PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 10: TUBERCULOSIS
NEMLC 23 FEBUARY 2023

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
10.1 Tuberculosis, Perinatal	mg/kg	mg/kg dosing removed, dosing table retained.
10.2.1 Non-Severe Tuberculosis Disease	TB regimen	Duration amended from 6 months to 4 months
10.7 TB preventative therapy	Ethambutol	Removed

General

The Tuberculosis chapter will be aligned with the available National Department of Health programme guidelines on TB preventative therapy (TPT) and Drug Resistant TB. These guidelines are not yet finalized, and thus certain changes will be actioned once they are formally published.

Terminology:
'M.tuberculosis PCR test' replaced with 'rapid TB molecular test (eg GeneXpert®)'.

- Tradename included to ensure test is identifiable.

10.1 TUBERCULOSIS, PERINATAL

mg/kg dosing: removed, dosing table retained

An external commenter outlined that the mg/kg doses recommended and the dosing table recommendations were not consistent. The Paediatric Committee recommended that the mg/kg doses be removed and the dosing in the weight band (using WHO dispersible tablets, rifampicin 75/isoniazid 50mg) the table be utilized.

The text was amended as follows:

Treatment for Drug Sensitive (DS) Tuberculosis
Newborn infant of mother with DS tuberculosis with newborn having any signs suggestive of illness.

Intensive phase
- Rifampicin, oral, ~~10 mg/kg/dose once daily~~ for 2 months.

PLUS
- Isoniazid, oral, ~~10 mg/kg/dose once daily~~ for 2 months.

PLUS
- Pyrazinamide, oral, ~~35 mg/kg/dose once daily~~ for 2 months.

Continuation Phase
- Isoniazid, oral, ~~10–15 mg/kg/dose once daily~~ for 4 months.

PLUS
- Rifampicin, oral, ~~10–15 mg/kg/dose once daily~~ for 4 months.

All asymptomatic neonates:
- Rifampicin/Isoniazid, oral once daily for 3 months (3RH) – HIV unexposed or HIV exposed uninfected not on NVP

Weight band	Daily rifampicin/isoniazid 75/50mg tablet	
	75/50	If dispersed in 10ml water
2-2.9 kg	½ tablet	5ml
3-3.9 kg	¾ tablet	7.5ml
4-5.9 kg	1 tablet	10ml
6-7.9 kg	1 ½ tablet	15ml

- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months (IPT) – HIV infected or HIV exposed on NVP

Weight band	Daily isoniazid (INH) 100 mg tablet
2–3.4 kg	¼ tablet
3.5–4.9 kg	½ tablet
5–7.4 kg	¾ tablet

During prophylaxis monitor the infant active TB disease (including growth monitoring) and re-evaluate for TB if necessary..
Administer BCG vaccine after completing TPT to prevent inactivation of BCG by TB medication.

10.2.1 NON-SEVERE TUBERCULOSIS DISEASE

Title amended as follows:

~~**UNCOMPLICATED**~~ **NON-SEVERE TUBERCULOSIS DISEASE** ~~**WITH LOW BACILLARY LOAD**~~

Children up to 8 years:

Regimen: Duration amended from 6 months to 4 months

The SHINE Trial[1], an open-label, treatment-shortening, non-inferiority, multi-center trial involving children with non-severe, symptomatic (presumably drug-susceptible), smear negative tuberculosis was undertaken to assess 4 months versus 6 months of standard first-line TB treatment. The primary efficacy outcome was unfavorable status (a composite of treatment failure, loss to follow-up or death), and the primary safety outcome was an adverse event of grade 3 or higher.

Each group had 602 children (median age 3.5 years). A total of 16 participants (3%) in the 4-month group had a primary outcome event, compared to 18 participants (3%) in 6-month group, (adjusted difference. -0.4 percentage points; 95% CI. -2.2 to 1.5). Findings were consistent across intention-to-treat and per protocol analyses. Adverse events of grade 3 or higher occurred in 95 participants (total of 115 adverse events) during treatment and up to 30 days after treatments (49 events in 47 participants in the 4-month group, and 66 events in 48 participants in the 6-month group).

