

Overcoming the Challenges in Access to TB Drugs for Children

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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

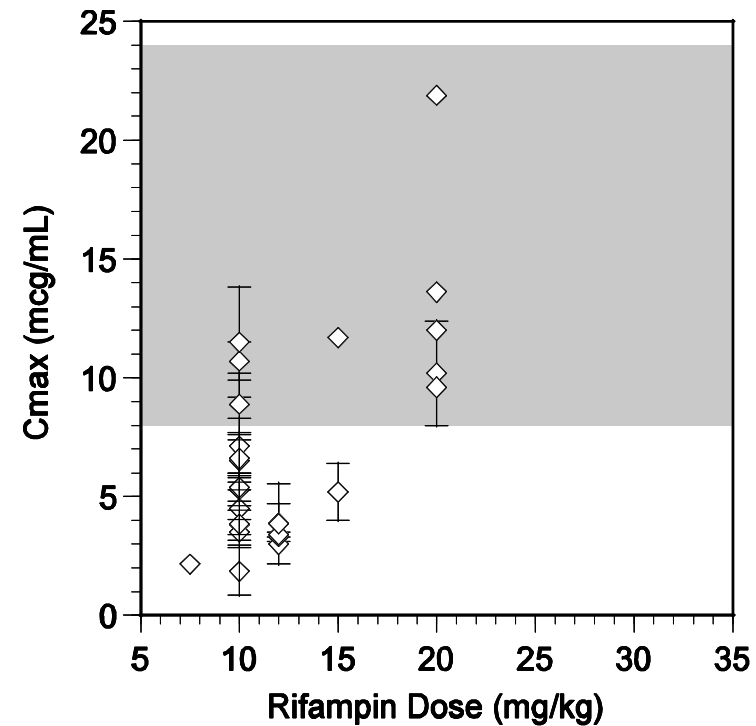
- poor adherence
- inadequate data regimen/dose

Pediatric PK for Second Line Agents

<input checked="" type="checkbox"/>	rifapentine	<input type="checkbox"/>	p-aminosalicylic acid
<input type="checkbox"/>	rifabutin	<input type="checkbox"/>	capreomycin
<input checked="" type="checkbox"/>	fluoroquinolones	<input checked="" type="checkbox"/>	aminoglycosides
<input type="checkbox"/>	cycloserine	<input type="checkbox"/>	clofazimine
<input type="checkbox"/>	terizidone	<input type="checkbox"/>	thiacetazone
<input type="checkbox"/>	ethionamide	<input type="checkbox"/>	diarlyquinolone
<input type="checkbox"/>	prothionamide	<input checked="" type="checkbox"/>	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

