

CHAPTER 10. TUBERCULOSIS

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TB guidelines are updated regularly. This STG should be read in conjunction with the most recent National Tuberculosis Control Programme Guidelines.

10.1. TUBERCULOSIS, DRUG-SUSCEPTIBLE

A15–A19

10.1.1. TUBERCULOSIS, PERINATAL

P37.0

*Notifiable condition.

DESCRIPTION

Perinatal tuberculosis (TB) is defined as TB acquired either congenitally (in-utero or during birth), or postnatally within the first 3 months of life.

- » Congenital TB:
 - Transplacental transmission – usually due to maternal extrapulmonary or disseminated TB.
 - Via swallowed or aspirated maternal blood or amniotic fluid during labour or delivery – usually due to maternal extrapulmonary TB.
- » Postnatal TB:
 - Inhalation of the bacilli during the neonatal period from a close contact with infectious pulmonary TB (PTB) – usually the mother but also other household contacts or visitors.

An infant may be the first identified person with TB. If the mother has not been diagnosed with TB, she should be assessed immediately.

History of Exposure

A newborn has had significant exposure to a person with infectious TB if:

- » The baby was born to a mother with TB and the mother:
 - started TB treatment within 2 months before delivery OR
 - demonstrates poor clinical response to TB treatment OR
 - is TB smear or acid-fast bacilli (AFB) or culture positive at delivery OR
 - is diagnosed with TB soon after delivery
- » The baby has been exposed to an adult or adolescent with PTB who shared the same enclosed space for one or more nights or for frequent or extended day time periods (e.g., day mother, visitors to the home, crèche) during the three months before the source patient started appropriate TB treatment.

Clinical Presentation

- » The clinical presentation may vary from asymptomatic or vague symptoms to severe acute or chronic illness.
- » Symptom onset in young infants is often acute over days.
- » Infants with congenital TB may become symptomatic within the first days of life but typically become ill between 2 and 4 weeks of age. Some may be diagnosed as late as five months of age.

- » The signs of perinatal TB can be non-specific and include poor feeding, fever, lethargy, irritability, growth faltering.
- » Congenital TB often presents with acute respiratory distress, jaundice, hepatosplenomegaly, abdominal signs, poor feeding and failure to thrive and/or a clinical picture of “neonatal sepsis”.
- » Postnatal TB often presents with cough, tachypnoea, wheeze or stridor.
- » Given the high risk of TB disease, the non-specific clinical presentation of infants, and high morbidity and mortality, a low threshold for rapid referral of unwell TB-exposed neonates and young infants is warranted.

DIAGNOSIS

Diagnosis relies on the history of exposure, a suggestive clinical examination and diagnostic investigations, including:

- » Chest X-ray (anteroposterior and lateral).
- » Abdominal ultrasound. Hypoechoic liver or splenic lesions, ascites, intra-abdominal or retroperitoneal lymphadenopathy are suggestive of TB.
- » Bacteriological confirmation and drug susceptibility testing (DST).
 - Gastric aspirate or induced sputum from the infant for TB-NAAT testing, microscopy for AFB, and TB culture, and/or stool for GeneXpert.
 - Repeated specimens may be needed to confirm the diagnosis.
- » Lumbar puncture for CSF if clinically indicated, miliary TB, or presumed congenital TB.
- » Sputum or other samples from the mother (or other TB source patient) that are positive for *M. tuberculosis*, with or without a suggestive chest X-ray. Always review DST results from the source patient.

GENERAL AND SUPPORTIVE MEASURES

- » All healthy newborns, regardless of HIV status or TB exposure status should receive BCG at discharge from the delivery unit.
 - BCG is a live attenuated *M.bovis* vaccine which is killed by anti-TB medicines.
 - If the baby starts TPT or TB treatment in the first 6 weeks of life, the BCG vaccine must be repeated one day after completion of TPT or TB treatment.
 - Babies with HIV should receive the repeat BCG dose after completion of TPT or TB treatment if they are on ART, clinically well, and have a CD4 > 25%.
- » In infants with a history of TB exposure have a low threshold for starting presumptive treatment based on clinical assessment.
- » In infants with a history of TB exposure, where TB disease has been excluded, TB preventive therapy (TPT) is indicated (refer to Figure 1: Management of the newborn exposed to TB).

- » If the TB source patient has drug-resistant TB, refer or discuss with an expert. In these infants, always send specimens, including a gastric aspirate or induced sputum for TB culture and DST.
- » Check the HIV status of the mother and, if positive, test the infant for HIV using HIV PCR.
- » Screen all other household contacts for TB.
- » Monitor the nutritional status of the neonate closely.
- » It is not recommended that infants be separated from their mothers after birth, even if the mother is known to still be contagious. Establishing breastfeeding and bonding with the newborn infant is important.
 - The mother should be started on effective anti-TB treatment (refer to Adult Hospital Level STGs and EML, Chapter 26: Tuberculosis) and the infant on TPT or TB treatment, as appropriate.
 - The mother should be advised on infection prevention and control measures, such as wearing a mask when handling or feeding the infant until she has been on effective therapy for at least two weeks and/or her sputum is smear-negative for acid-fast bacilli.
 - Other measures include sleeping in a separate room if feasible and allowing ventilation in the home.

MEDICINE TREATMENT

Treatment for perinatal drug-susceptible (DS) pulmonary TB and extrapulmonary TB (excluding TBM/CNS TB/ Miliary TB)

Intensive Phase (2 months)	Continuation Phase (4 months)
• Rifampicin ^w, oral. PLUS • Isoniazid, oral. PLUS • Pyrazinamide, oral. PLUS • Ethionamide, ora.l* OR • Ethambutol, oral.*	• Rifampicin ^w, oral. PLUS • Isoniazid, oral.

**Ethionamide should be used preferentially, especially in infants younger than three months or weighing < 3 kg due to challenges with ethambutol administration*

LoE IIIa^{i,ii}

TB drug doses should be adjusted as the child grows, and as outlined in Table 1. If the infant weighs less than 2 kg, consult an expert.

Table 1: TB dosing chart for infants with perinatal drug-susceptible pulmonary TB and extrapulmonary TB (excluding TBM/CNS TB/ Miliary TB)

Target dose (Range; mg/kg/ day)	Intensive phase Once daily (7 days a week)			Continuation phase Once daily (7 days a week)
	Duration: 2 months			Duration: 4 months
	Rifampicin (R): 15 (10–20) Isoniazid (H): 10 (7–15) Pyrazinamide (Z): 35 (30–40)			Ethionamide (Eto): 17.5–22.5 Ethambutol (E): 20 (15–25)
Formulation	Ethionamide OR Ethambutol			RH
Body Weight (kg)	RHZ 75/50/150 mg dispersible tablet (scored) OR 50/75/150mg/4ml suspension *	Ethionamide 250 mg tablet (not scored) OR 250 mg/8 ml suspension #	Ethambutol 400 mg tablet (not scored) OR 400mg/8ml suspension ##	RH 75/50 mg Dispersible tablet (scored) OR 50/75mg/4ml suspension*
< 2 kg	Obtain expert advice			
2–2.9 kg	½ tablet or 2 mL	1.5 mL	1 mL	½ tablet or 2 mL
3–3.9 kg	¾ tablet or 3 mL	2 mL	1.5 mL	¾ tablet or 3 mL
4–7.9 kg	1 tablet or 4 mL	2.5 mL	2.5 mL	1 tablet or 4 mL
Note: *If oral suspension required, for each dose, disperse 1 x RHZ 75/50/150 mg or 1 x RH 75/50 mg tablet in 4 mL of water, administer required dose, discard unused suspension. # To make an ethionamide oral suspension, 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. ## If oral suspension is required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 mL of water to prepare a concentration of 400 mg/8 mL (50 mg/mL), administer required dose as indicated in above chart, discard unused suspension.				

CAUTION

In infants living with HIV on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed by weight-band **twice daily (12 hourly)**. Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer to Chapter 9: Human Immunodeficiency Virus infection.

AND

In addition, administer pyridoxine to all breastfed infants, malnourished infants, and infants living with HIV (CLHIV). Acute malnutrition refers to wasting, evidenced by a weight-for-length z-score < -2, or bilateral pitting oedema.ⁱⁱⁱ

- Pyridoxine, oral, once daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).

LoE Ivb^{i,ii}

For weight-based treatment of infants with perinatal drug-susceptible central nervous system TB, TBM or miliary TB, see Section 10.1.2.1: Miliary TB (Table 5) and Section 10.1.2.2: TBM (Table 6) below.

