

Preventing Child Deaths from Drug-Resistant Tuberculosis

The Use of Practical Tools and Approaches to the Diagnosis and Treatment of Children with DR-TB

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International Union Against Tuberculosis and Lung Disease
14th November 2012

Practical Tools and Approaches

- When to suspect
- Diagnostic strategy
- Contact management
- Disease treatment
- HIV co-infection
- Drug usage, preparation and dosing
- Adverse events

Caring for Children with Drug-Resistant Tuberculosis

Practice-based Recommendations

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American Journal of Respiratory and Critical Care Medicine 2012

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



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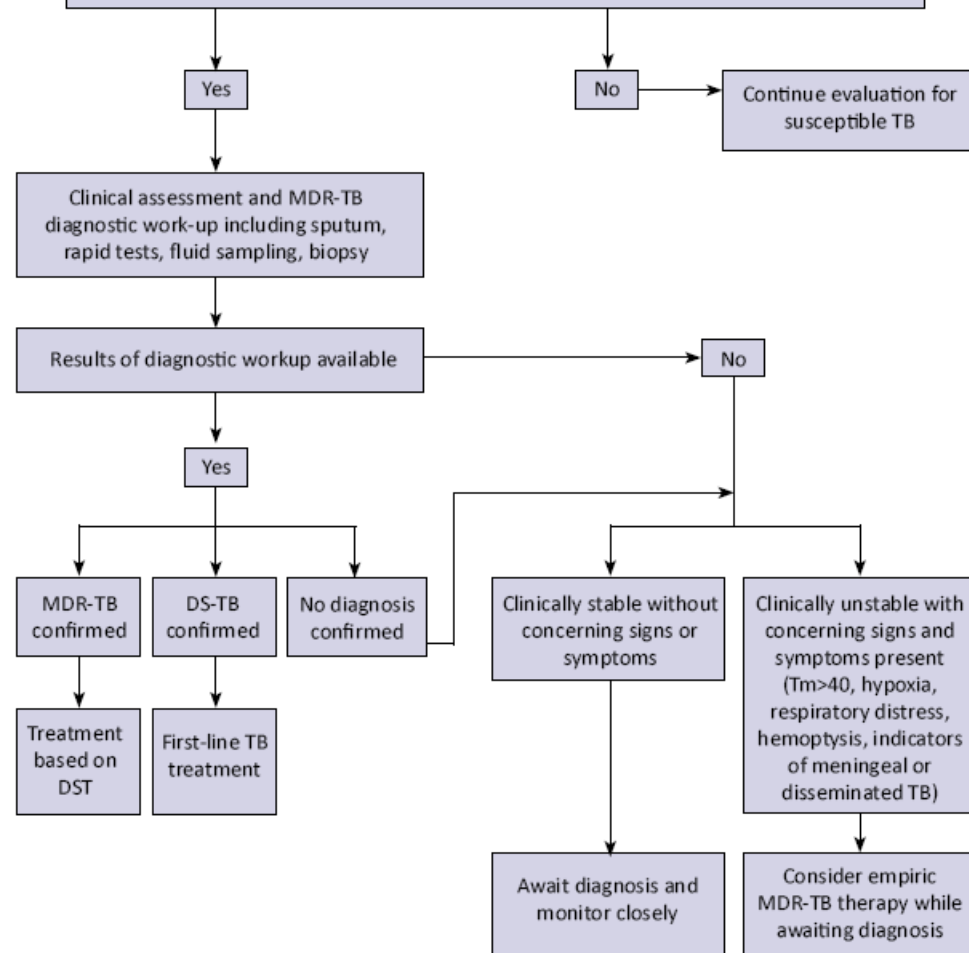
First Edition: November, 2012

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.

When to Suspect Drug-Resistant Tuberculosis in Children

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 improvement is frequently delayed)



