Treatment of DR-TB in children and preventive therapy for children exposed to DR-TB

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Diagnosis : M/XDR-TB in children

- DR TB is a microbiological diagnosis
- In children often difficult (paucibacillary TB):
  - Confirmed if DR *M. tuberculosis* strain is isolated from a child
  - Probable DR-TB if known contact with an adult DR PTB case (>78-90% concordance in several studies)
  - Suspect DR-TB if:
    - a child gets worse on Rx, failing adherent Rx
    - an adult source case with unknown DST result is a treatment failure, a retreatment case or died of TB during adherent Rx

Not all resistance is MDR/XDR

Focus today is on MDR-TB and more (e.g. XDR-TB)

However, consider the following:

- INH monoresistance/polyresistance:
  RIF and PZA most likely still susceptible, but need at least one more bactericidal drug if diagnosed early.
  Ethionamide resistance if *inhA* promoter region mutation.
  Consider drug-penetration in CSF if TBM/miliary TB
- RIF monoresistance:
  Becoming more prevalent; majority of these not resistant to other drugs.
  Beware interpretation of Xpert MTB/RIF as RMR!!!
  Keep INH, add FQN, EMB and other depending on extent of disease – many will treat as MDR-TB

Principles of childhood MDR-TB Rx

- Confirm the MDR-TB in the child if at all possible
- If MDR-TB is confirmed, also do DST for 2nd-line drugs
- Management – at a specialized MDR-TB clinic
- Use the adult index case's isolate DST pattern if no isolate from child is available. (Standardised MDR-TB treatment if empirical treatment for treatment failure)
- DOT with daily treatment only in DR-TB
- Counsel patients/parents at every visit for support, about adverse events, and importance of adherence
- Follow-up is essential; clinical, radiological and cultures

Principles of childhood MDR-TB Rx

- Give 4 or more drugs to which the patient's isolate is susceptible and/or naïve (depends on extent of disease and availability of drugs)
- Be aware of the different drug groups and cross-resistance (and co-resistance) amongst these drugs
- 2nd-line drugs are generally more toxic than 1st-line drugs
- Adverse effects more difficult to assess in children, but screen regularly
- Not complete if I don't add: NEVER add one drug to a failing regimen

Tuberculosis 92 (2012) 9–17

Contents lists available at SciVerse ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

REVIEW

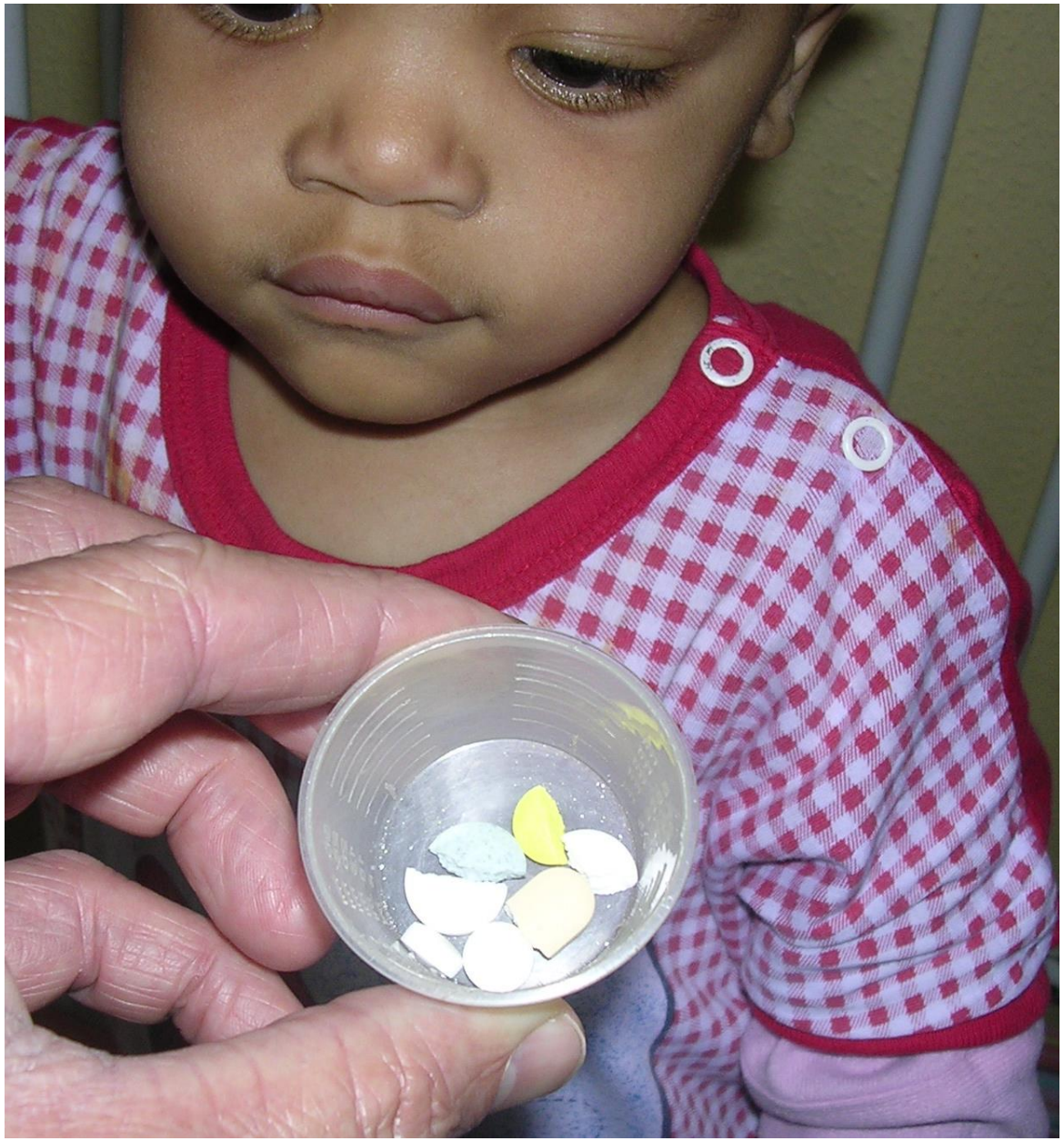
Paediatric use of second-line anti-tuberculosis agents: A review

