Overcoming the Challenges in Access to TB Drugs for Children

Gregory L. Kearns, PharmD, PhD
Professor of Pediatrics and Pharmacology, University of Missouri
Marion Merrell Dow / Missouri Chair in Pediatric Medical Research
Associate Chairman, Department of Pediatrics
Director, Pediatric Pharmacology Research Unit
The Children's Mercy Hospital, Kansas City, MO USA

Member, Committee on the Selection and Use of Essential Medicines
World Health Organization

Stop TB Symposium
26 October 2011
Lille, France

Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate data in pediatric patients

Rifampin (1967-2009)

	limited sampling	PK profile
micro	10	5
other	1	2

Isoniazid (1958-2010)

	limited sampling	PK profile
micro	3	0
other	8	15

Pyrazinamide (1987-2008)

	limited sampling	PK profile
micro	0	0
other	1	6

Ethambutol (1971-2006)

	limited sampling	PK profile
micro	2	1
other	0	2

Factors Contributing to Sub-therapeutic Drug Concentrations

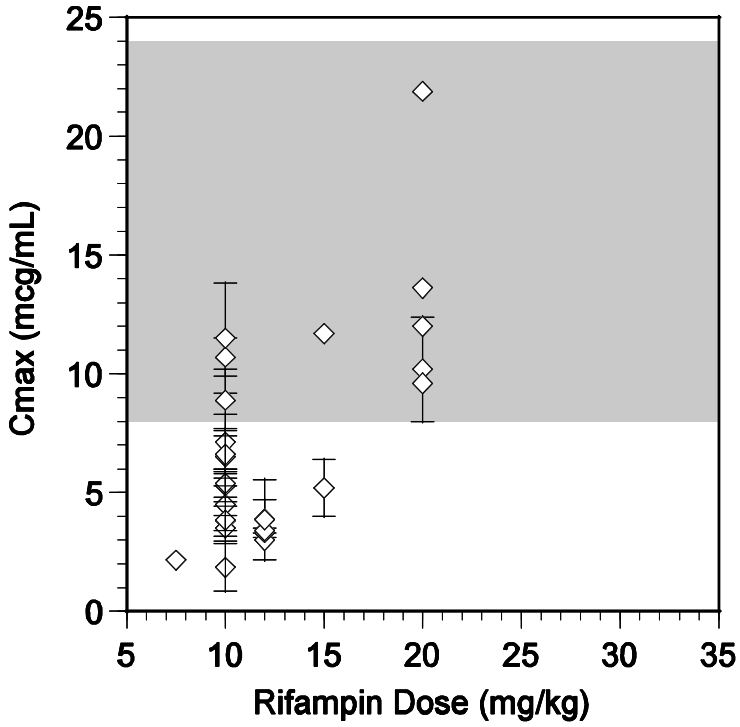
- poor adherence
- inadequate data regimen/dose

Pediatric PK for Second Line Agents

- ☑ rifapentine
- ☒ rifabutin
- ☑ fluoroquinolones
- ☒ cycloserine
- ☒ terizidone
- ☒ ethionamide
- ☒ prothionamide
- ☒ p-aminosalicylic acid
- ☒ capreomycin
- ☑ aminoglycosides
- ☒ clofazimine
- ☒ thiacetazone
- ☒ diarlyquinolone
- ☑ linezolid

Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate regimen/dose



Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate regimen/dose
- drug unavailable/sporadically available
- substandard/counterfeit generics
- drug-drug/drug-disease interactions
- genetics
- diet/nutritional status

