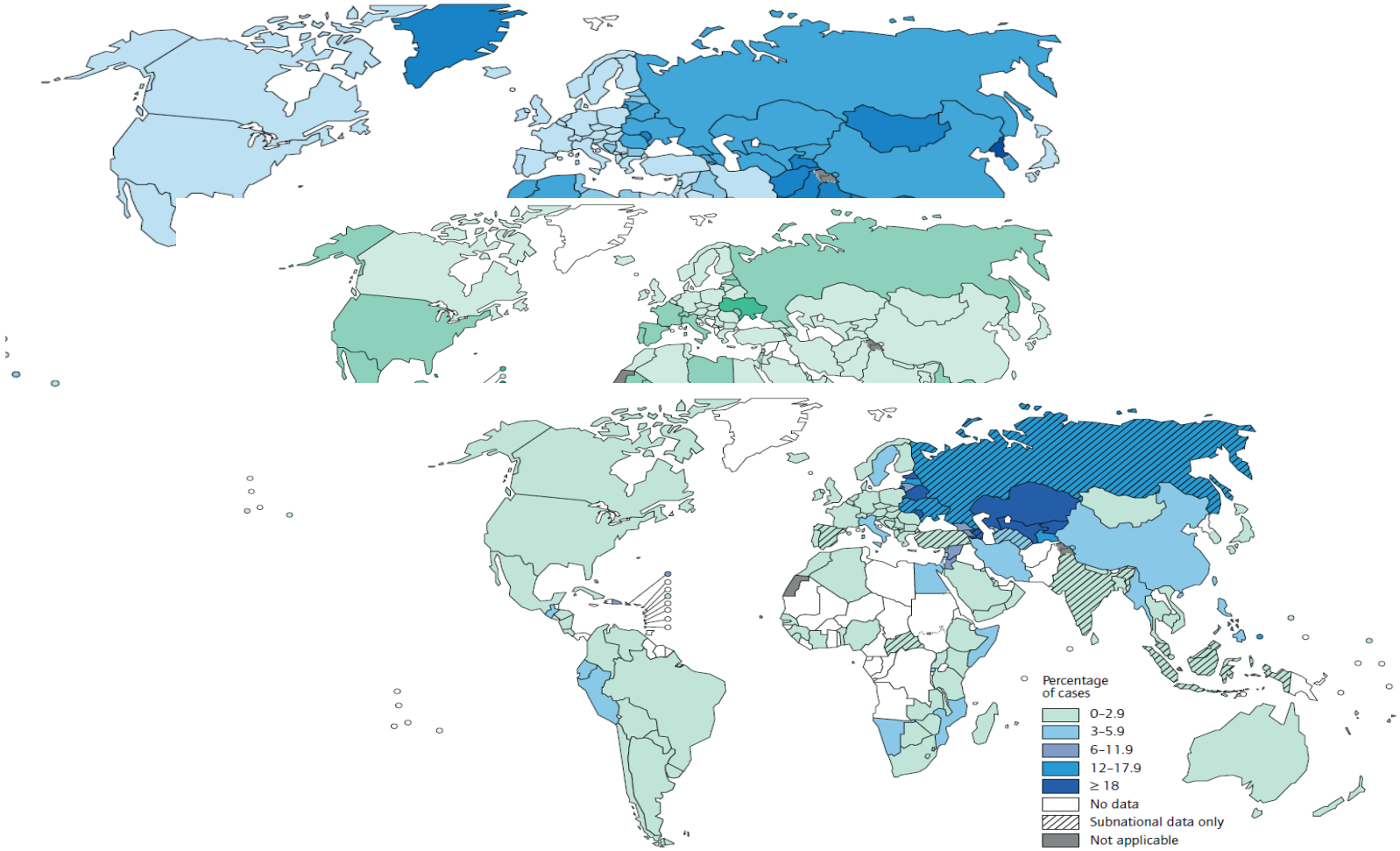
Imperial College London

Managing Drug-Resistant Tuberculosis in Pregnancy, Mothers and Newborns

James Seddon

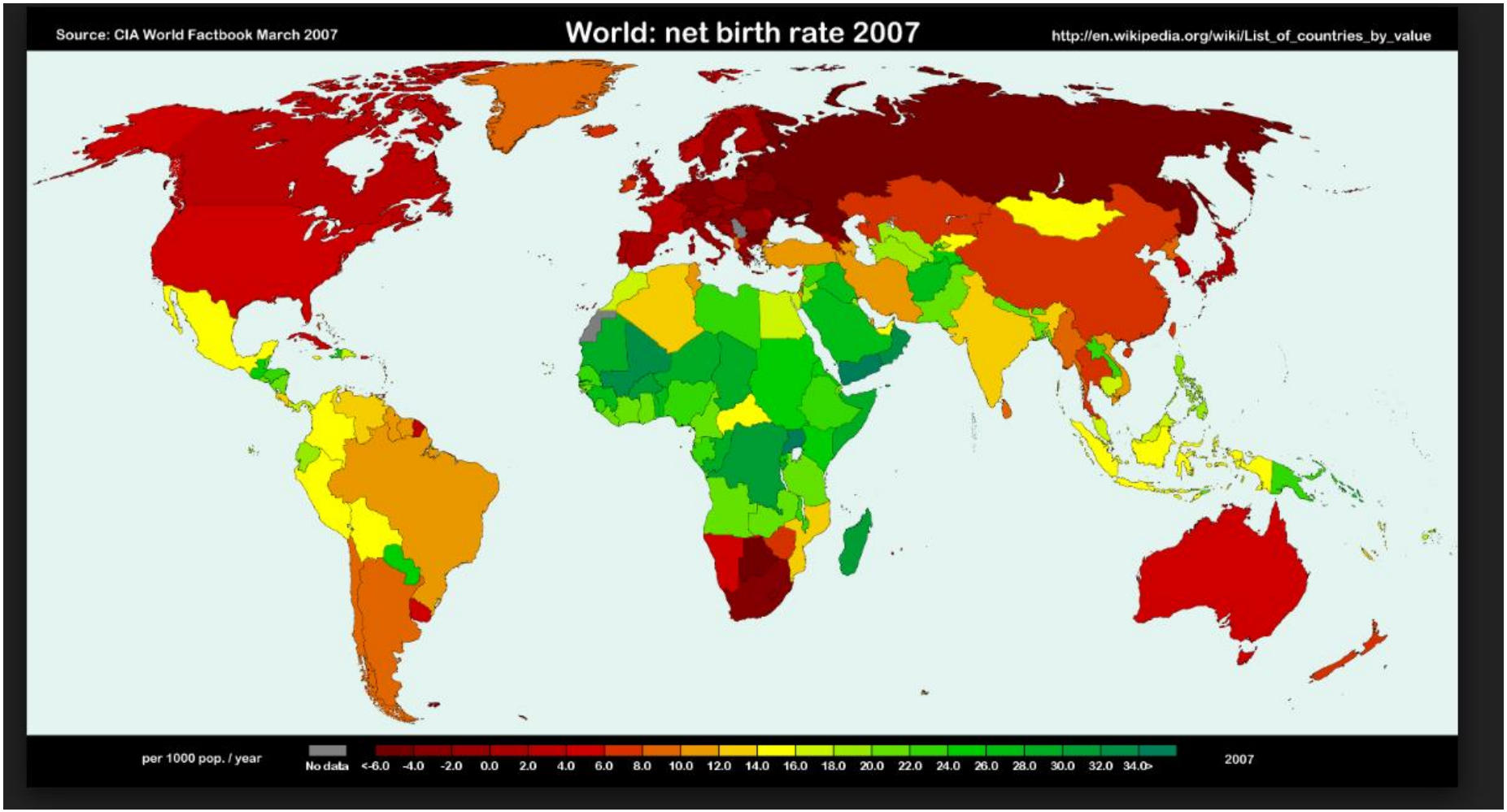
Postgraduate Course 31st October 2013

Epidemiology

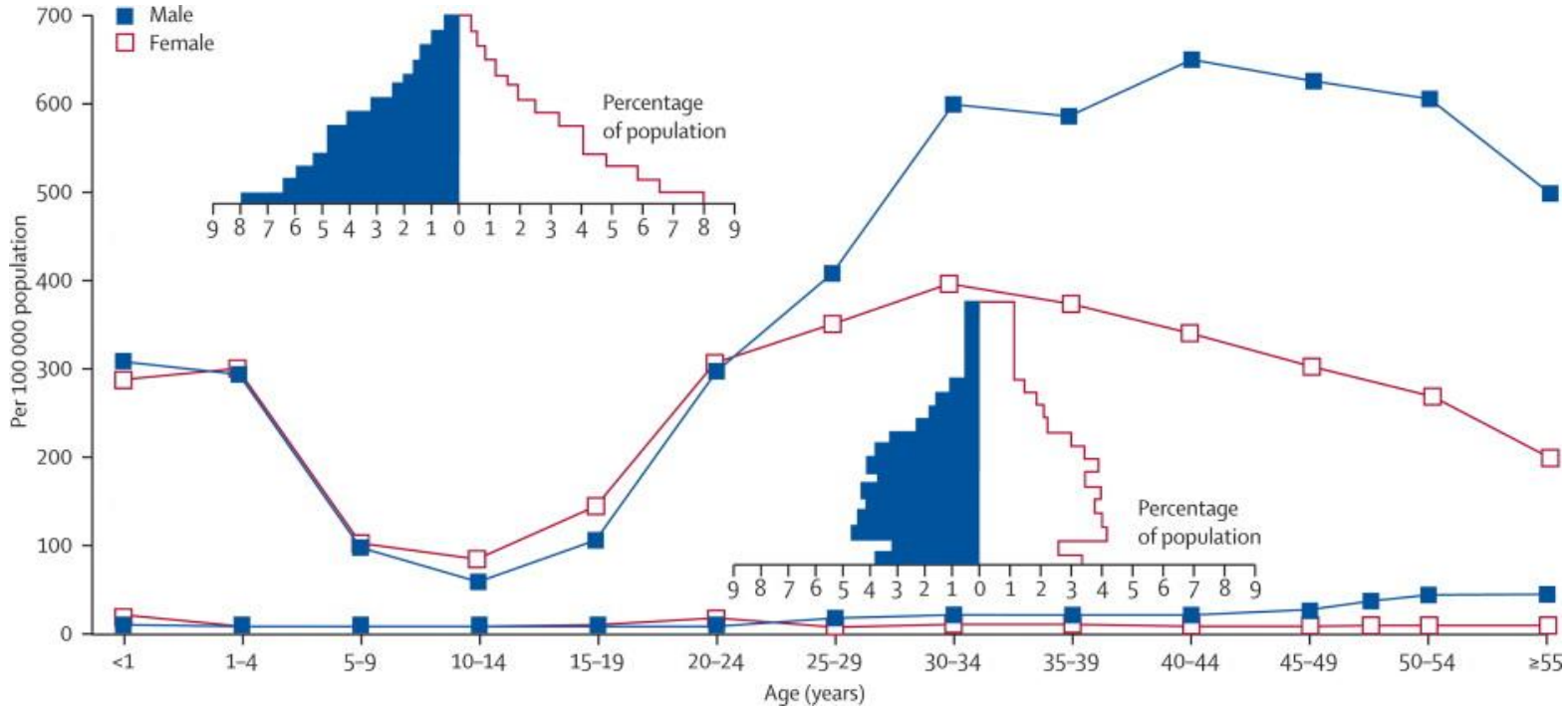


WHO Global Tuberculosis Report 2012

