

# INCLUSION OF CHILDREN IN TB TRIALS: HOW, WHY, WHAT?

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**WHO AND WHEN?**

**WHY?**

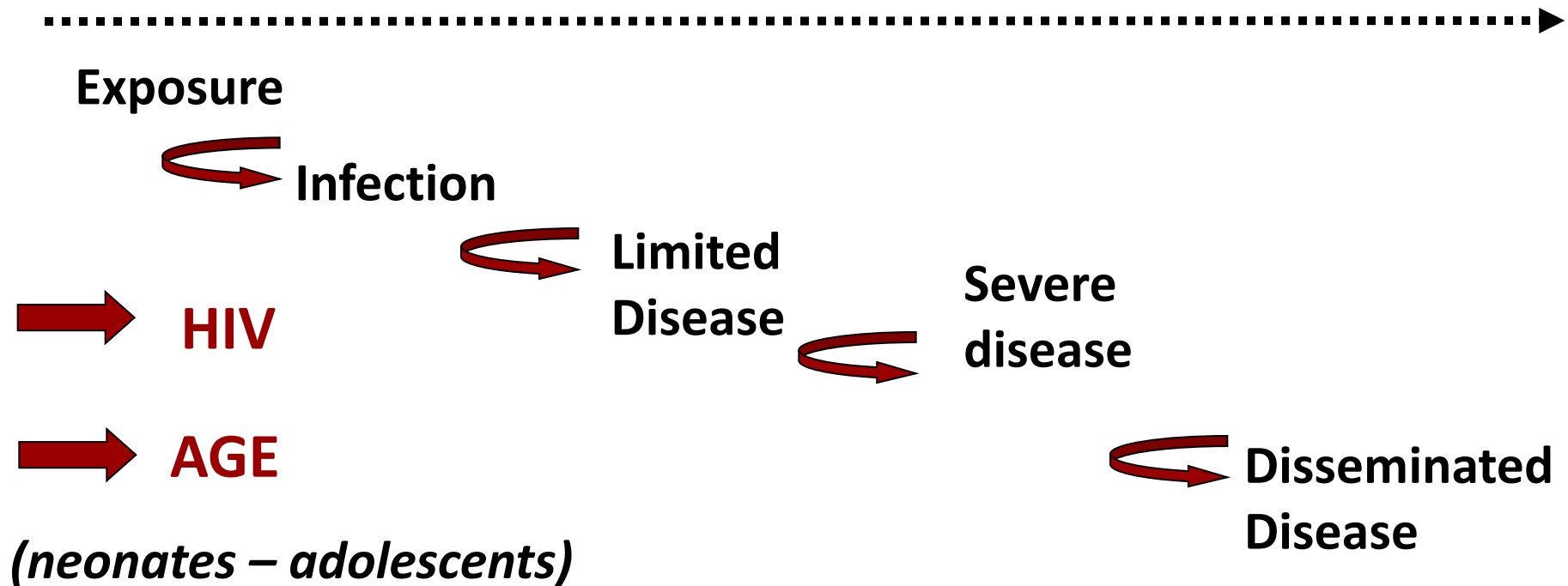
# WHO ESTIMATED TB CASES BY AGE, 2006

Country	Total Cases	Cases in Children < 15	% in Children
Myanmar	78,489	8,007	10.2
Nigeria	261,404	32,310	12.4
Pakistan	244,736	61,905	25.3
The Philippines	230,217	12,167	5.3
Russian Fed.	183,373	7,778	4.2
<b>South Africa</b>	<b>220,486</b>	<b>35,449</b>	<b>16.1</b>
Thailand	85,928	2,317	2.7
Uganda	75,250	12,099	16.1
Tanzania	117,489	18,890	16.1
Viet Nam	143,023	7,559	5.3
Zimbabwe	76,296	12,267	16.1
Total	6,678,188	630,722	9.4