This study showed that 4-month standard treatment was non-inferior to 6 months' treatment in children with drug-susceptible, non-severe, smear-negative TB.

[1] Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer A, Kinikar S. Shorter Treatment of Nonsevere Tuberculosis in African and Indian Children. NEJM. 2022, 386 (10): 911-922.

The Paediatric ERC thus recommended the duration of TB therapy in non-severe TB be reduced from 6 months to 4 months.

Children > 8 years (and > 25kg) of age and adolescents
Regimen: Duration amended from 6 months to 4 months

As per SHINE Trial above.

10.2.1 SEVERE TUBERCULOSIS DISEASE

Title amended as follows:

~~**COMPLICATED**~~ **SEVERE TUBERCULOSIS DISEASE** ~~**WITH PRESUMED HIGH BACILLARY LOAD**~~

10.5 DRUG RESISTANT TB (DR-TB)

The DR-TB therapy was removed, and a referral was added to the National Department of Health Clinical Reference Guide: Management of Rifampicin-Resistant Tuberculosis, 2019.[2]

The National Department of Health TB programme is currently reviewing the TB therapy including DR-TB, this section will be updated in line with these recommendations, pending approval from NEMLC.

TB PREVENTATIVE THERAPY (TPT) FOR TB EXPOSURE/INFECTION

Preventive therapy in case of drug-susceptible TB contact
Recommendations retained. These will be updated to be aligned with the National Department of Health TB Programme Guidelines when finalized.

Preventive therapy in case of drug-resistant TB contact (rifampicin susceptible and isoniazid susceptible)

Recommendations were amended in line with the National Department of Health, Clinical Reference Guide: Management of Rifampicin-Resistant Tuberculosis, November 2019. These will be further considered on release of the National Department of Health TB programme guidelines.

Preventative therapy in case of MDR-TB with second line sensitivity:
Ethambutol: Removed
The recommendations were updated as follows:

[2] National Department of Health. Management of Rifampicin-Resistant Tuberculosis. November 2019. https://www.health.gov.za/wp-content/uploads/2020/11/management-of-rifampicin-resistant-tb-booklet-1219-v6.pdf

MDR-TB with second line sensitivity

- Levofloxacin 15-20mg/kg daily for 6 months 500mg

AND/OR

- Isoniazid, oral, 15-20mg/kg daily for 6 months 300mg
- ~~Ethambutol, oral, 20-25mg/kg daily for 6 months 400mg~~
- ~~Levofloxacin 15-20mg/kg daily for 6 months 500mg~~

Refer case or discuss with specialist if simplification of prophylaxis regimen is required

Also see the National Department of Health Clinical Reference Guide: Management of Rifampicin-Resistant Tuberculosis, 2019[Error! Bookmark not defined.] for further guidance.

10.6 MENINGITIS, TUBERCULOSIS (TBM)

The following dosing table guidance was added:

The 75/50 RH and 75/50/150 RHZ formulations are not suitable for achieving the required doses in disseminated TB & TBM, so the 60/60 RH formulation should be used for such children.

Body weight (kg)	Single phase of treatment, 6-9 months Once daily; 7 days a week		
	Rifampicin/isoniazid (RH)	Pyrazinamide (Z)	Ethionamide (Eto)
	60/60 mg dispersible tablet (scored)	500 mg tablet (scored) or 500 mg/8 ml suspension	250 mg tablet (scored) or 250 mg/8 ml suspension
<2	**Obtain Expert Advice**		
2-2.9	¾ tablet or 3 ml	1 ml	1.5 ml
3-3.9	1 tablet or 4 ml	2 ml	2 ml
4-4.9	1 ½ tablets or 6 ml	2.5 ml	2.5 ml
5-5.9	1 ¾ tablets or 7 ml	3 ml	3 ml
6-6.9	2 tablets or 8 ml	½ tablet or 4 ml	½ tablet or 4 ml
7-8.9	2 ½ tablets or 10 ml		
9-9.9	3 tablets or 12 ml	¾ tablet or 6 ml	¾ tablet or 6 ml
10-11.9	3 ½ tablets or 14 ml		
12-12.9	4 tablets or 16 ml	1 tablet or 8 ml	1 tablet or 8 ml
13-14.9	4 ½ tablets or 18 ml		
15-16.9	5 tablets or 20 ml		1 ¼ tablet or 10 ml
17-17.9	5 ½ tablets or 22 ml	1 ¼ tablets or 10 ml	
18-19.9			1 ½ tablets or 12 ml
20-24.9	6 tablets or 24 ml	1 ½ tablets or 12 ml	