Epidemiology



Epidemiology



Donald et al. Lancet 2010; 375: 1852-1854

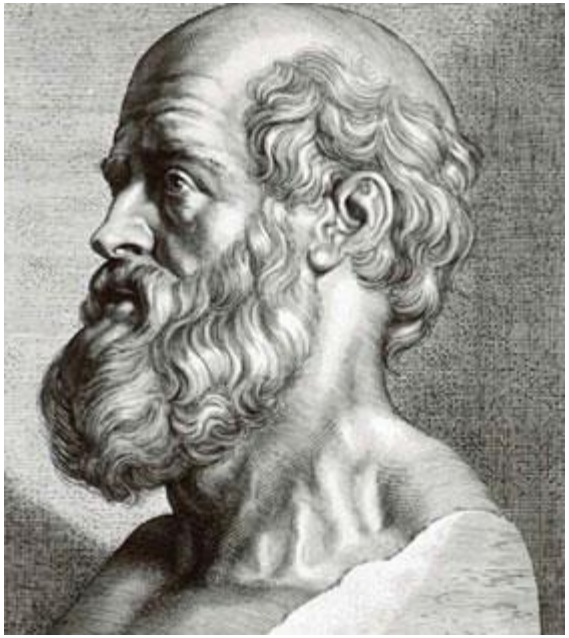
Epidemiology

- Limited data on TB in pregnancy
- TB disease in up to 8% HIV+ pregnant women in high burden countries
- TST+
  - Up to 34% HIV- women India
  - Up to 50% HIV + women SA

Mathad et al. Clin Infect Dis 2012; 55: 1532-49