# RISK OF TB DISEASE PROGRESSION (NO IPT)

- **Young age**
  - 43% of **infants** (children < 1year)
  - 25% of children aged one to five years
  - 15% of **adolescents**
- **Recent infection (1-2 years):** children with close contact
- Malnutrition
- **HIV**

# CONTINUUM OF TB INFECTION AND DISEASE STATES IN CHILDREN



## Incidence of culture-+TB in HIV-infected and uninfected South African infants (per 100 000 infant population)

	All infants	HIV-uninfected	HIV-infected	Relative risk
All tuberculosis	<b>83.1</b> (72.9-93.7)	<b>65.9</b> (56.7-75.3)	<b>1595.9</b> (1151.3-2131.5)	<b>24.2</b> (16.9-33.6)
Pulmonary tuberculosis	<b>78.7</b> (68.6-89.0)	<b>62.5</b> (53.3-71.7)	<b>1505.6</b> (1075.2-2022.8)	<b>24.1</b> (16.7-33.7)
Extrapulmonary tuberculosis	<b>28.2</b> (22.2-34.4)	<b>22.9</b> (17.5-28.6)	<b>481.8</b> (257.0-750.8)	<b>21.0</b> (10.7-35.0)
Disseminated tuberculosis	<b>16.6</b> (11.9-21.2)	<b>14.1</b> (9.7-18.3)	<b>240.9</b> (86.6-431.7)	<b>17.1</b> (6.0-33.7)
Miliary tuberculosis	<b>10.9</b> (7.2-14.7)	<b>9.3</b> (5.8-12.7)	<b>150.6</b> (30.8-301.0)	<b>16.2</b> (3.4-37.1)
Tuberculosis meningitis	<b>9.2</b> (5.8-12.6)	<b>7.9</b> (4.7-11.1)	<b>120.1</b> (27.7-257.9)	<b>15.2</b> (2.9-38.7)

# PAEDIATRIC CONSIDERATIONS: TB DRUGS

- Children typically achieve lower serum levels for most 1stline TB drugs vs. adults, given same mg/kg dosages
- **Secondline drugs?**
- **Novel agents?**
- Age, HIV infection, ART, nutritional status, genetic profile important considerations
- Disease: paucibacillary
- Spectrum of disease varied
- Drug delivery

*Schaaf HS, BMC Med. 2009; Schaaf HS,. Arch Dis Child. 2005; McIlleron H, Clin Infect Dis. 2009; Graham SM,. Antimicrob Agents Chemother. 2006; Roy V, Int J Tuberc Lung Dis.2010; Donald PR, Eur J Clin Pharmacol. 2007*

# WHAT?

- Exposure/infection: DS/DR
- Disease: spectrum
- MDR disease
- Existing agents: first and secondline
- Regimens
- Novel agents (n=6; PIPs?)

# DO WE NEED EFFICACY TRIALS?

- Preventive therapy – short course: YES
- Shortened duration limited TB disease: YES
- Novel agents, regimens: **Extrapolate adults; appropriate paediatric data needed**
- PK dosing, safety, tolerability, formulations, interactions, limited efficacy

# TOXICITY IN CHILDREN?

- Monitoring in children: growth, psychiatric wellbeing and/or neurocognitive development.
- Young children: adverse effects under detected unless actively monitored
- First-line well tolerated
- 2ndline drugs in children? Adverse effects, overlapping toxicities between ARV and 1stline TB drugs well-described in adults
- Children: injectables, ETH, Quin?
- Novel agents?

