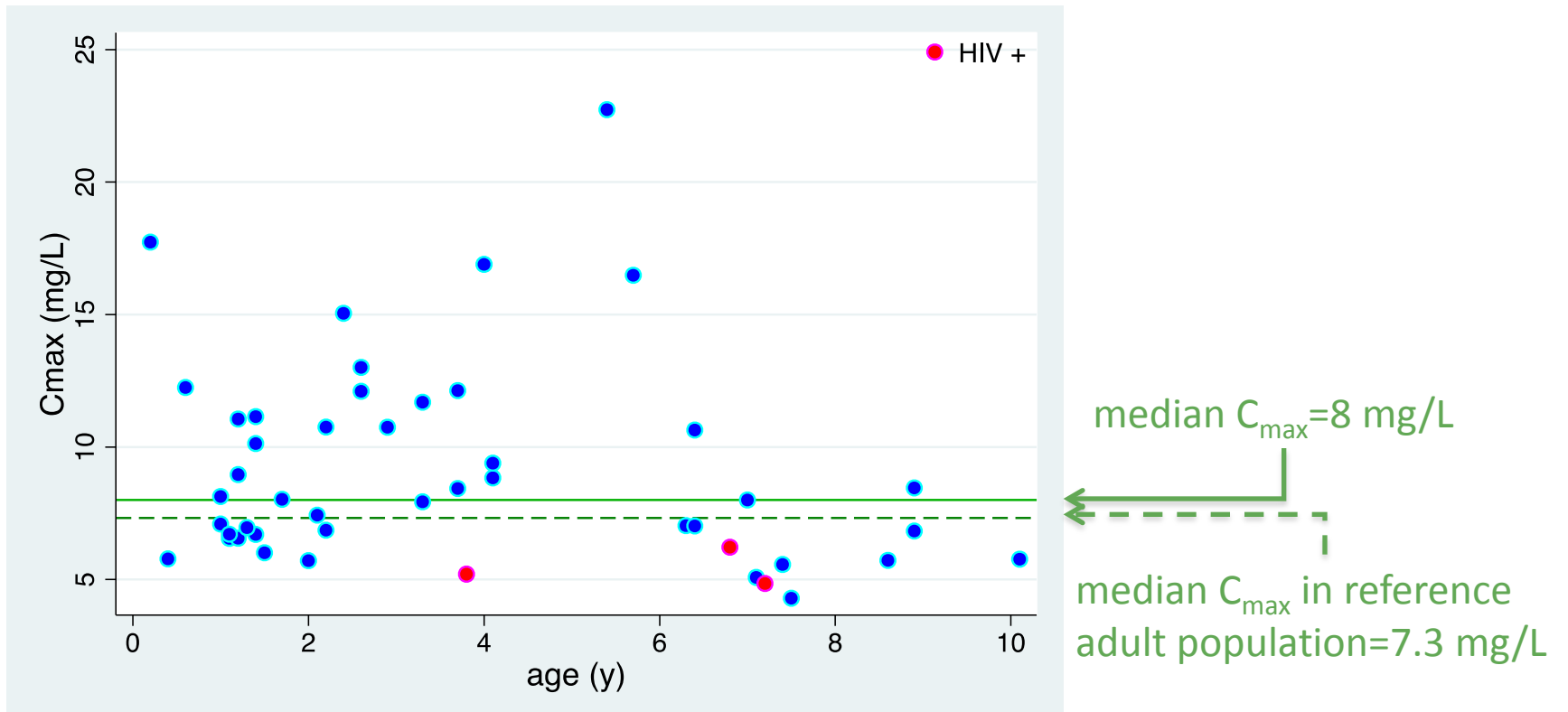
Population NLME models built using NONMEM7

- allometric scaling and maturation functions were tested
- covariate effects tested
 - age, sex and HIV, albumin and c-reactive protein on model parameters.
- individual AUC_{0-24} and C_{max} estimated (post-hoc Bayesian estimates)