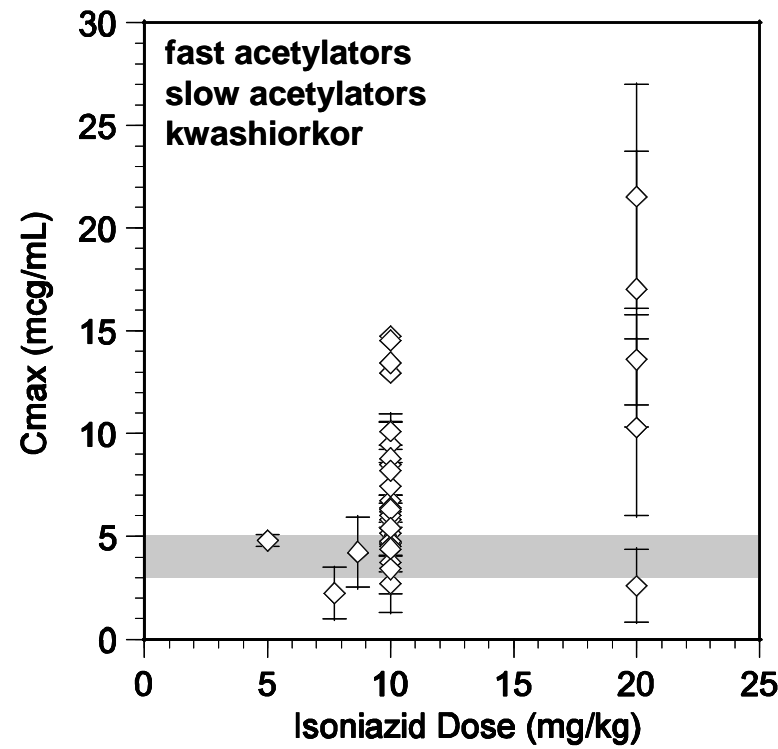
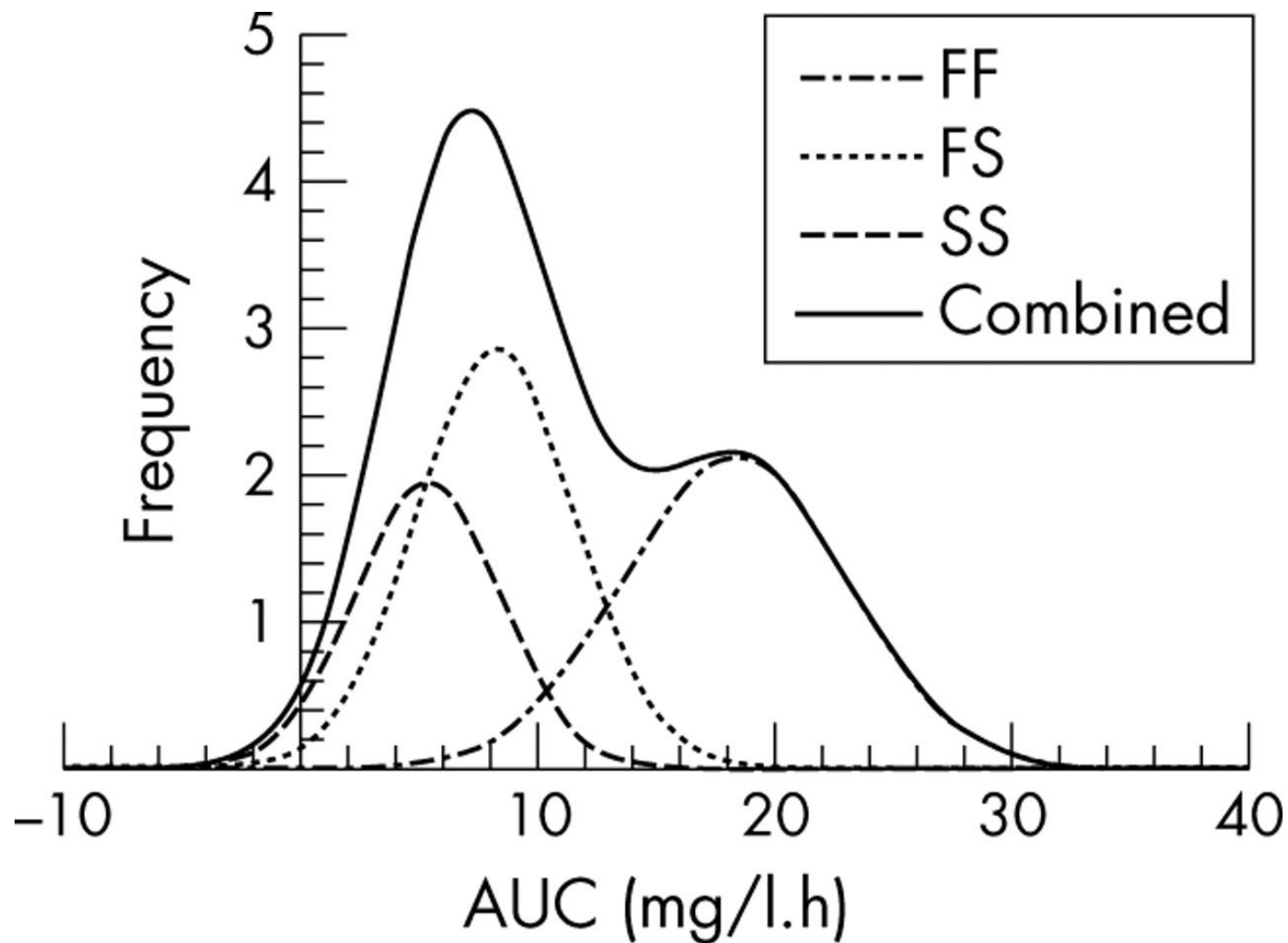
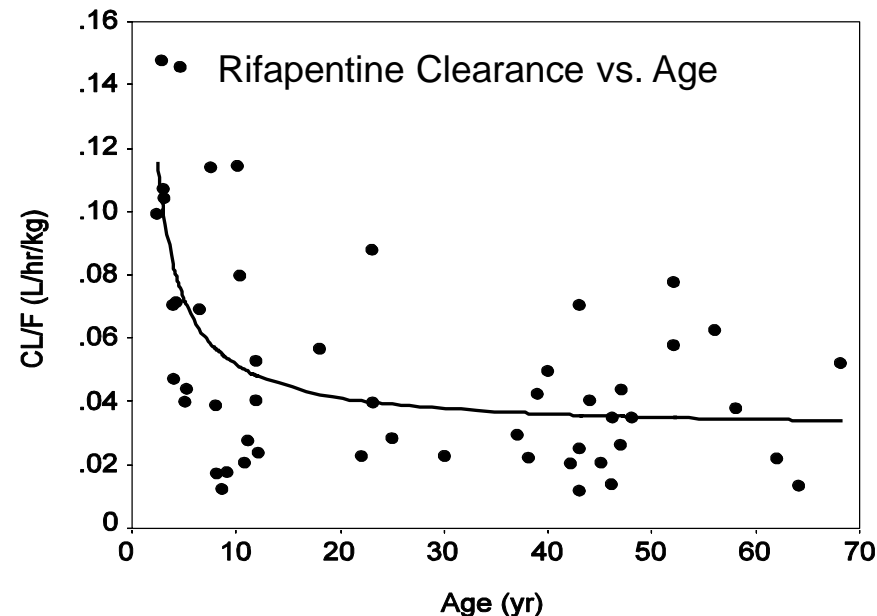