Child MDR-TB Suspect Criteria

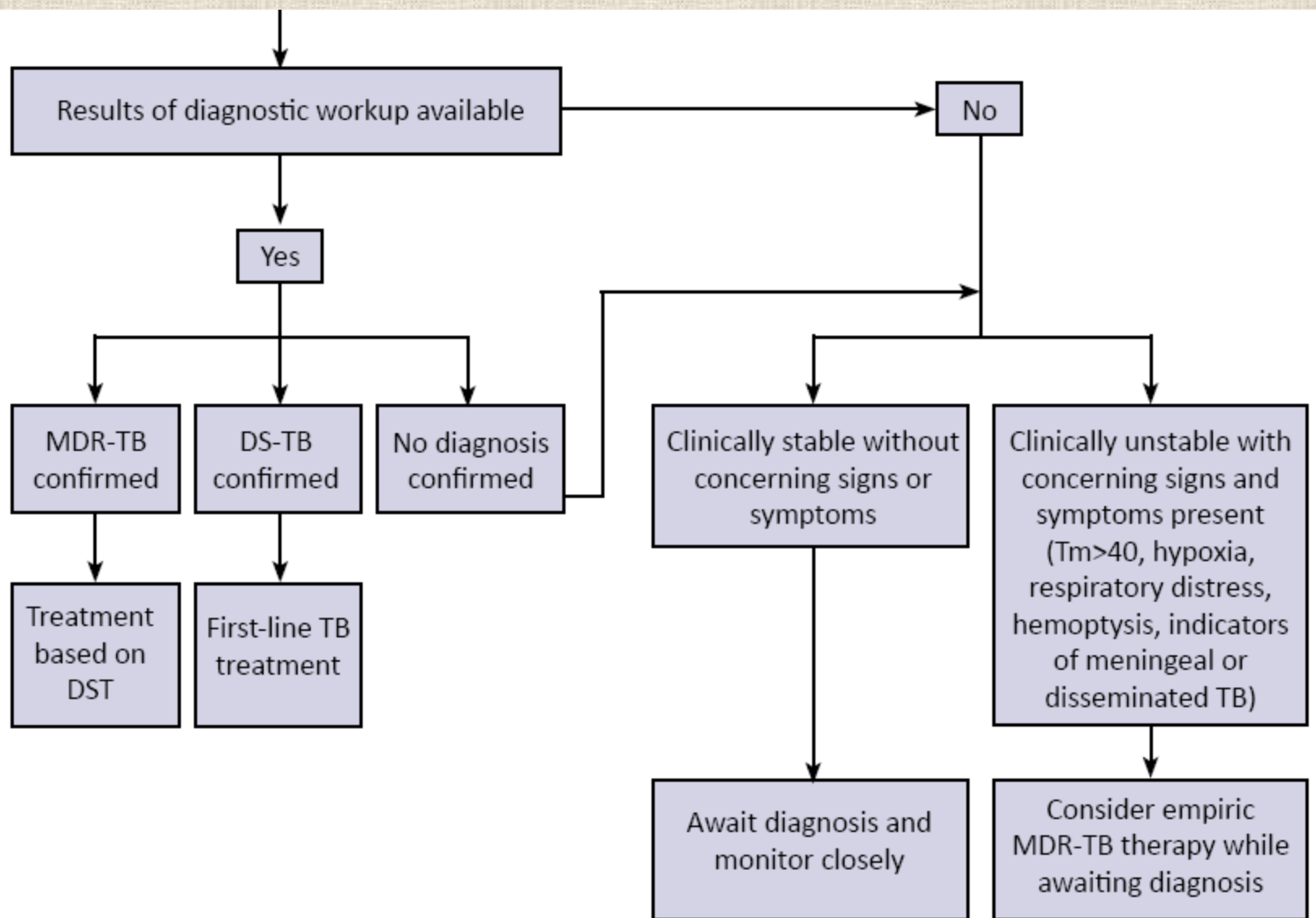
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Yes

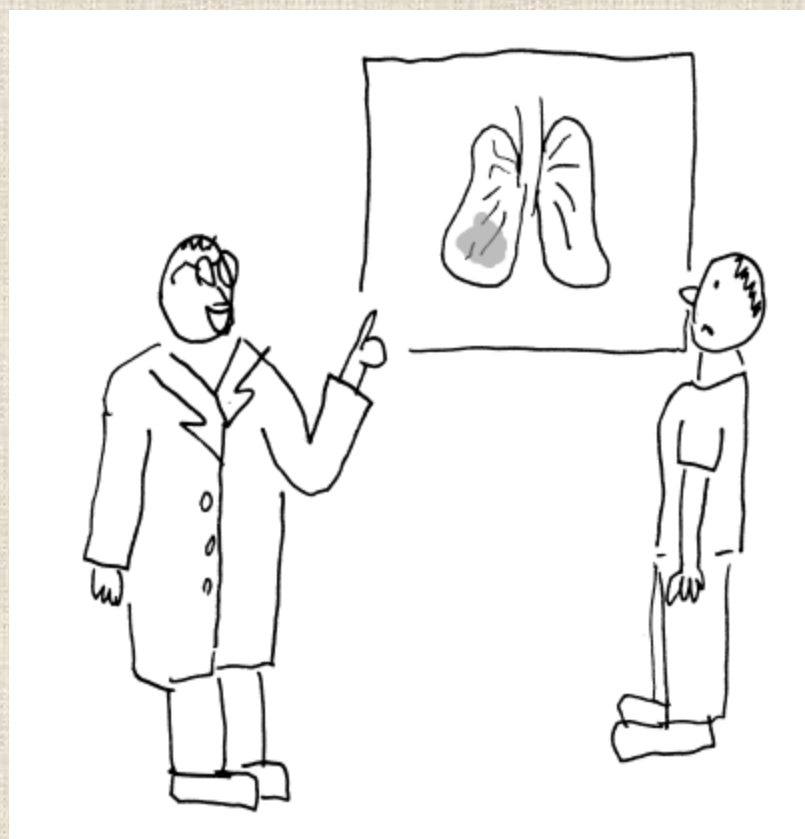
Clinical assessment and MDR-TB diagnostic work-up including sputum, rapid tests, fluid sampling, biopsy