Effect of Pregnancy on TB

- Pregnancy suppresses Th1 response
- Increased susceptibility
  - New infections
  - Reactivation
- Reversal post-partum (IRIS)



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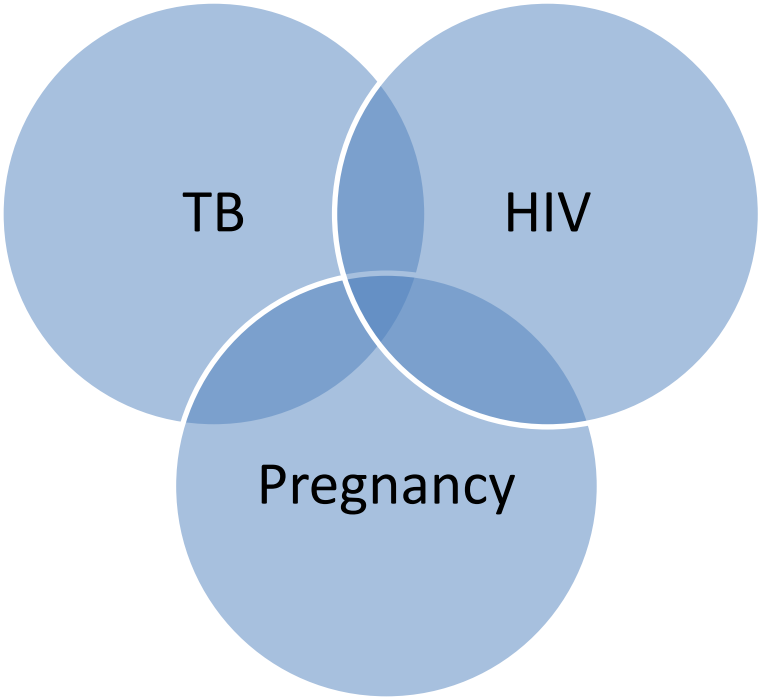
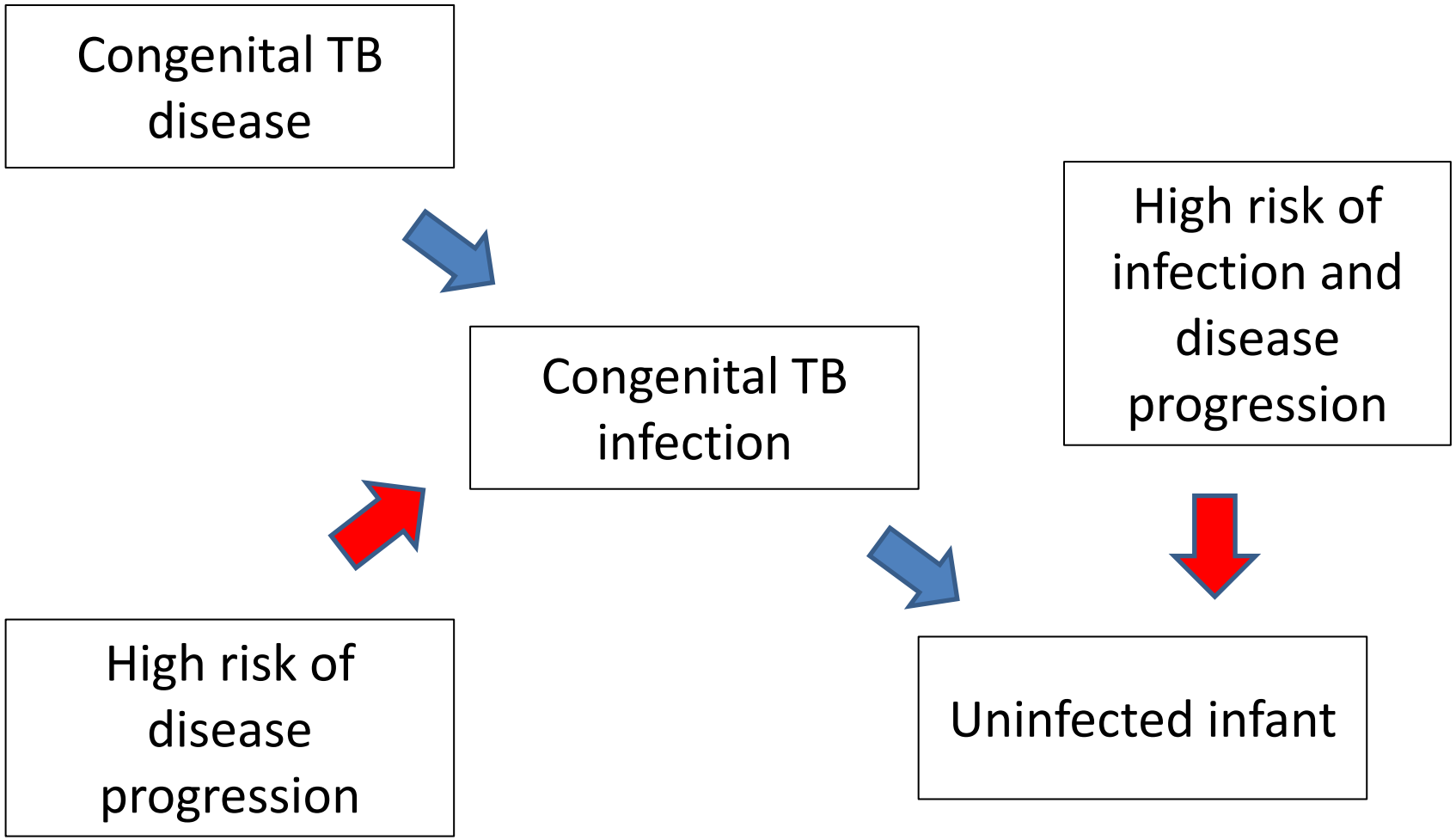
Effect of TB on Pregnancy