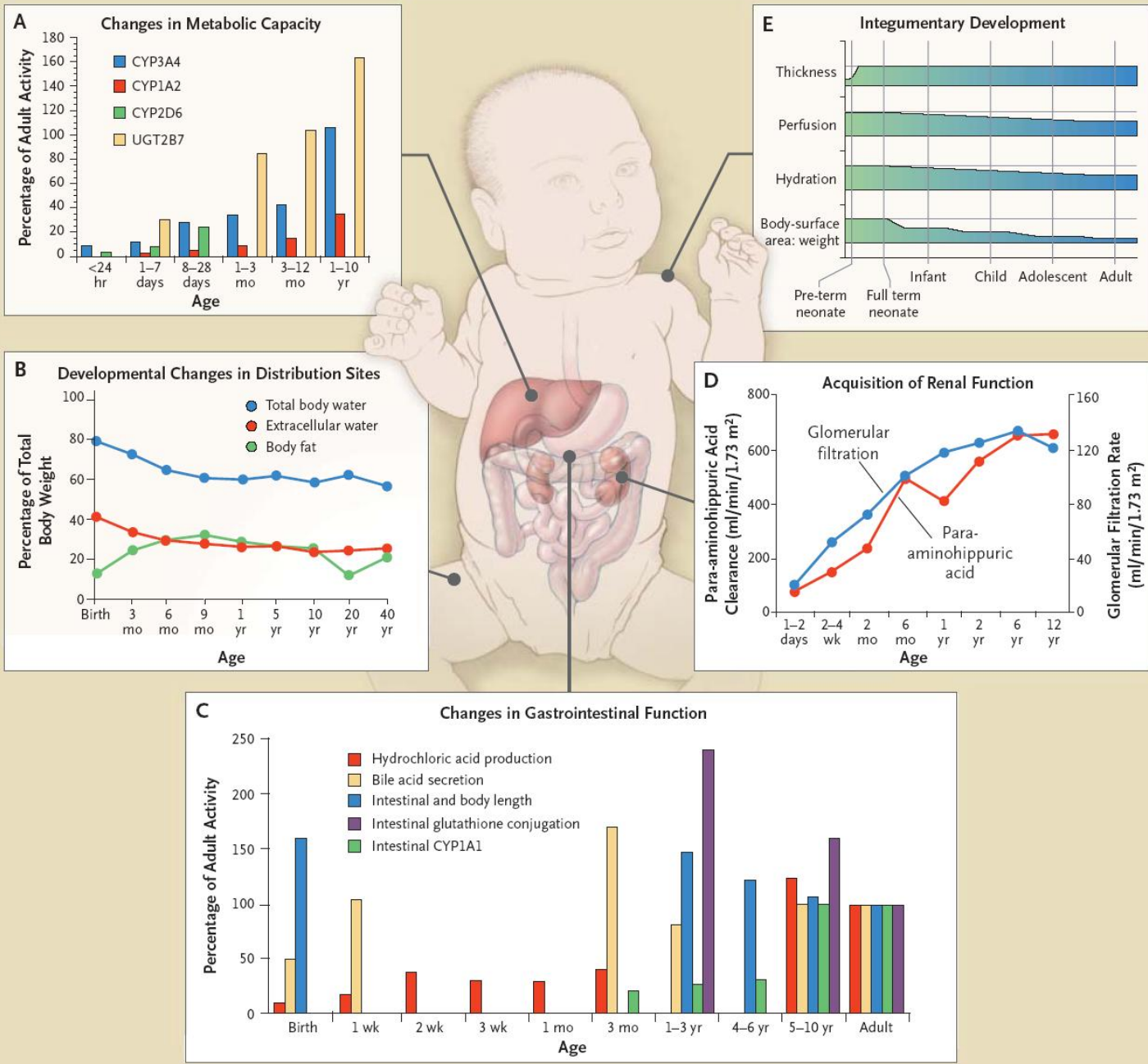
Figure 1 Distribution of AUC values based on genotype. This graph is based on the isoniazid AUC distribution data from Schaaf et al.