Note: Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication if possible

* If oral suspension required, for each dose, disperse 1 x HR 60/60 mg tablet in 4 ml of water, administer required dose as indicated in above chart, discard unused suspension
**If oral suspension is required, crush 1 x 500 mg Pyrazinamide tablet to a fine powder, disperse in 8 ml water to prepare a concentration of 500 mg/8 ml (62.5 mg/ml), administer required dose as indicated in above chart, discard unused suspension
*** If oral suspension is required, crush 1 x 250 mg Ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 250 mg/8 ml (31.3 mg/ml); administer required dose as indicated in above chart; discard unused suspension

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CHAPTER 10: TUBERCULOSIS
NEMLC 24 FEBRUARY 2022

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
10.1 Tuberculosis, Perinatal	Rifampicin/Isoniazid for 3 months (3RH)	Added for HIV unexposed or HIV exposed uninfected neonates not on nevirapine
	Isoniazid daily for 6 months	Added for HIV infected or HIV exposed neonates on nevirapine
10.2 Tuberculosis, Pulmonary	Dispersible formulation: RHZ 75/50/150 and RH 75/50	Moved above RH 60/60 dosing table –as first recommendation
10.5 Drug resistant TB (DR-TB)	Recommendations to be aligned with NDoH	
10.6 TB Preventative Therapy (TPT)	Recommendations to be aligned with NDoH	

General

The Tuberculosis chapter will be aligned with the available National Department of Health (NDoH) programme guidelines on TB preventative therapy (TPT) and Drug Resistant TB. These guidelines are not yet finalized, and thus certain changes will be actioned once these for formally published.

10.1 TUBERCULOSIS, PERINATAL

Tuberculosis Preventative Therapy

Rifampicin/Isoniazid daily for 3 months: Added for HIV unexposed or HIV exposed uninfected neonates not on nevirapine.

Isoniazid daily for 6 months: Added for HIV infected or HIV exposed neonates on nevirapine.

The text was included as follows:

All asymptomatic neonates:

- Rifampicin/Isoniazid, oral once daily for 3 months (3RH) – HIV unexposed or HIV exposed uninfected not on NVP

Weight band	Daily rifampicin/isoniazid 75/50mg tablet	
	75/50	If dispersed in 10ml water
2-2.9 kg	½ tablet	5ml
3-3.9 kg	¾ tablet	7.5ml
4-5.9 kg	1 tablet	10ml
6-7.9 kg	1 ½ tablet	15ml

- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months (IPT) – HIV infected or HIV exposed on NVP

Weight band	Daily isoniazid (INH) 100 mg tablet
2–3.4 kg	¼ tablet
3.5–4.9 kg	½ tablet
5–7.4 kg	¾ tablet

During prophylaxis monitor the infant for active TB disease. Administer BCG vaccine after completing TPT .

10.2 TUBERCULOSIS, PULMONARY

Uncomplicated with low bacillary load

The following text was added:

Indications:

Includes smear negative pulmonary TB with no more than mild to moderate lymph node enlargement and/or lung field opacification, or simple pleural effusion.

Dosing:

» Adjust treatment dosages to current body weight.
» If calculating dosages, rather give ½ tablet more than ½ tablet less.

Children up to 8 years:

The Paediatric Committee recommended that the dosing tables for the new dispersible combination tablets be listed first (over the older formulations), with dosing tables amended in line with the Primary Healthcare Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) 2020 edition .