- TB in pregnancy leads to increased rates
  - Maternal mortality
  - Hospitalization
  - Miscarriage
- Situation complicated by HIV
  - Increased susceptibility
  - Diagnostic challenges

Mathad et al. Clin Infect Dis 2012; 55: 1532-49

Epidemiology Newborns



Perfect Storm

- Epidemiology coincides
- HIV coincides
- Immunosuppression of pregnancy
- TB negative effect on pregnancy
- Intense exposure for vulnerable infants

Studies of MDR-TB treatment in pregnancy

Author	Journal	Year	Number	HIV
Bosco de Oliveria	Rev da Soc Bras Med Trop	2011	7	2
Tabarsi	IJTLD	2011	5	?
Palacios	CID	2009	38	3
Khan	IJTLD	2007	5	3
Tabarsi	Infection	2007	1	?
Shin	CID	2003	7	?
Lessnau	Chest	2003	1	?
Nitta	CID	1999	4	0

Very low numbers

Drug-Resistant Tuberculosis and Pregnancy: Treatment Outcomes of 38 Cases in Lima, Peru

Eda Palacios,[1,a] Rebecca Dallman,[3,a] Maribel Muñoz,[1] Rocio Hurtado,[4] Katiuska Chalco,[1] Dalia Guerra,[1] Lorena Mestanza,[1] Karim Llaro,[1] Cesar Bonilla,[2] Peter Drobac,[5,6] Jaime Bayona,[1] Melissa Lygizos,[7] Holly Anger,[1] and Sonya Shin[5,6]

3089 MDR-TB patients 1996 to 2005

- 1033 (33%) women age 15–45 years
- 38 (4%) pregnant
- 14 (37%) no changes in treatment regimen
- 14 (37%) treatment suspended until after pregnancy
- Remainder suspended and restarted

Palacios et al. Clin Infect Dis 2009; 48: 1413-9

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Treatment outcome	Healthy	Dead	In treatment	Unknown	Total
Cure	21	2			23
Death		5			5
Default	3			2	5
Failure		1	1		2
In treatment			2		2
Not known				1	1
Total	24	8	3	3	38

Palacios et al. Clin Infect Dis 2009; 48: 1413-9

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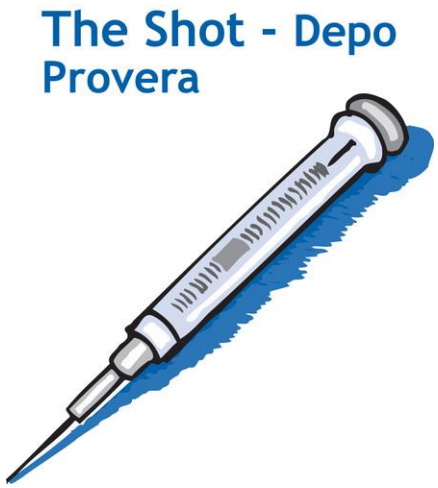
Follow up in 26/38 children

- 2 IPT
- 1 MDR-TB at 19/12
- 1 died pneumonia
- 25 healthy
- 2 minor health problems unrelated to TB

Palacios et al. Clin Infect Dis 2009; 48: 1413-9

Management in pregnancy

- Woman being treated for MDR-TB
  - Avoid pregnancy
  - Continue the same MDR-TB treatment
  - Stop MDR-TB treatment when pregnant
  - Adjust treatment for pregnancy
  - Terminate pregnancy



- Woman is pregnant and diagnosed with MDR-TB
  - Start normal MDR-TB treatment
  - Start a pregnancy adjusted MDR-TB treatment
  - Delay starting treatment
  - Terminate pregnancy

Management in pregnancy

Adverse effects of maternal TB treatment on foetus

Adverse effects of maternal TB on foetus

TB Drugs in Pregnancy

Safety of MDR-TB medications during pregnancy		
Medication	**Safety class***	**Comments**
Ethambutol	A	Experience in gravid patients suggests safety
Pyrazinamide	C	Experience in gravid patients suggests safety
Streptomycin Kanamycin Amikacin Capreomycin	D	Avoid use. Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use when possible.
Fluoroquinolones	C	Use with caution. No teratogenic effects seen in humans when used for short periods of time (2-4 weeks). Associated with permanent damage to cartilage in weight-bearing joints of immature animals. Experience with long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.
Ethionamide Protionamide	C	Avoid use. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.
Cycloserine Terizidone	C	Significant experience in gravid patients: animal studies have documented toxicity.

