Management of Multidrug-Resistant TB in Children

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Sentinel Project, Director of Capacity Building

Objectives

- To review data on best practices for diagnosis, treatment and prevention of DR-TB in children
- To discuss new tools and strategies for decreasing the impact of DR-TB on children
- To discuss challenges in field implementation of best practices for children affected by DR-TB

Issues in Pediatric DR-TB

- Burden of disease estimates
- Current diagnostic situation
- Treatment
- PK data and child friendly formulations
- Prevention
- Integration with vertical programs for TB and child health
- Training and capacity building
- Advocacy and funding

Burden of Child DR-TB

- Previous estimates 6-10% of adult TB cases
- Jenkins et al., 2014 Lancet approach
- Estimated 33,000 incident DR-TB cases among children per year
- Large gap even between the lowest estimates and the actual number of children treated
- Important to consider children affected by DR-TB, infected with DR-TB, and sick with DR-TB

DR-TB in the Philippines

- 4000 cases in 2013
- 2.8-3.8 children per household (average 3.4)
- 13,600 children affected by DR-TB in 2013

Diagnosis Versus Bacteriologic Confirmation

- Treating ONLY children with bacteriologically confirmed MDR-TB means that you are under-treating and children are being missed and dying
- Situation different from that of pan-susceptible TB
- You should always obtain samples to try and obtain confirmation
- In high-risk, sick children, you should almost never wait to treat

Opportunities for Diagnostic Innovation: Sample Collection

- Multiple specimens better
- Sputum from older children
- Induced Sputum
- Gastric aspirate (https://www.youtube.com/watch?v=IWl_TY_LbZk&feature=youtu.be)
- "Sweet string"
- Need to ensure adult and referral sites have access to basic sampling equipment

Opportunities for Diagnostic Innovation: Diagnostic Tests

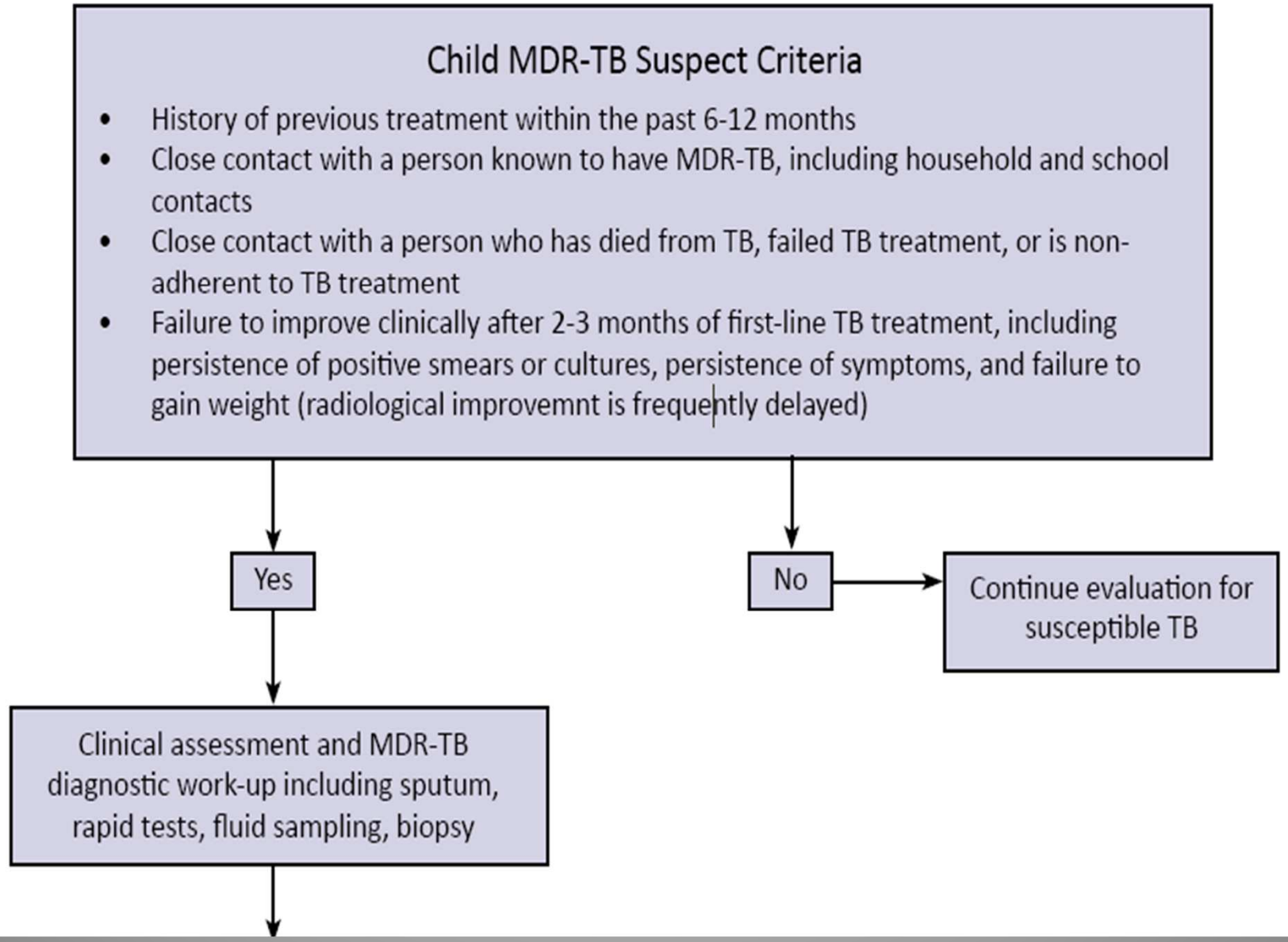
- Xpert MTB/RIF has higher sensitivity than smear
- Other molecular tests
- Liquid culture
- Solid culture
- Other methods not promising (i.e. LAM)