Factors Contributing to Sub-therapeutic Drug Concentrations

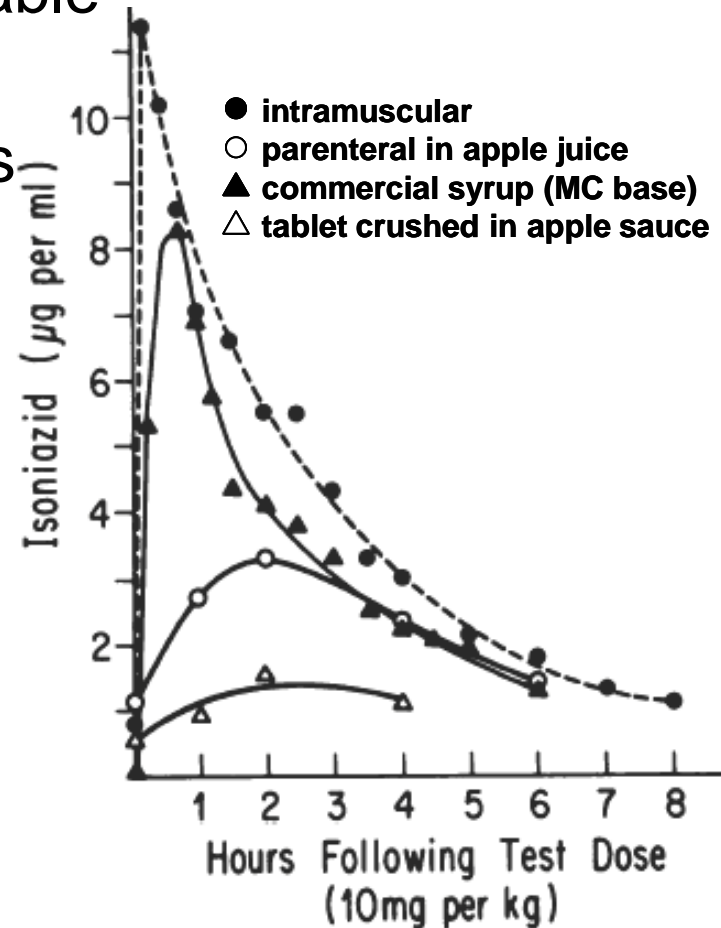
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- age