James A. Seddon [a,b,*], Anneke C. Hesseling [a], Ben J. Marais [c], Helen McIlleron [d], Charles A. Peloquin [e], Peter R. Donald [f], H. Simon Schaaf [a,f]

Tuberculosis. 2012; 92: 9-17

Building a regimen: Drugs in M/XDR-TB Rx

- Group 1: 1st-line drugs – susceptibility to EMB, PZA?
- Group 2: A 2-nd line injectable drug, kanamycin, amikacin or capreomycin: high rates of cross-resistance
- Group 3: A fluoroquinolone – OFX, LFX or MFX. Best of 2nd-line drugs available
- Group 4: Other oral 2nd-line drugs in combination:
  - Ethionamide/prothionamide (*inhA* mutation?)
  - Terizidone/cycloserine
  - PAS
- Group 5:
  - high-dose INH – as added drug in low-level INH resistance (or *inhA* promoter region mutation)
  - reserve drugs for XDR-TB – especially linezolid, clofazimine



Absence of child-friendly drugs and dosages

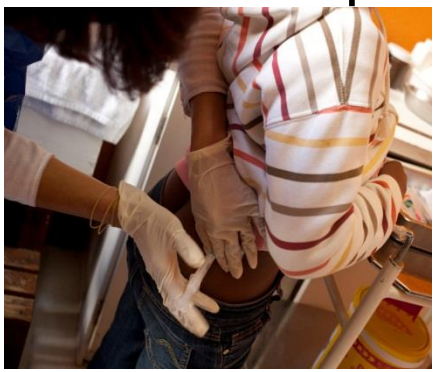
11-month-old with morning tablets MDR-TB Rx

Difficult to accurately break tablets to correct dosage.

Also receives an injectable

Dosages for 2nd-line drugs in children

- Only recently PK studies done in children – ongoing, therefore watch this space!
- 2nd-line Injectable drugs: IM or IV – high concentrations achieved with amikacin at 20mg/kg in children compared to adults at 15mg/kg:
  Suggested dosage 15-20mg/kg/day



	C_{max} (µg/ml)			T_{max} (h)			AUC_{0-8} (µg·h/ml)		
	N	Median (IQR)	p-value	N	Mean (SD)	p-value	N	Median (IQR)	p-value
Age group									
0-2 years	6	43.65 (42.20 - 49.20)		6	1.00 (0.00)		6	103.85 (96.80 - 119.10)	
2-5 years	7	49.10 (40.70 - 59.20)		7	1.14 (0.38)		7	124.15 (97.75 - 162.05)	
6-15 years	15	49.60 (40.30 - 56.40)	0.845	15	1.13 (0.35)	0.593	14	159.25 (124.20 - 179.48	0.016

Drugs for treatment of MDR-TB

Group 3: Fluoroquinolones – PK data still needed in all

Drug	Daily dosage		Unit size in mg
	mg/kg	Maximum	
Fluoroquinolones: ↔			
- Ofloxacin	15-20	800mg	200/400
- Levofloxacin*	15-20	1000mg	250/500
- Moxifloxacin	7.5-10	400mg	400
- Ciprofloxacin (Ciprofloxacin NOT recommended)	30-40	2.0g	250/5ml 250/500

2nd-line anti-TB drugs

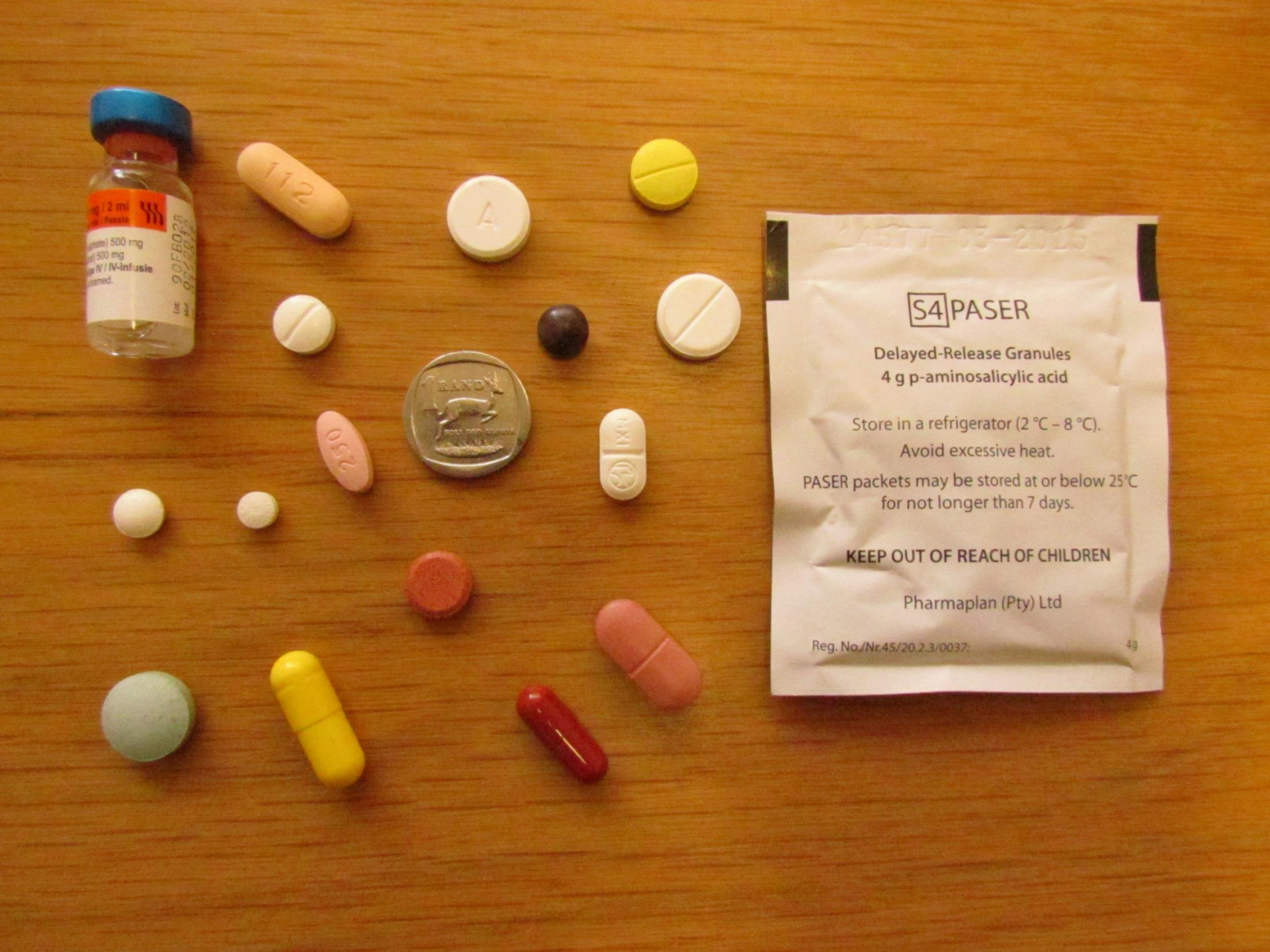
Group 4: Second-line oral bacteriostatic drugs