# EFFECT OF ETHIONAMIDE: THYROID

- 137 children (median age 2.9y; range 0.3-15.8y)
- Abnormal TFTs recorded in 79 children (58%); 30 elevated serum TSH and a suppressed fT4, 20 an isolated elevated serum TSH, 28 children an isolated low serum fT4 and one an isolated low TSH.
- 12 (8.8%) children developed biochemical hypothyroidism on treatment
- Hypothyroidism associated with **PAS** use (OR 9.17, CI 95% 2.29-36.73, p=0.001) and **HIV**-infection (OR 3.27, 95% CI 1.23-8.67, p=0.015)

**HOW?**

# PAEDIATRIC CHALLENGES TO ACCESS TRIALS: PREVENTIVE AND TREATMENT

- 1. Diagnostic challenges** - case definitions: rigorous and pragmatic case definitions
- 2. Treatment outcome definitions:** more pragmatic to allow children access into drug trials?
- 3. Practical challenges:** enrolling children into trials (adequate samples, PK, consent, experience, regulatory)

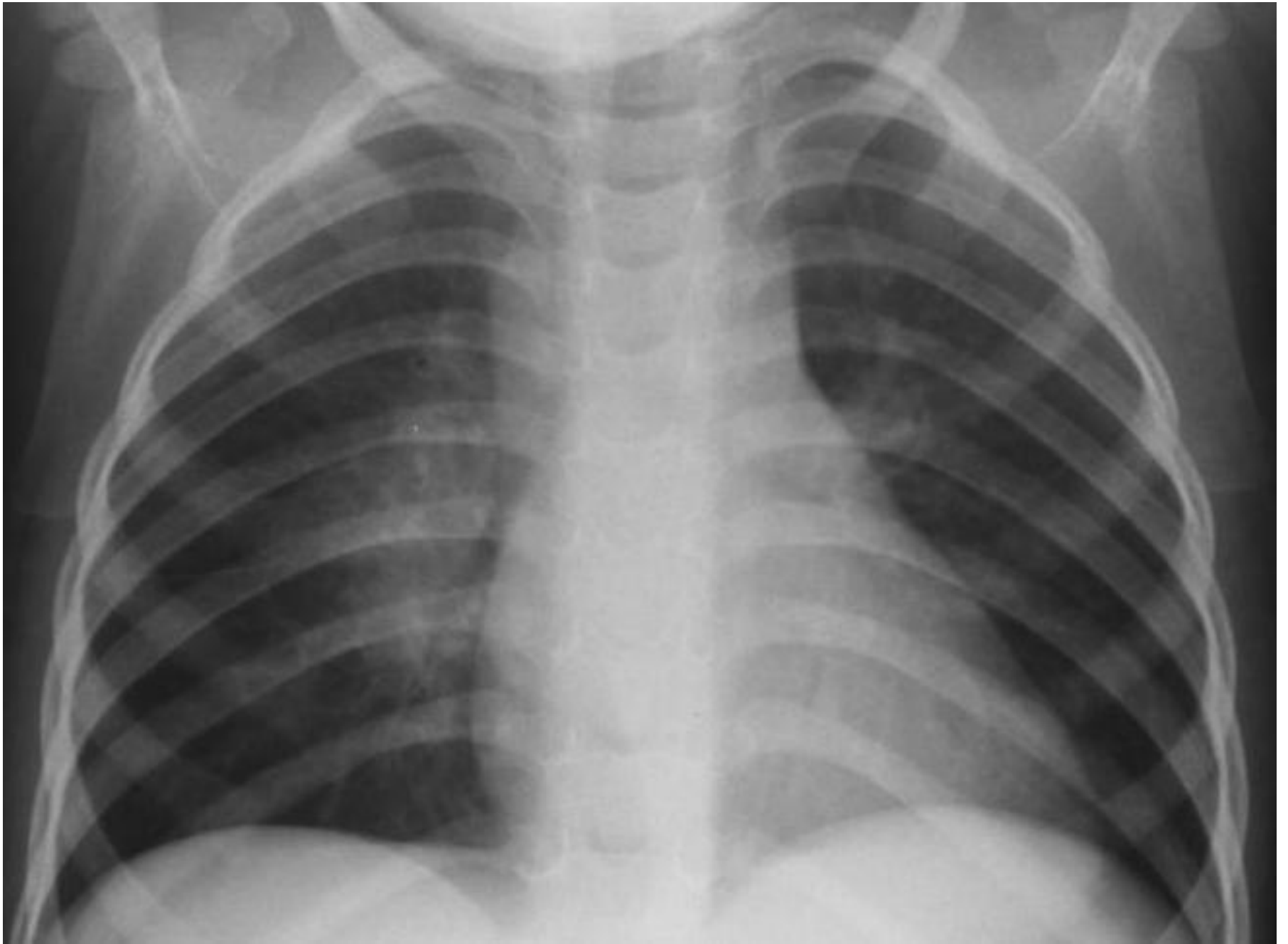
# WHEN?