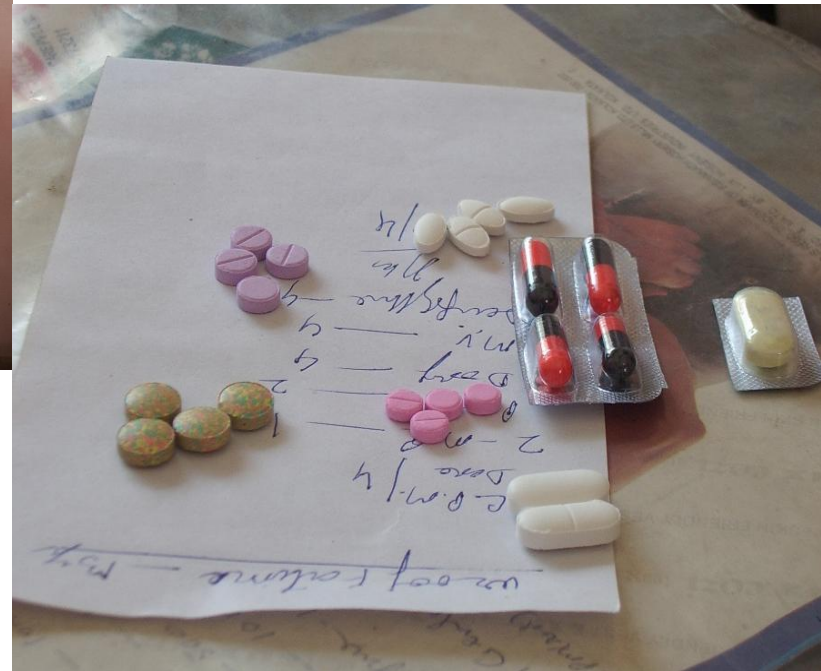


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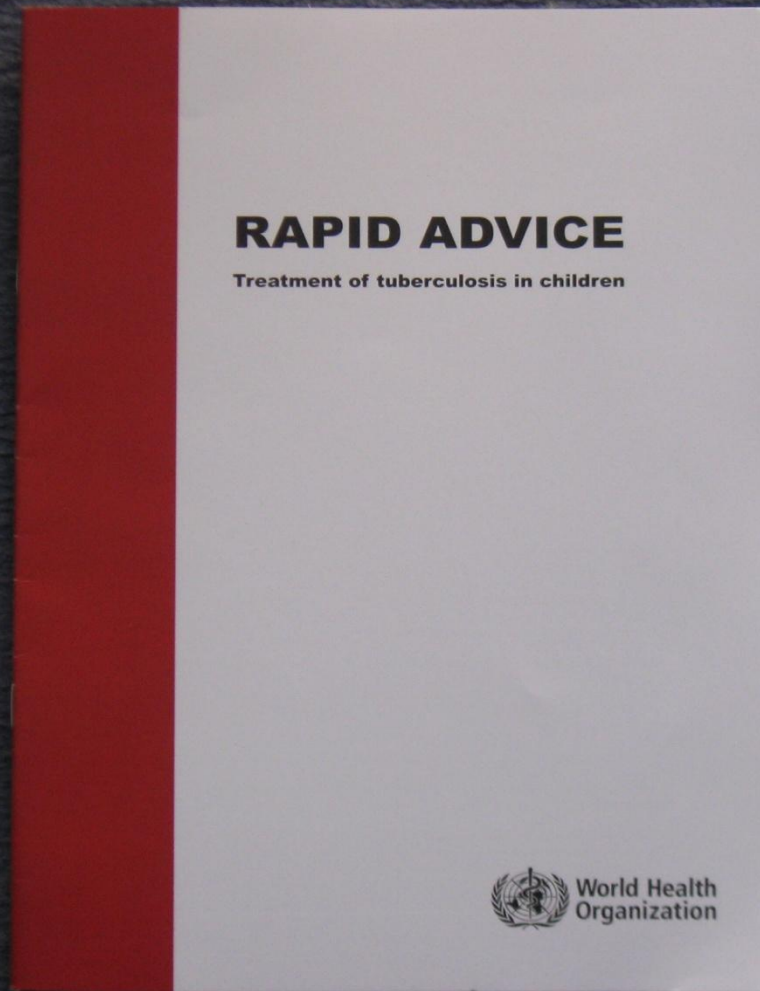
- poor adherence
- inadequate regimen/dose
- drug unavailable/sporadically available
- substandard/counterfeit generics
- drug-drug/drug-disease interactions
- genetics
- diet/nutritional status
- age
- extemporaneous compounding