Complicated TB with presumed high bacillary load

The following text was added:

Indications:

» Includes all other forms of pulmonary TB, such as smear positive TB, cavitatory pulmonary TB, bronchopneumonic TB, severe or extensive pulmonary TB lesions, tuberculous empyema.
» Includes all HIV/TB co-infected cases.
» All other forms of severe TB. i.e. extensive pulmonary TB, spinal or, osteo-articular TB or abdominal TB.
» Exclude TB meningitis in all cases of miliary TB, refer if this cannot be safely done at current level of care.

Dosing:

» Weigh at each visit and adjust treatment doses to body weight. If calculating dosages, rather give ½ tablet more than ½ tablet less.
» Keep strictly to the correct dose and the duration of treatment.
» The patient should be weighed regularly and the dose adjusted according to the current weight.

10.3 MILIARY TB

Miliary TB was moved up from the end of the chapter.

10.5 DRUG RESISTANT TB (DR-TB)

This will be aligned with the NDoH programmatic guideline recommendations.

10.6 TB PREVENTATIVE THERAPY (TPT) FOR TB EXPOSURE/INFECTION

This will be aligned with the NDoH programmatic guideline recommendations.

Tuberculin skin test (TST)

General screening was separated out, i.e. firstly screening for symptoms, weight loss etc. If patients screen positive they will then be further investigated.

Preventative therapy in case of drug-susceptible TB contact

The NDoH programme guidelines on this are still to be ratified by the National Health Council. The recommendations will propose inclusion of rifapentine. The Committee recommended aligning once this is finalised.

10.7 MENINGITIS, TUBERCULOSIS (TBM)

The following dosing table guidance was added:

The 75/50 RH and 75/50/150 RHZ formulations are not suitable for achieving the required doses in disseminated TB & TBM, so the 60/60 RH formulation should be used for such children.

Body weight (kg)	Single phase of treatment, 6-9 months Once daily; 7 days a week		
	HR	Z	Eto (Ethionamide)
	60/60 mg dispersible tablet (scored)	500 mg tablet (scored) or 500 mg/8 ml suspension	250 mg tablet (scored) or 250 mg/8 ml suspension
<2	**Obtain Expert Advice**		
2-2.9	¾ tablet or 3 ml	1 ml	1.5 ml
3-3.9	1 tablet or 4 ml	2 ml	2 ml
4-4.9	1 ½ tablets or 6 ml	2.5 ml	2.5 ml
5-5.9	1 ¾ tablets or 7 ml	3 ml	3 ml
6-6.9	2 tablets or 8 ml	½ tablet or 4 ml	½ tablet or 4 ml
7-8.9	2 ½ tablets or 10 ml		
9-9.9	3 tablets or 12 ml	¾ tablet or 6 ml	¾ tablet or 6 ml
10-11.9	3 ½ tablets or 14 ml		
12-12.9	4 tablets or 16 ml	1 tablet or 8 ml	1 tablet or 8 ml
13-14.9	4 ½ tablets or 18 ml		
15-16.9	5 tablets or 20 ml		1 ¼ tablet or 10 ml
17-17.9	5 ½ tablets or 22 ml	1 ¼ tablets or 10 ml	
18-19.9			1 ½ tablets or 12 ml
20-24.9	6 tablets or 24 ml	1 ½ tablets or 12 ml	

Note: Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets so as to avoid large volumes of liquid medication if possible

* If oral suspension required, for each dose, disperse 1 x HR 60/60 mg tablet in 4 ml of water, administer required dose as indicated in above chart, discard unused suspension

**If oral suspension is required, crush 1 x 500 mg Pyrazinamide tablet to a fine powder, disperse in 8 ml water to prepare a concentration of 500 mg/8 ml (62.5 mg/ml), administer required dose as indicated in above chart, discard unused suspension

*** If oral suspension is required, crush 1 x 250 mg Ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 250 mg/8 ml (31.3 mg/ml), administer required dose as indicated in above chart, discard unused suspension