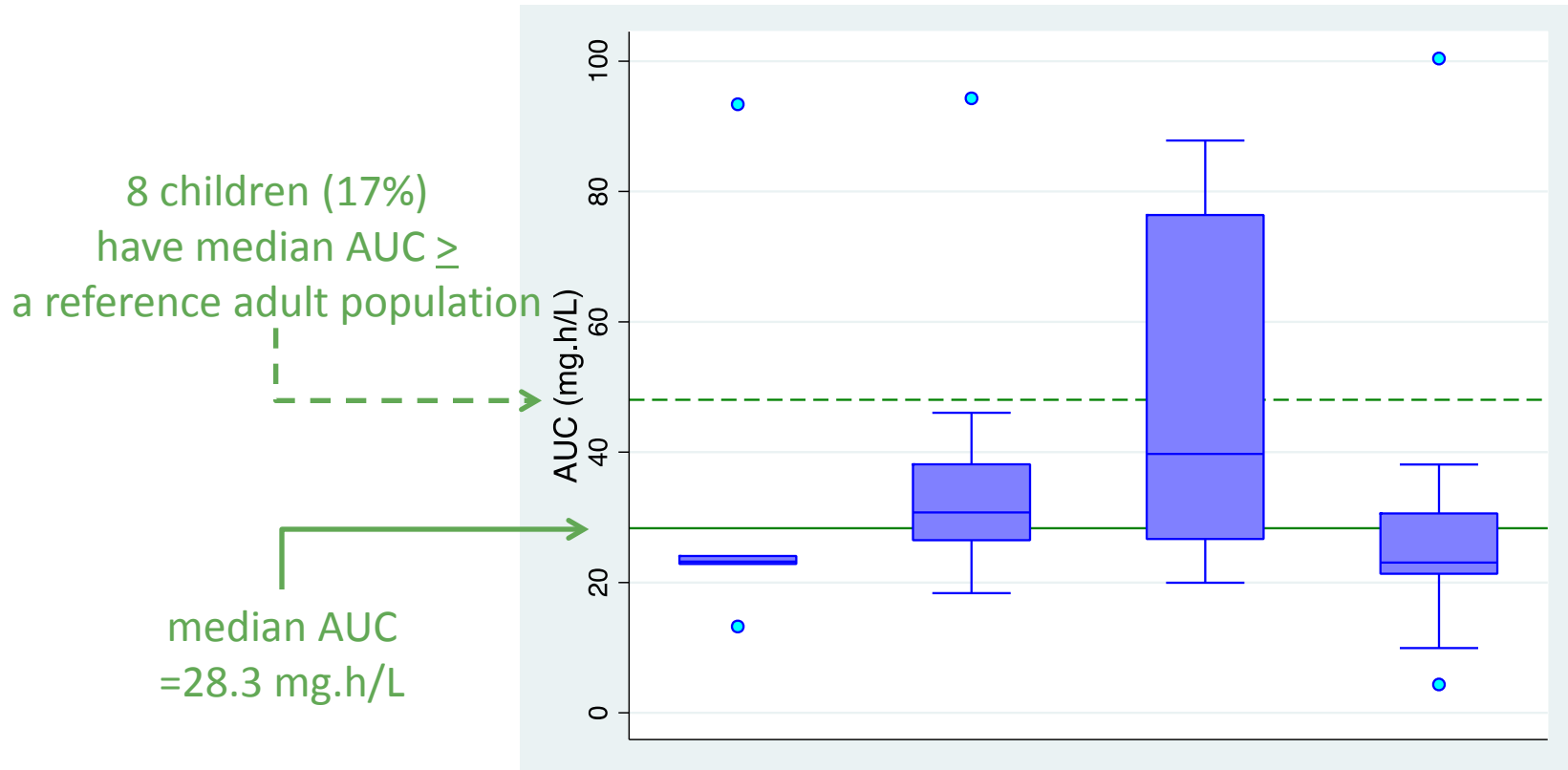
characteristics for 47 children

	n	median	IQR	range
age (years)	47	2.9	(1.4, 6.4)	0.2, 10.1
weight (kg)	47	13.4	(10.1, 18.4)	
girls		18/47 (38%)		
HIV		3/47 (6%)		
wt-for-ht z-score	41	0	(0, 1)	
C-reactive protein (mg/L)	46	1.85	(1, 6.5)	
Albumin (g/L)	46	40	(38, 42)	
rifampicin dose (mg/kg)	47	15.8	(13.4, 17.8)	
isoniazid dose (mg/kg)	47	12.0	(11.1, 13.5)	
pyrazinamide dose (mg/kg)	47	34.4	(32.1, 36.9)	

rifampicin peak concentration (C_{max})