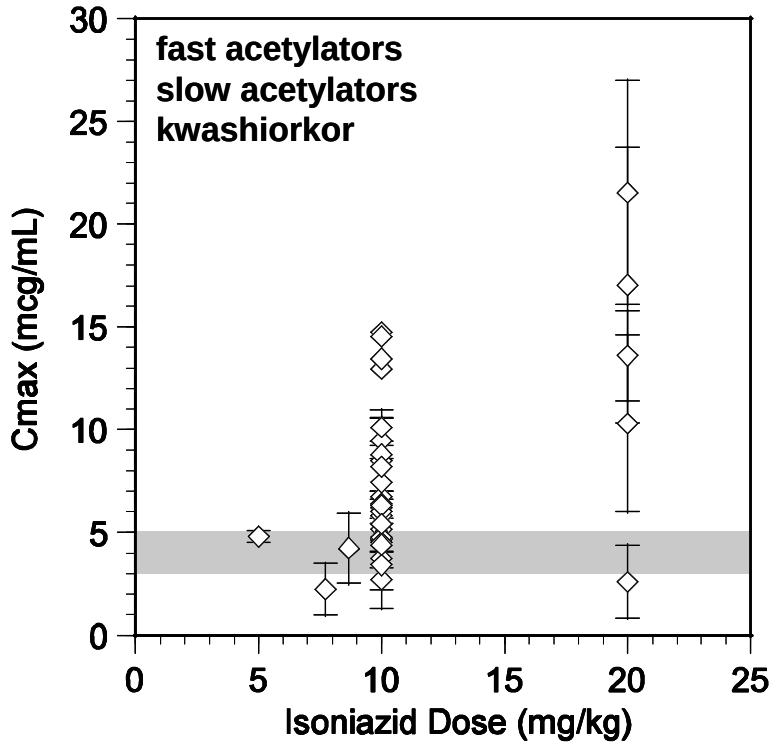
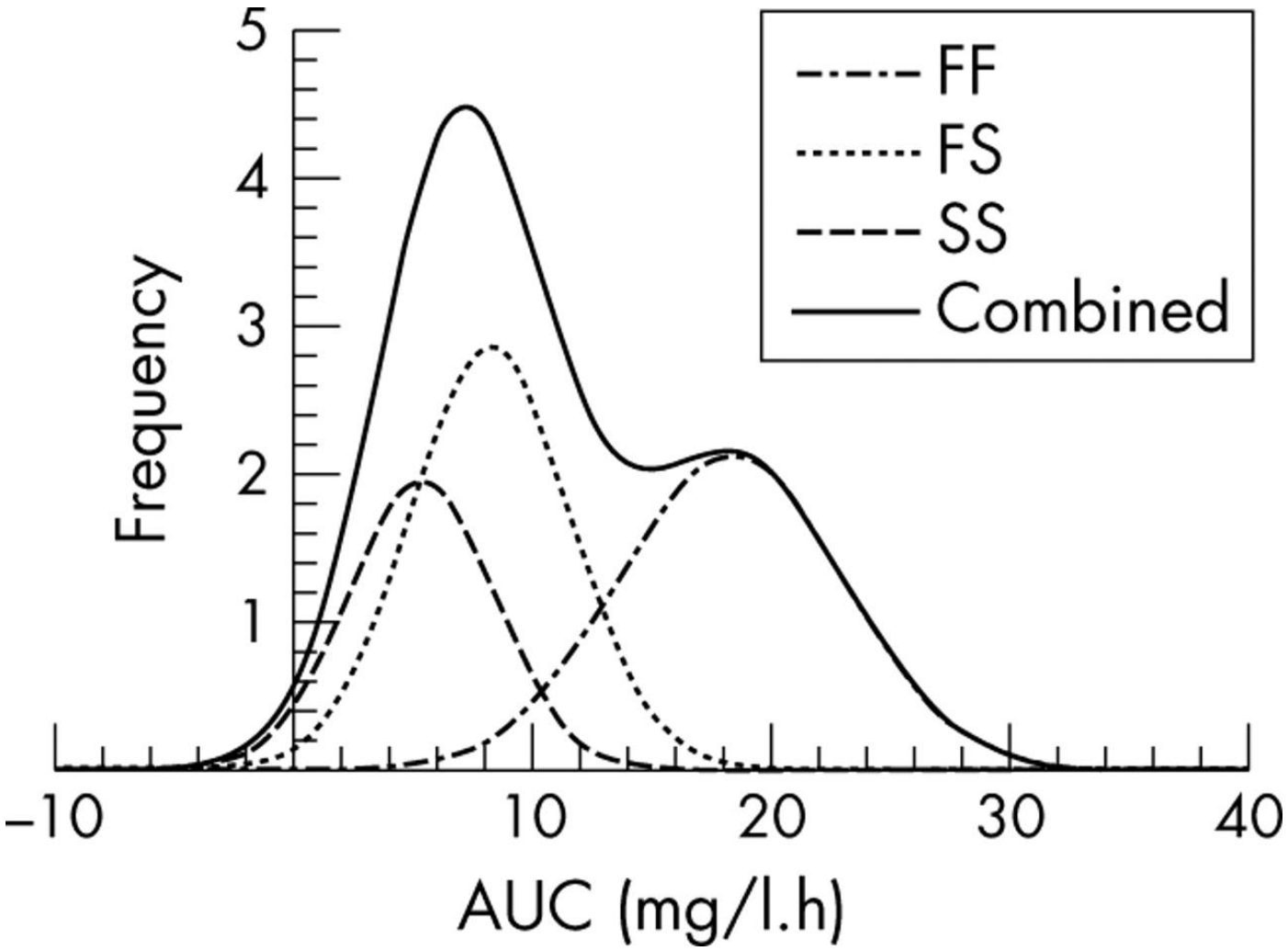


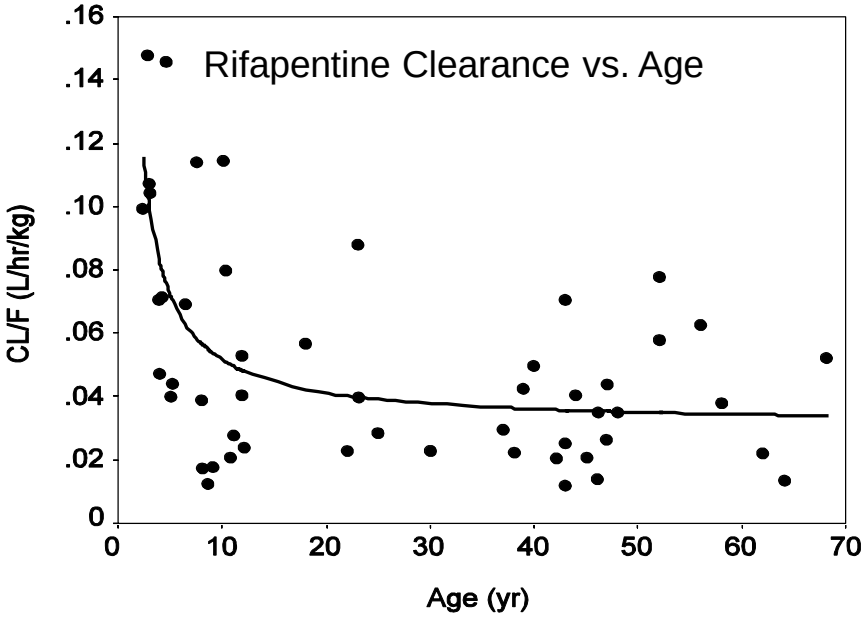
Figure 1 Distribution of AUC values based on genotype. This graph is based on the isoniazid AUC distribution data from Schaaf et al.