No

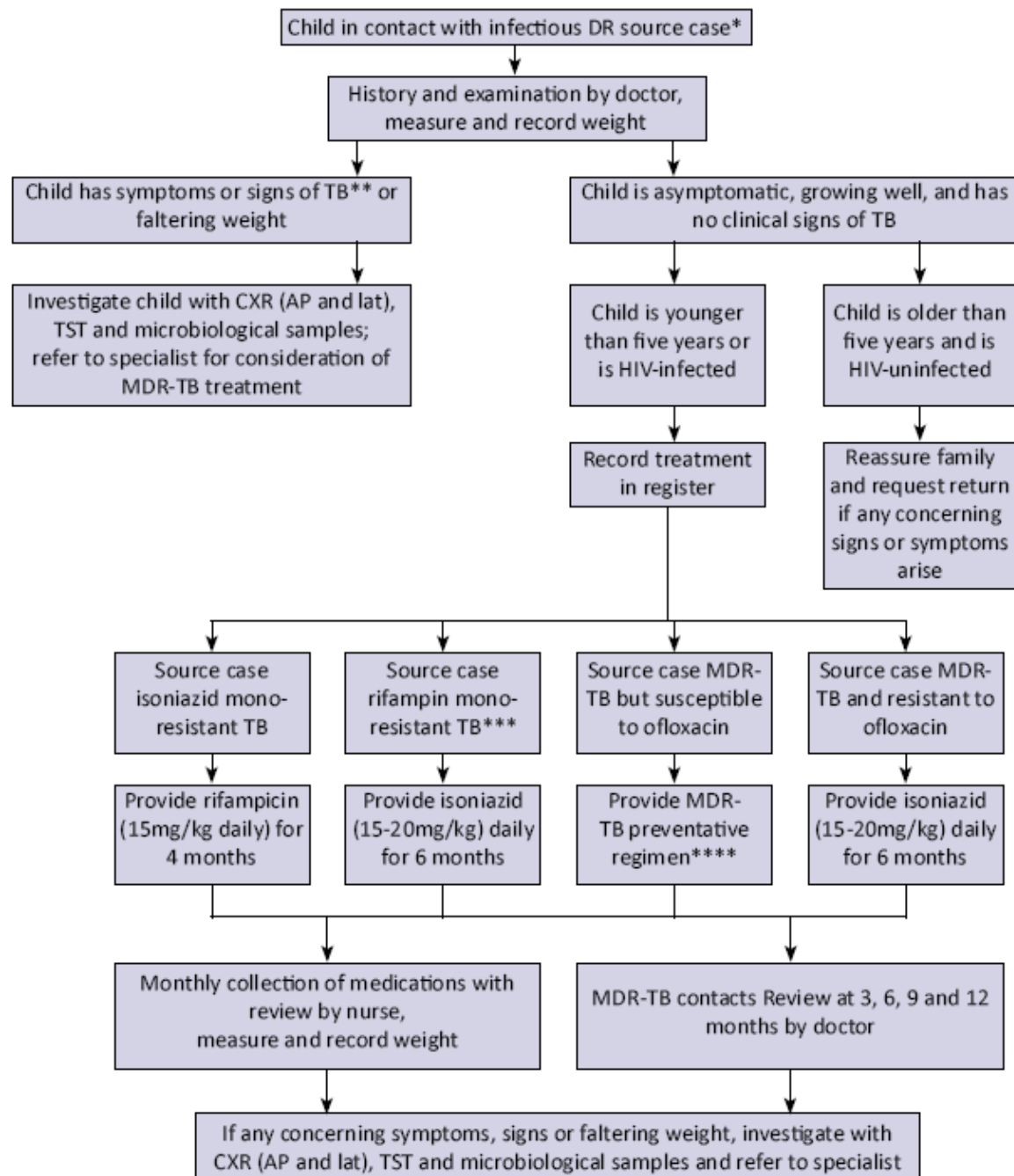
Continue evaluation for susceptible TB

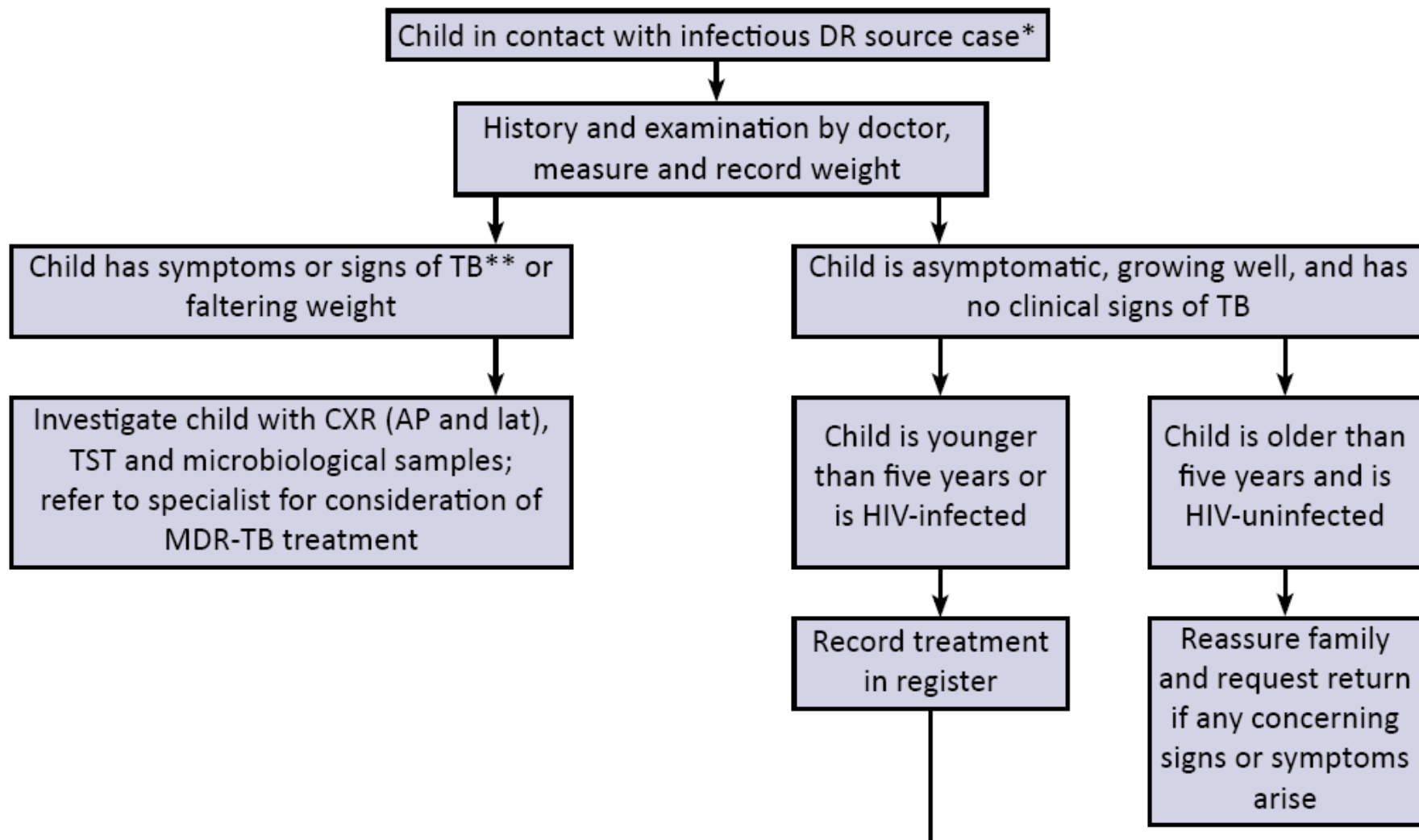


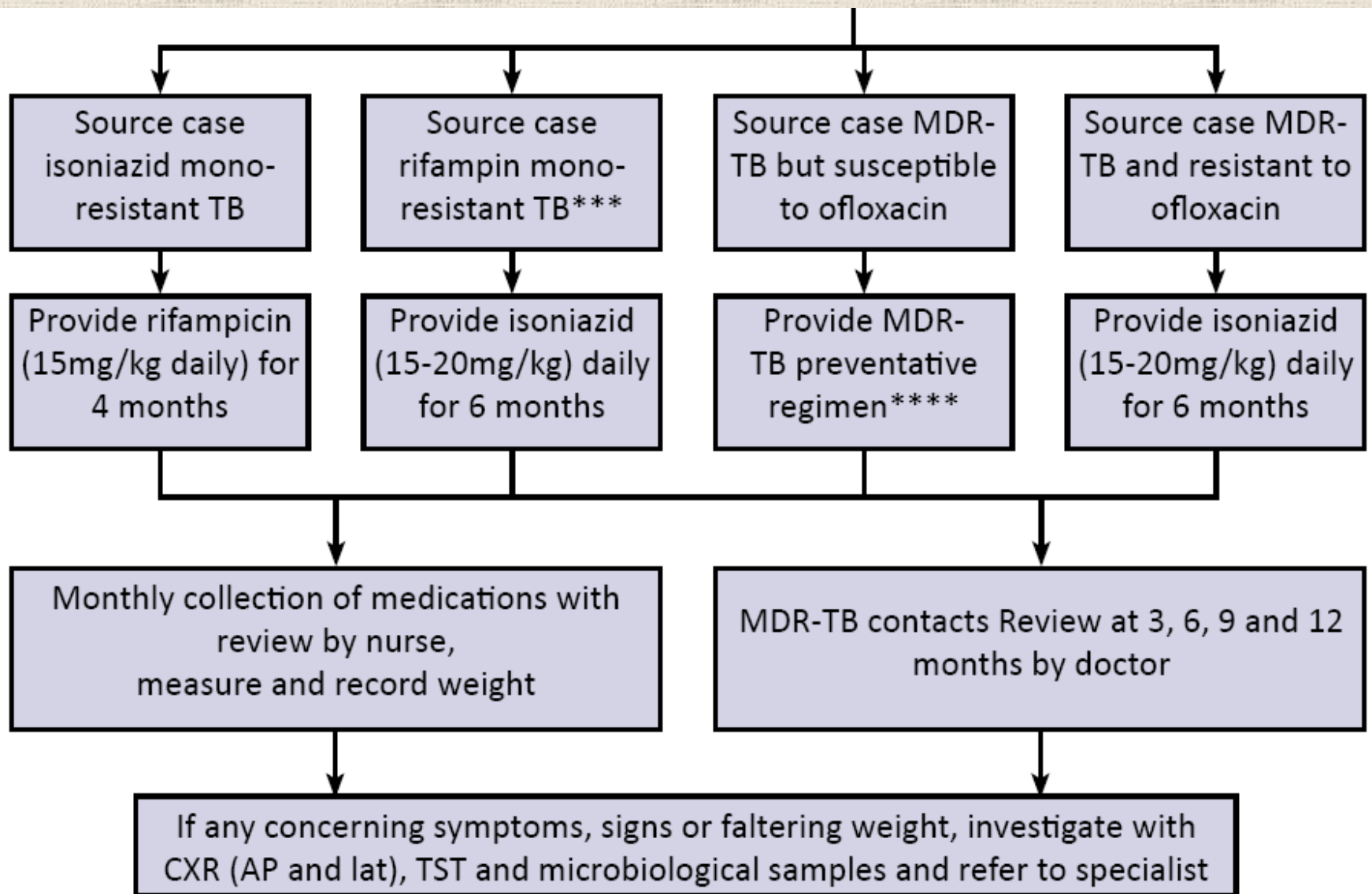
The Diagnostic Strategy



The Treatment of Children in Contact with Drug-Resistant Tuberculosis







Preventive Therapy in Western Cape

- Tygerberg Children's Hospital, Cape Town, South Africa
 - All children exposed to MDR-TB
 - May 2010 until April 2011
 - Ofloxacin, ethambutol and high dose isoniazid
or
 - High dose isoniazid
 - Six months therapy