Tuberculosis preventive therapy (TPT) for drug-susceptible (DS) perinatal tuberculosis exposure

- » In infants with a history of significant TB exposure, once TB disease has been excluded, TPT should be provided (refer to Figure 1 and Section 10.3 TPT for exposure/infection below).
- » During TPT, monitor the infant for active TB disease (including growth monitoring) and re-investigate for TB disease if necessary.

REFERRAL

- » Patients not responding to adequate therapy.
- » Perinatal TB with history of exposure to a person with drug-resistant TB – telephonic consultation with specialist.

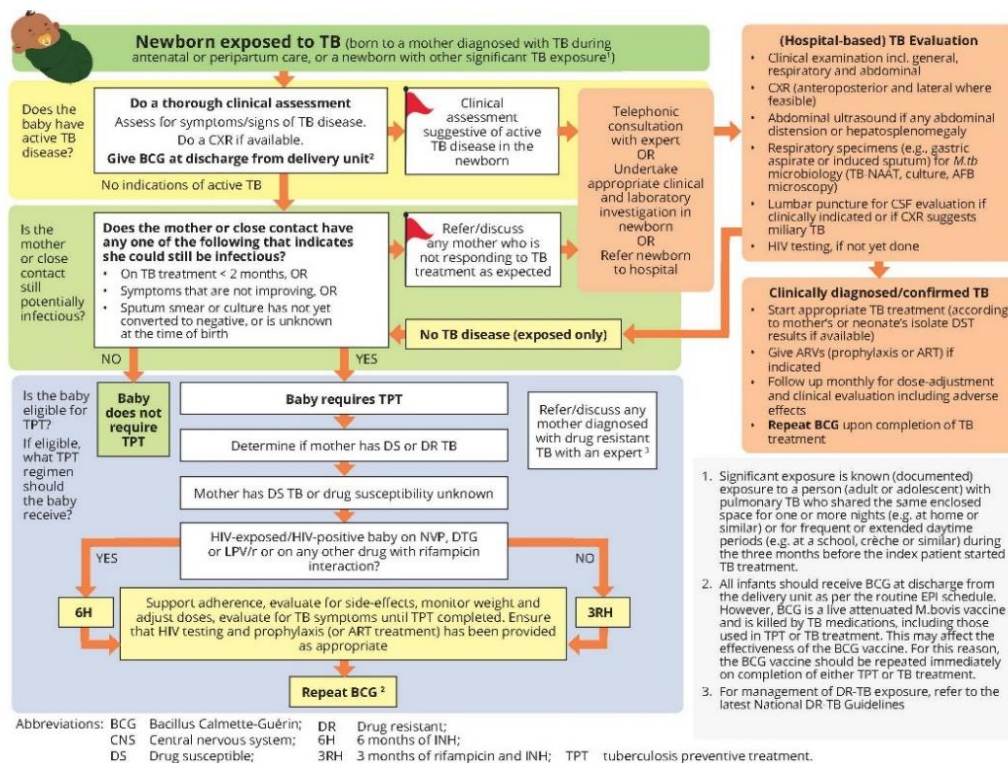


Figure 1: Management of the newborn exposed to TB

10.1.2. TUBERCULOSIS IN CHILDREN AND ADOLESCENTS < 15 YEARS

A15–A19

*Notifiable condition.

DESCRIPTION

Tuberculosis (TB) is a chronic, granulomatous disease caused by *M. tuberculosis*.

Most children develop TB after inhalation of droplets containing *M. tuberculosis*, which have been coughed or exhaled by adults or adolescents with pulmonary TB (e.g. the source patient). A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). The exposure must have occurred while the source patient was not on TB treatment OR if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment.

It is critical to identify the source patient with TB that the child was exposed to. Identify and screen all other child contacts of the source patient and offer TB preventive therapy (TPT) if appropriate.

Children < 2 years or living with HIV or severely malnourished may have few or atypical symptoms and are at high risk of rapid progression of TB disease with quick deterioration. Do not delay investigations for TB.

Complications of pulmonary TB in children include:

- » enlarged hilar and mediastinal lymphadenopathy with obstruction, e.g. tracheal or bronchial airway compression or occlusion with secondary atelectasis or hyperinflation;
- » local spread of infection, e.g. TB bronchopneumonia, pleural effusion or cavitation;
- » disseminated disease, e.g. miliary TB, TB meningitis and extrapulmonary involvement.

DIAGNOSIS

Signs and symptoms may include:

- » cough, acute (especially in infants or immunocompromised children) or persistent, unremitting cough for > 14 days that persists despite treatment;
- » loss of appetite;
- » unexplained weight loss or failure to thrive including insufficient weight gain and growth faltering;
- » lack of energy, child is less playful;
- » unexplained fever ($> 38^{\circ}\text{C}$) for ≥ 2 weeks;

- » drenching night sweats that are excessive and soak the bed or clothes;
- » noisy breathing or wheeze which may be the result of airway compression by lymph nodes;
- » lymphadenopathy (especially cervical and matted lymph nodes);
- » hepatosplenomegaly;
- » consolidation and pleural effusion on chest examination;
- » or back pain, limp or difficulty walking, lower limb weakness, spinal deformity.

SPECIAL INVESTIGATIONS

- » Chest X-ray (frontal and lateral views). Suggestive chest X-ray findings of TB include:
 - Enlarged hilar or mediastinal lymph nodes
 - Primary Ghon focus
 - Narrowing or compression of large airways
 - Parenchymal opacification
 - Lobar collapse
 - Miliary changes
 - Cavitation (in older children)
 - Pleural effusion
 - Pericardial effusion
 - Abnormality of the thoracic vertebra or paravertebral abscess.
- Note:** In children living with HIV (CLHIV), a nodular pattern on chest X-ray may be suggestive of miliary TB (bloodstream spread) or lymphoid interstitial pneumonitis (LIP). The miliary pattern of TB is micronodular (very small, 1–2 mm diameter) and extends into the periphery of the lungs, whereas LIP usually shows larger nodules and does not extend to the lung periphery.
- » Determine HIV status for all children and adolescents with presumed TB if the last test was negative or HIV status is unknown.
- » Tuberculin skin test (TST), e.g. Mantoux.
 - A TST provides no additional information in a child who is known to have a significant TB exposure.
 - A positive TST confirms a child has been infected with TB but does not differentiate between TB infection and TB disease.
 - A positive TST has an induration of ≥ 10 mm, or ≥ 5 mm in CLHIV or malnourished children.
 - A negative TST does not exclude TB infection or TB disease and a decision not to start TB treatment should not be based on a negative TST test.
 - A TST may be falsely negative due to incorrect administration or in the presence of malnutrition, immunosuppression (e.g. HIV, cancer chemotherapy, steroid therapy), following overwhelming viral infection (e.g. measles) or post-vaccination.
 - In these circumstances, a TST induration of ≥ 5 mm may be regarded as positive.

- » Urine lipoarabinomannan (U-LAM) for children or adolescents living with HIV (CALHIV):
 - Perform a U-LAM in CALHIV with current serious illness requiring hospital admission.
 - Perform a U-LAM in CALHIV seen in an outpatient setting who are symptomatic of TB with a CD4 count ≤ 200 or $\leq 25\%$ (if < 5 years) within the last 6 months, or who have advanced HIV disease.
 - A positive U-LAM provides clinical confirmation of TB disease in CALHIV. A negative U-LAM does not exclude TB.
- » TB nucleic acid amplification testing (TB-NAAT) and TB culture:
 - TB disease is microbiologically confirmed by a positive TB-NAAT or culture, on the following specimens:
 - Early morning gastric aspirate after no oral food intake for ≥ 4 hours
 - Expecterated sputum (older children) and induced sputum after no oral food intake for 3–4 hours
 - Nasopharyngeal aspirates
 - Stool for GeneXpert where testing is available
 - Cerebrospinal, pleural and/or ascitic fluid
 - Pus from cold abscess
 - Fine needle aspirate or biopsies of lymph nodes
 - Ear swabs in children with chronic otorrhoea

NOTE: Most children will not have microbiological confirmation of TB.

DIAGNOSTIC CRITERIA

Any child presenting with symptoms and signs suggestive of pulmonary TB is regarded as having TB disease if there is:

- » A chest X-ray suggestive of TB.
- AND/OR**
- » History of exposure to a person with infectious TB OR a positive TST (e.g. Mantoux).

Always collect sputum, induced sputum, gastric aspirates and/or nasopharyngeal aspirates for TB-NAAT and TB culture. A positive TB-NAAT or culture confirms TB disease and drug susceptibility. A negative TB-NAAT or TB culture does not rule out TB disease, particularly in children with severe or extrapulmonary disease.