Drug	Daily dosage		Unit size
	mg/kg	Maximum	in mg
Ethionamide/ Prothionamide	15-20	1.0g	250
Cycloserine/ Terizidone	15-20	750 mg	250
PAS (para-aminosalisylic acid)	150-200	8-12.0g	4 g sachets

2nd-line or reserve anti-TB drugs

Group 5: Drugs of unclear role in DR-TB treatment

Drug	Daily dosage	
	mg/kg	Maximum
Linezolid	10 mg/kg/dose 12 hrly	300-600/day
Clarithromycin	7.5 mg/kg/dose 12 hrly	1000/day
Amoxicillin/ Clavulanic acid	25 (amox) mg/kg/dose 8 hrly	
Clofazimine	3-5mg/kg daily	100/day
Thioacetazone	Not available – not in HIV-infected	
Imipenem/ cilastatin	20-40mg/kg IV every 8 hours	6000


S4 PASER
Delayed-Release Granules
4 g p-aminosalicylic acid
Store in a refrigerator (2 °C – 8 °C).
Avoid excessive heat.
PASER packets may be stored at or below 25°C
for not longer than 7 days.
KEEP OUT OF REACH OF CHILDREN
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MDR-TB Weight-Based Dosing Chart for Children

	Group 1: Oral first-line anti-TB drugs				Group 2:	Group 3: Fluoroquinolones					Group 4: Oral bacteriostatis agents					Group 5:		
	Ethambutol		Pyrazinamide		Injectable anti-TB drugs (injectable agents or parental agents)	Levofloxacin		Moxifloxacin		Ofloxacin	Cycloserine/Terizidone		PAS		Protionamide/ Ethionamide	Anti-TB drugs with unclear efficacy or unclear role in MDR-TB treatment	Isoniazid High Dose	
Target Dose	(15-25 mg/kg)		(30-40 mg/kg)			(15-20 mg/kg)		(7.5-10 mg/kg)		(15-20 mg/kg)	(15-20 mg/kg)		(150-200 mg/kg)		(15-20 mg/kg)		(15-20 mg/kg)	Target Dose
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: 30 mg/kg x 6.9 kg = 207 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: 200 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 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																		6-6.9
7-7.9																		7-7.9
8-8.9	2 tabs	4 mL							5 mL	1 tab								8-8.9
9-9.9			1 tab			.75 tab	7.5 mL				.75 cap	7.5 mL	2000 mg	1000 mg	.75 tab		2 tabs	9-9.9
10-10.9																		10-10.9
11-11.9																		11-11.9
12-12.9				1 tab		1 tab	10 mL				1 cap	1 cap	2500 mg	1250 mg	1 tab		3 tabs	12-12.9
13-13.9	3 tabs	6 mL																13-13.9
14-14.9																		14-14.9
15-15.9			1.5 tabs						7.5 mL	1.5 tabs								15-15.9
16-16.9	4 tabs	8 mL											3000 mg	1500 mg				16-16.9
17-17.9																		17-17.9
18-18.9																		18-18.9
19-19.9				1.5 tabs		1.5 tabs	15 mL	.5 tab			1.5 caps	15 caps			1.5 tabs			19-19.9
20-20.9									10 mL	2 tabs								20-20.9
21-21.9			2 tabs										4000 mg	2000 mg			4 tabs	21-21.9
22-22.9																		22-22.9
23-23.9																		23-23.9
24-24.9																		24-24.9
25-25.9																		25-25.9
26-26.9				2 tabs		2 tabs	20 mL				2 caps	20 mL	5000 mg	5000 mg	2 tabs			26-26.9
27-27.9	5 tabs	10 mL	2.5 tabs						12.5 mL	2.5 tabs							5 tabs	27-27.9
28-28.9													6000 mg	6000 mg				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 on pediatric drug-resistant tuberculosis

http://sentinel-project.org

Chart developed by Chelsie GawneMark

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/kw 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

What about the new drugs?