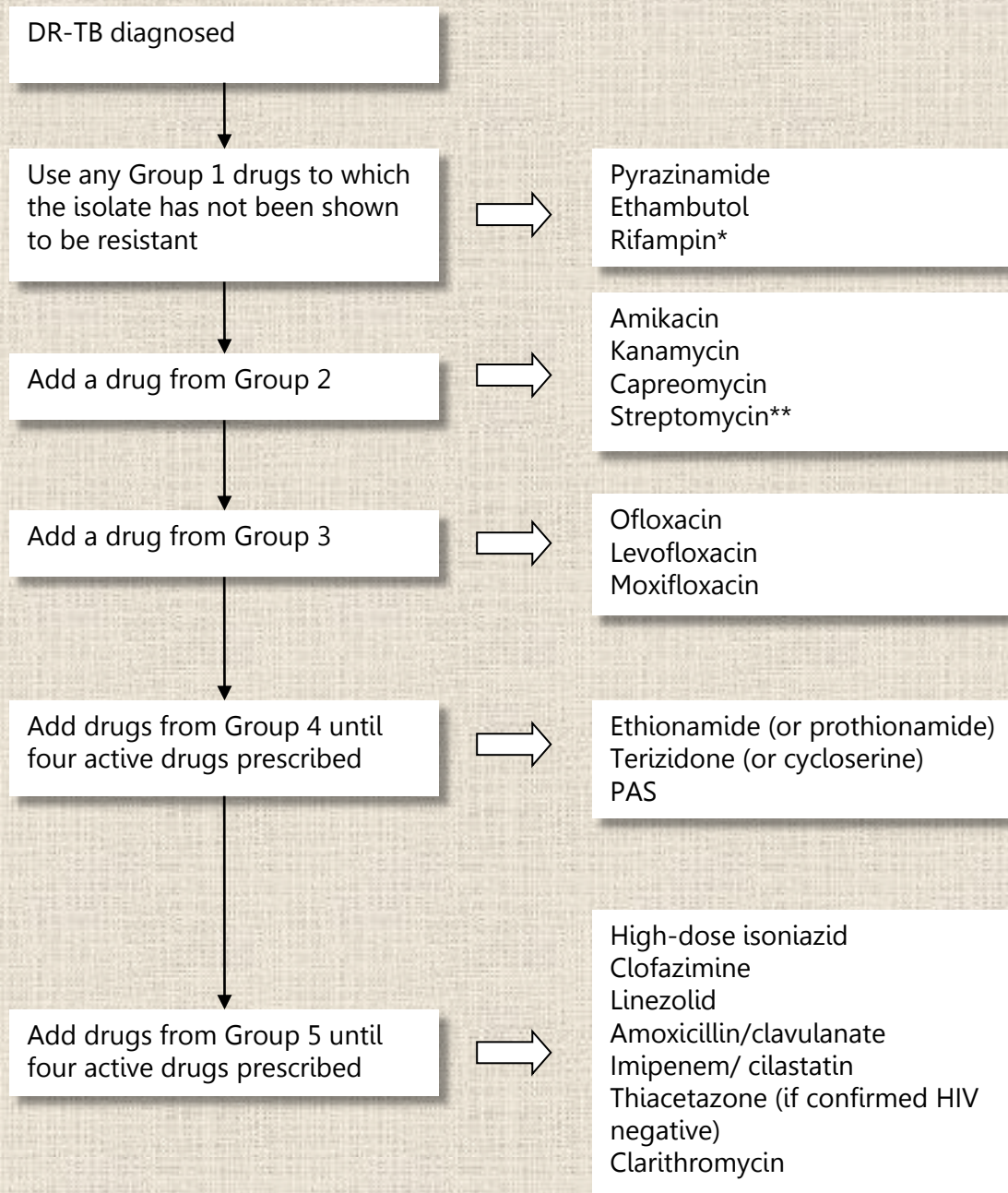
Toxicity and Tolerability

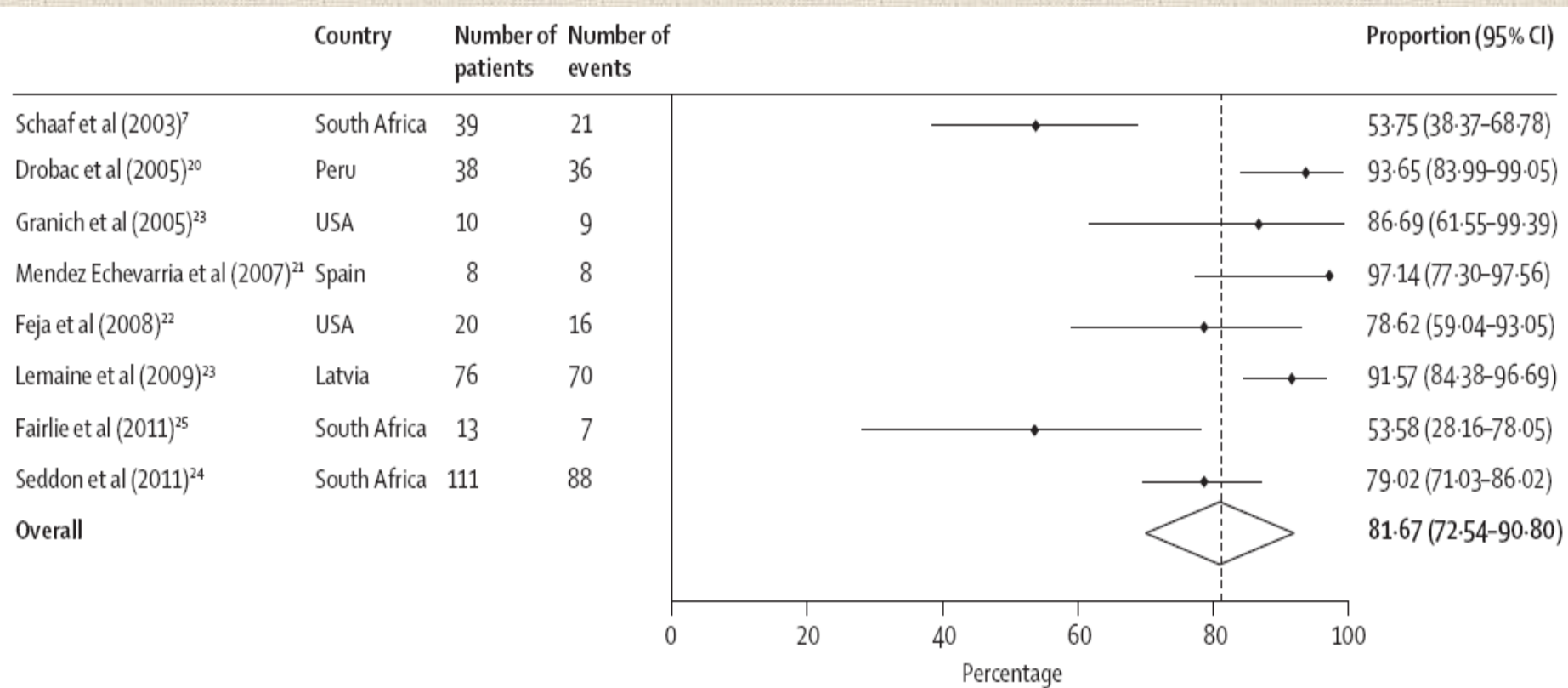
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Joint, muscle or bone pain*	183	5	1	0	0	189
Skin Rashes	144	42	6	1	0	193
Itchy skin	151	33	8	1	0	193
Headache*	155	3	2	0	0	160
Sleeping/mood	177	9	4	3	0	193
Lethargy	190	3	0	0	0	193
Visual problems	193	0	0	0	0	193
Vomiting	161	31	1	0	0	193
Diarrhoea	174	18	1	0	0	193
Jaundice	193	0	0	0	0	193
Loss of appetite/nausea	164	17	10	2	0	193

Outcome

		Number of events	Years of observation	Incidence rate with 95% CI (events per 1000 person years)	Rate Ratio (95% CI)	p-value
Age	0-12 months	5	51.6	97.0 (40.4-233.0)	1	-
	>12 months	3	197.0	15.2 (4.91-47.2)	0.16 (0.02-0.81)	0.02
Gender	Female	4	108.1	37.0 (13.9-98.6)	1	-
	Male	4	140.5	28.5 (10.7-75.9)	0.77 (0.14-4.13)	0.98
TST	Negative	4	149.6	26.7 (10.0-71.2)	1	-
	Positive	3	96.9	31.0 (10.0-96.0)	1.16 (0.17-6.84)	1.00
HIV status	Negative	6	229.5	26.1 (11.7-58.2)	1.0	-
	Positive	2	7.8	257.9 (64.5-1031.4)	9.87 (0.97-55.2)	0.05
Regimen	HEO	7	225.4	31.1 (14.8-65.2)	1	-
	H	1	23.2	43.0 (6.1-305.5)	1.39 (0.03-10.8)	1.0