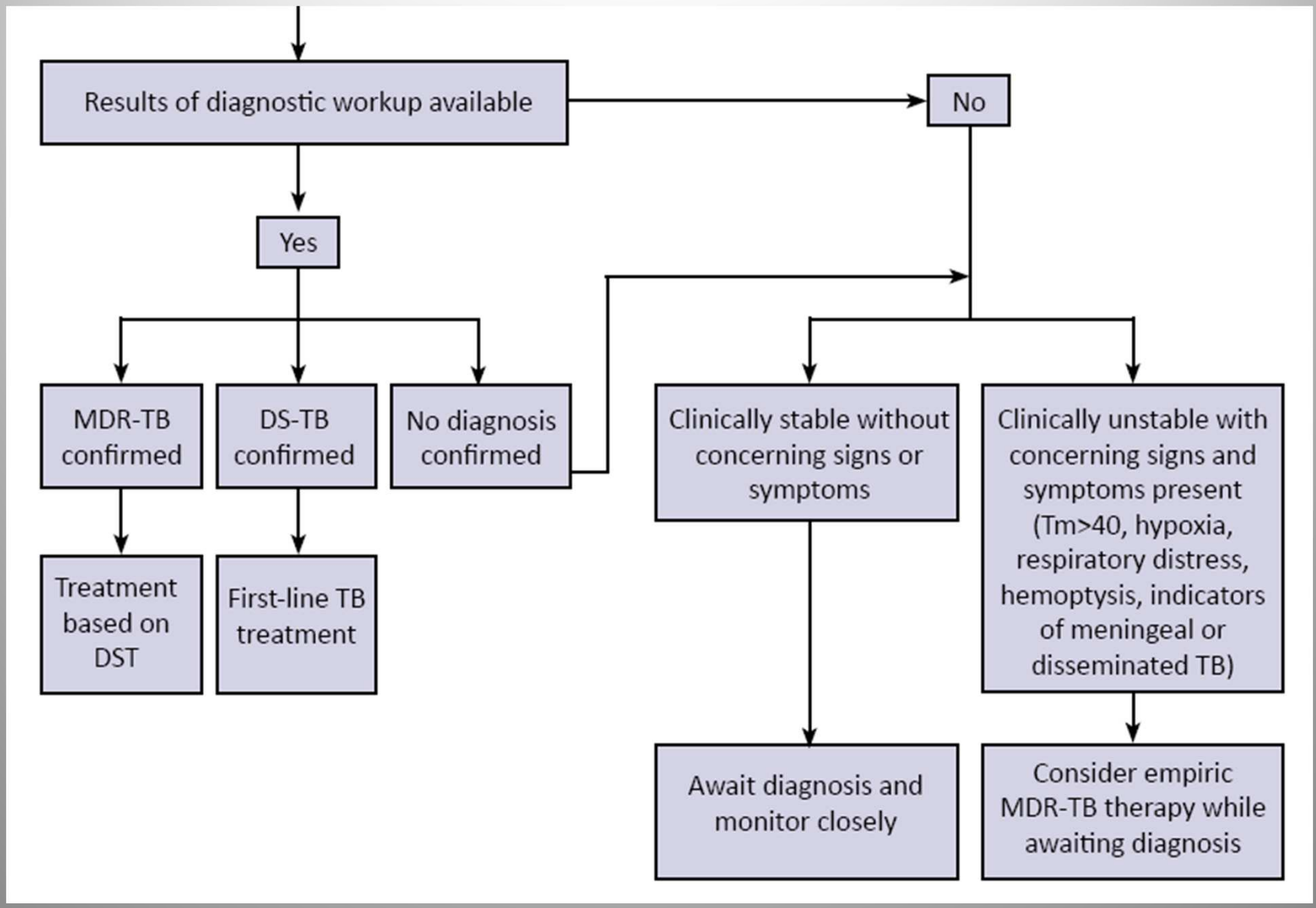
“Diagnosing” MDR-TB in Children

- Diagnosis can be done using relatively straight forward tools
- Confirming the disease bacteriologically may be challenging
- ***Need to treat in absence of confirmation in many cases***
- Contact history most important, not just for contacts with confirmed DR-TB but also those who died, failed, etc.

Excellent Treatment Outcomes with Timely Initiation of Therapy

- Meta-analysis of 318 patients show 80% success rate
- Follow same principles as adult DR-TB therapy
- Tolerate AEs well (except for hearing loss)
- May be able to reduce length of injectable therapy or length of regimen in cases with minimal disease
- Strategies for using and evaluating novel TB drugs in children
- Larger meta-analysis ongoing


Child MDR-TB Suspect Criteria
History of previous treatment within the past 6-12 months
Close contact with a person known to have MDR-TB, including household and school contacts
Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvemnt is frequently delayed)
Yes
No
Continue evaluation for susceptible TB
Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy


Results of diagnostic workup available
No
Yes
MDR-TB confirmed
DS-TB confirmed
No diagnosis confirmed
Clinically stable without concerning signs or symptoms
Clinically unstable with concerning signs and symptoms present (Tm>40, hypoxia, respiratory distress, hemoptysis, indicators of meningeal or disseminated TB)
Treatment based on DST
First-line TB treatment
Await diagnosis and monitor closely
Consider empiric MDR-TB therapy while awaiting diagnosis

Pediatric Providers: Action Items

- All children on TB treatment should be assessed for contacts with prior TB treatment, who died on TB treatment, who received injections, and known/confirmed DR-TB
- All children not gaining weight by the 3rd month of treatment should be assessed for DR-TB, including contact history, Xpert, and HIV

Drugs

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

MDR-TB Weight-Based Dosing Chart for Children

Target Dose	Group 1: Oral first-line anti-TB drugs				Group 2:	Group 3: Fluoroquinolones					Group 4: Oral bacteriostatis agents					Group 5:		Target Dose
	Ethambutol (15-25 mg/kg)		Pyrazinamide (30-40 mg/kg)		Injectable anti-TB drugs (injectable agents or parental agents)	Levofloxacin (15-20 mg/kg)		Moxifloxacin (7.5-10 mg/kg)		Ofloxacin (15-20 mg/kg)	Cycloserine/ Terizidone (15-20 mg/kg)		PAS (150-200 mg/kg)		Protionamide/ Ethionamide (15-20 mg/kg)	Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment	Isoniazid High Dose (15-20 mg/kg)	
Available Formulations	100 mg tablet	Suspend 400mg tab in 8 mL of water for a 50 mg/mL suspension	400 mg tablet	500 mg tablet		250 mg tablet	25 mg/mL suspension	400 mg tablet	20 mg/mL suspension	200 mg tablet	250 mg capsule	1 capsule in 10 mL water	Daily	Twice Daily	250 mg tablet		100 mg tablet	Available Formulations
Wt (kg)	Consult with a clinician experienced in pediatric MDR-TB prescribing for neonates (<28 days of age) and infants weighing <3 kg																	Wt (kg)
<3																		<3
3-3.9	1 tab	2 mL	.25 tab	.25 tab	To illustrate dose calculation, take the example of a child that weighs 6.9 kg. Both the low and high doses for the child's weight are calculated. For kanamycin: Low dose: 15 mg/kg x 6.9 kg = 103 mg High dose: 20 mg/kg x 6.9 kg = 138 mg A convenient dosing is then chosen between the two numbers. Select a dose between the two numbers and towards the higher number. In this case, choose: 125 mg per day, single dose. Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation.	.25 tab	2.5 mL	not recommended	1.5 mL	.5 tab	.25 cap	2.5 mL	500 mg	250 mg	.25 tab	Group 5 drugs are not recommended by the WHO for routine use in MDR-TB treatment because their contribution to the efficacy of MDR regimens is unclear. Their role in pediatric MDR-TB treatment is even less clear. Most of these drugs are expensive, and some require intravenous administration, and/or have severe side effects. However, they can be used in cases where adequate regimens are impossible to design with the medications from Groups 1-4. They should be used in consultation with an expert in the treatment of DR-TB.	.5 tab	3-3.9
4-4.9									2 mL				1000 mg	500 mg				4-4.9
5-5.9			.5 tab			.5 tab	5.0 mL		2.5 mL		.5 cap	5 mL	1500 mg	750 mg	.5 tab		1 tab	5-5.9
6-6.9		4 mL		.5 tab														6-6.9
7-7.9																		7-7.9
8-8.9	2 tabs					.75 tab	7.5 mL		5 mL	1 tab	.75 cap	7.5 mL	2000 mg	1000 mg	.75 tab		2 tabs	8-8.9
9-9.9			1 tab															9-9.9
10-10.9				1 tab														10-10.9
11-11.9																		11-11.9
12-12.9						1 tab	10 mL				1 cap	10 mL	2500 mg	1250 mg	1 tab			12-12.9
13-13.9	3 tabs	6 mL															3 tabs	13-13.9
14-14.9									7.5 mL	1.5 tabs								14-14.9
15-15.9			1.5 tabs					.5 tab					3000 mg	1500 mg				15-15.9
16-16.9				1 tab		1.5 tabs	15 mL				1.5 caps	15 mL			1.5 tabs			16-16.9
17-17.9									10 mL	2 tabs			4000 mg	2000 mg			4 tabs	17-17.9
18-18.9	4 tabs	8 mL																18-18.9
19-19.9			2 tabs															19-19.9
20-20.9				1.5 tabs									5000 mg	2500 mg				20-20.9
21-21.9						2 tabs	20 mL		12.5 mL	2.5 tabs	2 caps	20 mL			2 tabs		5 tabs	21-21.9
22-22.9													6000 mg	3000 mg				22-22.9
23-23.9	5 tabs	10 mL	2.5 tabs	2 tabs														23-23.9
24-24.9																		24-24.9
25-25.9																		25-25.9
26-26.9																		26-26.9
27-27.9																		27-27.9
28-28.9																		28-28.9
29-29.9																		29-29.9