Bedaquiline (TMC207): Janssen Pharmaceutical

- A diarylquinoline – unique mechanism of action – inhibits ATP synthesis - results in bactericidal activity
- Provisionally approved by FDA for use in MDR-TB – in addition to current MDR-TB regimen – in adults >18 yrs
- A strange drug with $t_{1/2}$ of >5 months
- No dosage established for children yet. Now phase 3 studies and planning child PK studies

Delamanid (OPC-67683): (Otsuka Pharmaceutical)

- A new Nitro-dihydroimidazo-oxazole derivative
- No cross-resistance with any current used anti-TB drugs
- Phase 2 b trials done
- No dosages or PK for children yet, but study ongoing

Adherence (and support)

- Treatment in hospital and in community needs to be observed – children are ingenuous when it comes to making plans how NOT to take their treatment!
- Ask children/caregivers to identify the tablets/capsules and how many of each are taken – can check on dosage
- Phone the clinics who dispense the treatment – do they collect the drugs regularly or is there DOT?
- Pill counts and other methods may be used
- Most important: identify a reliable caregiver to provide the drugs and observe the child taking it
- Monitor adverse effects and address these, as could lead to defaulting treatment

Adherence (and support)

- Teenagers – notoriously difficult group to adhere to treatment: Communication (clinic staff) and peer pressure (stigma/mocking) – both common problems
- Nutritional support and financial support often required by families – especially if caregivers/parents also ill

Additional treatment

- Pyridoxine (Vit B6)
  Levels of B6 remain low in HIV-infected children despite multivitamin supplementation
  With terizidone and high-dose INH supplementation with pyridoxine recommended
  Cilliers K et al. Pyridoxal-5-phosphate plasma concentrations in children receiving tuberculosis chemotherapy including isoniazid. Acta Paediatr. 2010;99(5):705-710

- Cotrimoxazole
  Outcome of TB/HIV co-infected adults improved if given CTX preventive therapy. Role in TB treatment?
- Start ART early iv HIV-infected – within 2 weeks of starting anti-TB treatment
- Nutritional rehabilitation

Drug-drug interactions

- Data on pharmacokinetic interactions between ART and the 2nd-line anti-TB drugs are incomplete, therefore unanticipated interactions may occur.
- The potential for clinically important changes in ART or anti-TB drug concentrations is less for 2nd-line anti-TB regimens compared to RIF-containing 1st-line regimens.
- ART and 2nd-line anti-TB drugs have many adverse effects in common.

Seddon et al. Tuberculosis 2012;92:7-12

Duration of treatment

- Optimal duration of treatment in children is not known
- Cavitary or extensive pulmonary TB: as for adults 18 months after first negative culture (XDR-TB possibly longer?)
- Primary, non-cavitary MDR-TB - Often culture-negative (paucibacillary): 12-15 months treatment probably sufficient in most cases (contacts of MDR-TB cases)
- Intensive phase including 2nd-line injectable drug, continuation phase mainly stop injectable drug
- In carefully selected cases (paucibacillary, no 2nd-line resistance) may elect not to use injectable drug

Table 2 Treatment and outcome in children treated for MDR-TB (n=149 unless otherwise stated)

Feature/outcome	Variable	Number (%) unless otherwise indicated
Admitted to hospital		103 (69.1)
Median duration of admission in months (n=103; IQR)		5 (3–7)
Treated with injectable drugs (n=142)*		94 (66.2)
Median duration of injectable drug use (n=94; IQR)		4 (4–6)
Median duration of total treatment (n=137; IQR)†		13 (11–18)
Median weight gain (IQR; kg)	3 months (n=115)	0.6 (0.2–1.5)
	6 months (n=102)	1.4 (0.7–2.2)
	12 months (n=84)	2.9 (1.0–4.0)
Median number of months to culture conversion (n=40)‡		1 (0.5–2)
Outcome	Cure	36 (24.2)
	Probable cure§	101 (67.8)
	Transferred out	1 (0.7)
	Lost to follow up	8 (5.4)
	Died¶	3 (2.0)

Thorax Online First, published on September 24, 2013 as 10.1136/thoraxjnl-2013-203900
Tubercu

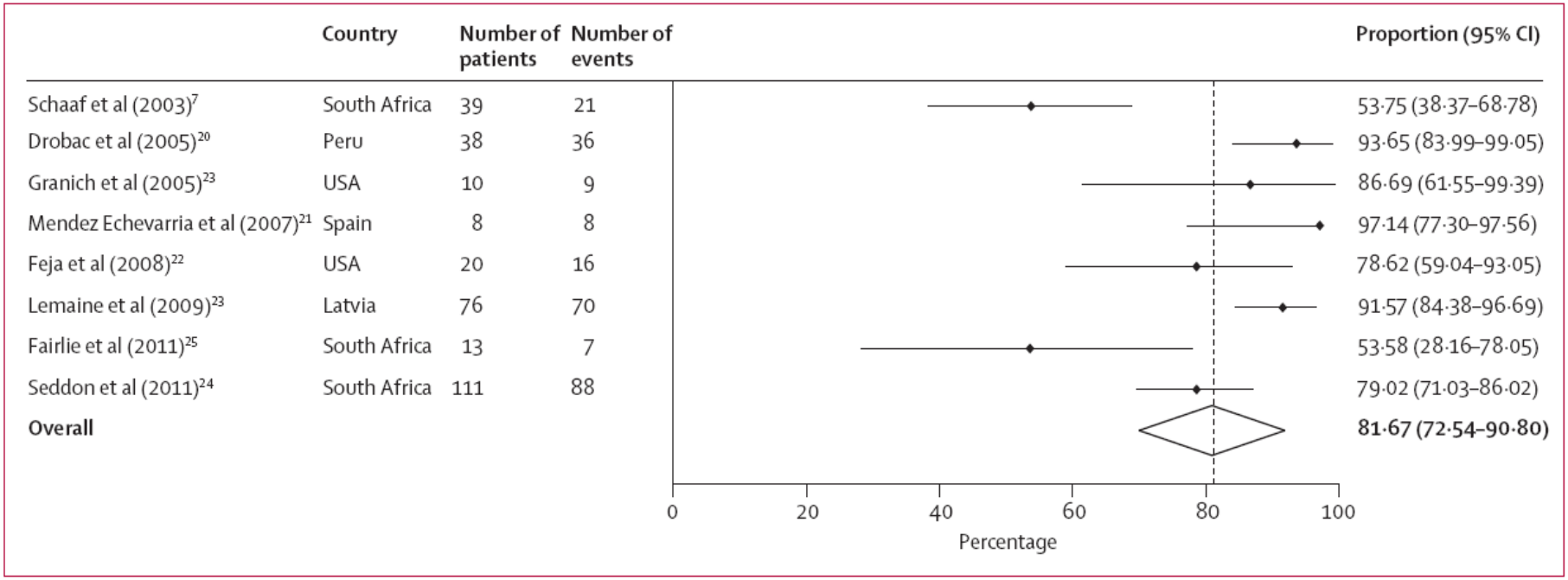
ORIGINAL ARTICLE

High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study

James A Seddon,[1,2,3] Anneke C Hesseling,[1] Peter Godfrey-Faussett,[2] H Simon Schaaf[1,4]

Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

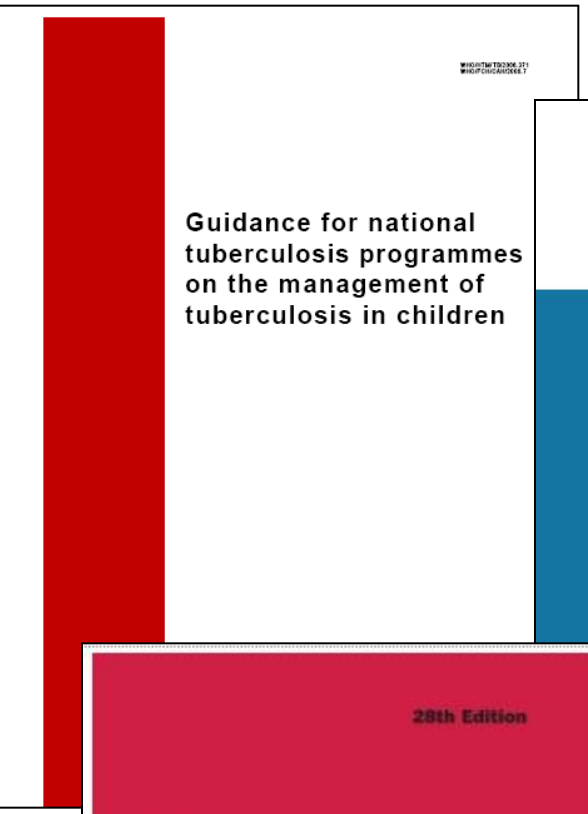
Dena Ettehad, H Simon Schaaf, James A Seddon, Graham S Cooke, Nathan Ford**