Negative results should be reviewed in the context of history and clinical and radiological findings. Treatment may be started if the overall picture suggests TB, even if the TB-NAAT or culture are negative. If the child is not severely ill and there is uncertainty about diagnosis, especially if low risk (>2 years of age, not living with HIV, not severely malnourished), consider treating the most likely non-TB condition, and follow-up in 1–2 weeks to reassess weight and symptoms. The parent/caregiver should be encouraged to return earlier if there is any deterioration of symptoms. This decision should consider the ability of the child to return for reassessment.

GENERAL AND SUPPORTIVE MEASURES

- » When a child is diagnosed with any form of TB, the parents and other household members should be evaluated to identify any undiagnosed TB.
- » Identify and screen all other child contacts of the identified adult with TB and offer TPT, if appropriate and only after TB disease is excluded.
- » Children with TB usually have paucibacillary disease and pose a low risk of infection to adults and other children.
- » However, children or adolescents who are sputum smear-microscopy or TB-NAAT positive, or older children (≥ 8 years) and adolescents with adult-type pulmonary TB (e.g. cavities on chest X-ray) pose higher infection risk to others.
 - All close contacts of these children with TB should be evaluated for TB symptoms, and where TB disease is excluded, TPT may be indicated.
- » Ensure that appropriate infection prevention and control measures are implemented at the facility with an adult, older child or adolescent with TB, including:
 - Adequate ventilation,
 - Isolation of older children, adolescent or adult with confirmed or suspected infectious pulmonary TB,
 - Use of personal respiratory protection by healthcare workers (e.g. respiratory masks).
- » Institute measures to prevent TB transmission in homes with an adult or older child with TB.
 - Instruct patients to cover their mouth and nose with their sleeve or a tissue when coughing or sneezing. After that, they should wash their hands and throw their tissue in the bin.
 - Windows and doors must be kept open (weather permitting) to increase the ventilation.
 - Where possible, sleep alone and not in a room shared with other household members.
 - During the first two weeks of treatment, when the source patient is still considered infectious, provide them with surgical masks to wear at home, during transportation and for medical consultations.
 - Refrain from having visitors in the home.
- » Monitor the nutritional status (e.g. measure and plot weight, height, mid-upper arm circumference) of the child at baseline and during follow-up to assess response to treatment and to adjust treatment dosing.
- » Energy needs increase in children with TB. Advise the caregiver on how to meet additional energy needs using food available at home. Refer for nutrition support.
- » At every visit ensure the caregiver can confidently crush, mix and give the correct volume of medicines themselves.

MEDICINE TREATMENT

Refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024¹

The specific TB treatment regimen is determined by drug susceptibility results for the child, the TB source patient (e.g., drug-susceptible TB, drug-resistant TB), and the site of TB disease. The duration of TB treatment is determined by the site of TB disease, disease severity at the start of therapy, and treatment response towards the end of treatment. Disease severity is based on clinical, radiological, and microbiological features. In CALHIV, treatment duration is also determined by duration on ART and HIV viral load.

Children and adolescents with non-severe drug-susceptible PTB and drug-susceptible cervical TB lymphadenitis are treated with a shortened 4-month treatment regimen (2 months intensive phase and 2 months continuation phase), provided they adhere to therapy and respond appropriately. CALHIV who meet eligibility criteria based on ART and viral suppression are also eligible for a shortened 4-month regimen. See Table 3 below: Determining eligibility for shortened course DS-TB treatment regimen.

Children and adolescents with severe pulmonary disease, extrapulmonary disease (except isolated cervical TB lymphadenitis), miliary TB, and TB meningitis (TBM) have severe disease and are **NOT** eligible for shortened regimens.

If unsure regarding which duration of therapy to provide, provide a longer course of therapy.

Table 2: Determining eligibility for shortened course DS-TB treatment regimen.

DETERMINE ELIGIBILITY FOR SHORTENED COURSE DS-TB TREATMENT REGIMEN	
Work through steps 1–6 below to assess eligibility to start shortened course of DS-TB treatment:	
INCLUSION CRITERIA FOR SHORT-COURSE	EXCLUSION CRITERIA FOR SHORT-COURSE
STEP 1. AGE OF THE CHILD	
• If no CXR available: child between ages of 3 months and 8 years • If CXR available: child between ages of 3 months and less than 15 years	• Child is under 3 months old • Child is aged 8 years or older & CXR is not available • Child is aged 15 years or older
STEP 2. SITE AND FEATURES OF DISEASE	
• PTB • Cervical lymphadenitis • Simple TB pleural effusion • First episode	• Extrapulmonary TB • Disseminated TB • Miliary TB • TB meningitis • TB bone or joint • Previous TB treatment
STEP 3. HIV STATUS	
• HIV negative • CLHIV on ART for at least 3 months AND VL < 1000 in the last 3 months	• Newly diagnosed HIV • On ART for < 3 months • Unsuppressed VL (VL ≥ 1000 in the last 3 months)
STEP 4. CLINICAL AND NUTRITIONAL STATUS	
• Clinically well without severe acute malnutrition	• Any danger signs * • Severe acute malnutrition (weight-for-height Z-score < -3 OR mid upper arm circumference [MUAC] < 11.5 cm) • Asymmetric or persistent wheezing
STEP 5. RADIOLOGICAL SEVERITY (if x-ray available)	
• Uncomplicated hilar lymphadenopathy: with no airway obstruction/compression • Uncomplicated TB pleural effusion • Consolidation/opacification: < 1 lobe involved • No cavities • No miliary pattern	• Complicated hilar lymphadenopathy: i.e., airway obstruction/ compression, deviation and/or hyperinflation or collapse. • Complicated TB pleural effusion: i.e., loculated effusion, empyema or associated pneumothorax • Consolidation/opacification: ≥ 1 lobe involved • Cavities • Miliary infiltrates
STEP 6. BACTERIOLOGICAL SEVERITY	
• No sputum sample that is AFB smear positive	• AFB smear positive on sputum sample
If NO exclusion criteria, child is ELIGIBLE for shortened TB treatment regimen: start short-course regimen (4 months in total). If ANY exclusion criteria, child is NOT ELIGIBLE for shortened TB treatment regimen: start 6–12 months TB treatment. Decide on duration according to site of disease/HIV status.	
IF ON SHORT COURSE, REASSESS ELIGIBILITY AT THE END OF MONTH 1 AND 4	
• Adherent to TB treatment • MONTH 1: TB signs and symptoms improved • MONTH 4: All TB signs & symptoms resolved and appropriate/improving weight trend	• Non-adherent to treatment • MONTH 1: TB signs and symptoms persisting (not improved) • MONTH 4: TB signs and symptoms have not completely resolved or weight trend not improving
Treatment may be stopped once child completed 4 months. Extend treatment to 6 months.	

NOTE:

- » If no chest X-ray (CXR) is available to confirm that the radiological criteria outlined in Table 23.1 for non-severe pulmonary TB are met, children and adolescents ≥ 8 years are **NOT** eligible for the shorter 4-month treatment regimen.
- » Children and adolescents with a sputum sample that is AFB smear-positive are **NOT** eligible for the shorter 4-month treatment regimen. Lymph node fine needle aspiration smear positivity is not an exclusion.
- » Children and adolescents who are not eligible for the shortened treatment regimen should receive the standard six-month drug-susceptible TB treatment regimen outlined below.
- » If there is any uncertainty about whether a child or adolescent is eligible for treatment shortening or not, rather treat for the full 6 months.
- » In children and adolescents with TB lymphadenitis, if cervical lymph nodes did not decrease in size by month 4 of treatment, continue to 6 months of treatment. If there is not a significant reduction in size of the lymph nodes, or if there is enlargement in lymph nodes, especially if TB was not bacteriologically confirmed, refer for further investigation.

***Danger signs that require urgent attention and precluding use of the shortened regimen**

<u>General danger signs</u> » Unable to drink or breastfeed » Vomits everything » Convulsions » Unconscious or lethargic » Any signs of shock	<u>Signs of severe dehydration (2 of the following)</u> » Unconscious or lethargic » Sunken eyes » Unable to drink, or poor drinking efforts » Skin pinch goes back very slowly
<u>Signs of severe respiratory illness (any of the following)</u> » Chest indrawing » Stridor in calm child » Oxygen saturation < 92% on room air » Central cyanosis	<u>Signs of meningitis (any of the following)</u> » Neck stiffness » Bulging fontanelle » Restless, continuously irritable
	<u>Signs of severe anaemia (any of the following)</u> » Severe palmar pallor » HB < 7 g/dl

Table 3: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed drug-susceptible non-severe pulmonary TB, severe pulmonary TB, and extrapulmonary TB (excluding TBM/CNS TB/ Miliary TB).

