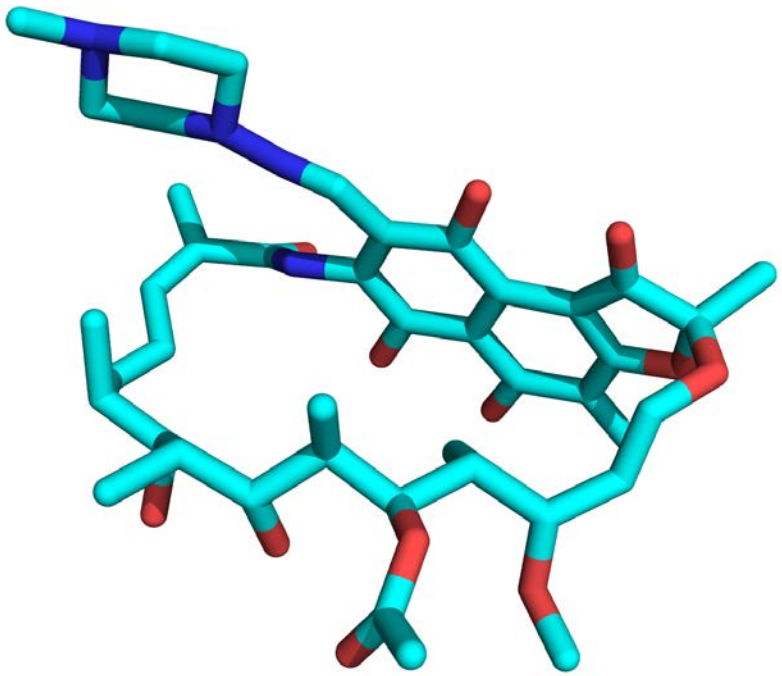
A simultaneous population pharmacokinetic analysis in Malawian adults and children of rifampicin

Rifampicin



- Rifampicin (RIF) remains a central component of first-line therapy since its introduction in 1967.
- rapidly kills the majority of bacilli in tuberculosis lesions
- inducer of many enzymes of the cytochrome P450 superfamily
- intensely red solid, and the small fraction which reaches body fluids is known for imparting a harmless red-orange colour to the urine

Malawi

Characteristic	Value
Total population (2008)	13,066,320
Life expectancy at birth (male/female) (years) (2006)	49/51
Gross national income per capita (2006) (US$)	720
Population living below US$1 a day (%) (2004)	20.8
Prevalence of tuberculosis (per 100,000) (2006)	**322**
HIV prevalence rate (%) (2006)	**11.9%**
Tuberculosis death rate (per 100,000)	**97**
Tuberculosis detection rate under DOTS, 2004	**40%**

Malawi is among the Sub-Saharan African (SSA) countries with worst health indicators . The majority of disease burden remains communicable diseases including malaria, tuberculosis and HIV/AIDS.

Sources: [NSO (2008), WHO 2006 database]

Data

Parameter		Median (range)
Study participants n [M/F]	165 [97/68]	
Adults	115	
Children	50	
Age (years) Children		6.125 (0.58-14)
Weight (kg) Children		15 (4.8-29)
Age (years) Adults		33 (14-65)
Weight (kg) Adults		49 (30-87)
HIV positive Children %	62%	
HIV positive Adults %	70%	

- *Rich PK data was collected from 40 adults and 22 children (up to 8 samples)*
- *Data collection: Queen Elizabeth Central Hospital, Blantyre, Malawi*
- *Quantification of drug levels: Liverpool School of Tropical Medicine*

Patient body weight FDC formulations in Malawi

Rifampicin ≈ 10 mg/kg/d (WHO recommendation 15 mg/kg/d)
Isoniazid ≈ 5 mg/kg/d
Pyrazinamide ≈ 25 mg/kg/d
Ethambutol ≈ 15 mg/kg/d