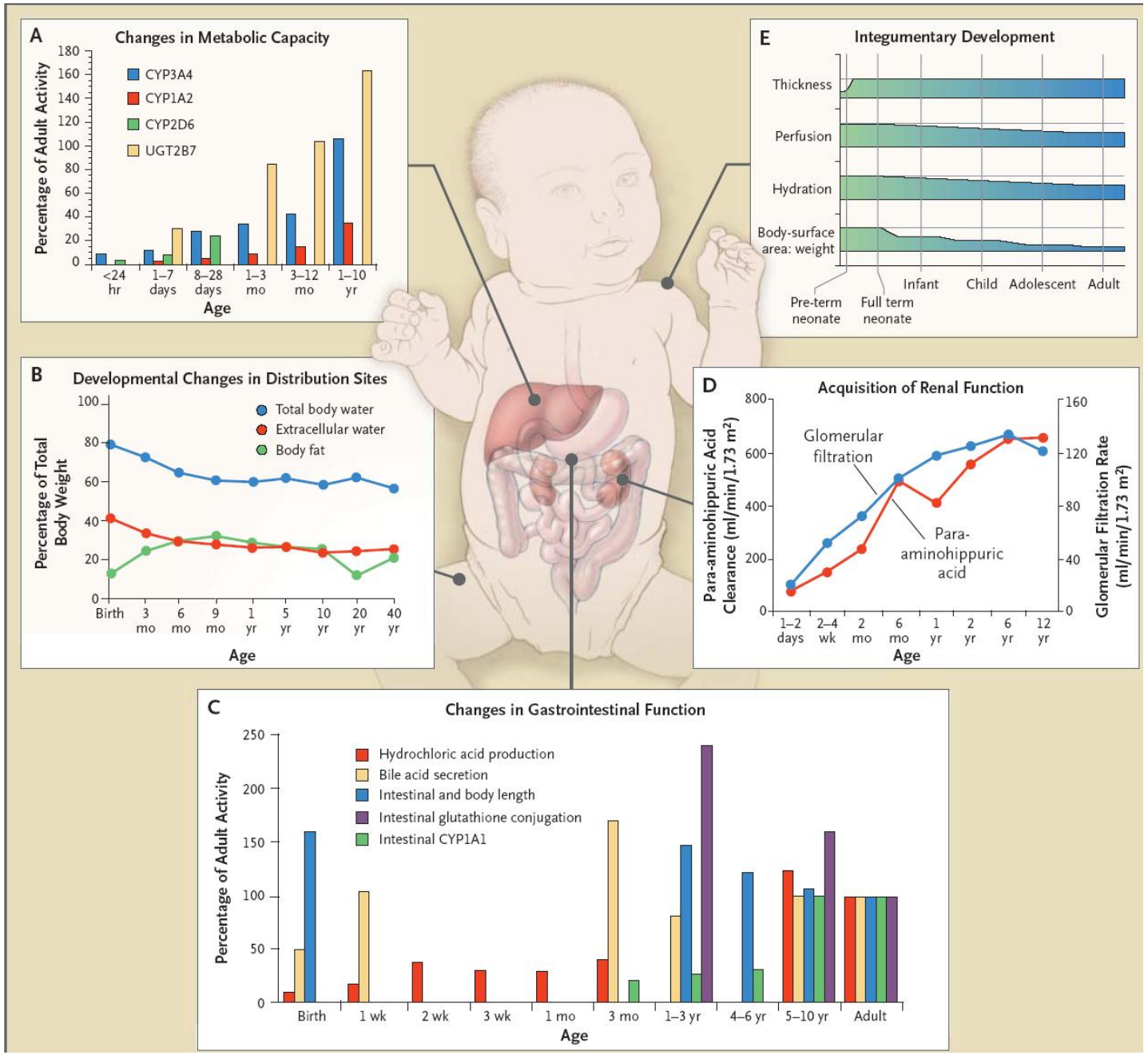
Cranswick, N et al. ***Arch Dis Child*** **2005;90:551-553**

Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate regimen/dose
- drug unavailable/sporadically available
- substandard/counterfeit generics
- drug-drug/drug-disease interactions
- genetics
- diet/nutritional status
- age



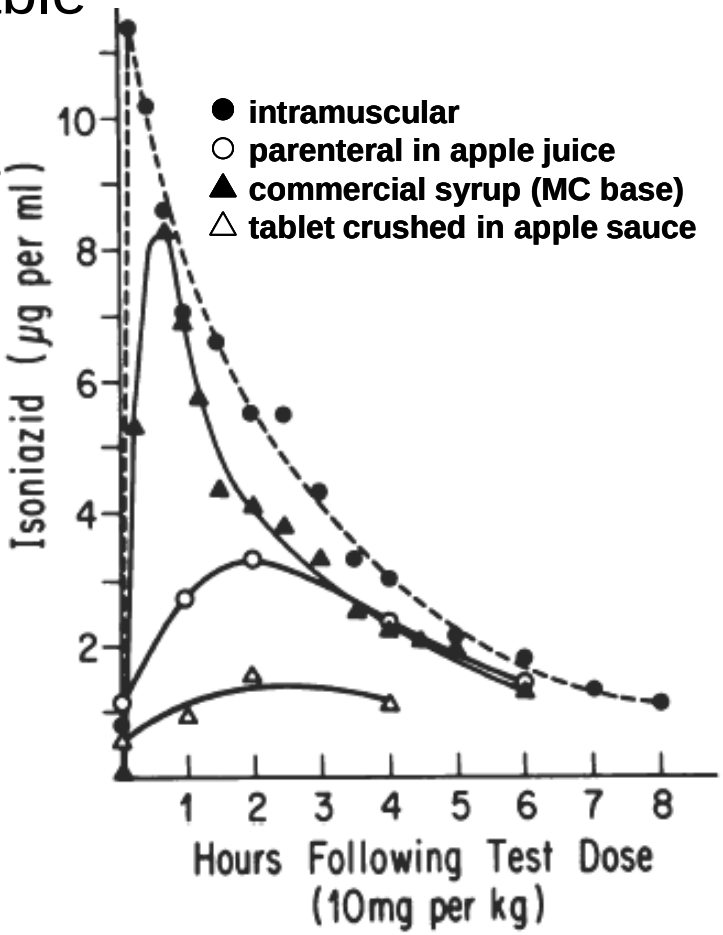
Adapted from Blake MJ, et al. PIDJ 2006;25:405-09



Kearns GL, et al. *N Engl J Med* 2003;349:1156-1167

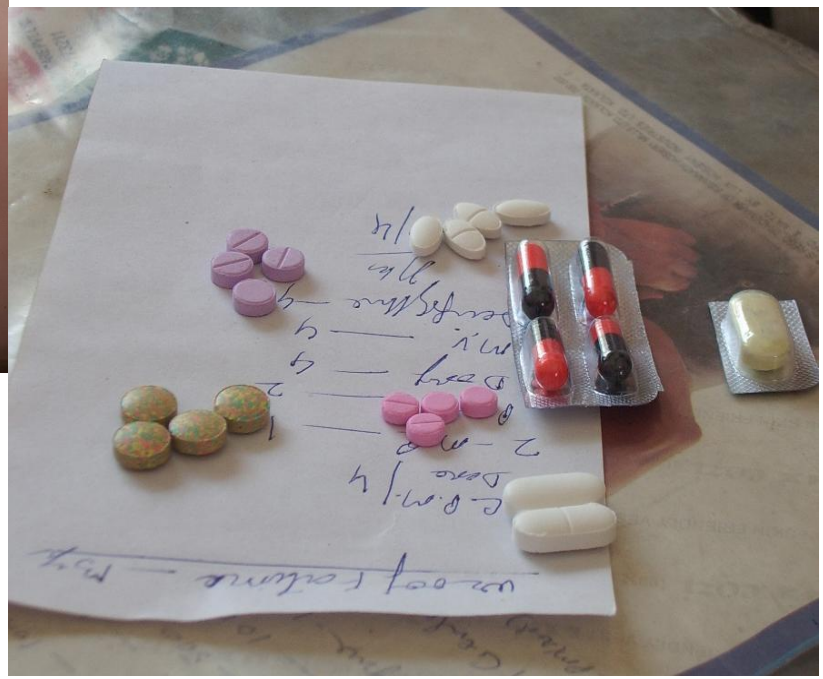
Factors Contributing to Sub-therapeutic Drug Concentrations