	Intensive phase Once daily, 7 days a week		Continuation phase Once daily, 7 days a week		
Target dose (range; mg/kg/day)	Duration 2 months		Non-severe TB Duration 2 months	Severe PTB and most EPTB Duration 4 months	Bone & joint TB Duration 10 months
	Isoniazid (H): 10 (7–15), Rifampicin (R): 15 (10–20)				
Formulation	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4 ml suspension *	E 400mg tablet (not scored) OR 400mg/8ml suspension #	RH 75/50mg Dispersible tablet (scored) OR 75/50mg/4ml suspension*		
Body Weight (kg)					
< 2	Obtain expert advice				
2–2.9	½ tab	1 ml	½ tab		
3–3.9	¾ tab (3 ml)	1.5 ml	¾ tab (3 ml)		
4–7.9	1 tab	2.5 ml	1 tab		
8–11.9	2 tabs	½ tab or 4 ml	2 tabs		
12–15.9	3 tabs	¾ tab or 6 ml	3 tabs		
16–24.9	4 tabs	1 tab or 8 ml	4 tabs		
	RHZE 150/75/400/275 mg tablet		RH 150/75 mg tablet		RH 300/150 mg tablet
25–29.9	2 tabs		2 tabs		1 tab
30–34.9	3 tabs		3 tabs		
35–64.9	4 tabs		4 tabs		2 tabs
≥ 65	5 tabs		5 tabs		
Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets to avoid large volumes of liquid medication.					
* To make an oral suspension, for weight band 3–3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) or 1 x RH 75/50 mg tablet (continuation phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all the suspension to the child orally or via nasogastric tube.					
# If oral suspension required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension					

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed by weight-band **twice daily (12 hourly)**.

Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer to Chapter 9: Human Immunodeficiency Virus infection.

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

For intra-thoracic TB lymphadenopathy with significant airway compression and/or TB pericarditis, consider corticosteroids:

Oral corticosteroids may be considered in children with TB and intra-thoracic lymphadenopathy with significant airway compression or TB pericarditis.

- Prednisone, oral, 2 mg/kg as a single daily dose for 4 weeks.
 - Maximum daily dose: 60 mg.
 - Taper to stop over further 2 weeks.

LoE: IVb^v

Common adverse drug reactions associated with DS-TB medicines in children:

Table 4: Common adverse effects of DS-TB medicines in children

Adverse effect	Responsible drug	Management
Hepatotoxicity (e.g. jaundice, new or persistent nausea, vomiting, tender or enlarged liver)	Pyrazinamide, ethionamide, isoniazid, rifampicin.	» Stop TB treatment and other hepatotoxic drugs (e.g. antiretroviral or cotrimoxazole) immediately. » For further management refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024: Section 14.4 Management of Adverse Drug Events.
Gastrointestinal intolerance (e.g. nausea, vomiting, abdominal pain)	Most DS-TB medicines	» If jaundiced or tender, enlarged liver, or new/persistent vomiting, stop all anti-TB treatment immediately and refer urgently. » If nausea/vomiting only after taking TB treatment without jaundice or tender/enlarged liver, advise taking treatment after eating or at night. If symptoms persist after 1 week, discuss/refer.

Adverse effect	Responsible drug	Management
Joint pain	Pyrazinamide	Symptomatic treatment with paracetamol 15 mg/kg (maximum 1g) 6 hourly as needed for 5 days.
Peripheral neuropathy (e.g. tingling pain or numbness in hands and feet)	Isoniazid	Ensure taking pyridoxine: » Body weight < 6 kg: 6.25 mg (¼ tablet) » Body weight ≥ 6 kg but age < 5 years old: 12.5 mg (½ tablet) daily. » Age ≥ 5 years: 25 mg (1 tablet) daily). If already taking pyridoxine and not responding – discuss/refer all cases. Note: Drug-induced peripheral neuropathy can be irreversible if the offending drug is not stopped promptly.
Dark or orange urine	Rifampicin	Reassure the child or adolescent and caregivers that this is normal and to be expected while taking rifampicin. No intervention required.
Rash	All DS-TB medicines	» For mild, itching rash, with no blistering, mucosal involvement or systemic involvement treat symptomatically. » If erythematous rash with fever, blistering, mucosal involvement, hepatitis, stop all medicines and discuss/refer urgently.
Optic neuritis (e.g. change in vision or visual impairment)	Ethambutol	Stop ethambutol immediately. Refer to ophthalmology for urgent assessment.

LoE:IIIb'

Refer to Management of Tuberculosis in Children and Adolescents. A Clinical Guideline for the Diagnosis and Treatment of Drug-susceptible TB in Children and Adolescents in South Africa. September 2024: Section 14.4 Management of Adverse Drug Events.

REFERRAL

- » Poor response to TB treatment.
- » Adverse drug reactions (ADR) requiring single drug combinations.
- » If the adult or adolescent with TB the child is or was exposed to has drug-resistant TB (DR-TB), refer the child or discuss with an expert.

10.1.2.1. MILIARY TUBERCULOSIS

A19.9

DESCRIPTION

Miliary tuberculosis is a severe form of TB disease that involves the spread of *M. tuberculosis* in the bloodstream to the lungs, brain, and other organs. Children with miliary TB are assumed to have central nervous system (CNS)

involvement and are treated accordingly. Children with miliary TB are treated with 4 drugs for 6 to 9 months and are **NOT** eligible for treatment shortening.

Note: Children with miliary tuberculosis should all be considered to have meningitis, even if no symptoms or neurological signs are present and even if CSF has a normal result. See Section 10.4: Meningitis, tuberculosis (TBM) in children for relevant special investigations and management considerations.

MEDICINE TREATMENT

Children and adolescents < 15 years:

A 6-to-9-month regimen of rifampicin, isoniazid, pyrazinamide and ethionamide, see table 5.

Note: Treatment duration is determined by clinical severity of disease, response to treatment and HIV co-infection. Discuss with an expert.

Table 5: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed drug-susceptible TBM/CNS TB/ Miliary TB)

Body weight	Single phase of treatment, 6–9 months Once daily; 7 days a week		
	RH 75/50 mg dispersible tablet (scored) OR 75/50 mg/4 mL suspension *	Z 500 mg tablet (scored) OR 500 mg/8 mL suspension**	Eto 250 mg tablet (scored) OR 250 mg/8 mL suspension***
	Isoniazid (H): 15–20 mg/kg, maximum dose 450 mg Rifampicin (R): 22.5–30 mg/kg, maximum dose 900 mg	Pyrazinamide (Z): 35–45 mg/kg, maximum dose 2 000 mg	Ethionamide (Eto): 17.5–22.5 mg/kg, maximum dose 1 000 mg
< 2	Obtain Expert Advice		
2–2.9	¾ tablet or 3 mL	1 mL	1.5 mL
3–3.9	1½ tablets	2 mL	2 mL
4–4.9	< 3 months: 1½ tablets ≥ 3 months: 2 tablets	2.5 mL	2.5 mL
5–5.9	2½ tablets	3 mL	3 mL
6–7.9	3 tablets	½ tablet or 4 mL	½ tablet or 4 mL
8–8.9	3½ tablets	¾ tablet or 6 mL	¾ tablet or 6 mL
9–9.9		1 tablet or 8 mL	1 tablet or 8 mL
10–11.9	4 tablets	1 tablet or 8 mL	1 tablet or 8 mL
12–12.9		1½ tablets or 12 mL	1½ tablets or 12 mL
13–14.9	4½ tablets	1½ tablets or 12 mL	1½ tablets or 12 mL
15–15.9	5 tablets	1½ tablets or 12 mL	1½ tablets or 12 mL
16–16.9	6 tablets	1½ tablets or 12 mL	1½ tablets or 12 mL
17–17.9		1½ tablets or 12 mL	1½ tablets or 12 mL
18–19.9	7 tablets	1½ tablets or 12 mL	1½ tablets or 12 mL
20–24.9		1½ tablets or 12 mL	1½ tablets or 12 mL

Body weight	Single phase of treatment, 6–9 months Once daily; 7 days a week		
	RH 75/50 mg dispersible tablet (scored) OR 75/50 mg/4 ml suspension *	Z 500 mg tablet (scored) OR 500 mg/8 mL suspension**	Eto 250 mg tablet (scored) OR 250 mg/8 mL suspension***
25–29.9	RH 300/150 mg tablet: 3 tablets	2 tablets	2 tablets or 16 ml
30–34.9		2 ½ tablets	2 ½ tablets or 20 ml
35–39.9		3 tablets	3 tablets or 24 ml
40–49.9		3 ½ tablets	3 ½ tablets or 28 ml
≥ 50		4 tablets	4 tablets or 32 ml
Children should be taught and encouraged to swallow whole tablets or, if required, fractions of tablets to avoid large volumes of liquid medication if possible. * To make an RH oral suspension for weight band 2–2.9 kg, for each dose, disperse 1 x RH 75/50 mg tablet in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all the suspension to the child orally or via nasogastric tube. ** To make an oral suspension, 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. ***To make an oral suspension, crush 1 x 250 mg ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration			

AND

- Pyridoxine, oral, once daily for 6–9 months for all children and adolescents:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed by weight-band **twice daily (12 hourly)**. Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer Chapter 9: Human Immunodeficiency Virus infection.