- Early?
- Later?
- Novel agents: Inclusion to allow for PK, safety, licensure, generalibility following initial adult data

# WHO?

- Target population likely to benefit
- Risk/benefit assessment
- Age spectrum (infants - adolescents)
- Disease spectrum (DR)
- HIV and ART
- Genetic differences
- Preventive and treatment groups

# UNCOMPLICATED LYMPH NODE DISEASE



# COMPLICATED LYMPH NODE DISEASE



# ADULT-TYPE DISEASE (SMEAR+)



# DISEASE SEVERITY PREDICTS CULTURE YIELD: Rx response?

Disease manifestation	Total (%) N = 439	Bacteriologic yield
Not TB	85 (19.4)	
<b>Intra-thoracic TB</b>	307 (69.9)	120/195 ( <b>61.5</b> )
Uncomplicated LN	147 (47.9)	22/64 ( <b>34.4</b> )
Complicated LN	106 (34.5)	59/80 ( <b>73.5</b> )
Other	54 (17.5)	39/51 ( <b>76.5</b> )
<b>Extra-thoracic TB</b>	72 (16.4)	31/46 ( <b>67.4</b> )
Cervical lymphadenitis	35 (48.6)	27/27 ( <b>100</b> )
TBM	14 (19.4)	1/10 ( <b>10.0</b> )
Other	23 (31.9)	5/9 ( <b>55.6</b> )
Intra+Extra	25 (5.7)	12/13 ( <b>92.3</b> )

# STANDARD CXR REPORTING FORMAT (DUAL BLINDED REVIEW)

<b>SDOCB</b>	<b>STANDARDISED CXR REPORT FORM</b>											
<table border="1" style="margin: auto;"> <tr> <td style="width:15%;">CXR NO</td> <td style="width:10%;">1</td> <td style="width:10%;">2</td> <td style="width:10%;">3</td> <td style="width:10%;">4</td> <td style="width:10%;">5</td> <td style="width:10%;">6</td> <td style="width:10%;">7</td> <td style="width:10%;">8</td> <td style="width:10%;">9</td> <td style="width:10%;">10</td> </tr> </table>	CXR NO	1	2	3	4	5	6	7	8	9	10	<div style="border: 1px solid black; width: 100px; height: 100px; margin: auto;"></div> <p style="text-align: center; margin-top: 5px;"><b>CHILD BARCODE</b></p>
CXR NO	1	2	3	4	5	6	7	8	9	10		
<table border="1" style="margin: auto;"> <tr> <td style="width:15%;">VISIT</td> <td style="width:15%;">0 - BASELN</td> <td style="width:15%;">1 - M3</td> <td style="width:15%;">2 - M6</td> <td style="width:15%;">3 - M15</td> <td style="width:15%;">4 - M27</td> <td style="width:15%;">5 - UNSCH 1</td> </tr> </table>	VISIT	0 - BASELN	1 - M3	2 - M6	3 - M15	4 - M27	5 - UNSCH 1					
VISIT	0 - BASELN	1 - M3	2 - M6	3 - M15	4 - M27	5 - UNSCH 1						

Reader name	RPG	HSS	BJM	CXR date	D	D	M	M	Y	Y	Y	Y
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QUALITY OF CXR	PA accepted	Yes	No	Lateral accepted	Yes	No
NORMAL CXR	YES	NO				