- poor adherence
- inadequate regimen/dose
- drug unavailable/sporadically available
- substandard/counterfeit generics
- drug-drug/drug-disease interactions
- genetics
- diet/nutritional status
- age
- extemporaneous compounding



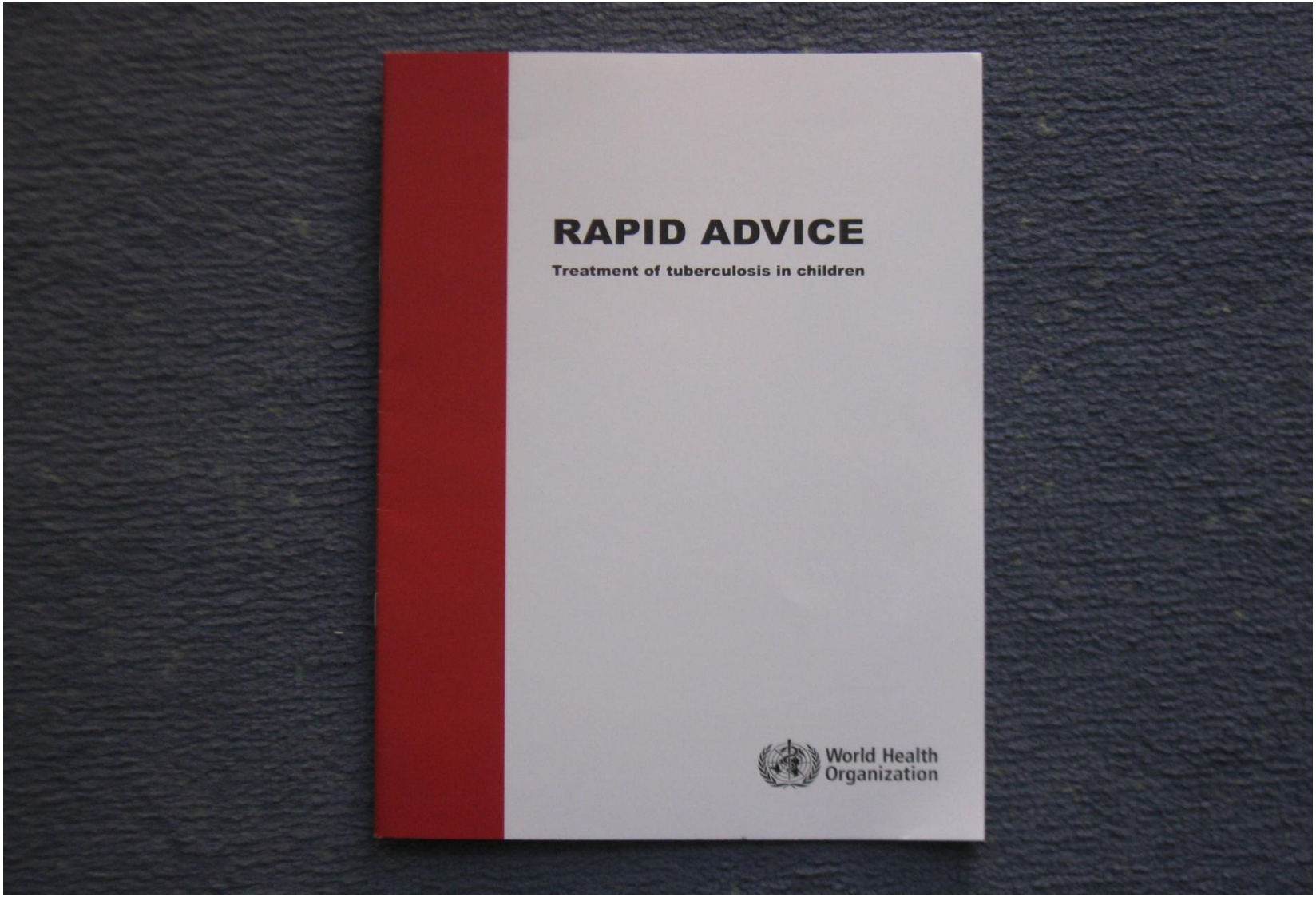
Notterman D, et al. Pediatrics 1986;77:850

In a rural health clinic, somewhere in India, a women with a sick child with TB saw the physician …..



..and these are the medicines which were given to the child

Courtesy of Dr. H. Hogerzeil, June 2008



http://www.who.int/tb/publications/2010

WHO THE STOP TB DEPARTMENT

Scope of revision – in the "Rapid Advice"

Literature review

- Dosing of 3 first line medicines: isoniazid, rifampicin and pyrazinamide
- Hepatotoxicity of anti-TB drugs
- Efficacy and safety of intermittent treatment regimens of TB in children
- Efficacy, safety and pharmacokinetics of the first line TB medicines in children less than 3 months of age
- Efficacy and safety of the first-line TB medicines in the treatment of TB meningitis
- Efficacy and safety of the first-line TB medicines in the treatment of osteo-articular TB
- The choice of fluoroquinolones for treatment of TB in children, including a review of safety

Recommendations at a glance

- Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of anti-tuberculosis medicines for the treatment of tuberculosis in children:
  - Isoniazid (H) – **10 mg/kg** (range 10–15 mg/kg); maximum dose 300 mg/day
  - Rifampicin (R) – **15 mg/kg** (range 10–20 mg/kg); maximum dose 600 mg/day
  - Pyrazinamide (Z) – **35 mg/kg** (30–40 mg/kg)
  - Ethambutol (E) – **20 mg/kg** (15–25 mg/kg)