10.1.2.2. TUBERCULOSIS MENINGITIS

A17.0

*Notifiable condition.

DESCRIPTION

Tuberculous meningitis is an infection of the meninges caused by *M. tuberculosis*. Early diagnosis and treatment improve the prognosis.

Differentiation from acute bacterial meningitis may be difficult. If there is any doubt, treat for both conditions.

Complications of TBM may be acute or long term:

- » Acute:
 - raised intracranial pressure,
 - cerebral oedema,
 - hemi/quadrilegia,
 - hyponatraemia
 - hydrocephalus,
 - brain infarcts,
 - convulsions,
- » Long-term neurological sequelae include intellectual disability, motor impairment, epilepsy, hydrocephalus, blindness and deafness.

DIAGNOSTIC CRITERIA**Clinical Presentation**

- » Usually includes a history of contact with an adult or adolescent with infectious TB.
- » Onset of symptoms may be gradual with vague complaints of drowsiness, fatigue, vomiting without diarrhoea, fever, weight loss, irritability and headache.
- » Later, symptoms such as convulsions and neurological fall-out may occur.
- » Younger children may present with regression of milestones and older children may present with behavioural changes.
- » Examination may reveal signs of meningeal irritation and signs of raised intracranial pressure, convulsions, cranial nerve palsies, localising signs (such as hemiparesis), altered level of consciousness or coma.
- » The degree of involvement is classified into 3 stages. Prognosis relates to the stage of the disease:
 - Stage 1: Alert and orientated but irritable with no focal neurological signs.
 - Stage 2a: Glasgow coma scale score of 15 (normal level of consciousness), signs of meningeal irritation, mild focal neurological signs like squint or hemiparesis.
 - Stage 2b: Glasgow coma scale score of 11–14, signs of meningeal irritation, mild focal neurological signs like squint or hemiparesis.
 - Stage 3: Stupor/coma, Glasgow coma scale score ≤ 10 , may have abnormal posturing, severe focal neurological signs, e.g., multiple cranial nerve palsies, quadriplegia.

Investigations

- » If a depressed level of consciousness, focal neurological signs, or features of raised intracranial pressure are present, a CT scan should be performed prior to lumbar puncture (LP) to determine if it is safe. Do not delay treatment of TBM until CT scan +/- LP is performed if there is a strong clinical suspicion of TBM. If tuberculoma detected on CT scan, discuss with expert.
- » Lumbar puncture once determined safe to perform.
 - CSF findings may vary depending on the stage and include:
 - Raised protein
 - Chloride and glucose are moderately low
 - Moderate leucocytosis with lymphocyte predominance. **NOTE:** polymorphs may predominate initially in about a third of patients.
 - Gram stain is negative and acid-fast bacilli are seldom found
 - Always send CSF for TB-NAAT and culture
 - A minimum of 3–5 ml CSF is required.
 - A negative TB-NAAT does not exclude TBM.
 - Bacilli may be cultured from the CSF, but results can take up to 4–6 weeks.
 - If TB culture is positive, drug susceptibility testing will be done.
 - Do not request a smear for AFB on the CSF as there is a low diagnostic yield from the low concentration of organisms and it wastes the CSF sample.
- » TST, if child < 5 years and in the absence of a known significant TB exposure and no previous history of TB disease.
- » Chest X-ray.
- » Gastric washings, induced sputum, or expectorated sputum in older children, for TB-NAAT and culture.
- » Electrolytes: check for hyponatraemia.

GENERAL AND SUPPORTIVE MEASURES

- » Hospitalise all children with presumed TBM.
- » Monitor respiratory rate and pattern, pulse rate, blood pressure, oxygen saturation.
- » Monitor neurological status on a regular basis:
 - Assess level of consciousness, posture and pupil responses.
 - Look for focal neurological signs.
- » A rapid deterioration in level of consciousness may indicate worsening hydrocephalus, hyponatraemia, new brainstem infarction, or cerebral oedema. Repeat neuroimaging, review sodium urgently and consider neurosurgical referral.
- » Ensure optimal nutrition and refer for nutritional support. Initially nasogastric feeding may be needed. Placement of percutaneous endoscopic gastrostomy (PEG) should be considered.

- » Refer for rehabilitative support including physiotherapy, occupational therapy, speech therapy.

MEDICINE TREATMENT

- » Differentiation from acute bacterial meningitis may be difficult.
- » If in doubt, treat for both conditions.
- » **NOTE:** Children and adolescents with TBM are treated with 4 drugs for 6–9 months and are **NOT eligible for treatment shortening**.
- » Treatment can be extended to 9 months in children with complex disease, where treatment interruptions or changes occurred, or in children with immune dysfunction (including CALHIV). Discuss with an expert.

Anti-tuberculosis treatment

A 6 to 9-month regimen of rifampicin, isoniazid, pyrazinamide and ethionamide, see table 6.

Note: Treatment duration is determined by clinical severity of disease, response to treatment and HIV co-infection. Discuss with an expert.

Table 6: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed drug-susceptible TBM/CNS TB/ Miliary TB)

Body weight	Single phase of treatment, 6–9 months Once daily; 7 days a week		
	Isoniazid (H): 15–20 mg/kg, maximum dose 450 mg Rifampicin (R): 22.5–30 mg/kg, maximum dose 900 mg	Pyrazinamide (Z): 35–45 mg/kg, maximum dose 2000 mg	Ethionamide (Eto): 17.5–22.5 mg/kg, maximum dose 1000 mg
	RH 75/50 mg dispersible tablet (scored) OR 75/50 mg/4ml suspension*	Z 500 mg tablet (scored) OR 500 mg/8 mL suspension**	Eto 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	1½ tablets	2 mL	2 mL
4–4.9	< 3 months: 1½ tablets ≥ 3 months: 2 tablets	2.5 mL	2.5 mL
5–5.9	2½ tablets	3 mL	3 mL
6–7.9	3 tablets	½ tablet or 4 mL	½ tablet or 4 mL
8–8.9	3½ tablets		
9–9.9		¾ tablet or 6 mL	¾ tablet or 6 mL
10–11.9	4 tablets	1 tablet or 8 mL	1 tablet or 8 mL
12–12.9			
13–14.9	4½ tablets		1¼ tablet or 10 mL
15–15.9	5 tablets	1½ tablets or 12 mL	
16–16.9	6 tablets	1¼ tablets or 10 mL	1½ tablets or 12 mL
17–17.9			
18–19.9		7 tablets	2 tablets or 16 ml
20–24.9			
25–29.9			
30–34.9			
35–39.9	RH 300/150 mg tablet: 3 tablets	3 tablets	3 tablets or 24 ml
40–49.9		3 ½ tablets	3 ½ tablets or 28 ml
≥ 50		4 tablets	4 tablets or 32 ml

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

* To make an oral suspension for weight band 2–2.9 kg, for each dose, disperse 1 x RH 75/50 mg tablet in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all of the suspension to the child orally or via nasogastric tube.

** To make an oral suspension, 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.

*** To make an oral suspension, crush 1 x 250 mg Ethionamide tablet to a fine powder, disperse in 8 ml of water to prepare a concentration

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin-containing TB treatment, dolutegravir is dosed by weight-band **twice daily** (12 hourly). Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer Chapter 9: Human Immunodeficiency Virus infection.