	<b>Lung area involved</b>
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PARENCHYMA			(tick applicable boxes)							
Alveolar (Consolidation)	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Ghon focus	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Expansile	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Bronchopneumonic	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Cavity	Y	N	RUL	RML	RLL	LUL	LING	LLL		
Nodular infiltr (>2mm)	Y	N	Peri-hilar			Peripheral			Right	Left
Miliary infiltr (up to 2 mm)	Y	N	Peri-hilar			Peripheral			Right	Left
Volume loss	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Hyperinflation	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Calcification (lung)	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Fibrosis	Y	N	RUL	RML	RLL	LUL	LING	LLL	Segm	Lobar
Peri-hilar streakiness	Y	N	Right			Left				

NODES					
Peri-hilar	Y	N	U	Right	Left
Paratracheal	Y	N	U	Right	Left
Calcification (nodes)	Y	N		Peri-hilar      Paratracheal	

AIRWAYS				
Bronchial compression	Y	N	Right	Left
Tracheal compression	Y	N		

PLEURA						
Effusion	Y	N	R	L	Small	Large
Thickening	Y	N	R	L	Loculated	Y
Pneumothorax	Y	N	R	L	N	U

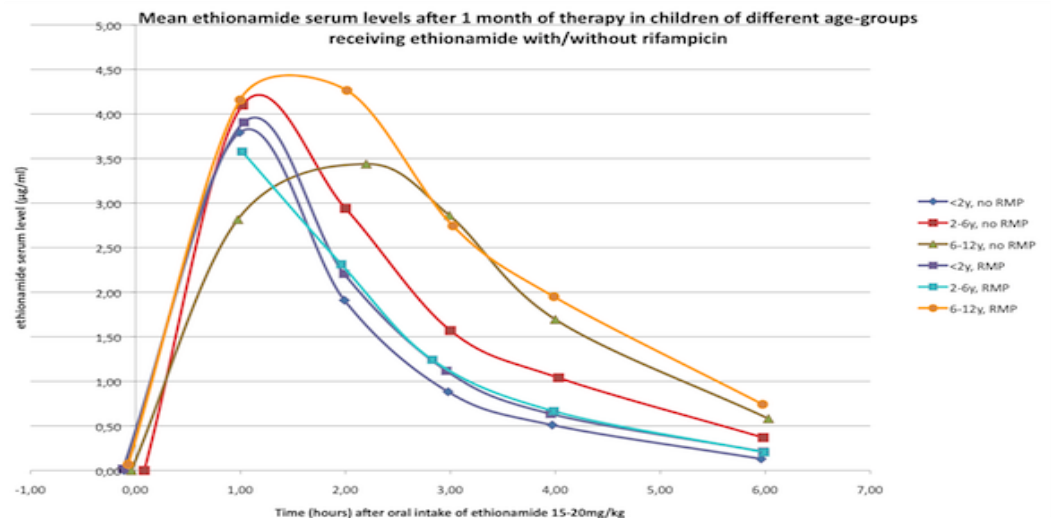
HEART					
Enlargement	Y	N	U	Pericardial Effusion	
				Y	N



Certainty of diagnosis	Certain TB	Uncertain TB	Not TB																		
<p><b>If certain TB, indicate TB disease classification</b> (circle all that apply, and classify as certain or uncertain)</p>	<ol style="list-style-type: none"> <li>1. Uncomplicated LN disease</li> <li>2. Complicated LN disease</li> <li>3. Expansile pneumonia</li> <li>4. Ghon focus</li> <li>5. Miliary TB</li> <li>6. Pleural effusion</li> <li>7. Cavities</li> <li>8. Adult type TB</li> <li>9. Calcification</li> </ol>	<table border="0"> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> </table>	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	
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<p><b>If not TB: alternative diagnosis</b> (circle all that apply, classify as certain or uncertain)</p>	<ol style="list-style-type: none"> <li>1. Lobar pneumonia</li> <li>2. Interstitial pneumonia</li> <li>3. Bronchopneumonia</li> <li>4. LAWO</li> <li>5. Congenital malformation</li> <li>6. LIP</li> <li>7. Cavity not TB</li> <li>8. Bronchiectasis</li> <li>9. Other (specify)</li> </ol>	<table border="0"> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> <tr><td style="border: 1px solid black; padding: 2px;">Certain</td><td style="border: 1px solid black; padding: 2px;">Uncertain</td></tr> </table>	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	Certain	Uncertain	
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<p><b>If abnormal previous CXR: current CXR improved?</b></p>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Uncertain	<input type="checkbox"/> Deteriorated																	