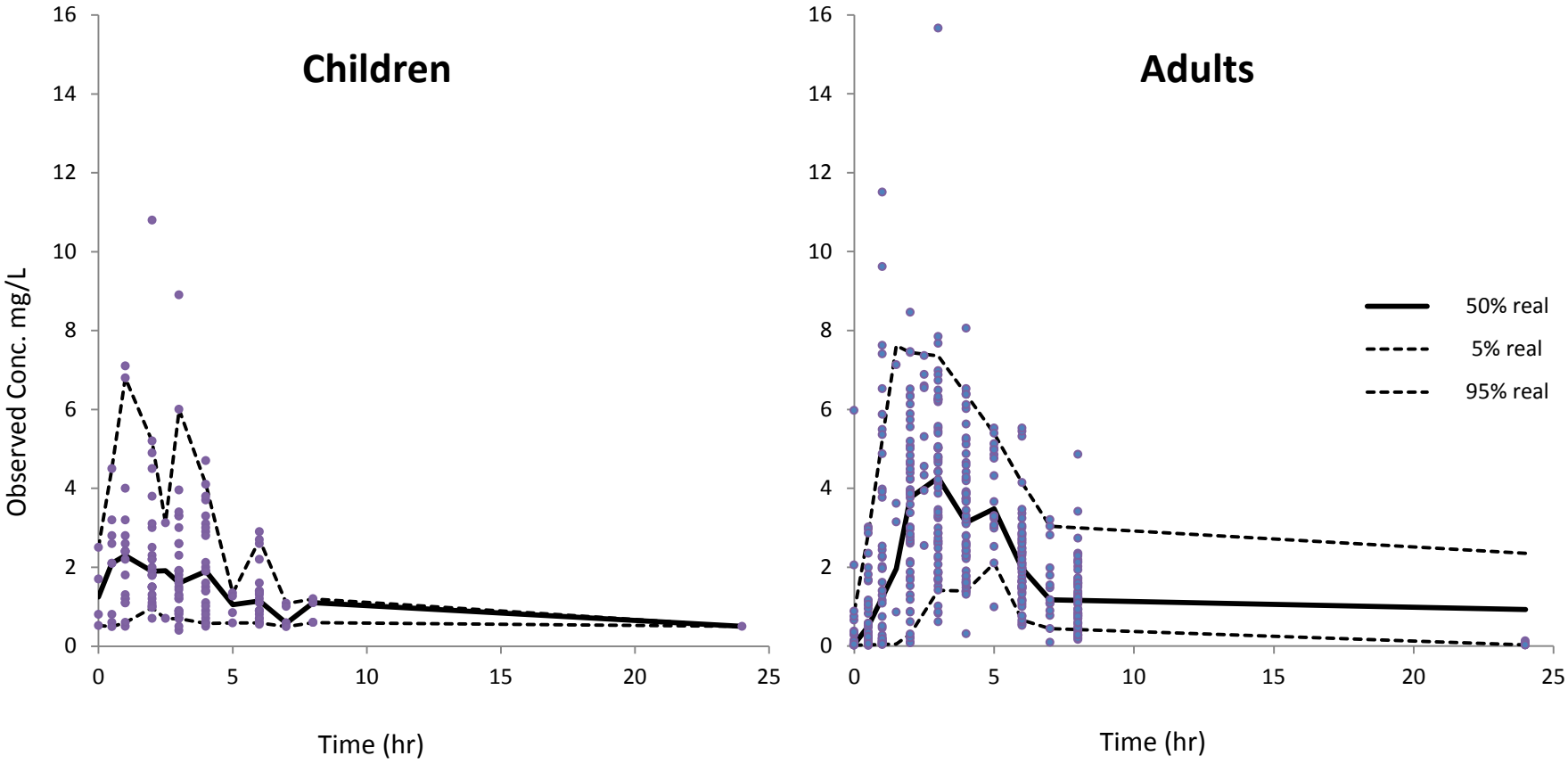
	Children		
Bands	Patients body weight (kg)	Initial phase	Continuation Phase
		RHZ (mg) [**R60**/H30/Z150]	RH (mg) [R60/H30]
1	**0-6**	1	1
2	**7-9**	1.5	1.5
3	**10-14**	2	2
4	**15-19**	3	3
5	**20-24**	4	4
6	**25-29**	5	5
	Adults		
		RHZE (mg) [**R150**/H75/Z400/E275]	RH (mg) [R150/H75]
1	**30-37**	2	2
2	**38-54**	3	3
3	**55-74**	4	4
4	**75 and over**	5	5