For preventive regimens, consult with experts regarding optimal regimen construction.
The doses of isoniazid, ethambutol, and fluoroquinolones for preventive regimens are the same as in this dosing chart.

Sentinel Project
an pediatric drug-resistant tuberculosis

http://sentinel-project.org

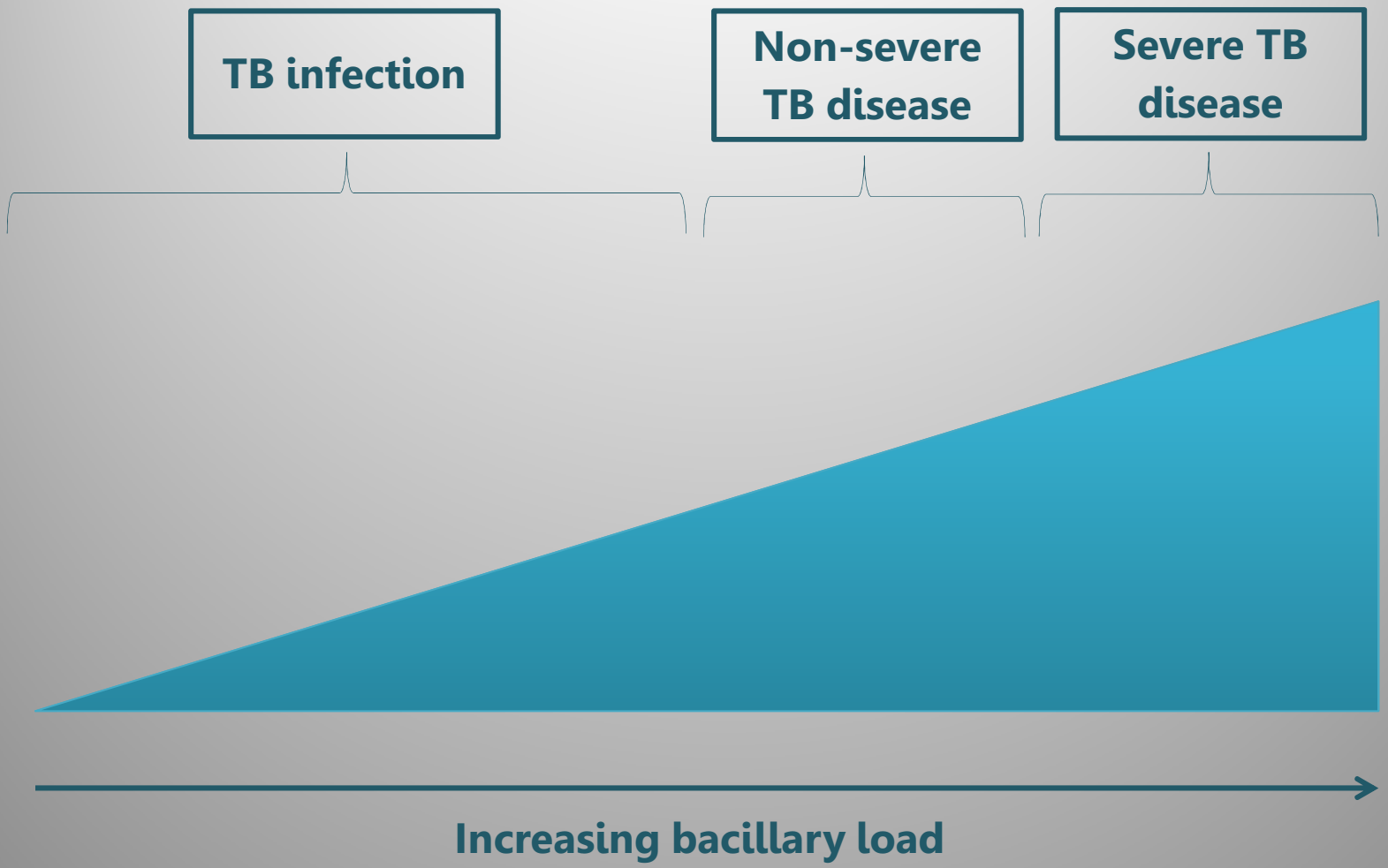
v1.1

Group 2	Steptomycin	Amikacin	Kanamycin	Capreomycin
Daily Dose	20-40 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily	15-20 mg/kg once daily
Maximum Daily Dose	1000 mg	1000 mg	1000 mg	1000 mg

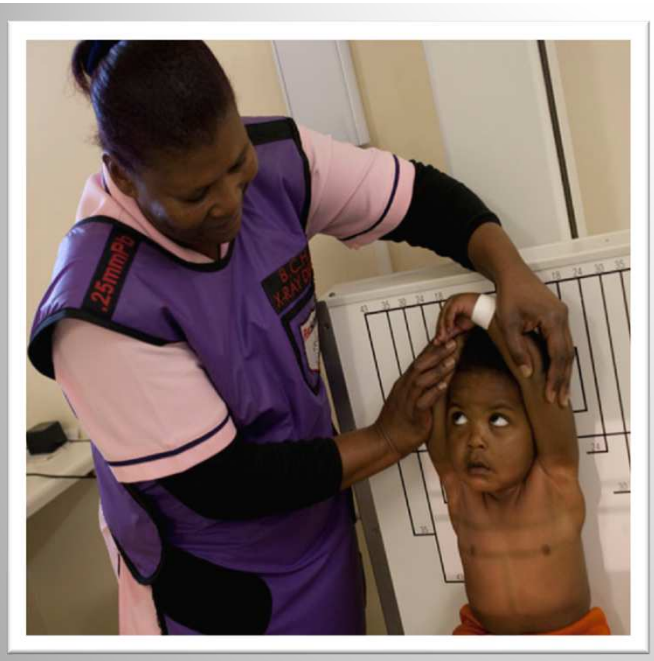
Group 5	Clofazimine (CFZ)	Amoxicillin-clavulanate (AMX-CLV)	Meropenem (MPN)	Linezolid (LZD)	Clarithromycin (CLR)
Daily Dose	2-3 mg/kg once daily; if the child is <25kg give 100mg every second day	80 mg/kg in two divided doses based on the amoxicillin component	20-40 mg/kg IV every 8 hours	10 mg/kg dose twice daily for children <10 years of age 300 mg daily for children >10 years of age (also give vitamin B6)	7.5 mg/kg twice daily
Maximum Daily Dose	200 mg	4000 mg amoxicillin and 500 mg clavulanate	6000 mg	600 mg	1000 mg

Do children need the same treatment as adults?