FDA Approved Labeled Doses for Anti-TB Drugs

- Isoniazid (INH): 10-15 mg/kg/day up to maximum dose of 300 mg/day
- Pyrazinamide (PZA): 15 to 30 mg/kg/day up to maximum dose of 2.0 gm per day
- Rifampin (RIF): 10 to 20 mg/kg/day up to maximum dose of 600 mg/day

Identifying Rational Parameter Estimates

- Rifampin

	Infants	Children
Tau (hr)	24	24
bioavailability (%)	0.5	0.5
Volume (L/kg)	1.1	0.53
ka (1/hr)	1.15	1.15
kel (1/hr)	0.25	0.31
lag time (hr)	0	0

- Isoniazid

	Infants/Children (fast acetylators)	Infants/Children (slow acetylators)	Malnourished Infants/Children (fast acetylators)	Malnourished Infants/Children (slow acetylators)	Infants/Children with kwashiorkor
Tau (hr)	24	24	24	24	24
bioavailability (%)	0.9	0.9	0.9	0.9	0.9
Volume (L/kg)	1.06	1.56	1.5	1.5	1.22
ka (1/hr)	1.57	1.57	1.57	1.57	1.57
kel (1/hr)	0.54	0.21	0.53	0.26	0.73
lag time (hr)	0	0	0	0	0

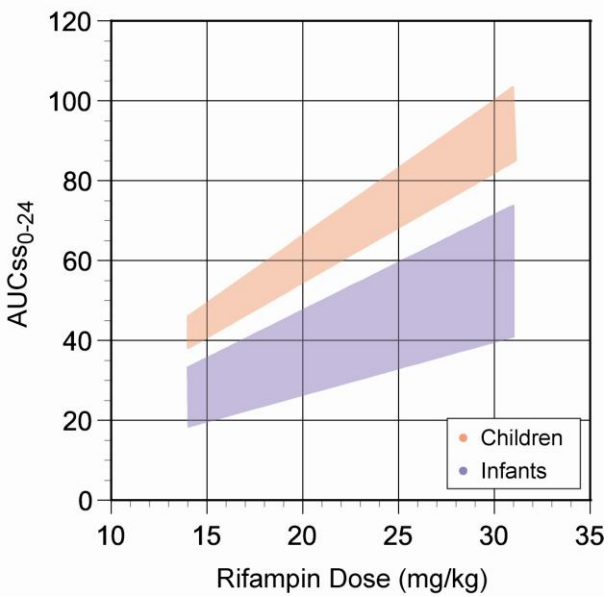
- Pyrazinamide

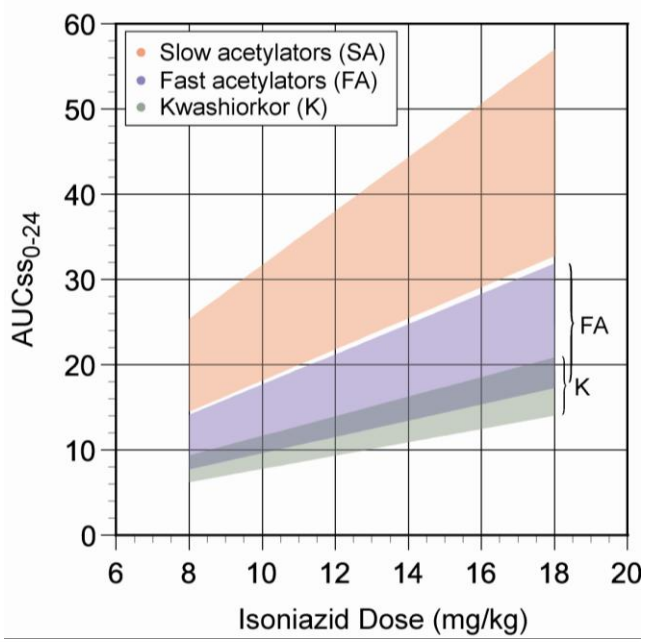
	Infants/Children (slow absorbers)	Infants/Children (fast absorbers)
Tau (hr)	24	24
bioavailability (%)	0.8	0.8
Volume (L/kg)	0.57	0.57
ka (1/hr)	1.25	3.56
kel (1/hr)	0.075	0.075
lag time (hr)	0	0