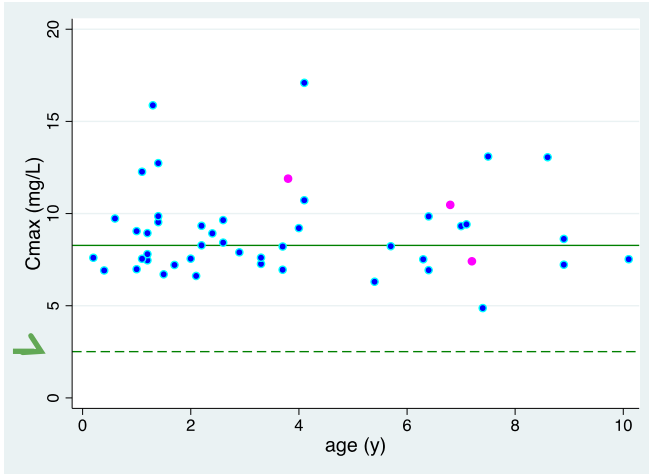


rifampicin AUC₀₋₂₄

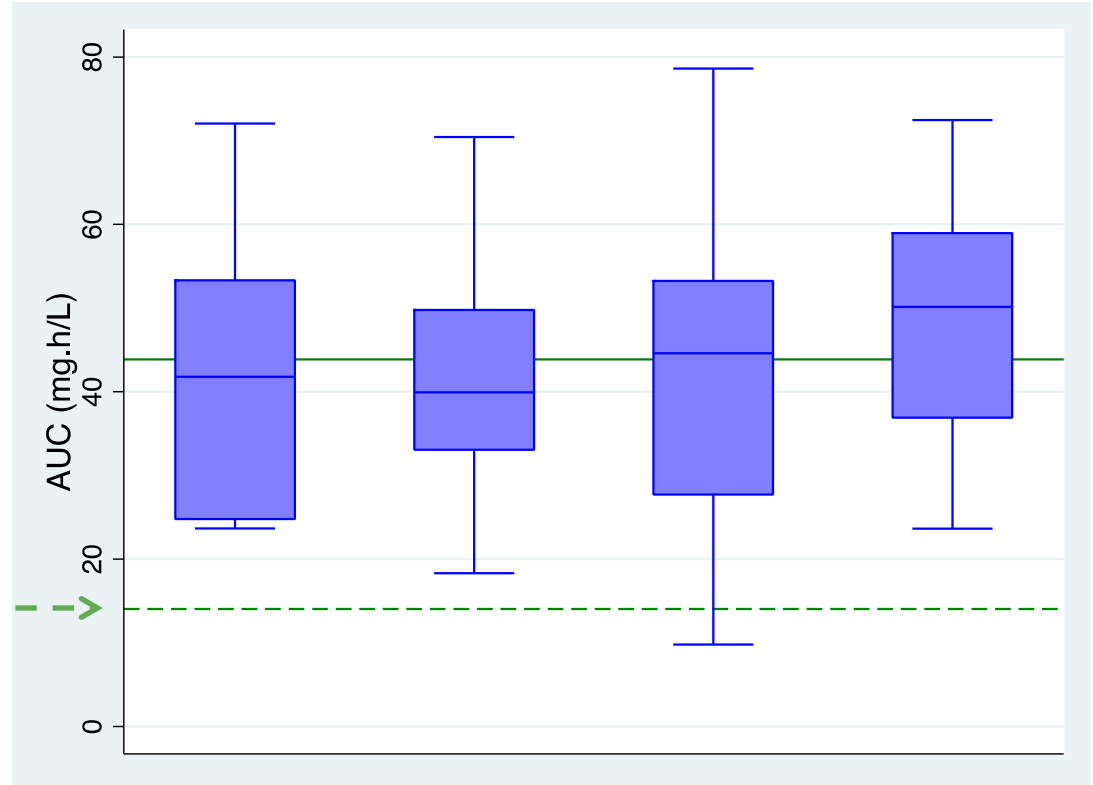


weight (kg)	<8	8-11.9	12-15.9	≥ 16
n	5	13	14	15
median age (y)	1.1	1.3	2.6	7.1
(range)	(0.4,1.4)	(0.2,3.8)	(1.5,5.4)	(4.1,10.1)
median dose (mg/kg)	11.3	15.8	15.4	14.5

isoniazid



median for reference
adult population



weight (kg)

<8

8-11.9

12-15.9

≥16

n

5

13

14

15

median age (y)

1.1

1.3

2.6

7.1

(range)

(0.4,1.4)

(0.2,3.8)

(1.5,5.4)

(4.1,10.1)

median dose (mg/kg)