WHO dosing instructions (2009)

Rifampicin ≈ 15 mg/kg/d (10 to 20 mg/kg/day)

Children			
Bands	Weight (kg)	Rifampicin, isoniazid, pyrazinamide dispersible (60,30,150)	Rifampicin, isoniazid dispersible (60,60)
1	5-7	1	1
2	8-14	2	1
3	15-20	3	2
		Rifampicin, isoniazid tablet (150,75)	Rifampicin, isoniazid dispersible (60,60)
4	21-33	2	2
Adults			
1	33-50	450 mg	
2	50-70	600 mg	

Adults and children plasma concentrations



Aims

- Investigate the pharmacokinetics of rifampicin in a Malawian population, adults and children (nonlinear mixed effect modelling, NONMEM)

- simulate likely population exposures following revised WHO dosing guidelines

- compare the ability of weight- and age-based dosing bands to achieve target rifampicin exposures using a growth standard curve for a Malawian population

Rifampicin popPK parameter estimates

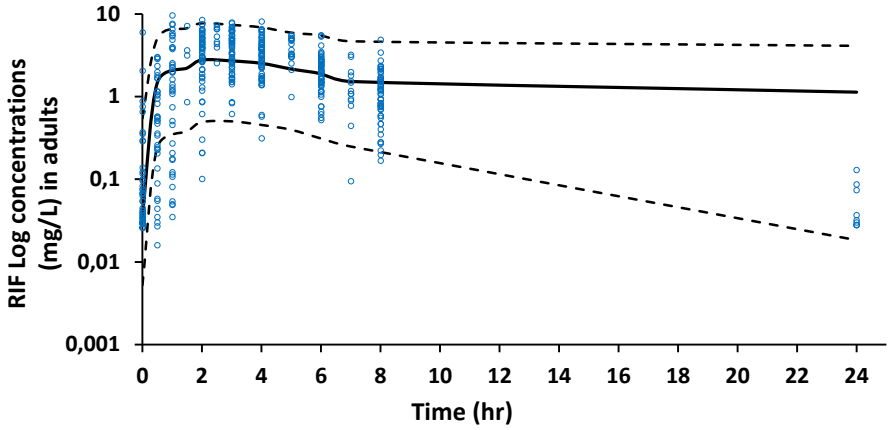
Parameter	Estimate	RSE (%)
CL/F (L/h)	23.9	6
V/F (L)	44.6	11
k_a (h^{-1})	0.236	3
F $_{\%\ relative\ bioavailability}$	51.7	18
IIV CL/F (%)	46.6	15
IIV V/F (%)	87.4	30
Residual error		
Proportional (%)	48	8
Factor associated with age on RIF CL/F	0.517	18