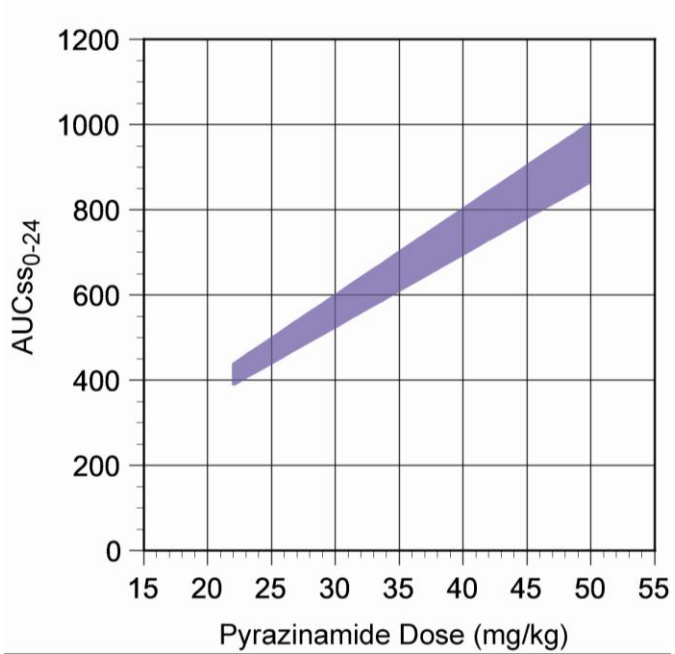
- Ethambutol

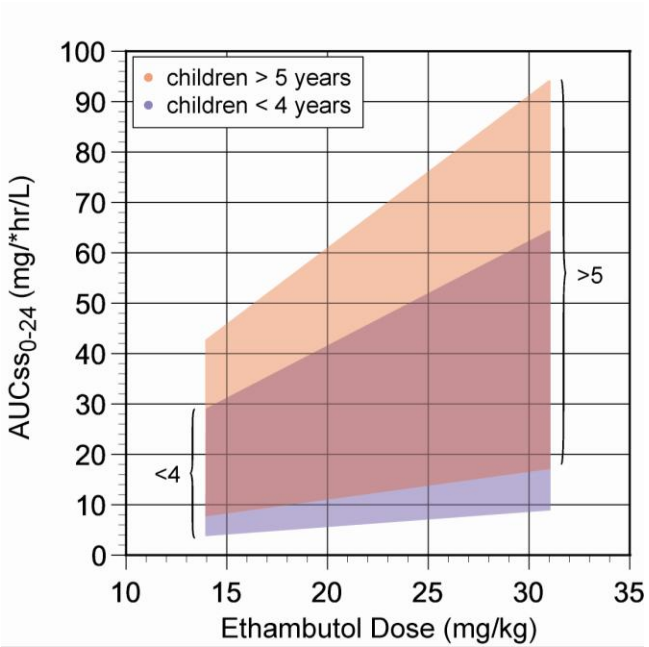
	Children (< 4 yr)	Children (≥ 5 yr)
Tau (hr)	24	24
bioavailability (%)	nested in Vd/F	nested in Vd/F
Volume/F (L/kg)	6-20	6-20
ka (1/hr)	0.68	0.68
kel (1/hr)	0.11	0.069
lag time (hr)	0	0