PLUS

- Pyridoxine, oral, once daily for 6–9 months for all children and adolescents:
 - Body weight < 6 kg: 6.25 mg ($\frac{1}{4}$ tablet).
 - Body weight $\geq$ 6 kg but age < 5 years: 12.5 mg ($\frac{1}{2}$ tablet).
 - Age $\geq$ 5 years: 25 mg (1 tablet).

PLUS

Corticosteroids

- Prednisone, oral, 2 mg/kg as a single daily dose for 4 weeks.
 - Maximum daily dose: 60 mg.
 - Taper to stop over further 2 weeks.

LoE ^{IV}

If there is concern around raised intracranial pressure: See Section 13.12: Raised intracranial pressure.

Hydrocephalus

- » Review by neurosurgeon or paediatric neurologist where possible.
- » Avoid low sodium IV fluids in these patients, i.e., products with sodium concentrations < 60 mmol/L.
- » Communicating hydrocephalus with severely raised intracranial pressure may be managed with medicines once hydration status is stable, and/or with serial lumbar puncture and specialist consultation (tertiary hospital care).

Treatment of communicating hydrocephalus

If dehydrated, rehydrate with sodium chloride 0.9%, IV.

Start diuretics as soon as the patient is well hydrated and serum electrolytes are within the normal range:

- Acetazolamide, oral, 50 mg/kg/day, divided into 3 doses and given 8 hourly for one month.
 - Maximum daily dose: 1000 mg.
 - Monitor for metabolic acidosis and serum potassium derangements.

PLUS

- Furosemide, oral, 1 mg/kg/day, divided into 2 doses, given 12 hourly for one month.
 - Maximum 40 mg per dose.
 - Taper slowly over 2 weeks if the intracranial pressure has normalised, as indicated by clinical response or resolution of hydrocephalus on follow-up scan.
 - Do not restrict fluids once on diuretics.

Hyponatraemia

Low serum sodium is common in children with TBM. Hyponatraemia (< 125 mmol/L) may precipitate seizures and worsen coma. Serum sodium < 120 mmol/L is life-threatening.

Low serum sodium in TBM may be due to:

- » The syndrome of inappropriate antidiuretic hormone (SIADH) causing fluid retention. SIADH is associated with lower serum uric acid and low urine output. Hyponatraemia from SIADH responds to fluid restriction.
- » Cerebral salt wasting with hypovolaemia. Cerebral salt wasting is associated with normal serum uric acid and high urine output. Hyponatraemia from cerebral salt wasting responds to fluid replacement with sodium chloride 0.9%.

Management of hyponatraemia depends on acuity, cause, severity and presence of symptoms. Too rapid correction of low sodium may be associated with life-threatening complications.

Table 7: Management of serum sodium in children with TBM

Classification of hyponatraemia/low serum sodium	Definition mmol/L	Action
Normal	135–145	None needed – continue normal fluid intake.
Mild	130–134	Review hydration status carefully and consider repeating after 24 hours if it remains clinically stable.
Moderate	120–129	Intravenous correction is usually needed: correction at 4 mmol/L over 24 hours. If neurological symptoms associated with low sodium occur, an initial bolus of 3 mL/ kg over 1 hour of 3% saline can be considered. If chronic hyponatraemia occurs, oral correction* can be considered, provided there are no symptoms of hyponatraemia.

Classification of hyponatraemia/ low serum sodium	Definition mmol/L	Action
Severe	< 120	Intravenous correction is usually needed: correction at 4 mmol/L over 24 hours with a maximum correction of 8 mmol/L for 24 hours. Regardless of neurological symptoms, an initial bolus of 3–5 mL/kg of 3% saline over 1 hour can be considered.
» Sodium deficit: $\text{Weight in kg} \times 0.6 \times (140 - \text{current serum sodium})$. » If sodium chloride (NaCl), 0.9% is used: – Volume of 0.9% NaCl required to address the sodium deficit = Sodium deficit / 0.154. » If NaCl, 3% is used: – Volume of 3% saline required to address the sodium deficit = Sodium deficit / 0.513. » Calculating the time (in hours) needed to correct the deficit: $= 2 \times (140 - \text{current serum sodium})$. » DO NOT CORRECT TOO FAST. Rapid correction can cause osmotic demyelination syndrome. Serum sodium should not increase > 8 mmol/L in 24 hrs. Stop additional sodium replacement when it reaches 135 mmol/L. » The same calculations apply for sodium deficit and the time to correct the deficit, whether for IVI or oral correction.		

Seizures

- » Generalised and focal seizures are common in children with TBM.
- » Seizures may occur acutely, and survivors of TBM may develop epilepsy.
- » Routine use of anti-seizure medications in children with TBM is not recommended.
- » To manage status epilepticus and seizures, refer to Sections 13.1: Epileptic Seizures and 13.2: Status Epilepticus.
- » Choice of antiseizures medication should consider drug interactions with rifampicin and other anti-TB medicines (e.g., avoid carbamazepine).

REFERRAL

- » For suspected or confirmed drug-resistant TBM, consult an expert.
- » TBM not responding to adequate therapy.
- » TBM with complications requiring investigations or interventions not available locally.
- » Suspicion of non-communicating hydrocephalus.

10.1.2.3. TREATMENT OF CHILDREN WHO WERE PREVIOUSLY SUCCESSFULLY TREATED FOR TB (RE-TREATMENT)

A child who was previously successfully treated for pulmonary TB is at increased risk for re-infection with TB. It is imperative to exclude drug-resistant TB by requesting a TB-NAAT plus culture with drug susceptibility testing (DST). Determine drug susceptibility of any known person with infectious

pulmonary TB in contact with the child. If the above does not indicate resistant TB, treat as drug-susceptible TB with close monitoring of response. Consider an extension of the duration of the continuation phase of therapy in the case of retreatment.

NOTE: Children and adolescents previously treated for TB are **NOT** eligible for the treatment shortening.

REFERRAL

» Poor clinical response to TB retreatment.

10.2. DRUG-RESISTANT TUBERCULOSIS (DR-TB)

U84.3

See the National Department of Health Updated Clinical Reference Guide: Clinical Management of **Rifampicin-Resistant Tuberculosis**, September 2023^{vii}

DESCRIPTION

Drug-resistant tuberculosis (DR-TB) occurs when *M. Tuberculosis* strains demonstrate resistance to one or more first-line or second-line anti-TB drugs.

Table 8 below presents key definitions and terminology for drug-resistant tuberculosis.

Table 8: Terminology and definitions for drug-resistant TB

Terminology	Description
Monoresistant TB	Resistant to only one anti-TB drug, without resistance to other drugs
Rifampicin-resistant TB (RR-TB)	Resistant to at least rifampicin ± resistance to another anti-TB drug. This includes MDR-TB, Pre-XDR-TB, rifampicin monoresistant TB, and XDR-TB
Multidrug resistant TB (MDR-TB)	Resistant to rifampicin and isoniazid (± resistance to other anti-TB drugs)
Pre-extensively drug-resistant TB (Pre-XDR-TB)	Resistant to rifampicin (± resistant to isoniazid) AND resistant to fluoroquinolones
Extensively drug-resistant TB (XDR-TB)	Resistance to: • Rifampicin (± resistant to isoniazid), AND • At least one fluoroquinolone (levofloxacin or moxifloxacin) AND • Bedaquiline OR linezolid

DIAGNOSTIC CRITERIA

The diagnosis of TB disease in children is made on history, clinical examination, and microbiological and radiological investigations (refer to Section 10.1: Tuberculosis, Drug-Susceptible above). Drug-resistant TB (DR-TB) disease is suspected in children with TB disease and a recent DR-TB exposure or who are failing first-line TB treatment despite good adherence.

Clinical Presentation

The clinical presentation is identical to drug-susceptible TB disease.

Investigations

- » DR-TB disease is microbiologically confirmed in a child with signs and symptoms of TB and a positive TB-NAAT or TB culture demonstrating rifampicin resistance and/or isoniazid resistance.
- » Always collect at least two good-quality specimens (sputum, induced sputum, gastric aspirates and/or nasopharyngeal aspirates) for TB-NAAT and TB culture with DST.
- » In children with EPTB fine needle aspirates of lymph nodes, biopsies, pleural fluid, ascitic fluid and cerebrospinal fluid should also be sent for microbiological confirmation.
- » Children who test positive for *M. tuberculosis* with rifampicin resistance must have additional specimens sent for DR-TB reflex testing that may include Xpert® MTB/XDR testing for fluoroquinolone resistance, targeted next generation sequencing (tNGS), and TB culture and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive.
- » Many children will not have microbiological confirmation of DR-TB due to paucibacillary or extrapulmonary disease.
 - In these children, treatment should be based on the drug susceptibility testing of the *M. tuberculosis* strain from the most likely source patient.