- Severe disease: yes
- May be able to use shorter duration of injectables in minimal/limited disease
- May be able to use shorter duration of therapy in minimal/limited disease
- Based on work from Cape Town (Simon Schaaf and colleagues)



Wiseman et al. Pediatr Infect Dis J 2021; 31(4): 347-352



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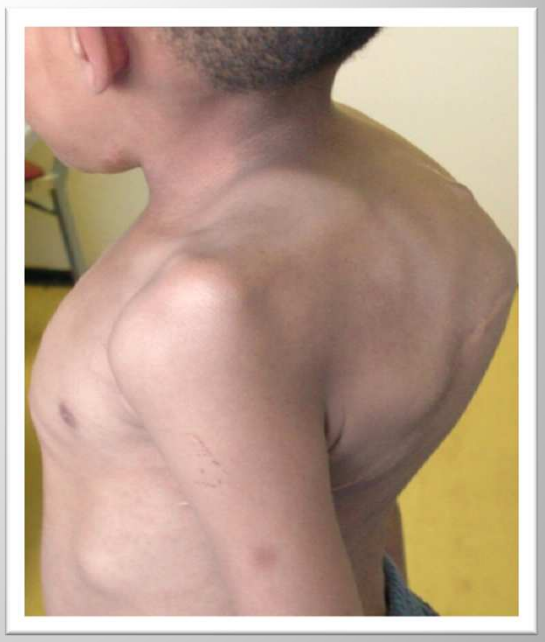