A = Safety established using human studies
B = Presumed safety based on animal studies
C = Uncertain safety, no human studies and animal studies show adverse effect
D = Unsafe, risk may only be justifiable under certain clinical circumstances.

Partners In Health 2003

TB Drugs in Pregnancy

- Avoid treatment in first trimester if possible
- Aim to have mother culture negative by the time of birth
- Risk benefit assessment in each case
- Include mother in treatment decisions
- Include pyridoxine

TB Drugs in Pregnancy

- ‘Safe drugs’
  - Isoniazid, rifampicin, ethambutol, PZA
- Unclear
  - Fluoroquinolones, cycloserine/terizidone, PAS
- Avoid if possible
  - Injectables, ethionamide/prothionamide

Infection Control

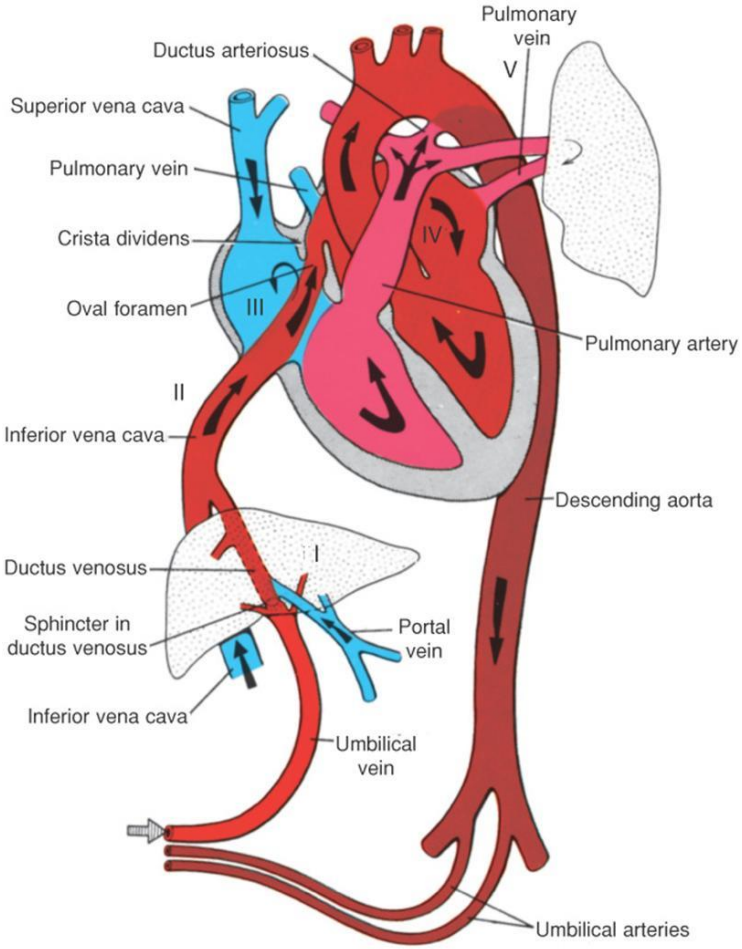
- Challenging!!!
- Consider delivery room and postnatal wards
- Ventilation (windows)
- Best form of infection control is effective treatment
- Consider masks for breastfeeding
- Consider sleeping in separate room until smear negative
- In extreme circumstances separate (XDR-TB?)

Breast feeding

- Generally should be encouraged
- Most drugs cross in small concentrations
- Injectables will not get into the neonate
- Give pyridoxine to infant

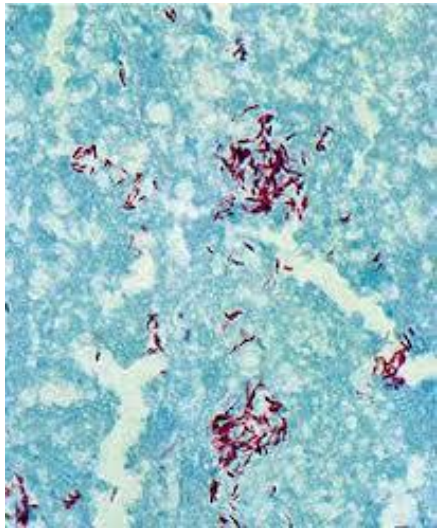
MDR-TB in neonates

- Assessment for TB disease
  - Non- specific signs (fever, irritability, poor feeding)
  - Liver/spleen enlargement
  - Lymphadenopathy
  - Cough/respiratory distress
  - CXR changes
- Examination of placenta