# AGE AND HIV EFFECT

- 31 children enrolled, 10 children 0-2 years, 11 children 2-6 years, 10 children 6-12years
- Sampling before and 1,2,3,4 and 6hours after ETH dosing
- ETH serum levels after oral intake (15-20mg/kg) correlated significantly with **age**
- RMP did not have an influence on ETH serum levels
- In **HIV-infected** children  $C_{max}$  as well as AUC were significantly lower (1/4 months therapy:  $C_{max}$   $p=0.05/0.02$ , AUC  $p=0.002/0.047$ )



# Pharmacokinetics (PK) and Genetics (PG) of Isoniazid (INH) in South African HIV-Exposed Infants - PACTG 1041

J. Kiser, R. Zhu, S. Nachman, C. Mitchell, G. McSherry, S. Madhi, M. Cotton, R. Bobat, S. Kim, H. Seifart, C. Werely, D.Z. D'Argenio, and C.V. Fletcher

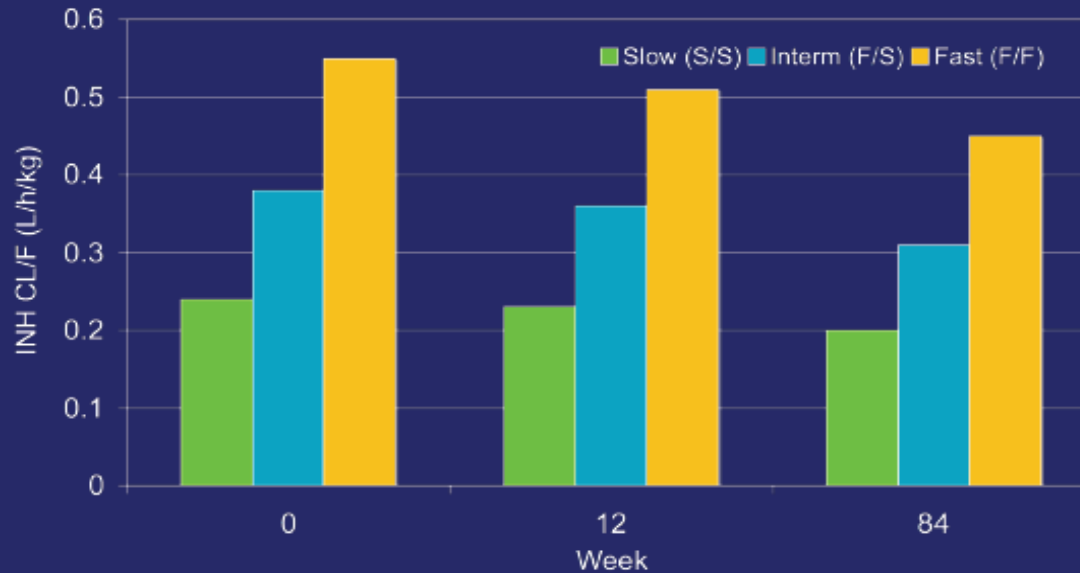
## Demographic Summary

Covariates	Symbol	Ratios	Mean (SD)	Quartiles		
				Min	Median	Max
Age (months)	AGE		8.2 (7.4)	3.0	5.8	23.9
Weight (kg)	WT		7.7 (2.6)	3.5	7.1	18.1
INH Dose (mg/kg/d)	DOSE		14 (3)			
Sex (male/female)	SEX	66/65				
Genotype (Slow/Inter/Fast)	GT	32/46/30 23 na				
HIV Status (uninfected/infected)	HIVS	78/53				

131 HIV-exposed and infected infants (mean age: 8.2 months)

# PK Modeling Results

- NAT2 phenotype and weight explained a significant portion of interindividual variability in CL/F and weight explained a significant portion of the variability in V/F.
- In the final model, variability (%SD) for CL/F and V/F was 49% and 32% versus 62% and 33% in the model without the explanatory covariates.
- Effect of NAT2 genotype on INH CL/F.