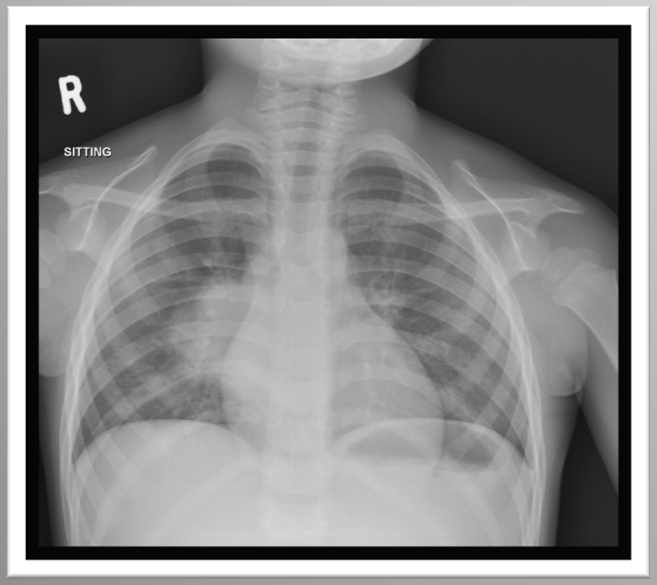

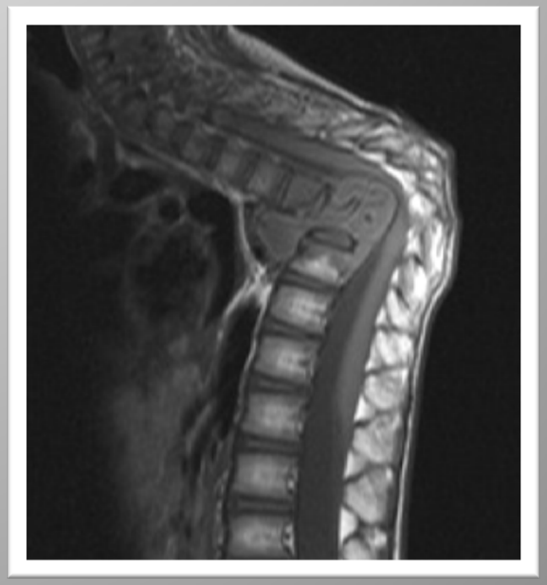

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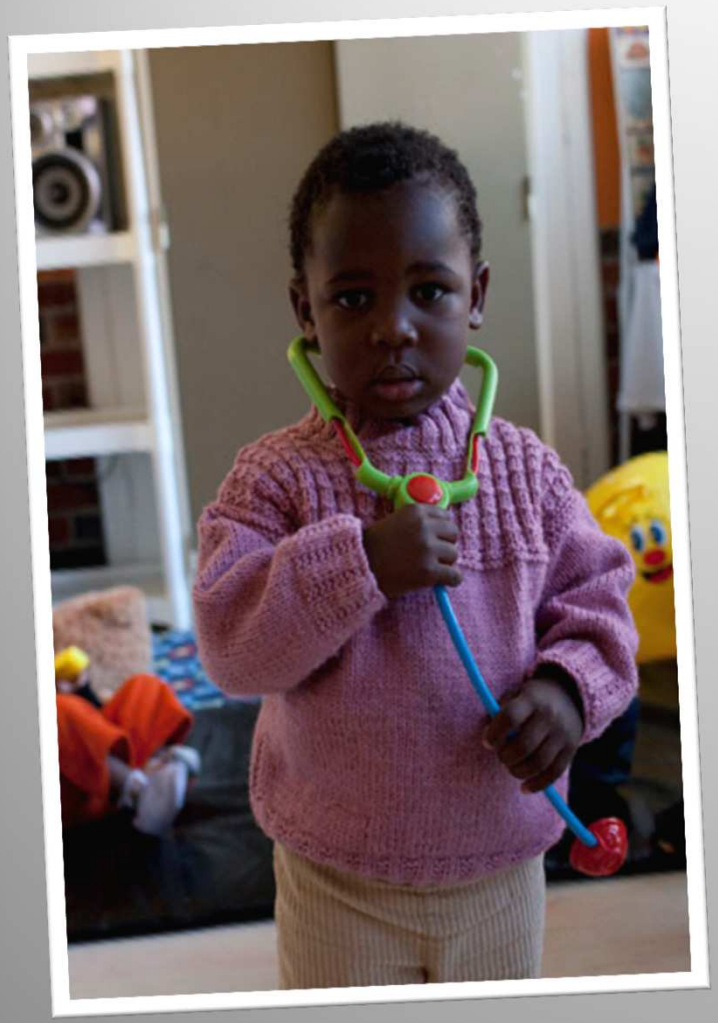
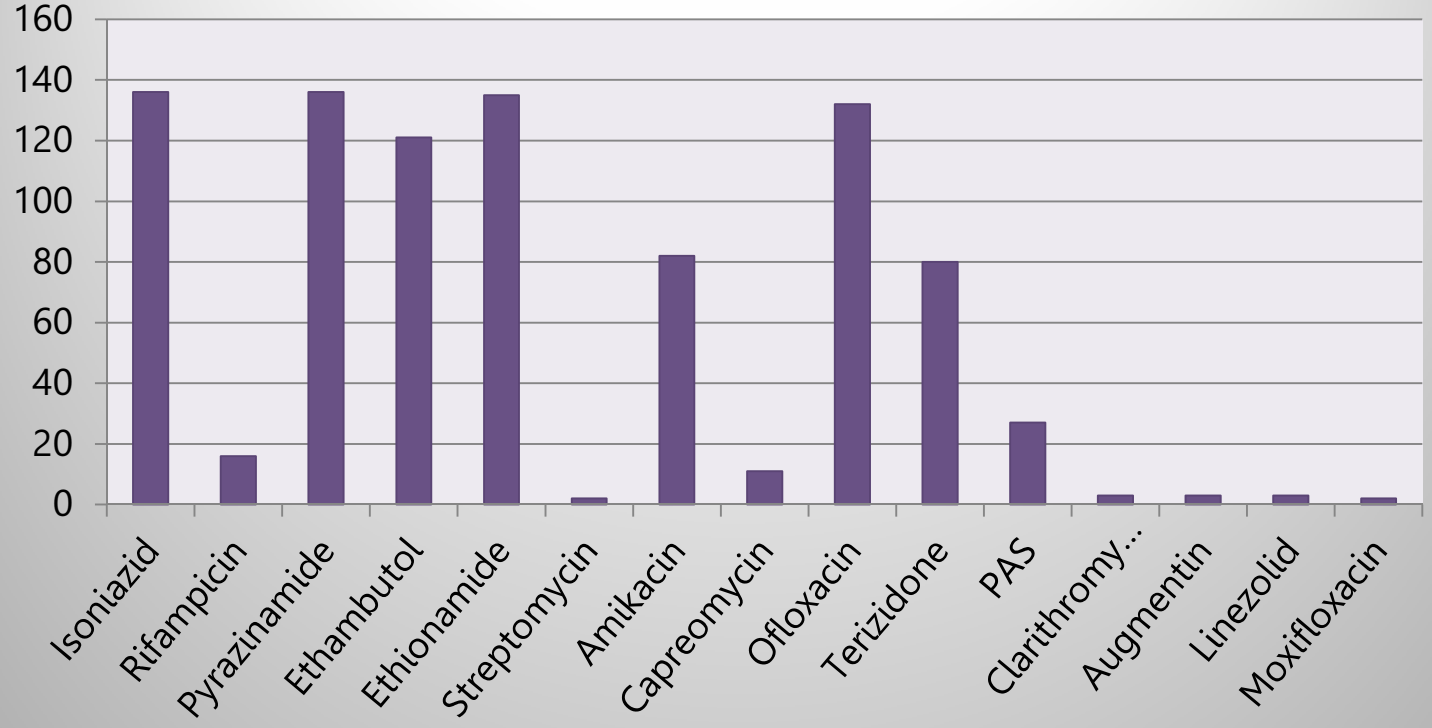
MDR-TB treatment Cape Town



- 149 children
- Median age: 36 months (IQR: 16-66)
- Male gender: 69 (46.3%)
- HIV-infected 32 of 146 tested (21.9%)

Thorax 2013 (in press)



Thorax 2013 (in press)

Treatment and Outcome

	Severe disease (n=45)	Non-severe disease (n=104)	OR (95% CI)	p-value
Hospital admission	42 (93.3)	61 (58.7)	9.87 (2.64-36.9)	<0.001
Injectable TB drug use	39/41 (95.1)	55/101 (54.5)	16.3 (3.27-81.3)	<0.001
Median duration of injectable drug	6 (4-6)	4 (3-5)		<0.001
Median total duration of therapy	18 (18-20)	12 (10-16)		<0.001
Mortality	3 (6.7)	0		0.008

Thorax 2013 (in press)

Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide

USAID
FROM THE AMERICAN PEOPLE

TB CARE II

Sentinel Project
on pediatric drug-resistant tuberculosis

First Edition: November, 2012

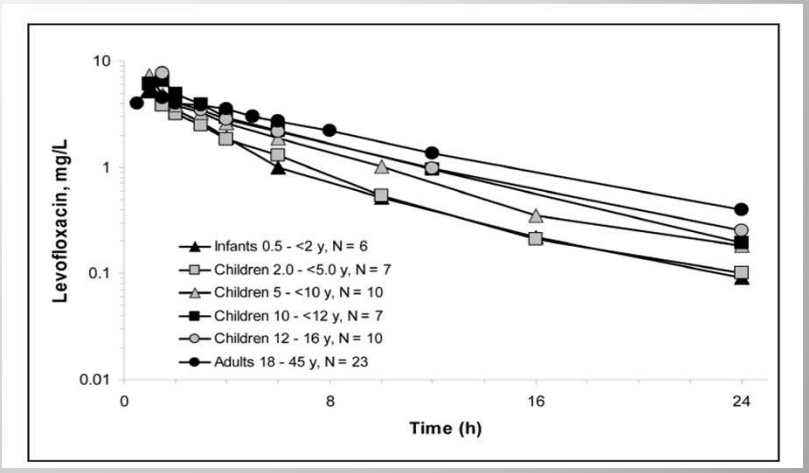
This handbook is made possible by the support of the American people through the United States Agency for International Development (USAID). The contents of this report are the sole responsibility of TB CARE II and The Sentinel Project on Pediatric Drug-Resistant Tuberculosis and do not necessarily reflect the views of USAID or the United States Government.

Treating with first-line and “see if they get better”?

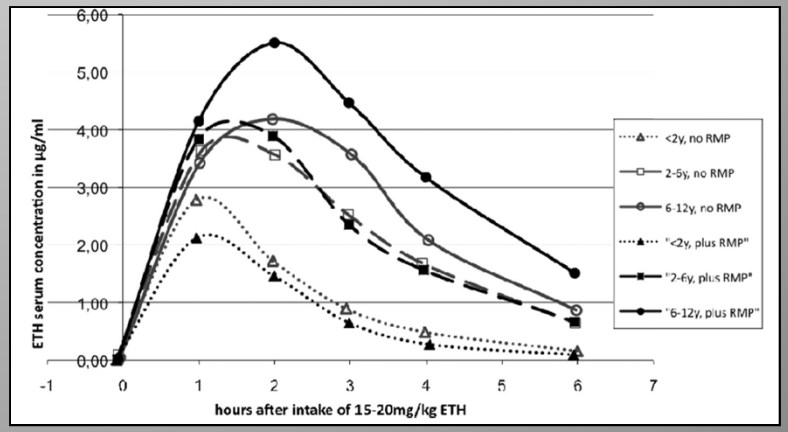
- If child has known risk for MDR-TB, this strategy is dangerous
- Risk of disease progression
- Risk of amplification
- Unclear rationale behind this approach