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



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



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

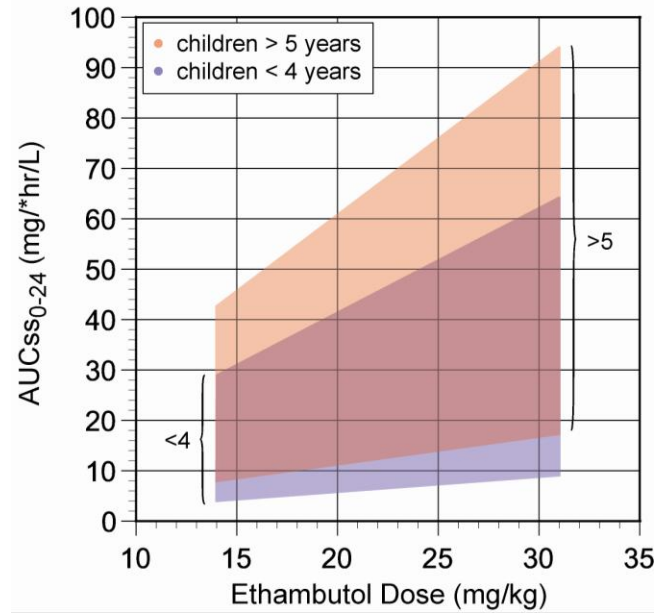
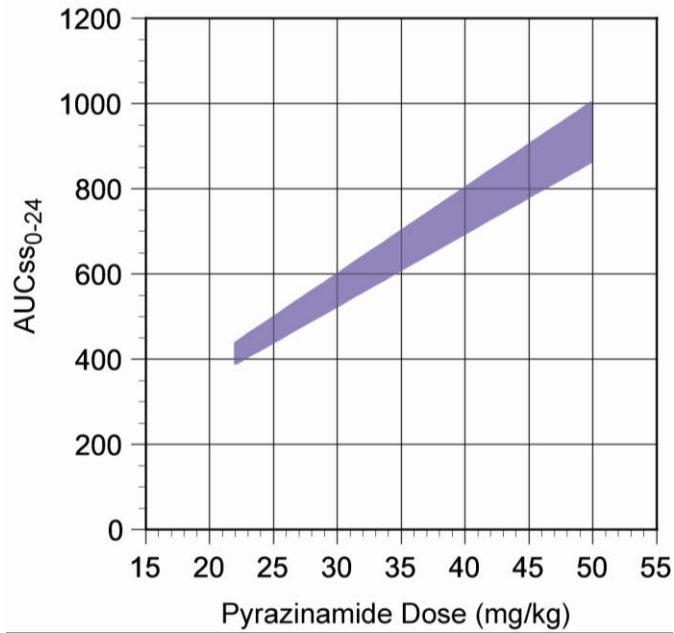
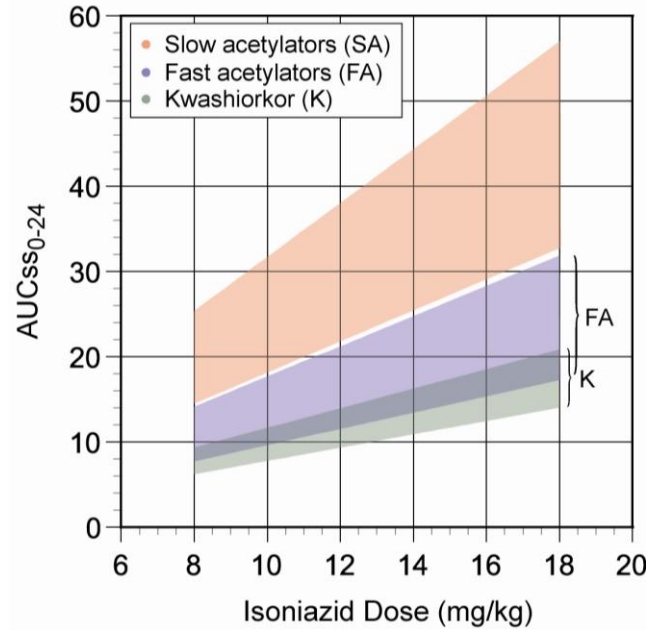
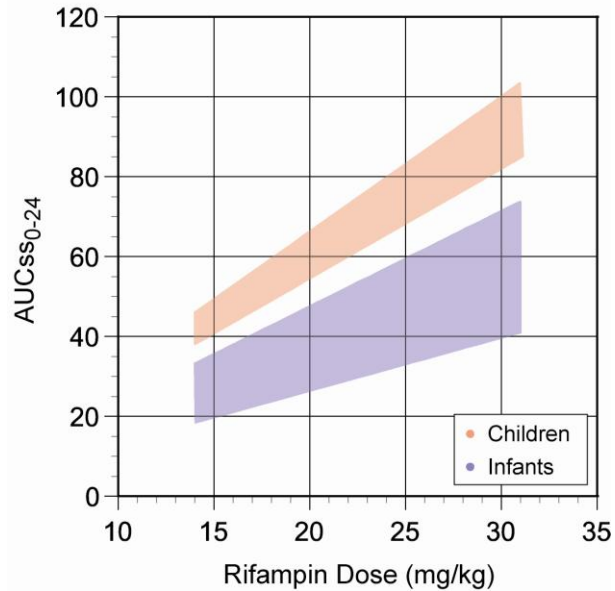
- Pyrazinamide