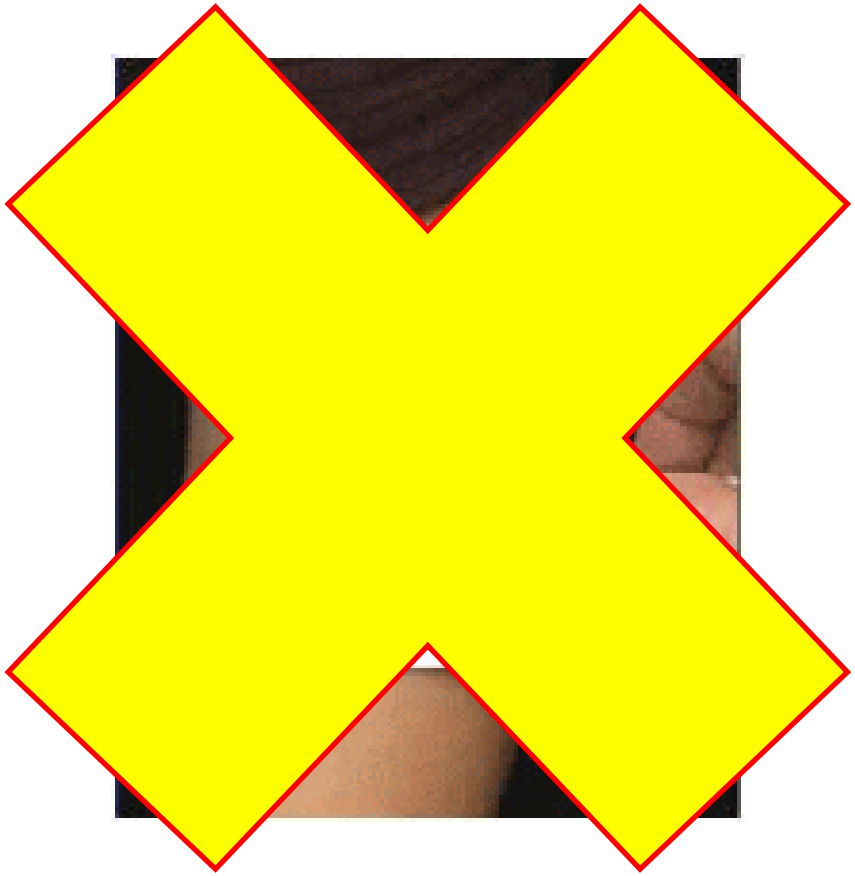
MDR-TB in neonates

- If MDR-TB disease suspected clinically
  - Immediate gastric aspirate
  - Repeat gastric aspirate x 3
  - Consider LP
  - CXR
  - AUSS
  - Send samples for culture
    - Blood
    - Swabs (ears, skin) if indicated
  - Start empiric treatment based on DST of mother



MDR-TB infection in neonates

- Assessment for TB infection
  - Assume if mother culture positive in last trimester of pregnancy or after delivery
  - TST/IGRA limited use
- Close follow up

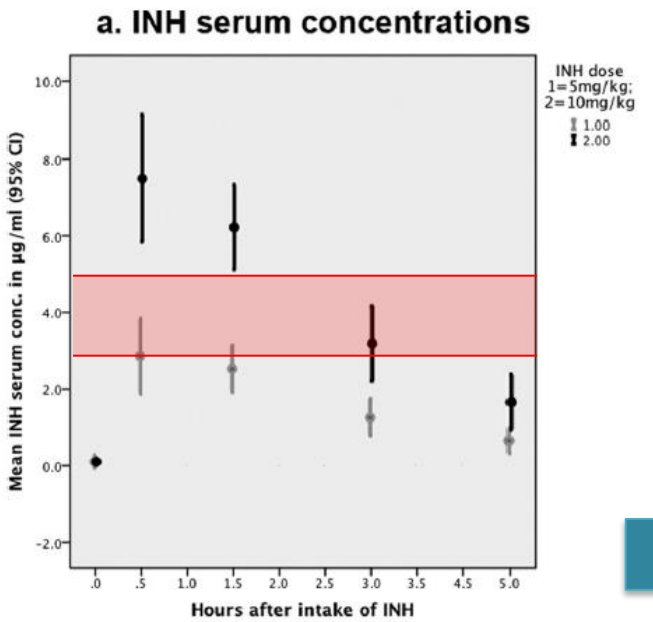


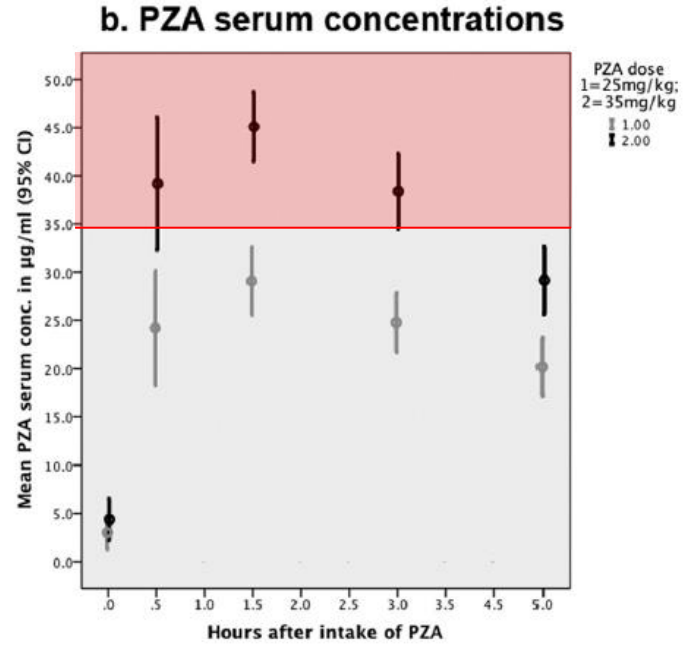
Treatment of MDR-TB in neonates

- Principles similar to older children
  - Infection
  - Disease
- Concern that in very young or premature neonates metabolism slower
  - May require lower dosages
  - May require more monitoring
- Remember BCG
- Close follow up

Pharmacokinetics in neonates

Author	Journal and year	Drug	Age	Findings
Thee	AAC 2011	INH, RMP, PZA	< 2 years	INH concentrations ↑ in < 12 months
Pullen	T Drug Mon 2006	RMP	29/40	RMP concentrations low with 8.5mg/kg
Tan	AAC 1993	RMP	35/40	RMP concentrations low with 10mg/kg
Le Doare	BMJ CR	RMP	26+2/40	>10mg/kg required for RMP dosing