PK data in children

- Efficacy can be determined from adult studies
- Specific issues around
  - Toxicity and tolerability
  - Formulations
  - Pharmacokinetics



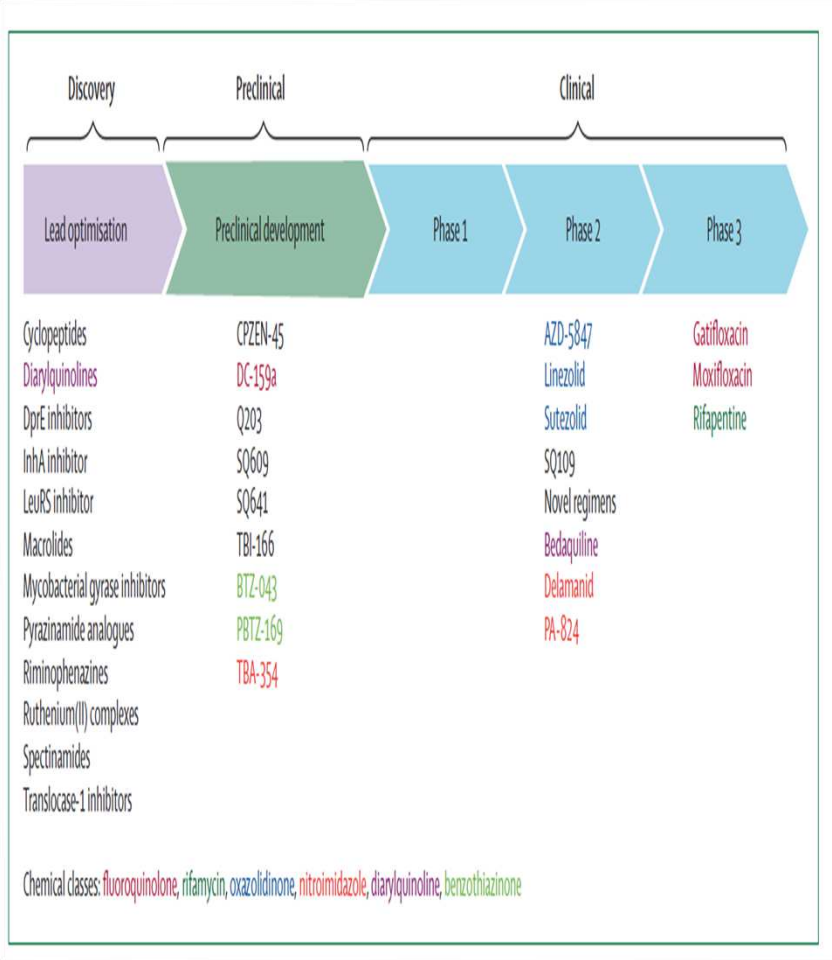
Chien et al. J Clin Pharm 2005; 45: 153-160



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

New Drugs

Zumla et al. Lancet Infect Dis 2014; 14: 327-40



- Children need to be included in clinical trials once safety and efficacy has been shown in adults
- Can use a definition of probable TB
- Adolescents should be included up front

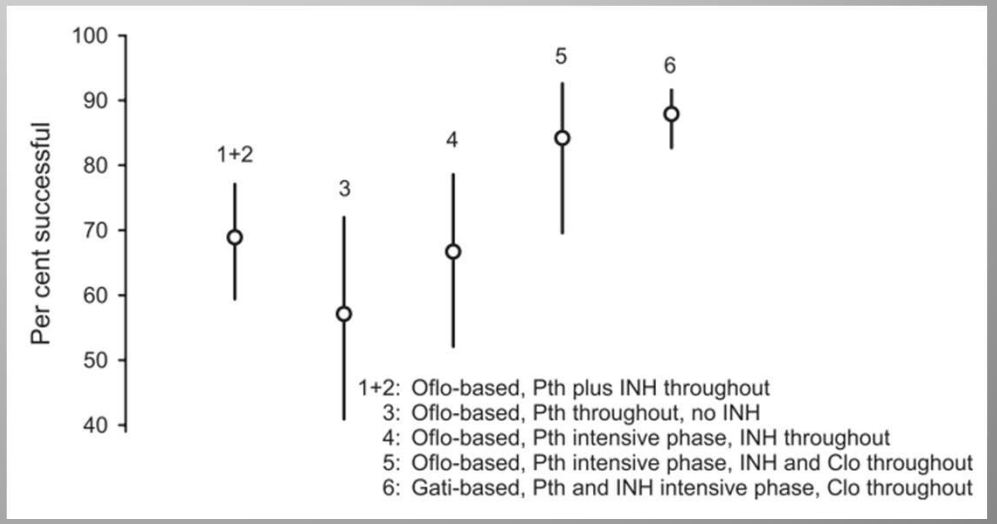
Delamanid Compassionate Use Program and Trials

- Available for children ages 13 and above
- Requires procedure for importation
- Request: medical@otsuka.de
- PK studies being done in children of all ages
- Clinical trial on long-term use enrolling children in South Africa and the Philippines
- Dispersible tablet (50mg scored)

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled	
				Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0