Simulating Pharmacokinetic Exposures

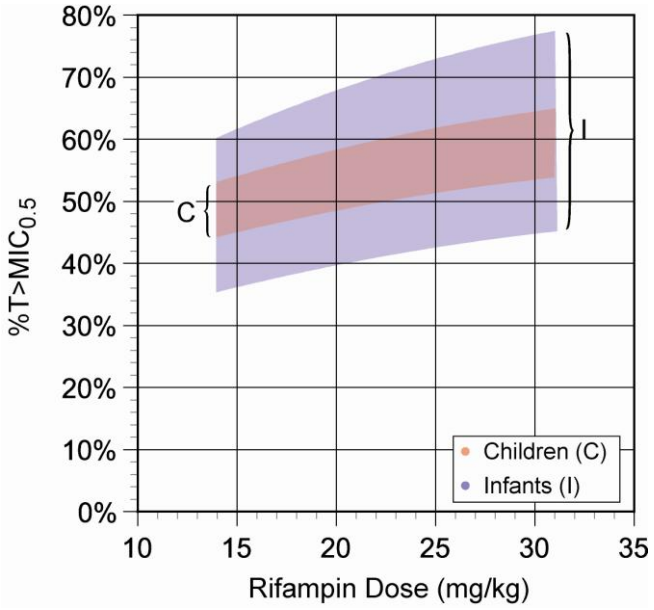


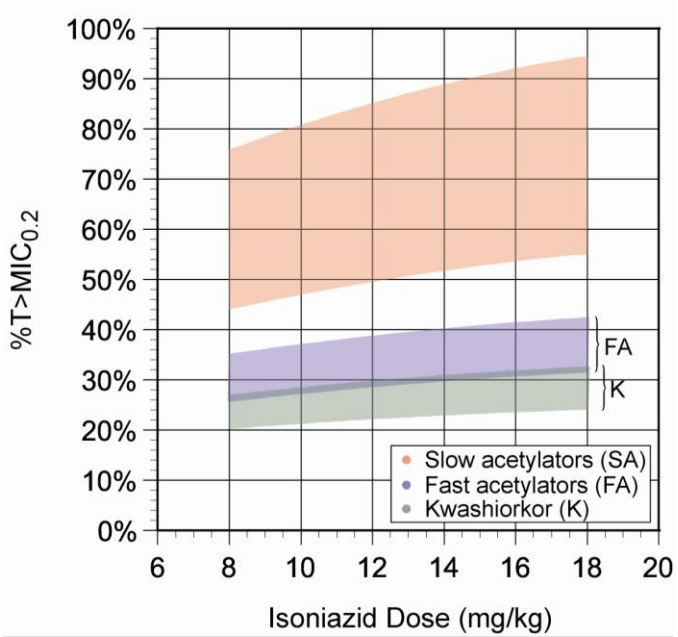


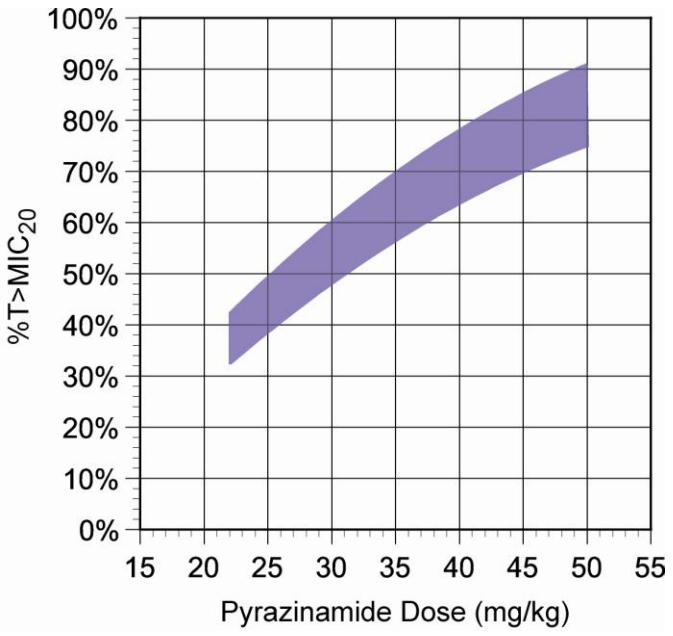


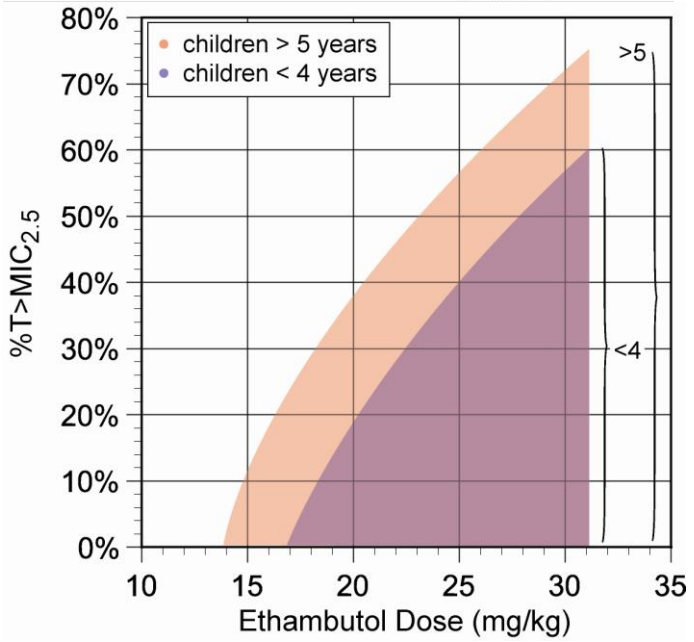


Simulating Pharmacodynamic Targets

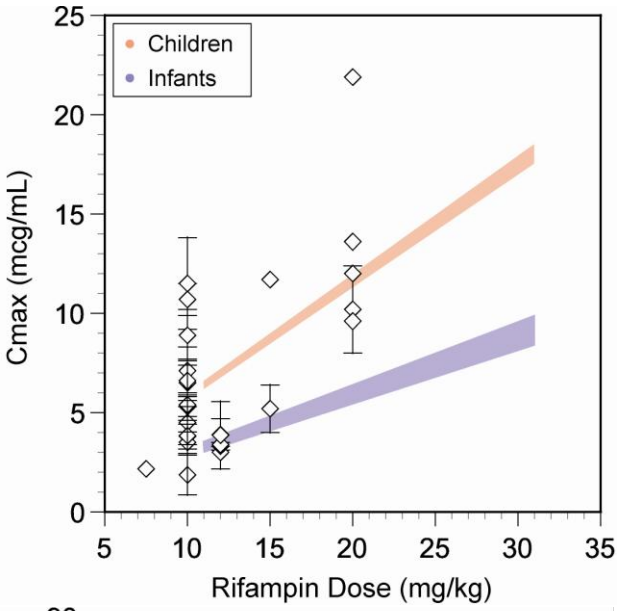


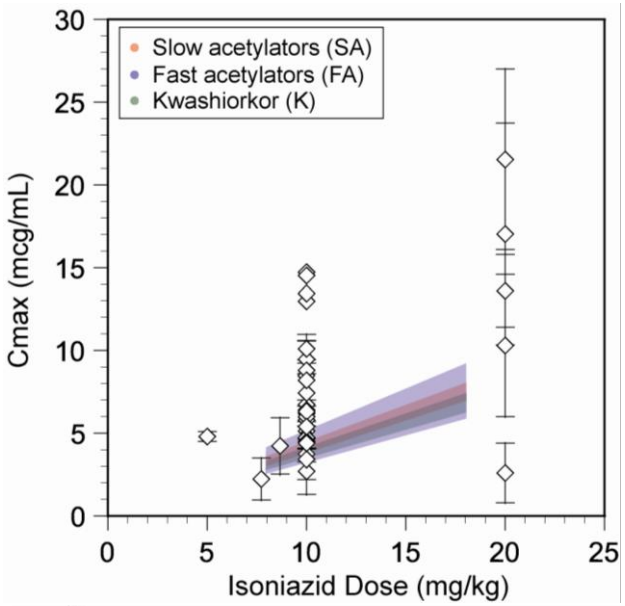


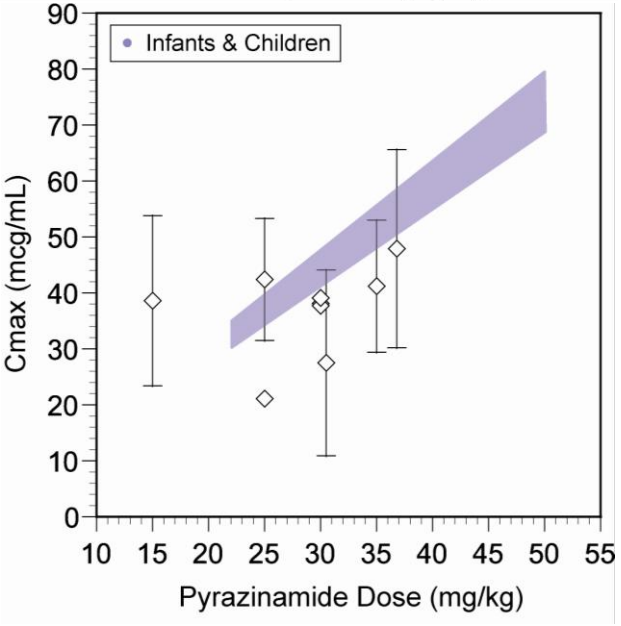


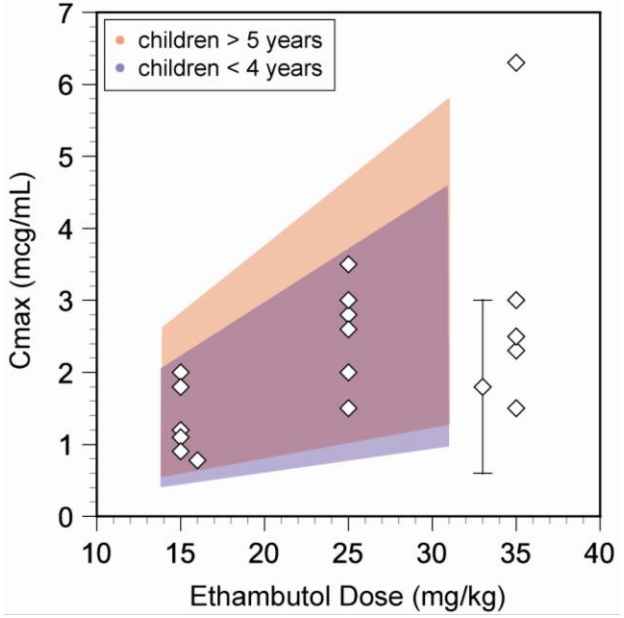


Interpreting the Results with Caution









World Health Organization

Table 1.B. : Interim recommendation for intensive phase using dispersible FDCs (rifampicin, isoniazid, pyrazinamide: 60+30+150 and rifampicin, isoniazid: 60+60) and ethambutol tablet (100mg)