	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

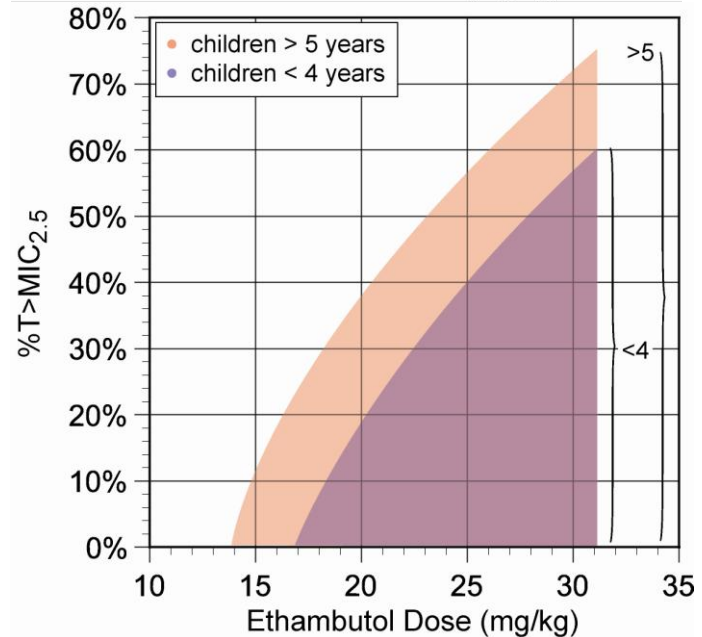
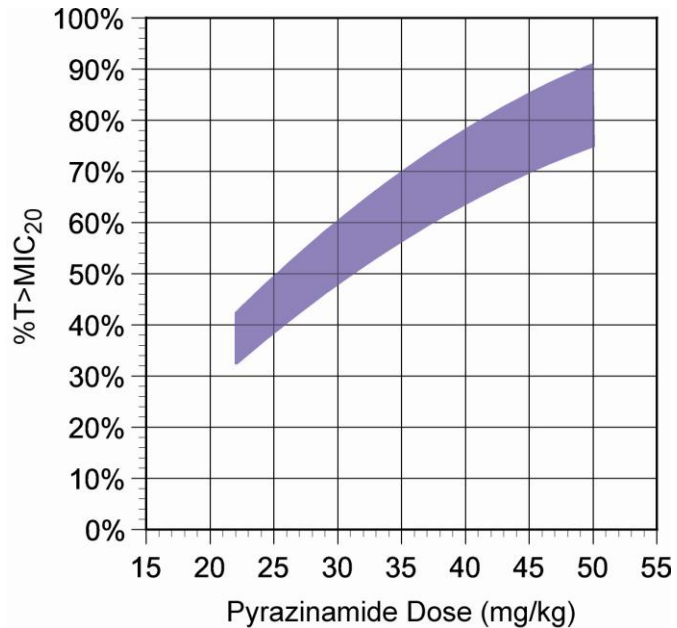
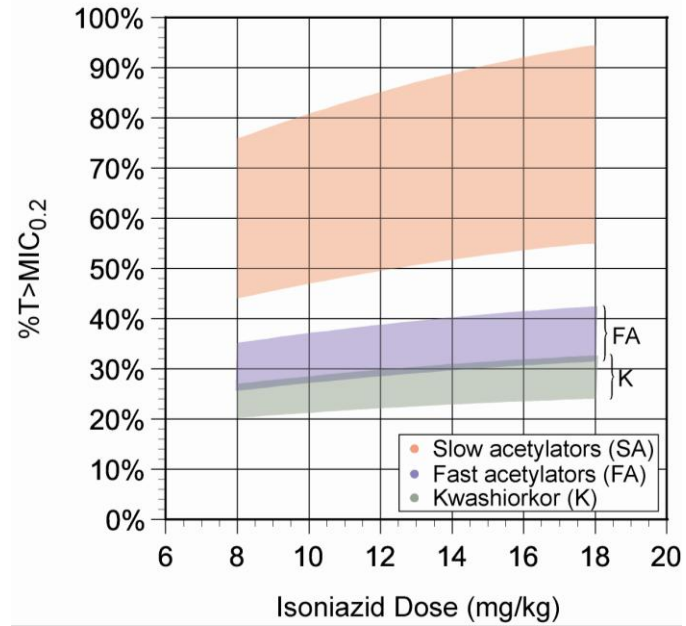
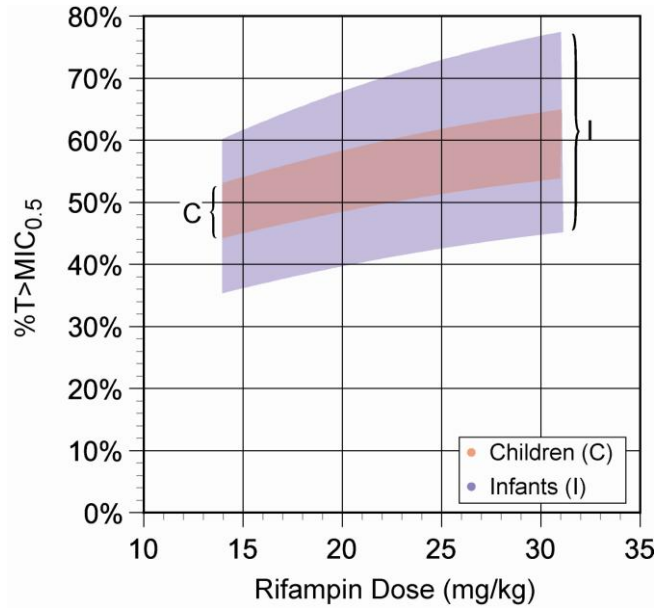
- Ethambutol