- INH PK at 10-20 mg/kg/d in infants similar to published data in older children (median 3.8 y) if weight adjusted.
- Influence of age-related enzyme maturation and genotype on INH PK in children

# MATERNAL AND INFANT PAIRS

- 715 HIV-infected women: TB incidence: 5.0 per 100 person-years (95% CI 3.2–7.4 cases per 100 person-years).
- Women with incident TB and their infants had a 2.2- and 3.4-fold increased probability of death, respectively, compared with women without active TB and their infants
- **Routine screening for TB during routine antenatal care as strategy for maternal/infant interventions (IMPAACT P1078: IPT trial - safety)**

*Gupta, Clin infect Dis 2007; Kali et al, J Acquir Immune Defic Syndr. 2006*

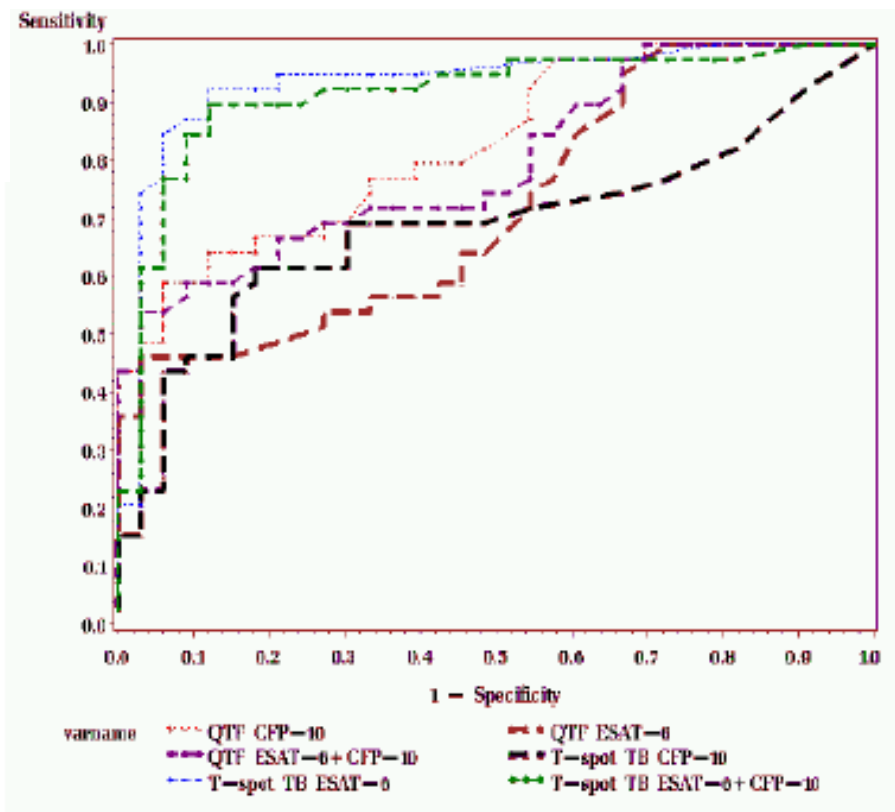
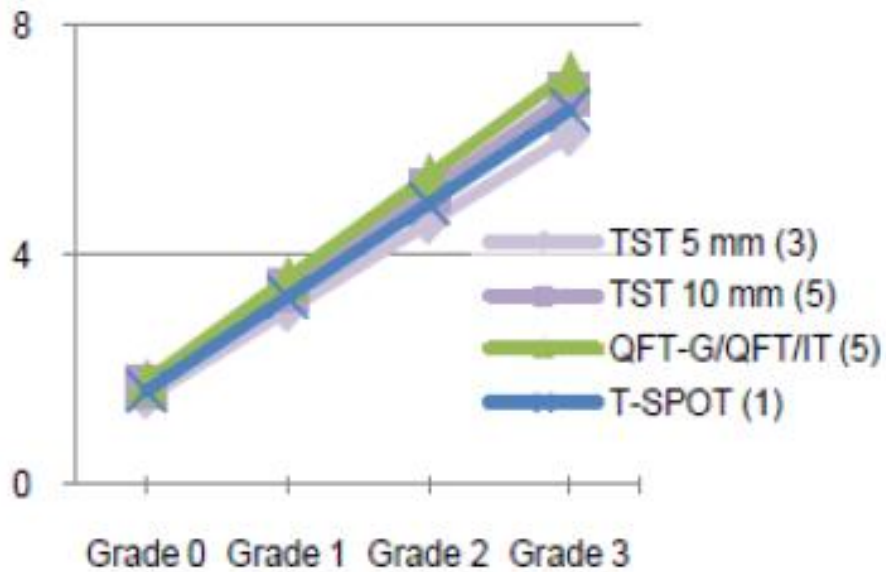