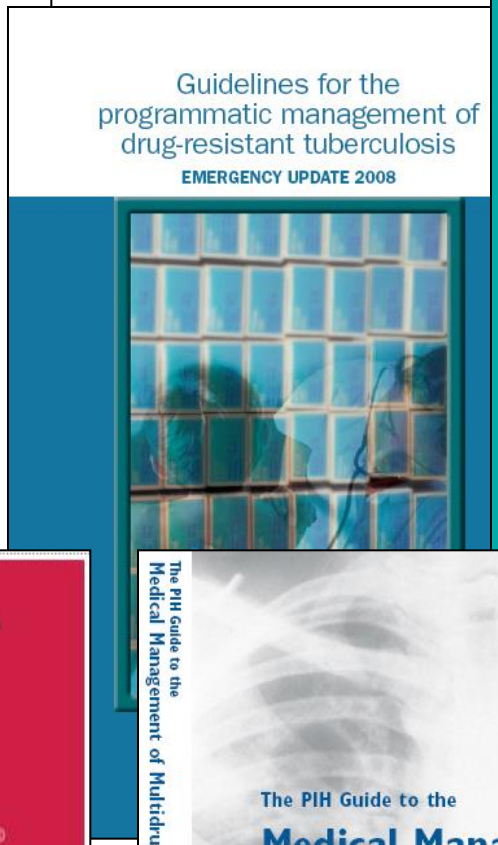


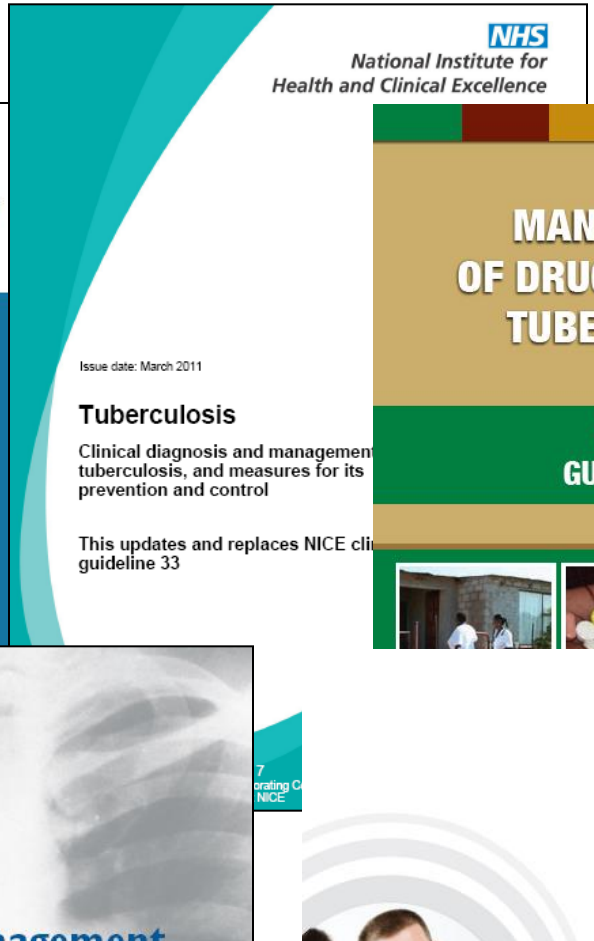
Lancet Infect Dis. 2012

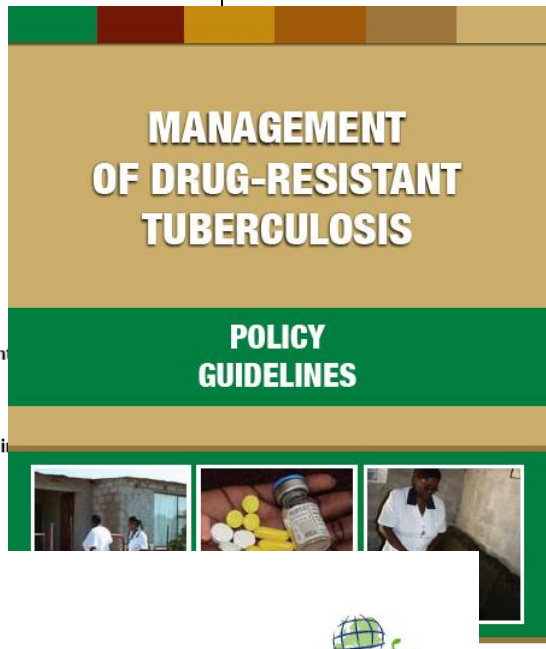
Management of DR-TB contacts

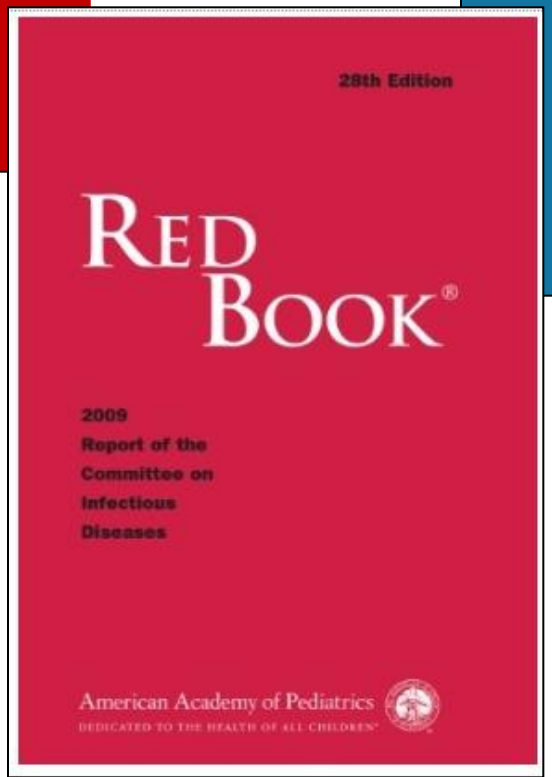
- Guidelines vary in opinion
  - NICE, WHO, RSA DOH – follow up and isoniazid
  - CDC, ATS, IDSA, AAP – regimen containing two drugs to which index case is susceptible
  - ECDC – Follow-up with or without preventive Rx
- Few studies have examined the treatment of contacts of cases with MDR-TB (or any other DR-TB) – no RCTs
- Early onset of ART in HIV-infected infants/children is important for both prevention of TB and improved outcome if they develop TB


Guidance for national tuberculosis programmes on the management of tuberculosis in children


Guidelines for the programmatic management of drug-resistant tuberculosis
EMERGENCY UPDATE 2008


NHS
National Institute for Health and Clinical Excellence
Issue date: March 2011
Tuberculosis
Clinical diagnosis and management
tuberculosis, and measures for its
prevention and control
This updates and replaces NICE cli
guideline 33


MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS
POLICY GUIDELINES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Report of the
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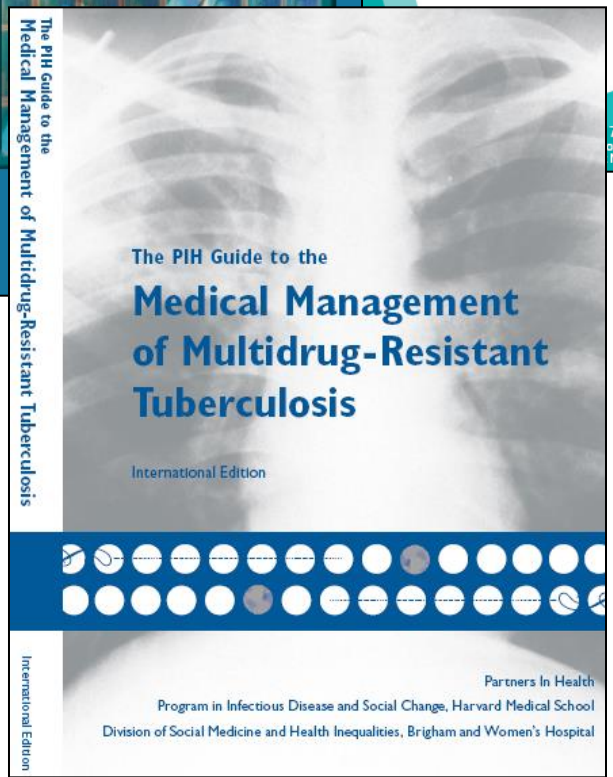
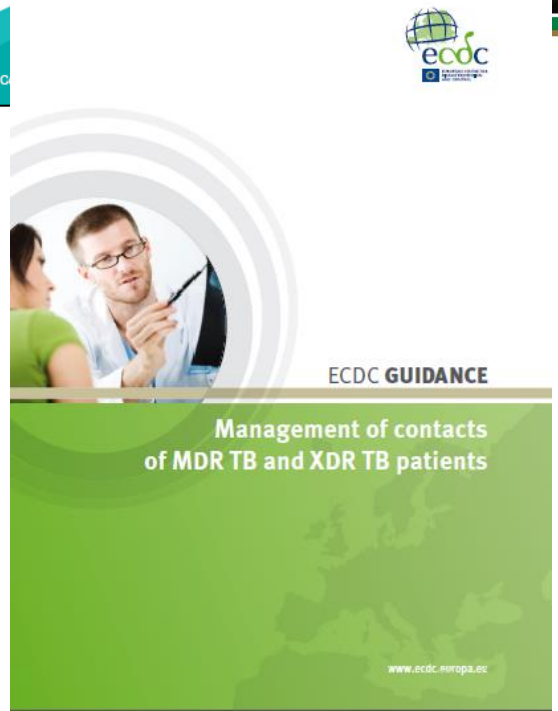
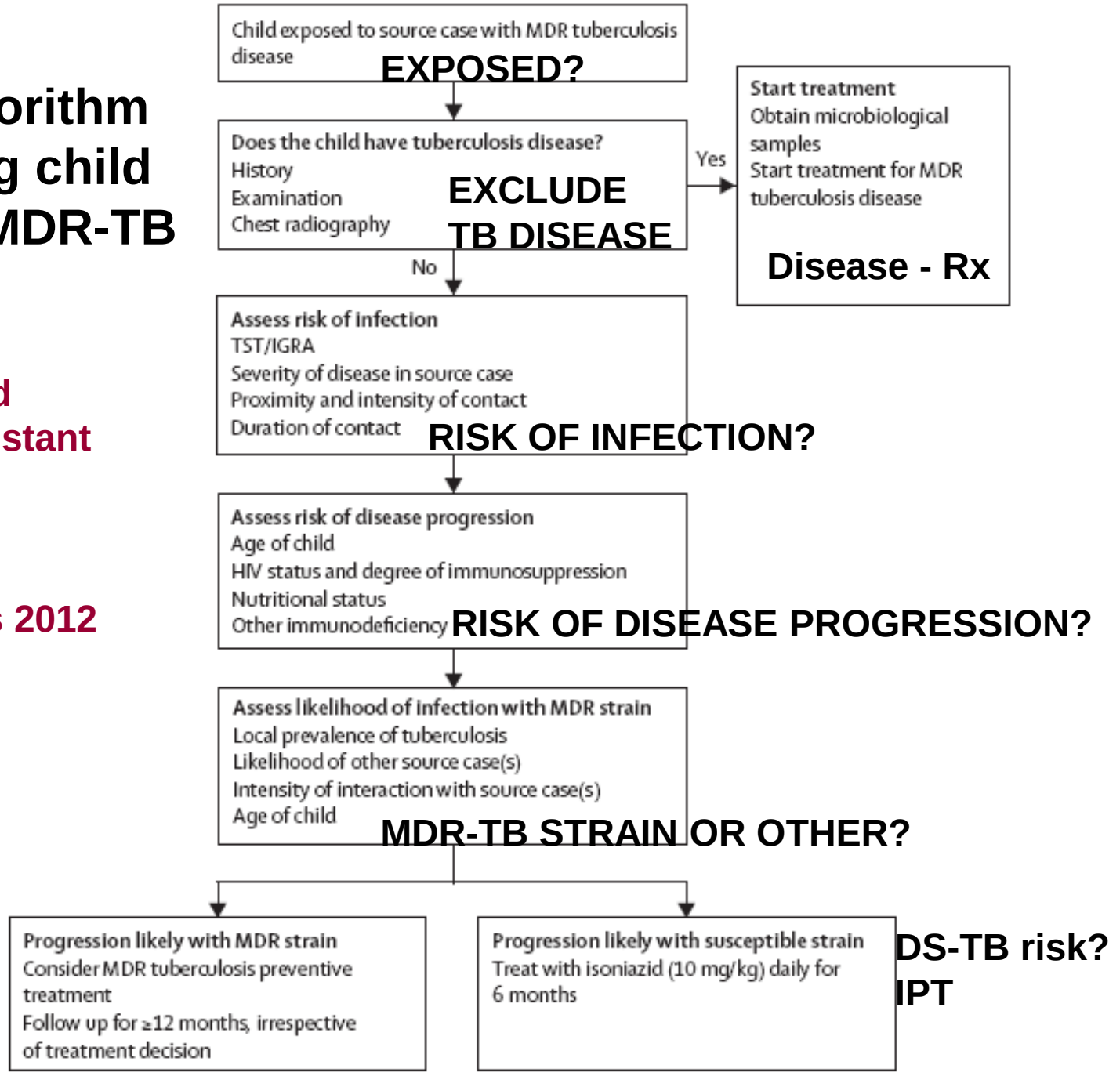

The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis
The PIH Guide to the
Medical Management of Multidrug-Resistant Tuberculosis
International Edition
Partners In Health
Program in Infectious Disease and Social Change, Harvard Medical School
Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital


ecdc
ECDC GUIDANCE
Management of contacts
of MDR TB and XDR TB patients
www.ecdc.europa.eu

Decision algorithm for assessing child contacts of MDR-TB

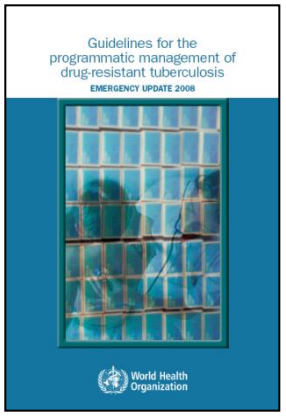
Management of children exposed to multidrug-resistant *Mycobacterium tuberculosis*.
Seddon JA et al.
Lancet Infect Dis 2012



High risk MDR-TB
Preventive Rx & follow-up

DS-TB risk?
IPT

WHO 2008 Guidelines for Drug-Resistant TB Management - Update



Key recommendations:

- DR-TB contact investigation should be a high priority
- Consider contact investigation of XDR-TB as an emergency situation
- Close contacts of DR-TB patients should receive careful clinical follow-up

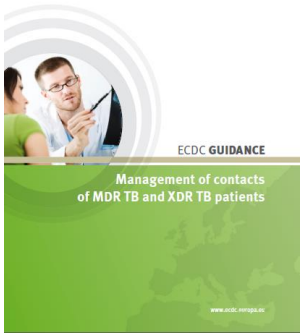
Definition of close contact:

- People living in the same household (adults & children)
- Spending many hours a day together with the patient in the same indoor living space

WHO Guidelines for Drug-Resistant TB Management - 2008 Update

- Contacts of MDR-TB patients may not be infected with the same strain; some may be infected with isoniazid-susceptible strains, particularly in high-burden areas
- Strain concordance of HH members with TB is high: In adults (50-67%) and in child contacts <5 years (75-88%)
- Close contacts of MDR-TB patients should receive careful clinical follow-up for at least two years
- If active disease is present or develops, prompt initiation of MDR-TB treatment is recommended (empiric MDR-TB regimen, even in adults, if DST and culture not available)
- WHO does not recommend the universal use of second-line drugs for preventive therapy in MDR-TB contacts

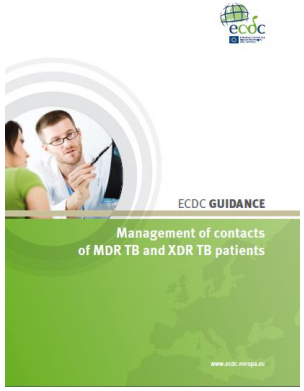
ECDC guidance (2012): Summary



- Expresses support for two different options:
  - preventive therapy and/or
  - careful clinical observation

  The central principle is that a comprehensive risk assessment should be part of the evaluation of any MDR-TB or XDR-TB contact.
- The individual risk assessment should consider:
  - the MDR-TB contact's risk for progression to TB disease
  - the DST pattern of the source case
  - the risk for adverse events upon initiating preventive Rx
- In case of XDR-TB, available drug regimens are limited and without proven efficacy, thus close observation is likely the only option.