Weight (kg)	Rifampicin, isoniazid, pyrazinamide *dispersible* (60,30,150)	Rifampicin, isoniazid *dispersible* (60,60)	Ethambutol *tablet* (100)	Rifampicin (mg/kg)	Isoniazid (mg/kg)	Pyrazinamide (mg/kg)	Ethambutol (mg/kg)
5	1	1	1	24.0[∞]	18[∞]	30.0	20.0
6	1	1	1	20.0	15.0	25.0[Y]	16.7
7	1	1	1	17.1	12.9	21.4[Y]	14.3[Y]
8	2	1	2	22.5[∞]	15.0	37.5	25.0
9	2	1	2	20.0	13.3	33.3	22.2
10	2	1	2	18.0	12.0	30.0	20.0
11	2	1	2	16.4	10.9	27.3[Y]	18.2
12	2	1	2	15.0	10.0	25.0[Y]	16.7
13	2	1	2	13.8	9.2[Y]	23.1[Y]	15.4
14	2	1	2	12.9	8.6[Y]	21.4[Y]	14.3[Y]
15	3	2	3	20.0	14.0	30.0	20.0
16	3	2	3	18.8	13.1	28.1[Y]	18.8
17	3	2	3	17.6	12.4	26.5[Y]	17.6
18	3	2	3	16.7	11.7	25.0[Y]	16.7
19	3	2	3	15.8	11.1	23.7[Y]	15.8
20	3	2	3	15.0	10.5	22.5[Y]	15.0

http://www.stoptb.org/assets/documents/gdf/whatis/Interim%20Paediatric%20FDCs%20detailed%20dosing%20instructions_Sept09.pdf

Proposed Dosing Schedule for a New Pediatric FCD for Tuberculosis: Rif-80mg; INH-70mg; PZA – 200 mg and ETH – 110 mg

Body Weight (kg)	**Number of Tablets per Day (single bolus)**
5 to 7	1
8 to 14	2
15 to 20	3
21 to 25	4
26 to 30	5

from Prof. B. Fourie, 2010

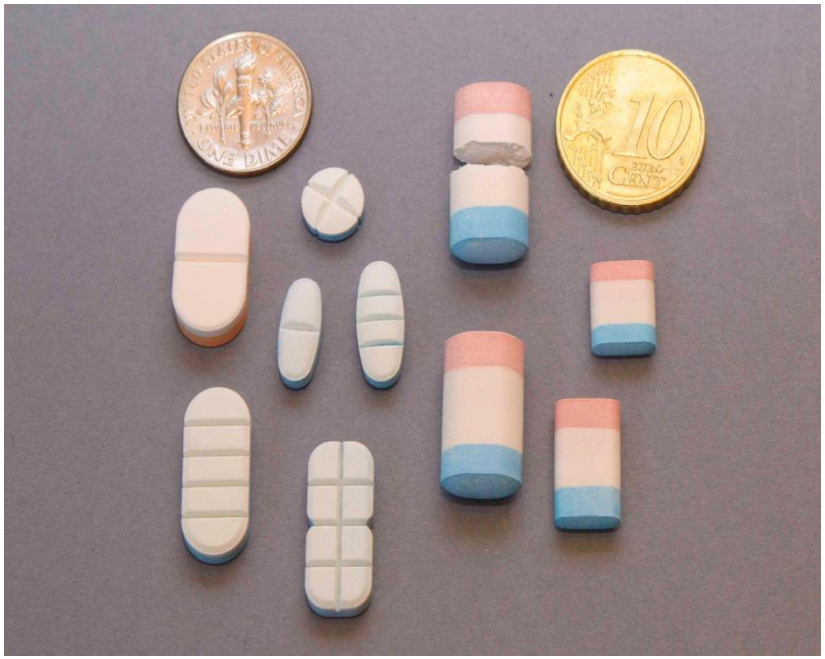
Proposed dosing strategy for a single FDC

Product		INH	Rifampin	Pyrazinamide
		150 mg	200 mg	400 mg
Weight	Dose			
5 kg	½ pill	15 mg/kg	20 mg/kg	40 mg/kg
6 kg	½ pill	12.5	16.7	33.3
7 kg	½ pill	10.7	14.3	28.5
8 kg	½ pill	9.4	12.5	25
9 kg	½ pill	8.8	11.1	22
8 kg	1 pill	18.7	25	50
9 kg	1 pill	16.7	22.2	44
10 kg	1 pill	15	20	40
11 kg	1 pill	13.5	18	36.4
12 kg	1 pill	12.5	16.6	33.3
13 kg	1 pill	11.5	15.4	30.1
14 kg	1 pill	10.7	14.3	28.6
15 kg	1 pill	10	13.3	26.6
16 kg	1 ½ pills	14.1	18.8	37.5
17 kg	1 ½ pills	13.2	17.6	35.3
18 kg	1 ½ pills	12.6	16.6	33.3
19 kg	1 ½ pills	11.8	15.8	31.6
20 kg	1 ½ pills	11.2	15	30
21 kg	1 ½ pills	10.7	14.3	28.5
21 kg	2 pills	14.8	19	38
22 kg	2 pills	13.6	18.2	36.4
23 kg	2 pills	13	17.4	34.8
24 kg	2 pills	12.5	16.6	33.3
25 kg	2 pills	12	16	32
26 kg	2 pills	11.5	15.4	30.1
27 kg	2 pills	11.1	14.8	29.6
28 kg	2 pills	10.7	14.3	28.5
29 kg	2 pills	10.4	13.8	27.5
30 kg	2 pills	10	13.3	26.6

Kearns GL and Spielberg SP; 2009

What we got…

FDCs for tuberculosis - what we need…



Formulations needed for developing countries…..

- Affordable, commercially viable
- Stable
- Accurately divisible
  - One dose form for all is ideal
- Transportable and low bulk/weight
- Minimal administration frequency
- Minimum, non-toxic excipients
- Convenient, easy, reliable administration
  - Palatable
  - Minimal manipulation
- Confirmatory studies
  - Relative bioavailability
  - Additional PK data
  - Exposure – response data

Acknowledgements…

- Prof. S. Abdel-Rahman
- Prof. P. Donald
- Prof. T. Nunn
- Dr. S. Hill

- Dr. Malgosia Grzemska
- Ms. Lisa Hedman

WHO

THE STOP TB DEPARTMENT