GENERAL AND SUPPORTIVE MEASURES

- » When a child is diagnosed with any form of DR-TB, the parents and other household members should be evaluated to identify those with undiagnosed TB.
 - Identify and screen all other child contacts of the identified adult with DR-TB and offer TB preventive therapy (TPT) if appropriate and only after TB disease is excluded.
- » Children with TB usually have paucibacillary disease and pose a low risk of infection to adults and other children.
- » However, children or adolescents who are sputum AFB or TB-NAAT positive, or older children (≥ 8 years) and adolescents with adult-type pulmonary TB (e.g. cavities on chest X-ray) pose higher infection risk to others.
- » All contacts of these children with DR-TB should be evaluated for TB symptoms, and where TB disease is excluded, appropriate TPT should be provided.

- » Institute measures to prevent TB transmission in homes with an adult or older child with TB
 - Instruct patients to cover their mouth and nose with their sleeve or a tissue when coughing or sneezing. After that, they should wash their hands and throw their tissue in the bin.
 - Windows and doors must be kept open (weather permitting) to increase the ventilation
 - Where possible, sleep alone and not in a room with other household members.
 - During the first two weeks of treatment when the patient is still considered infectious, provide them with surgical masks to wear at home, during transportation and medical consultations.
 - Refrain from having visitors in the home.
- » Monitor the nutritional status (e.g. measure and plot weight, height, mid-upper arm circumference) of the child at baseline and during follow-up to assess response to treatment and to adjust treatment dosing.
- » Energy needs increase in children with TB. Advise the caregiver on how to meet additional energy needs using food available at home. Refer for nutrition support.
- » At every visit ensure the caregiver can confidently crush, mix and give the correct volume of medicines themselves.
- » Preparation and administration of medications to treat DR-TB in children can be complicated and intensive adherence support should be provided to the family throughout treatment.

10.2.1. ISONIAZID MONORESISTANT TUBERCULOSIS IN CHILDREN AND ADOLESCENTS < 15 YEARS

A15.0–3/A15.7–8/A16.0–2/A16.4/A16.7–9 + (U50.00–01+U50.10–11) + (B20.0)/U50.00/U50.1/U50.10/U50.11

DESCRIPTION

Isoniazid monoresistant TB is TB disease caused by *M. tuberculosis* that is resistant to isoniazid but susceptible to rifampicin. If isoniazid monoresistance is detected > 28 days after starting treatment with RHZE for drug-susceptible TB, repeat TB-NAAT testing to rapidly assess for rifampicin resistance.

MEDICINE TREATMENT

Treatment should be given for at least 6 months.

Confirmed isoniazid monoresistant TB and fluoroquinolone susceptible:

- RHZ plus E at standard weight-based dosing, oral, daily.

AND

- Levofloxacin, oral, daily.

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg ($\frac{1}{4}$ tablet).
 - Body weight $\geq$ 6 kg but age < 5 years: 12.5 mg ($\frac{1}{2}$ tablet).
 - Age $\geq$ 5 years: 25 mg (1 tablet).

Table 9: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed isoniazid mono-resistant pulmonary or extrapulmonary TB (excluding TBM, CNS TB, Miliary TB, bone/joint TB)

Single phase, 6 months duration Oral, 7 days a week			
Formulation	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4ml suspension*	E 400mg tablet (not scored) OR 400mg/8ml suspension**	Levofloxacin 250 mg tablet OR 500 mg tablet OR 25 mg/ml suspension***
Body Weight (kg)			
Target dose (range; mg/kg/day)	Isoniazid (H): 10 (7–15) mg Rifampicin (R): 15 (10–20) mg Pyrazinamide (Z): 35 (30–40) mg Ethambutol (E): 20 (15–25) mg Levofloxacin: 15–20 mg		
3–3.9	¾ tab (3 ml)	1.5 ml	2 ml
4–4.9	1 tab	2.5 ml	
5–7.9	1 tab	2.5 ml	5 ml or ½ x 250 mg tablet
8–9.9	2 tabs	½ tab or 4 ml	
10–11.9	2 tabs	½ tab or 4 ml	10 mL or 1 x 250 mg tablet
12–12.9	3 tabs	¾ tab or 6 ml	
13–15.9	3 tabs	¾ tab or 6 ml	
16–24.9	4 tabs	1 tab or 8 ml	15 mL or 1 ½ x 250 mg tablet
≥ 25	HRZE 75/150/400/275 mg tablet		
25–29.9	2 tabs		1 x 500 mg tablet or 2 x 250 mg tablet or 20 mL
30–34.9	3 tabs		1 ½ x 500mg or 3 x 250mg tablets daily
35– < 45.9 kg	4 tabs		
46–65 kg	4 tabs		2 x 500mg or 4 x 250mg tablets daily
≥ 65	5 tabs		
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			
* To make an oral suspension, for weight band 3–3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) in 4 ml of water. administer 3 ml, discard			

unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all of the suspension to the child orally or via nasogastric tube.

** If oral suspension required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

***For levofloxacin 25mg/ml suspension: Crush and disperse 1 x 250mg tablet in 10 mL water.

Confirmed isoniazid mono-resistant TB and fluoroquinolone susceptible AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, 15 to 20 mg/kg daily.

REFERRAL

- » Discuss children with isoniazid mono-resistant TB, miliary TB or bone/joint TB with an expert as they may require a different regimen or duration of treatment.
- » Children and adolescents not responding to appropriate TB treatment.
- » If unsure of appropriate treatment regimen – Telephonic consultation with specialist.

10.2.2. RIFAMPICIN-RESISTANT, PRE-XDR AND XDR-TB IN CHILDREN AND ADOLESCENTS < 15 YEARS

U50.0, U50.2, U50.20, U50.21, U50.5

DESCRIPTION

Rifampicin-resistant tuberculosis (RR-TB) is TB disease caused by *M. tuberculosis* that is resistant to rifampicin, with or without resistance to other anti-TB drugs. Pre-XDR-TB is TB disease caused by *M. tuberculosis* that is resistant to rifampicin (with or without resistance to isoniazid) and to at least one fluoroquinolone (either levofloxacin or moxifloxacin). Extensively drug-resistant TB (XDR-TB) is TB disease caused by *M. tuberculosis* that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid.

DIAGNOSIS

All children and adolescents with signs and symptoms of TB should have a specimen sent for TB-NAAT testing. Some TB-NAATs test for both rifampicin and isoniazid resistance (e.g. BD MAXTM MDR-TB). Xpert[®] MTB/RIF Ultra, a

type of TB-NAAT, only tests for rifampicin resistance. A rifampicin resistant result detected by Xpert® MTB/RIF Ultra, or other TB-NAAT, is sufficient to start a patient on RR-TB treatment. All children and adolescents who test positive for *M. tuberculosis* with rifampicin resistance must have additional specimens sent for DR-TB reflex testing that may include Xpert® MTB/XDR testing for fluoroquinolone resistance, targeted next generation sequencing (tGNS), TB microscopy and culture, and phenotypic drug susceptibility testing for bedaquiline and linezolid if culture positive. Many children will not have microbiological confirmation due to paucibacillary or extrapulmonary disease. In children, without microbiological confirmation of RR-TB/Pre-XDR-TB, treatment should be based on the drug susceptibility of the *M. tuberculosis* strain from the most likely source patient.

MEDICINE TREATMENT

The composition and duration of RR-TB/Pre-XDR-TB treatment regimens is based on the drug susceptibility (or that of the most likely source patient), as well as site and severity of TB disease.

Severe TB disease in children < 15 years	Non-severe TB disease in children < 15 years
» Chest x-ray: bilateral disease (consolidation, infiltrates), or presence of cavities. » Mediastinal lymph nodes causing airway compression. » Extrapulmonary forms of disease other than isolated peripheral lymph nodes or simple pleural effusion.	» Isolated peripheral lymphadenopathy. » Chest x-ray: unilateral disease (consolidation, infiltrates in < 1 lobe in total) without cavities. » Small/simple pleural effusions. » Mediastinal lymph nodes without airway compression.

- » Regimens should include at least 4 drugs considered to be effective, with the addition of a 5th drug in severe disease.
- » Children with non-severe RR-TB/Pre-XDR-TB disease are likely to be successfully treated with 6-month regimens containing at least 4 effective drugs.
- » Children with more severe disease are likely to require longer treatment for 9 or 12 months.
- » There is no specified intensive or continuation phase for paediatric RR-TB/Pre-XDR-TB regimens and most drugs should be continued through treatment.
- » All-oral regimens must be prioritised.
- » Toxicity, and feasibility of adverse effect monitoring for specific medicines, may limit the use of certain medicines.
- » Drug dosing is based on the child's weight, and dosing must be modified as children gain or lose weight.
- » Child-friendly formulations of anti-TB medications should be used whenever possible.