Damien Schumann

## Measures of *M. tb* infection in relation to exposure and age in adults and children in recent household contact with TB

	Measures of <i>M. tb</i> infection					
	TST positive		T SPOT.TB positive		QTF positive	
	Unadjusted	Age adjusted	Unadjusted	Age adjusted	Unadjusted	Age adjusted
Covariates	OR (95% CI) *	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
<b><i>M. tb</i> contact score <math>\geq 4</math></b>	1.56 (0.59 – 4.15)	<b>3.83</b> (1.05-14.03)	62.42 (7.67 – 508.69)	<b>38.40</b> (7.59- 616.11)	9.60 (3.02 – 30.54)	<b>14.94</b> (4.02-55.58)
<b>Age in years</b>	-	1.07 (1.02 – 1.11)	-	1.01 (0.96 – 1.06)	-	1.04 (1.01-1.08)



Hesseling et al, Thorax, 2008, Mandalakas, WHO REPORT. 2010

# MDR DISEASE AND CONTACTS

<i>Total number of children on treatment for on MDR and XDR disease over 2 years: BCH and TBCH, by age and HIV status</i>												
	<i>HIV-infected</i>			<i>HIV-uninfected</i>			<i>Total DR</i>	<i>Total DR HIV+</i>	<i>Total DR HIV-</i>	<i>Total by age stratum</i>		
<b>Age</b>	<2	2-5	>5	<2	2-5	>5				<2	2-5	>5
<b>MDR</b>	18	21	23	52	72	78	<b>264</b>	62	202	70	93	101
<b>XDR</b>	2	1	2	2	2	3	<b>12</b>	5	7	4	3	5
<b>Total</b>	20	22	25	54	74	81	<b><u>276</u></b>	67	209	74	96	106

<i>Total number children on MDR prophylaxis over 2 years: TBCH, BCH and OPD, by age and HIV status</i>												
	<i>HIV-infected</i>			<i>HIV-uninfected</i>			<i>Total</i>	<i>Total HIV+</i>	<i>Total HIV-</i>	<i>Total by age stratum</i>		
<b>Age</b>	<2	2-5	>5	<2	2-5	>5				<2	2-5	>5
	16	18	14	280	236	0	<b><u>564</u></b>	48	516	296	254	14



# SUMMARY

1. Early PK and dosing, toxicity, formulations (new, 2ndline)
2. Early inclusion children (age, HIV, target populations, DR)
3. Infection and disease
4. Regimens vs. drugs
5. Efficacy? Limited adequate novel agents
6. Disease: case definitions standardized - prevention, limited efficacy
7. Treatment outcome: bacteriological; CXR improvement, weight gain (limited efficacy)
8. Family-based approaches