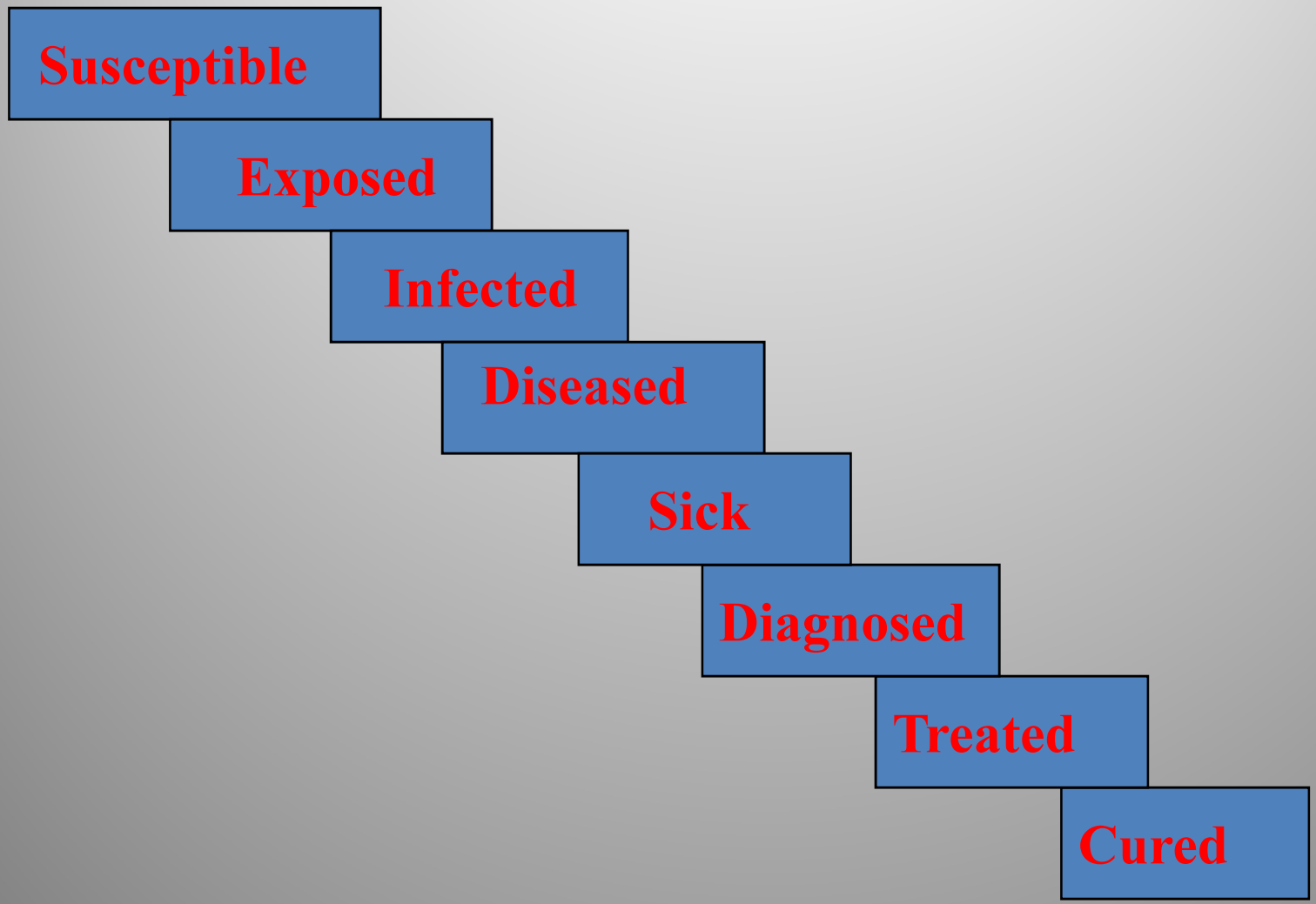


Van Deun et al. AJRCCM 2010; 182(5): 684-692

DR-TB and Adolescents

- Program data from India and South Africa suggests adolescents with MDR-TB may have worse outcomes: a significant proportion of this (apprx. 20%) is due to early death

Cascade in Childhood DR-TB



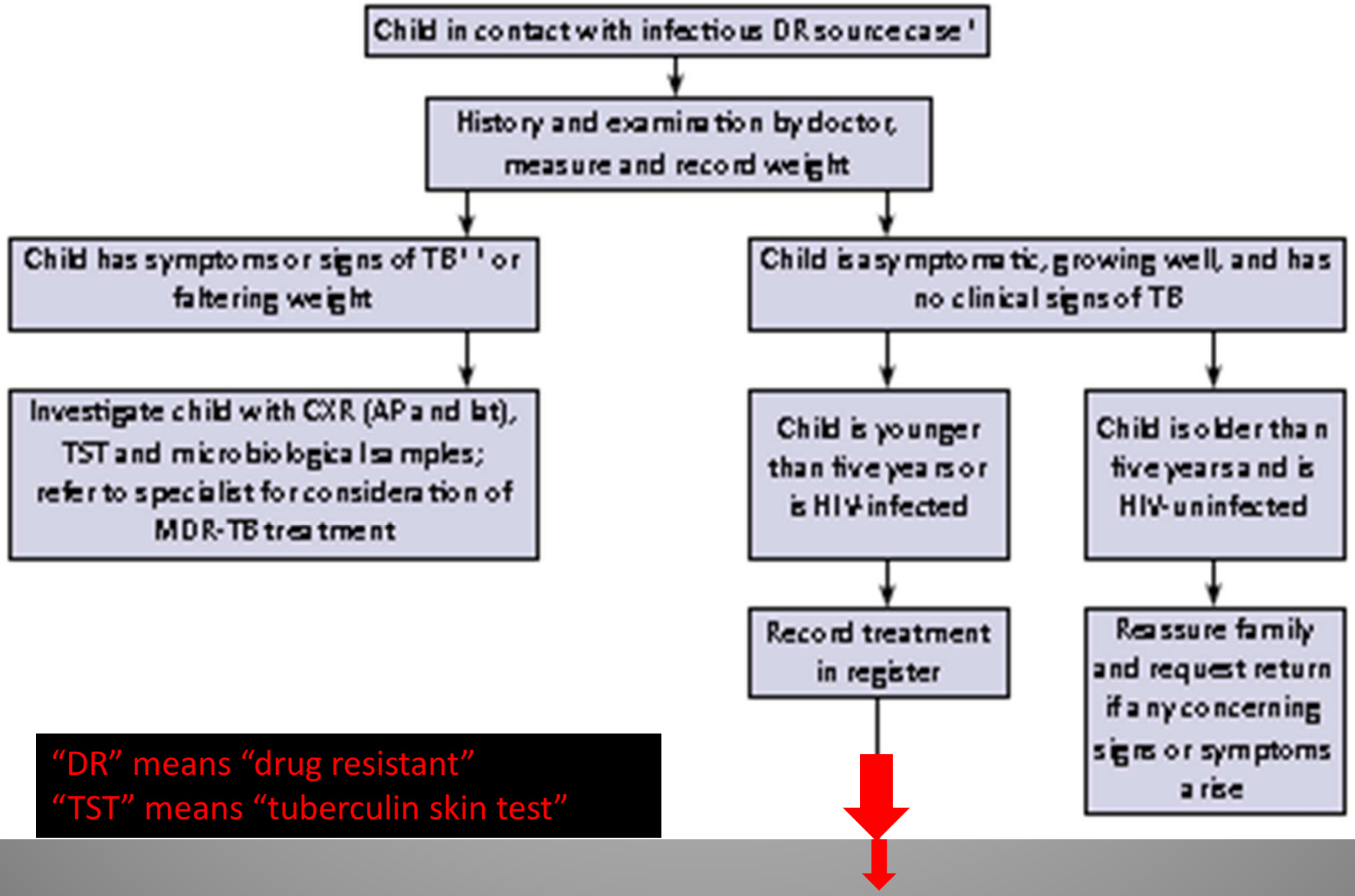
Meta-analysis by Shah et al., 2013 CID

- 25 total studies
- Evaluated a median of 111 household contacts of patients with DR-TB
- Pooled yield of 7.8% for active DR-TB and 47.2% for LTBI
- 50% concordance with exact same DST pattern of source case; higher rates of concordance seen when looking at strains
- Majority of cases detected within 1 year of source case identification

Post-Exposure Protocol: Need for Best Practices

- Need to define “household”
- Most contact tracing is done on a “one time only” basis, with minimal information obtained on household.
- Contact tracing tends to focus on children under the age of 5 and those with HIV who are currently in the household and present at the visit.
- Lack of careful follow-up for contacts in settings where TB programs are overwhelmed
- Role of TST unclear

Management Algorithm for Child Contacts of MDR-TB cases



"DR" means "drug resistant"
"TST" means "tuberculin skin test"