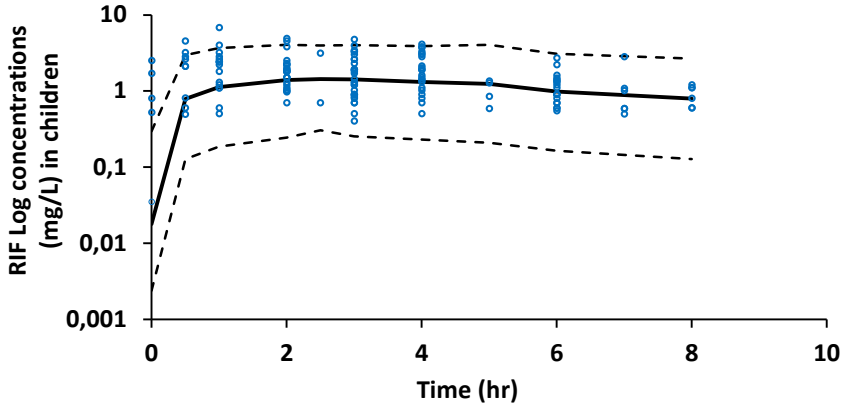
1- compartment

$CL = \theta_1 \times (wt_i/70)^{**}0.75$

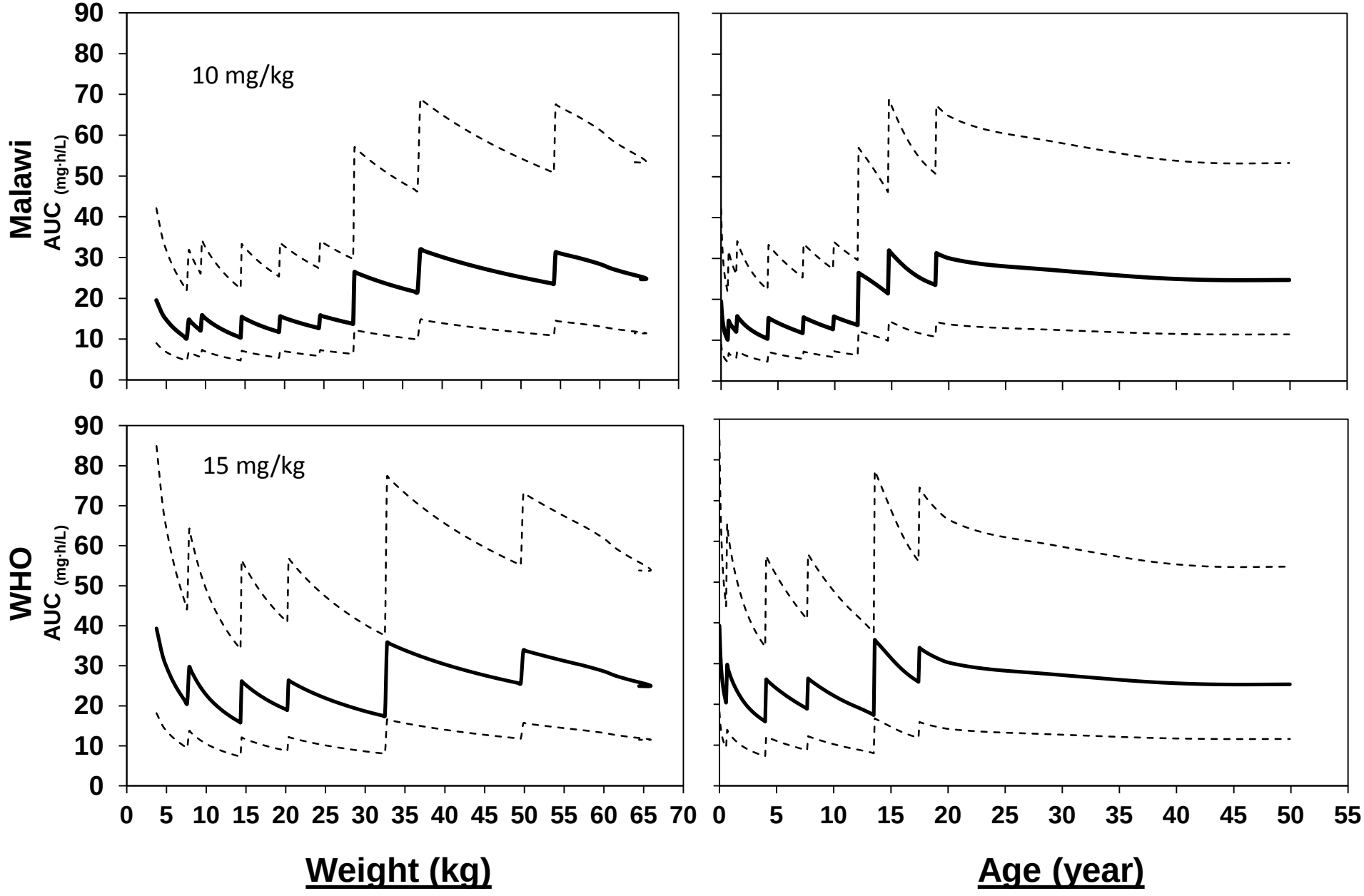
$V = \theta_2 \times (wt_i/70)^{**}1$

$CL = \theta_1 \times (AGE/28)^{**}\theta_{age}$





AUC simulations



Conclusions

- Malawian children have allarming low rifampicin plasma concentrations
- Need of new formulations
- Using age as surrogate for weight (?)
- Is WHO dosing recommendations appropriate?

Thank you

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