ECDC Guidance: Summary



- Urgent need for further research, specifically in two areas:
  - studies evaluating the benefit of preventive therapy in MDR-TB and XDR-TB contacts
  - cost-benefit analyses of implementing preventive Rx
- Acknowledge that there are on-going studies which appear to support the use of preventive therapy, but these results need to be confirmed in larger studies and other settings
- Additional drugs may become available for treatment of MDR-TB, which will necessitate an update of this guidance document

Problems faced with child MDR-TB contacts

- High risk of infection and disease in children <3 years of age, especially breastfeeding infants
- HIV-infected children similar or higher risk
- Extensively drug-resistant (XDR)-TB contacts increasing – which drugs for prevention?
- High TB burden areas:
  - clinical follow-up challenging over long periods
  - >1 source case not uncommon
- Failure of adherent low-dose (4-6mg/kg/d) INH and combination (INH/RMP) preventive Rx common in our experience

Studies supporting preventive therapy?

Preventive Rx in MDR-TB contacts - systematic review

- Two observational studies met inclusion criteria.
- A prospective cohort study found individualised tailored treatment to be effective for preventing MDR-TB disease in children (OR 0.20, 95%CI 0.04–0.94) (Schaaf et al Pediartrics 2002)
- A retrospective cohort study found INH not to be effective (OR 0.46, 95%CI 0.07–2.32)

Fraser et al. IJTLD 2006

CDC - Chuuk study, Micronesia

- Contacts of 2 source cases: strain (A) resistant to HRZES; strain (B) resistant to HREth
- Evaluation of MDR-TB contacts: 15 had MDR-TB disease, 5 had DS-TB, and 119 had LTBI with positive TST.
- LTBI contacts were offered preventive Rx. 14 of the 119 cases refused, preventive Rx was initiated in 105 contacts
- A FQN-based regimen was used: FQN alone or in combination with Eth (strain A) or E (strain B)
- All therapy was DOT x 12 months
- 93 completed the MDR preventive Rx – no TB disease
- 28 contacts (15 initial screen & 11 additionally linked MDR-TB cases in persons not previously identified as contacts, and 2 out of 14 who refused preventive therapy) developed MDR-TB disease

Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study

- Aim: To study the tolerability and toxicity of a standard preventive therapy regimen, given to children exposed to MDR-TB, and explore risk factors for poor outcome.
- Method: HEO x 6 months to contacts <5 years or HIV-infected <15 years as preventive therapy

Seddon JA, Schaaf HS, et al. Clin Infect Dis (Advance Access September 24, 2013)

RESULTS

- 186 children, median age 34 months (IQR: 14-47)
- Of 179 children tested for HIV, 9 (5.0%) were positive
- Adherence was good in 141 (75.8%) children
- Only 7 (3.7%) children developed Grade 3 adverse events
- One child (0.5%) died and 6 (3.2%) developed incident TB during 219 patient years of observation time
- Factors associated with poor outcome were:
  - age <1 year (RR: 10.1; 95%CI: 1.65-105.8; p=0.009)
  - HIV-pos status (RR: 10.6; 95%CI: 1.01-64.9; p=0.049)
  - exposure to multiple source cases (RR: 6.75; 95%CI: 1.11-70.9; p=0.036)
  - poor adherence (RR: 7.50; 95%CI: 1.23-78.7; p=0.026)

Conclusions

- This three-drug preventive therapy regimen was well tolerated and few children developed TB or died if adherent to therapy.
- The provision of preventive therapy to vulnerable children following exposure to MDR-TB should be considered.

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Preventive Rx for DR-TB contacts

- No RCT available.
- Failure of INH or INH/RMP to prevent MDR-TB reported.
- INH mono-resistance: RMP x 4 mo
- RMP-monoresistance: INH x 6 mo (LPA and Xpert?)
- MDR-TB: FQN & EMB (or ETH) x 6-12 mo (hd INH?)
- Pre-XDR or XDR-TB – only hd INH (15-20mg/kg)?
- In both MDR and XDR-TB regular clinical follow-up is indicated: both ECDC and WHO recommends 2 years of follow-up (minimum is 1 year – 95% disease in 1 year). Pendulum swinging towards preventive treatment.

Conclusions

- Appropriate MDR preventive Rx – using 2 drugs with/without high-dose INH – could be effective in preventing MDR-TB in children
- There is an urgent need to address this issue in a randomised controlled trial(s)
- Single drug preventive therapy with a FQN (e.g. levofloxacin) or novel anti-TB agent considered ?
- Until such a trial is conducted, routine clinical data collected as part of existing TB control programmes could be useful
- What about XDR-TB contact? Careful follow-up and possibly high-dose INH are probably the only options – treat as XDR-TB if TB develops

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Why consider high-dose INH?

- In one study, 38 of 45 INH resistant isolates were resistant at 0.1-0.2µg/mℓ but susceptible at 5.0µg/mℓ. Only 7 resistant at 5µg/mℓ or more

Schaaf et al. Eur J Clin Microbiol Infect Dis 2007

- *inhA* promoter region mutations, which make up 60% of current MDR-TB cases and 80-90% of XDR-TB cases' INH conferring mutations (WC & EC provinces) usually causes low-level INH resistance

- High-dose INH at 15-20mg/kg/day could still add value preventive therapy of child contacts of MDR/XDR-TB cases