<u>Ofloxacin</u> DST of source case	Susceptible	7	225.5	31.0 (14.8-65.1)	1	-
	Resistant	1	14.2	70.6 (9.9-500.9)	2.27 (0.05-17.7)	0.77
Adherence	Good	2	189.7	10.5 (2.6-42.2)	1	-
	Poor	6	58.9	101.8 (45.8-226.7)	9.66 (1.73-97.9)	0.006

The Treatment of Children with Drug-Resistant Tuberculosis Disease





HIV Co-Infection

Child diagnosed with DR-TB

Child:

- HIV positive *and*
- Already on HAART

Start DR-TB treatment
ASAP

Child:

- Found to be HIV positive *or*
- Known to be HIV positive but not on HAART yet

Aim to start HAART two weeks after
starting DR-TB treatment

Watch for signs of IRIS

- Worsening symptoms or signs
(respiratory or lymphadenopathy)
- Fever
- Weight loss
- Abdominal pain

Treat with steroids if IRIS detected
If severe or life-threatening consider
stopping HAART and restarting when
DR-TB more established

Avoid if possible or monitor closely:

- D4T
- The combination of efavirenz and cycloserine/terizidone
- The combination of tenofovir and injectables

Drug Usage, Preparation and Dosing

Drugs

	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
	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