	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

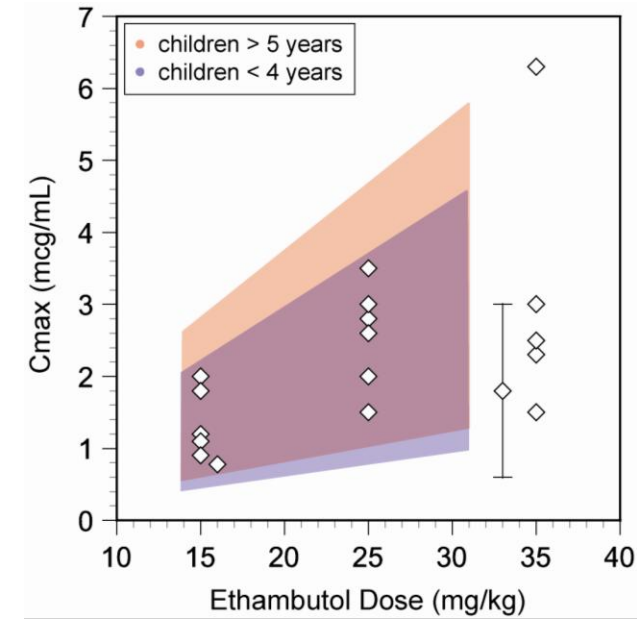
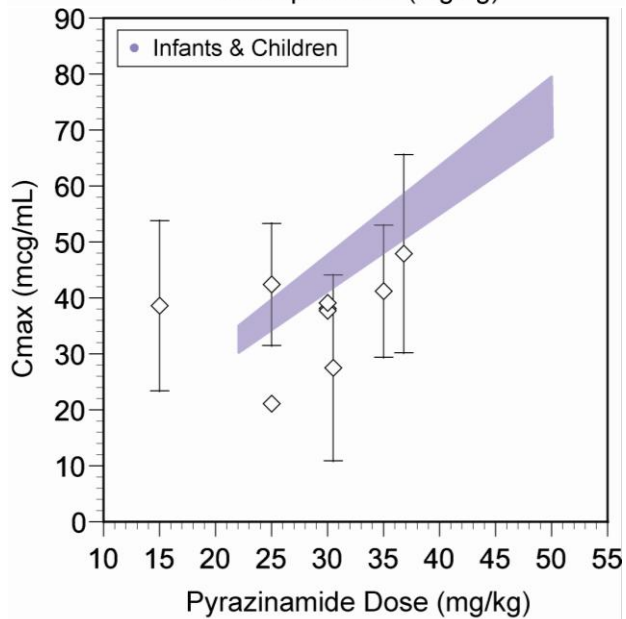
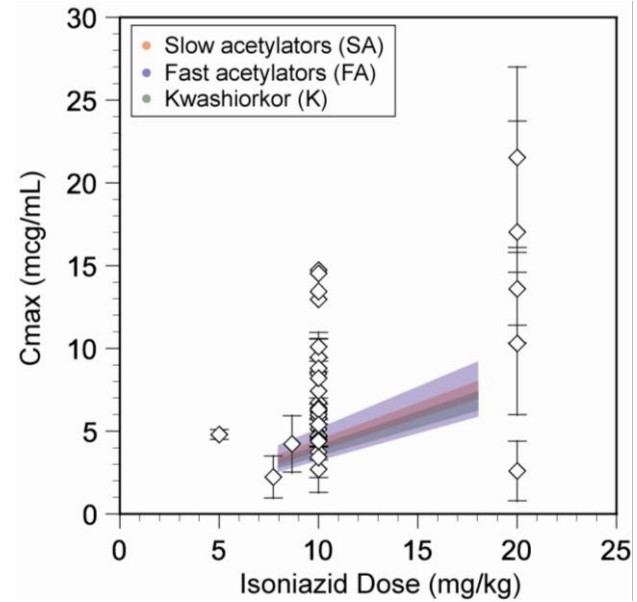
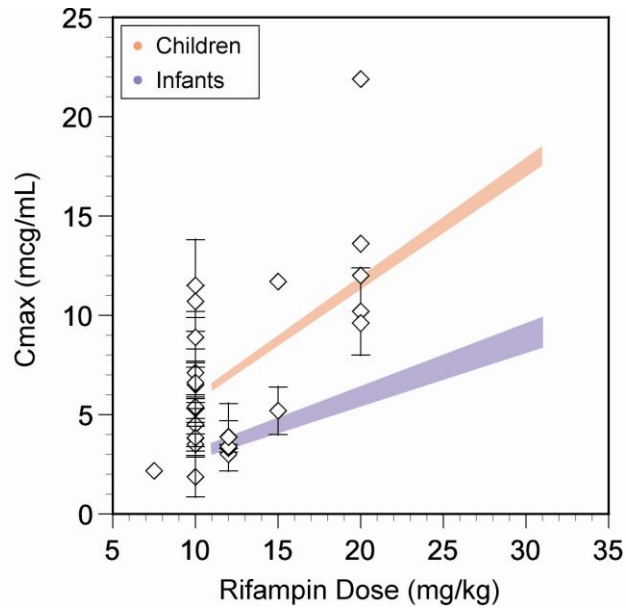


Table 1.B. : Interim recommendation for intensive phase using dispersible FDCs (rifampicin, isoniazid, pyrazinamide: 60+30+150 and rifampicin, isoniazid: 60+60) and ethambutol tablet (100mg)

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 ^X	23.1 ^Y	15.4
14	2	1	2	12.9	8.6 ^X	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 ^X	15.8
20	3	2	3	15.0	10.5	22.5 ^Y	15.0

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



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

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



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