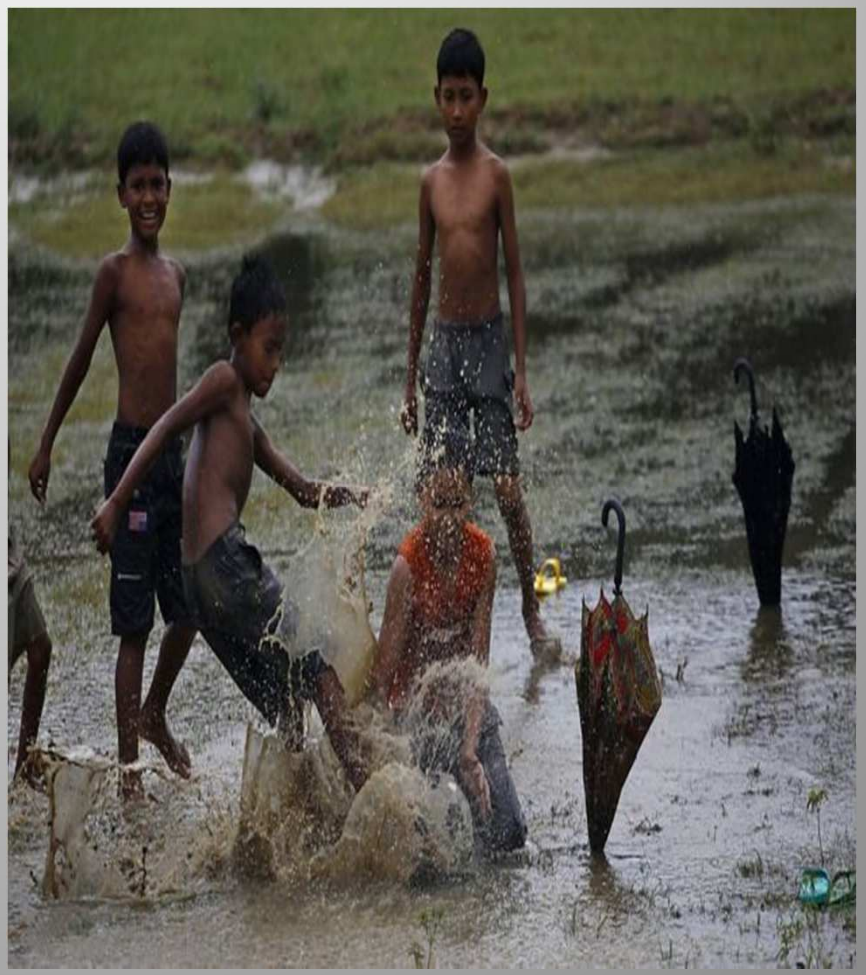
Management of Child Contacts of MDR TB Cases

Further Details on Treatment Algorithm

- MDR TB preventative regimen depends on the national program. Examples include:
  1. Fluoroquinolone and high dose INH
  2. Fluoroquinolone, high dose INH and EMB (Seddon et al., 2012, Lancet ID)
  3. Fluoroquinolone and EMB
  4. High dose INH alone
  5. Fluoroquinolone alone

Opportunities for Integrated Care

- Most children do not present to TB clinics but rather to primary health clinics or for vaccinations or with their mothers
- Many children with MDR-TB are actually first seen by adult MDRTB providers
- Projects should be planned with colleagues in these areas
- Best practices for family-centered approach, including school, parental work situation, etc.



Advocacy and Psychosocial Support

- Children historically overlooked in global TB approaches
- Available funding has been increasing
- Also need increased psychosocial support, school, etc.

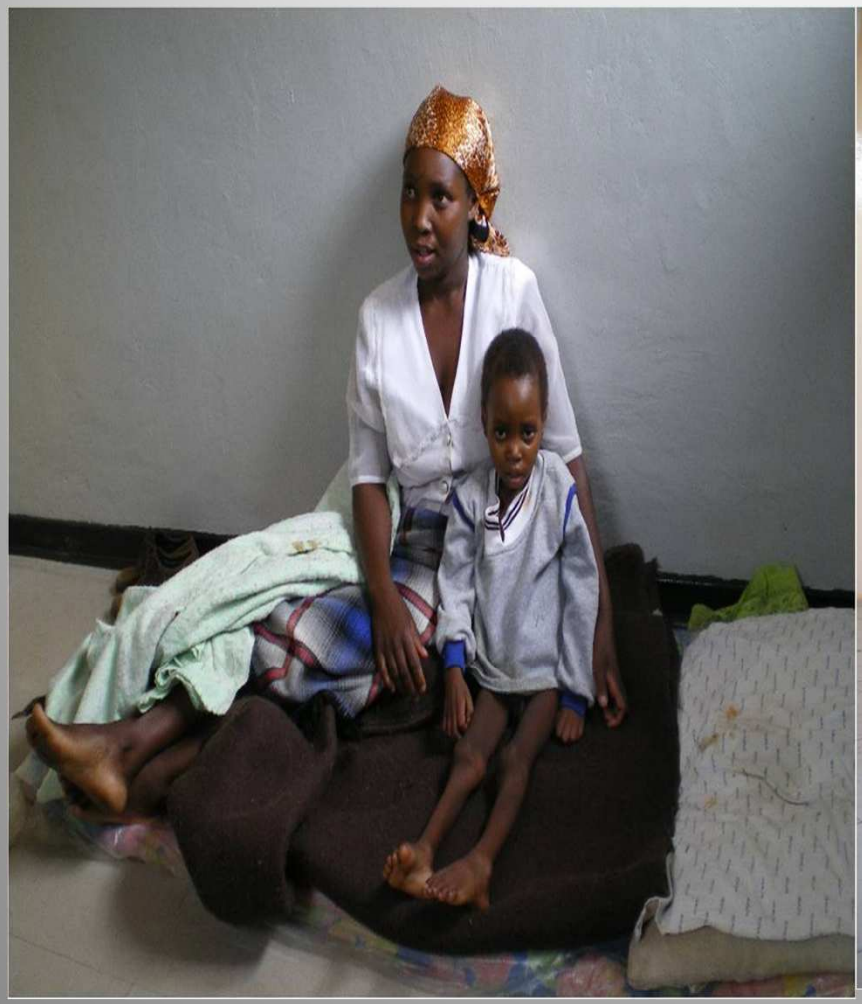
Pediatric DR-TB Recommendations

- Move away from a fear-based practice where we think we are protecting children by not offering optimal care
- Utilize a “family centered approach”, including active contact tracing and psychosocial family support
- Use of Xpert MTB/RIF® as primary screening tool in children instead of smear microscopy (still need culture)
- ***Allow for treatment of high-risk children, even in the absence of bacteriologic confirmation***
- Treatment advisory committee(s) for possible pediatric cases (international support available)

Pediatric DR-TB Recommendations

- Develop child-friendly formulations (i.e. scoring, granules, compounding)
- Adolescents need extra support
- Provide integrated care, coordinated with child health efforts
- Focus on capacity building with all levels of providers
- Advocate, advocate , advocate!

Do NOT be afraid of treating



Be afraid of NOT treating

Courtesy of Tara Loyd

Thank you!

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www.sentinel-project.org