		Isoniazid	Pyrazinamide	Ethambutol		Ofloxacin		Levofloxacin ¹	Moxifloxacin	Terizidone	Ethionamide	PAS
	Dosing range (mg/kg)	15-20	30-40	20-25		15-20		7.5-10	7.5-10	15-20	15-20	150
Weight (kg)	Tablet size (mg)	100	500	400	100	200	400	250	400	250	250	4000
3-4.9		50 (1/2 tab)	125 (1/4 tab)	100 (1/4 tab)	100 (1 tab)	100 (1/2 tab)	100 (1/4 tab)	*	*	62.5 (1/4 cap)	62.5 (1/4 tab)	500 (1/8 sach)
5-6.9		100 (1 tab)	250 (1/2 tab)	100 (1/4 tab)	150 (1½ tab)	100 (1/2 tab)	100 (1/4 tab)	62.5 (1/4 tab)	*	125 (1/2 cap)	125 (1/2 tab)	1000 (1/4 sach)
7-9.9		150 (1 ½ tab)	250 (1/2 tab)	200 (1/2 tab)	200 (2 tabs)	150 (3/4 tab)	200 (1/2 tab)	125 (1/2 tab)	*	187.5 (3/4 cap)	187.5 (3/4 tab)	1500 (3/8 sach)
10-13.9		200 (2 tabs)	500 (1 tab)	300 (3/4 tab)	300 (3 tabs)	200 (1 tab)	200 (1/2 tab)	125 (1/2 tab)	100 (1/4 tab)	250 (1 cap)	250 (1 tab)	2000 (1/2 sach)
14-19.9		300 (3 tabs)	500 (1 tab)	400 (1 tab)	400 (4 tabs)	300 (1 ½ tab)	300 (3/4 tab)	187.5 (3/4 tab)	200 (1/2 tab)	375 (1 ½ caps)	375 (1 ½ tab)	3000 (3/4 sach)
20-29.9		400 (4 tabs)	750 (1 ½ tab)	600 (1 ½ tab)	600 (6 tabs)	400 (2 tabs)	400 (1 tab)	250 (1 tab)	200 (1/2 tab)	500 (2 caps)	500 (2 tabs)	4000 (1 sach)
30-39.9		400 (4 tabs)	1000 (2 tabs)	800 (2 tabs)	800 (8 tabs)	600 (3 tabs)	600 (1 ½ tab)	312.5 (1 ¼ tabs)	300 (3/4 tab)	625 (2 ½ caps)	625 (2 ½ tabs)	6000 (1 ½ sach)
>40		400 (4 tabs)	1500 (3 tabs)	1200 (3 tabs)	1200 (12 tabs)	800 (4 tabs)	800 (2 tabs)	375 (1 ½ tabs)	400 (1 tab)	750 (3 caps)	750 (3 tabs)	8000 (2 sach)

If rifampin is given, dose as for drug-susceptible tuberculosis; ¹A suspension is available for a number of the drugs in some contexts, which might be preferable for smaller children

*Unable to create an appropriate fraction of a tablet for a child of this weight; ¹For children less than five years this dosage of levofloxacin should be given twice a day

Cycloserine / Terizidone (10-20 mg/kg)		
kg	250 mg capsule	1 capsule in 10 mL water
1-2	not recommended	
3-5	0.25 cap	2.5 mL
6-9	0.5 cap	5 mL
10-11	0.75 cap	7.5 mL
12-22	1 cap	10 mL
23-30	2 caps	—

The Monitoring and Management of Adverse Events

Monitoring

- Reasons for monitoring
 - Response to treatment
 - Adverse events
 - Promote adherence
- Types of monitoring
 - Clinical
 - Radiological
 - Microbiological
 - Laboratory

Proposed Monitoring Schedule

All children	Baseline	Month										Ongoing
		1	2	3	4	5	6	9	12	15	18	
HIV status	•											
Toxicity (symptoms, signs)	•	•	•	•	•	•	•	•	•	•	•	•
Height and weight	•	•	•	•	•	•	•	•	•	•	•	•
Audiology ¹	•	•	•	•	•	•	•					
Colour vision testing ²	•	•	•	•	•	•	•	•	•	•	•	•
CR ³	•			•			•					
TB culture and DST ⁴	•	•	•	•	•	•	•					
Creatinine and potassium ¹	•	•	•	•	•	•	•					
TSH, T ₄ ⁵	•			•			•	•	•	•	•	•
Haematology (FBC with differential) ⁶	•	•	•		•		•	•	•	•	•	•
HIV-infected												
LFTs, Cholesterol	•						•			•		•
CD4 count and viral load	•						•			•		•

Other Issues to Consider

- Other Co-infections
- Infection Control
- Morbidity
- Adherence
- Multidisciplinary care