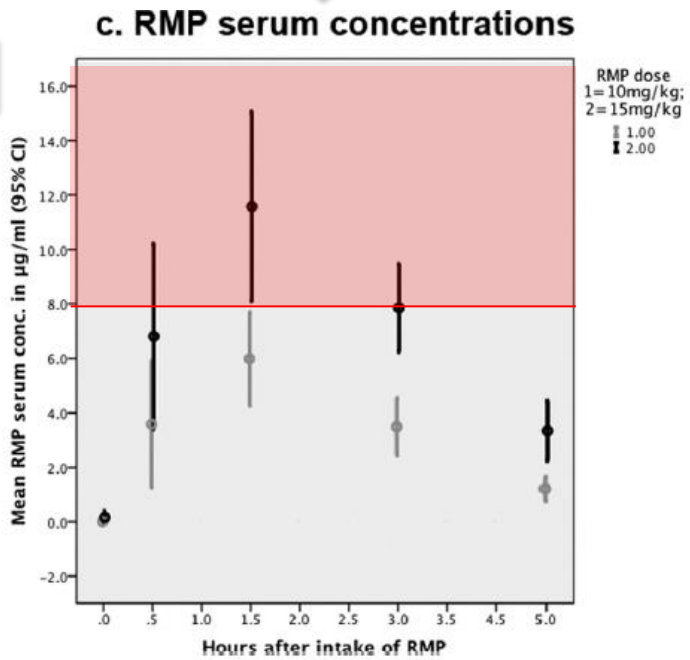




Target >8µg/ml

Target 3-5µg/ml

Target >35µg/ml



Thee et al. AAC. 2011; 55(12): 5560-5567

Recommended Drug Dosages in Children

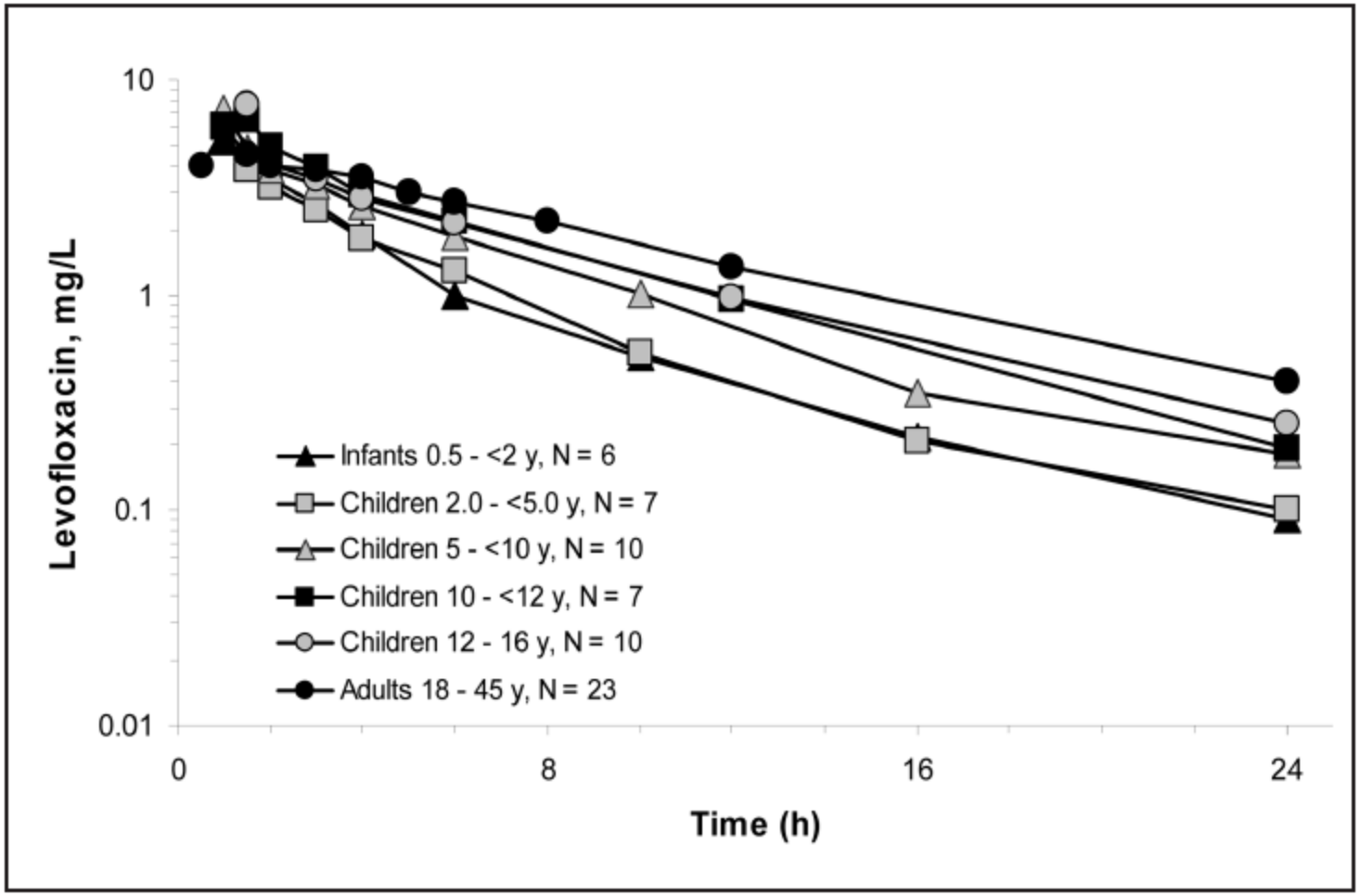
	Drug	Dose
Group 1	Isoniazid	15-20mg/kg
	Pyrazinamide	30-40mg/kg
	Ethambutol	20-25mg/kg
Group 2	Amikacin	15-22.5mg/kg
	Capreomycin	15-30mg/kg
Group 3	Ofloxacin	15-20mg/kg
	Levofloxacin	7.5-10mg/kg daily or bd
	Moxifloxacin	7.5-10mg/kg
Group 4	Ethionamide	15-20mg/kg
	Terizidone	15-20mg/kg
	PAS	150mg/kg
Group 5	Clofazimine	3-5mg/kg
	Linezolid	10mg/kg daily or bd
	Thiacetazone	5-8mg/kg
	Augmentin	15mg/kg tds
	Clarithromycin	7.5mg/kg bd

The injectables

- Unclear which drug to use
- IM vs. IV
- Effect of lignocaine
- C_{max} dose-dependent