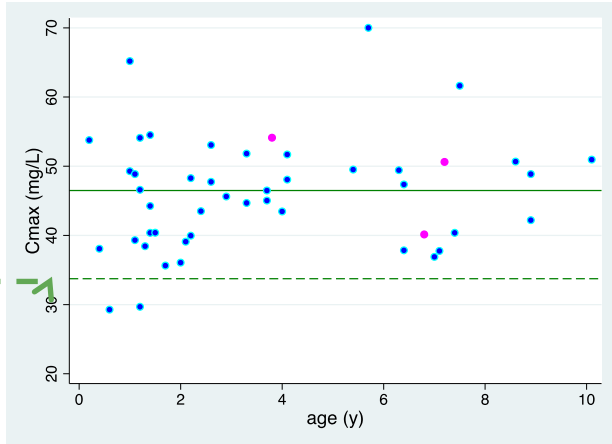
13.9

13.5

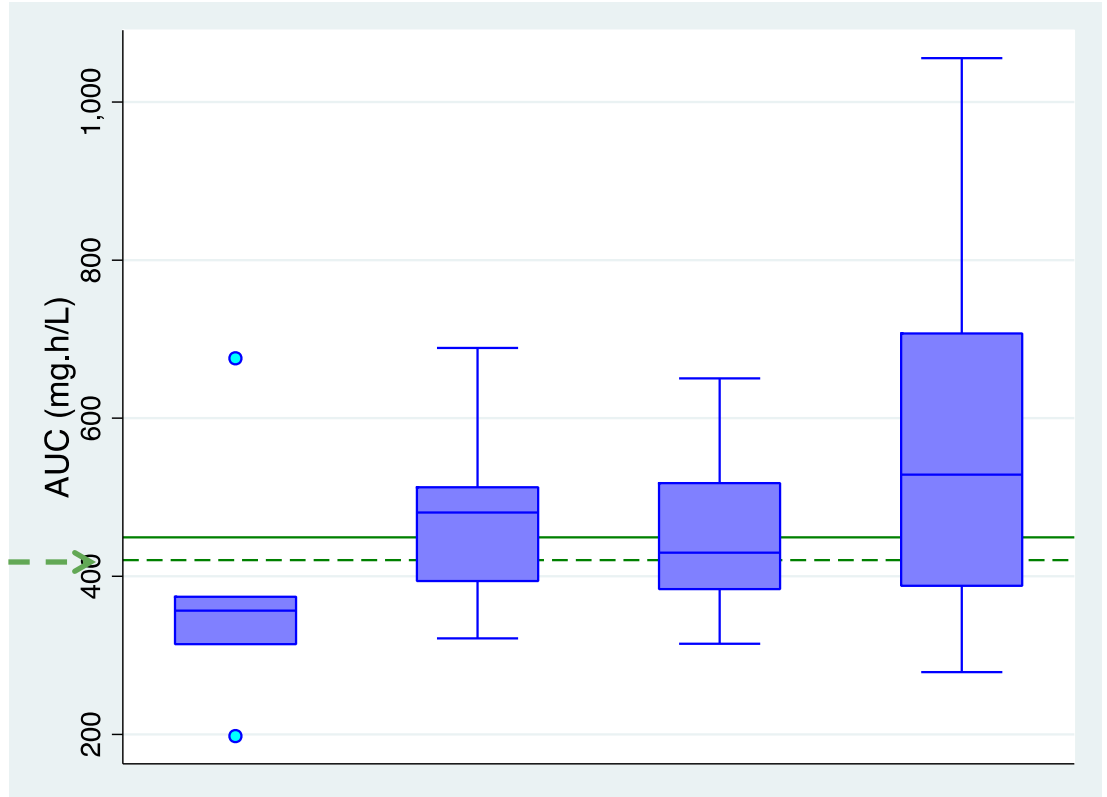
11.4

11.2

pyrazinamide



median for reference
adult population



weight (kg)

<8

8-11.9

12-15.9

≥16

n

5

13

14

15

median age (y)

1.1

1.3

2.6

7.1

(range)

(0.4,1.4)

(0.2,3.8)

(1.5,5.4)

(4.1,10.1)

median dose (mg/kg)

31.7

37.5

34.1

33.7

Population pharmacokinetics of rifampicin, pyrazinamide and isoniazid in children with tuberculosis: *in silico* evaluation of currently recommended doses

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J Antimicrob Chemother. 2014 May;69(5):1339-49.

Combined model to evaluate Δ bioavailability against previous study

similar population: similar age

HIV 36%

Formulations - dispersible FDC

Doses – prior to revised guidelines

RIFAMPICIN

ISONIAZID

PYRAZINAMIDE

+10%

+53%

+9%

conclusions

- Compared to an adult reference population
 - rifampicin AUC is low
 - isoniazid AUC and C_{\max} are high
 - pyrazinamide C_{\max} is high
- Wide variability in drug concentrations
 - the same mg/kg dose may not be optimal for all children 0-12 years old
 - part of larger study which will allow better definition of covariate effects (age, size, HIV, anthropometry, pharmacogenetics)
- Need definition of:-
 - the key PK measures e.g. C_{\max} vs. AUC
 - appropriate target levels for the PK measures
 - the effects of formulation by age, dose preparation and administration methods

acknowledgements

- Participating children and their care-givers.
- Annelies van Rie
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