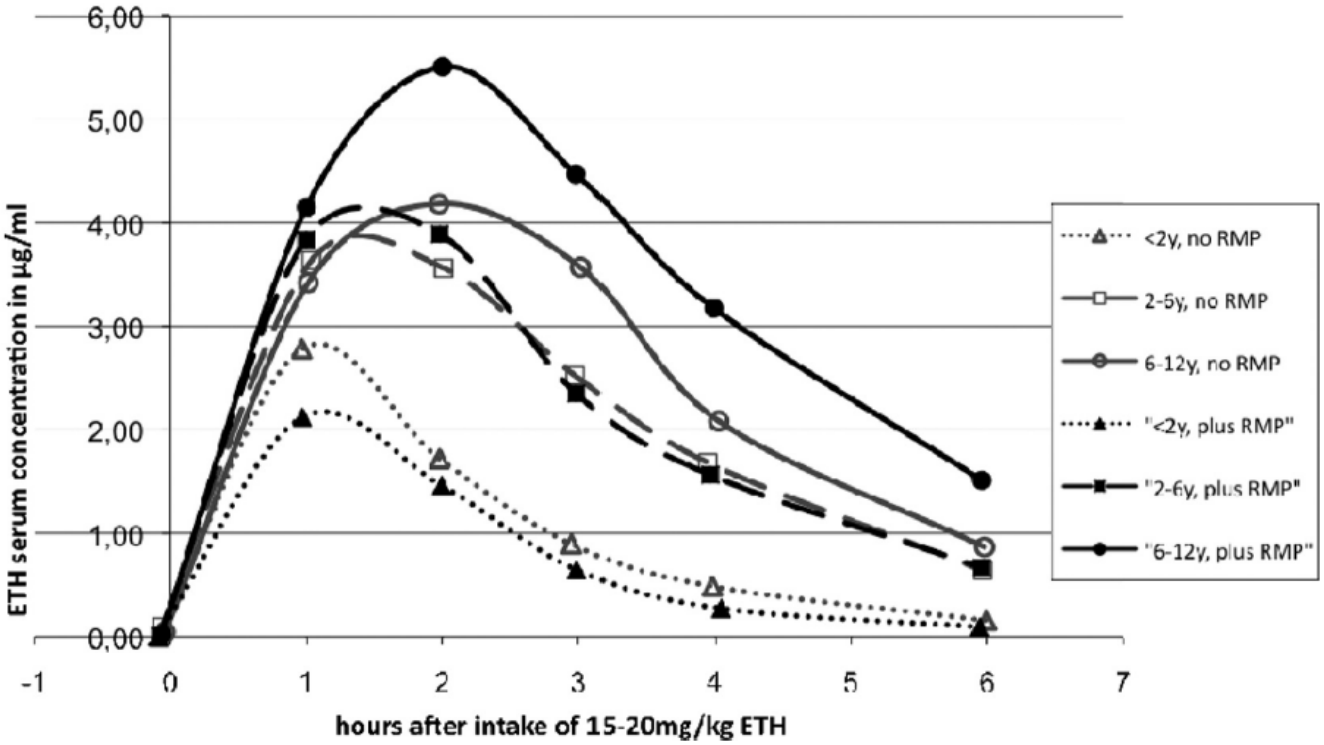
Jureen et al. J Clin Microbiol. 2010;48:1853-1858.

Fluoroquinolones



Chien et al. J Clin Pharm 2005; 45: 153-160

Ethionamide



Thee et al. AAC 2011; 55: 4595-4600

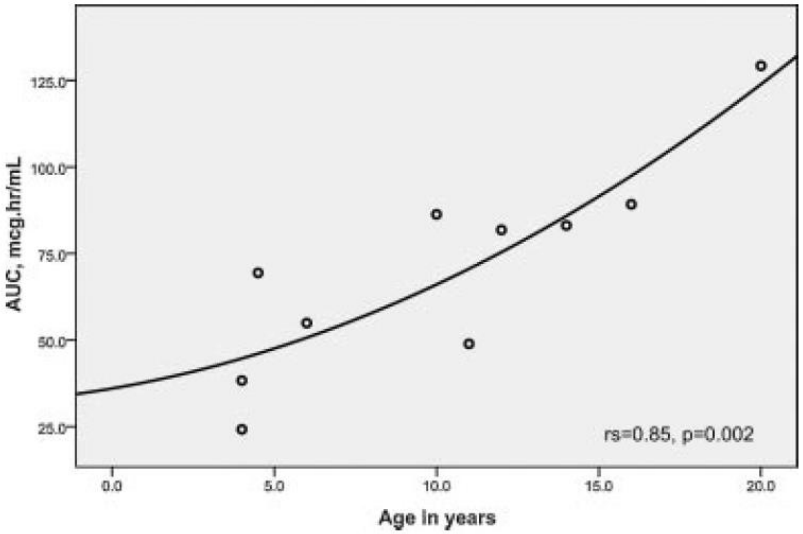
Other drugs

- Cycloserine /Terizidone
  - Poorly studied and unstable
  - No PK data to guide dosing in children of different ages and +/- HIV
- PAS
  - One study of 4 children
  - C_{max} 6.25-12µg/ml after 300mg/kg/day given 5 times/day

Zitkova et al. Chemotherapy. 1974; 20: 18-28 , Rastogi et al. Curr Microbiol. 1996; 33: 167-175
Soderhjelm et al. Tex Rep Biol Med. 1949;7:471-479

Other drugs

- Clofazimine
  - No paediatric PK data
- Linezolid
  - Limited data in children
- Thiacetazone
  - No PK data in children
- Amoxicillin/carbapenems + clavulanic acid
- Clarithromycin
- New agents
  - TMC-207, OPC-67683, PA-824



Santos et al. Ped Pulmonology 2009; 44: 148-154

Rastogi et al. Curr Microbiol. 1996; 33: 167-175, Jungbluth et al. Pediatr Infect Dis J. 2003; 22: S153-157

Thank You!