- » All cases of RR-TB/Pre-XDR-TB with confirmed or presumed resistance to bedaquiline, clofazimine, or linezolid should be referred to a paediatric RR-TB expert or infectious diseases specialist or to the National clinical advisory committee (NCAC) (Email: NCAC@witshealth.co.za).

Examples of anti-tuberculosis drugs used in RR-TB treatment

- Levofloxacin
- Bedaquiline
- Linezolid
- Clofazimine
- Terizidone
- Ethambutol
- Delamanid
- Pyrazinamide
- Ethionamide
- Para amino salicylic acid
- High-dose isoniazid

Refer to latest programmatic guidelines for specific treatment regimens and weight-based dosing charts (National Department of Health. Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis. September 2023).

REFERRAL

- » Children and adolescents not responding to appropriate TB treatment.
- » If unsure of appropriate treatment regimen - Telephonic consultation with specialist.

10.3. TB PREVENTIVE THERAPY (TPT) FOR TUBERCULOSIS EXPOSURE/INFECTION

Screen all infants, children and adolescents with a history of significant exposure to a TB source patient. A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). The exposure must have occurred while the source patient was not on TB treatment OR if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment.

In addition, a newborn has had significant exposure to a person with infectious TB if the baby was born to a mother with TB and the mother:

- » started TB treatment within 2 months before delivery OR

- » demonstrates poor clinical response to TB treatment OR
- » is TB smear or acid-fast bacilli (AFB) or culture positive at delivery OR
- » is diagnosed with TB soon after delivery.

Screening includes history taking, clinical examination and appropriate investigations. For guidance on screening in infants < 3 months, see Section 10.1.1 Tuberculosis, perinatal. Give full anti-tuberculosis treatment if the diagnosis of TB disease is confirmed or suspected (See Sections 10.1.1 Tuberculosis, perinatal; and 10.1.2 Tuberculosis in children and adolescents < 15 years). If there is a history of a significant exposure, and TB disease has been excluded consider the need for TB preventive therapy (TPT). Never give TPT to children with active TB disease.

Indications for TPT:

- » All asymptomatic infants and children < 5 years, and children or adolescents with HIV (CALHIV), who are clinically well, with a normal chest X-ray, irrespective of TST, in close contact with someone with infectious pulmonary TB should receive TPT.

NOTE: Previous TPT or TB treatment does not protect a child against subsequent TB exposure/infection. If there is a new exposure to someone with infectious pulmonary TB after completion of a course of TPT, it can be repeated. TPT should be repeated after each episode of documented TB exposure. In the case of a new exposure to someone with infectious pulmonary TB while the child is on TPT, the duration of TPT should continue for at least as long as the source patient remains infectious.

10.3.1. TUBERCULOSIS PREVENTIVE THERAPY (TPT) AFTER DRUG-SUSCEPTIBLE TUBERCULOSIS EXPOSURE

TPT for significant drug-susceptible TB exposure:

- » In HIV-negative children < 25 kg, the preferred regimen is 3RH (rifampicin plus isoniazid daily for 3 months).
- » In CALHIV, the preferred regimen is 6H (isoniazid daily for 6 months).

If HIV-negative or HIV-exposed not on nevirapine and < 25 kg:

- Rifampicin/isoniazid 75/50 mg daily for 3 months

Weight (kg)	RH (Daily) fixed dose combination		Duration
	75/50 mg	If crushed and mixed in in water	
2–2.9	½ tablet	Mix 1 tablet in 4 mL of water. Give only 2 mL of this mixture.	3 months
3–3.9	¾ tablet	Mix 1 tablet in 4 mL of water. Give only 3 mL of this mixture.	
4–5.9	1 tablet	Mix 1 tablet in 4 mL of water and give ALL of this mixture.	
6–7.9	1 ½ tablets	Mix 1 ½ tablets in 5–10 mL of water and give ALL of this mixture.	
8–11.9	2 tablets	Mix 2 tablets in 5–10 mL of water and give ALL of this mixture.	
12–15.9	3 tablets	Mix 3 tablets in 5–10 mL of water and give ALL of this mixture.	
16–24.9	4 tablets	Mix 4 tablets in in 5–10 mL of water and give ALL of this mixture.	
≥ 25	Use adult formulations and doses		

AND

In addition, administer pyridoxine to all breastfed infants, malnourished children, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 3 months.:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).

If CALHIV or HIV-exposed on nevirapine:

- Isoniazid, oral, 10 mg/kg daily for 6 months.

Weight (kg)	Daily isoniazid 100mg tablet	Duration
2–3.4	¼ tablet	6 months
3.5–4.9	½ tablet	
5–7.4	¾ tablet	
7.5–9.9	1 tablet	
10–14.9	1 ½ tablets	
15–19.9	2 tablets	
20–24.9	3 tablets (or one 300 mg tablet)	
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

In addition, administer pyridoxine to all breastfed infants, malnourished children, CALHIV, or those with existing neuropathy. Acute malnutrition refers

to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

10.3.2. TUBERCULOSIS PREVENTIVE THERAPY (TPT) AFTER DRUG-RESISTANT TUBERCULOSIS EXPOSURE

Isoniazid mono-resistance (rifampicin-susceptible):

- Rifampicin , oral, for 4 months.

Daily dose		Dose calculation/preparation (depending on available rifampicin formulation)	Notes
< 10 years old	15 mg/kg daily	<u>15 mg/ml solution</u> Rifampicin 150mg capsule: open capsule into 10 ml of water.	If rifampicin alone is unavailable, discuss alternative with expert.
≥ 10 years old	10 mg/kg daily	<u>30 mg/ml solution</u> - Rifampicin 300mg capsule: open capsule into 10 ml of water. <u>60 mg/ml solution</u> - Rifampicin 600mg capsule: open capsule into 10 ml of water.	

CAUTION

In CALHIV on dolutegravir-based ART and rifampicin TPT, dolutegravir is dosed by weight-band **twice daily (12 hourly)**. Continue twice daily dosing of dolutegravir until 2 weeks after stopping rifampicin. Refer Chapter 9: Human Immunodeficiency Virus infection.

Rifampicin-mono-resistance (source patient is confirmed isoniazid-susceptible by culture-based drug susceptibility testing):

- Isoniazid, oral, 10 mg/kg daily for 6 months.

Weight (kg)	Daily isoniazid 100mg tablet	Duration
2–3.4	¼ tablet	6 months
3.5–4.9	½ tablet	
5–7.4	¾ tablet	
7.5–9.9	1 tablet	
10–14.9	1 ½ tablets	
15–19.9	2 tablets	
20–24.9	3 tablets (or one 300 mg tablet)	6 months
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

In addition, administer pyridoxine to all breastfed infants, malnourished children, CALHIV, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

Rifampicin-resistant TB (susceptible to fluoroquinolones):

- Levofloxacin ^W 15–20 mg/kg daily for 6 months (maximum dose: 1000 mg).

OR

- Isoniazid, oral, 15–20 mg/kg daily for 6 months (maximum dose: 600 mg). LoE: IVb^{III}
 - Only if susceptible to high-dose isoniazid (e.g., low-level INH resistance).

Weight	Levofloxacin 250 mg tablet (scored) OR 500 mg tablet (scored)		OR	Isoniazid 100 mg tablet OR 300 mg tablet	
	250 mg tablet	500 mg tablet		100 mg tablet	300 mg tablet
3–4.9 kg	2 mL*		OR	5 mL*	
5–6.9 kg	5 mL* or			1 tablet	
7–9.9 kg	0.5 tablet			1.5 tablets	
10–15.9 kg	1 tablet			2 tablets	
16–23.9 kg	1.5 tablets			3 tablets	1 tablet
24–29.9 kg	2 tablets	1 tablet		4 tablets	1.5 tablets
30–35.9 kg	3 tablets	1.5 tablets		4.5 tablets	
36–45.9 kg					
46–55.9 kg	4 tablets	2 tablets			2 tablets
56–69.9 kg					
≥ 70 kg					
*Dissolution of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide.					

AND

If isoniazid TPT, administer pyridoxine to all breastfed infants, malnourished children, CALHIV, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months:
 - Body weight < 6 kg: 6.25 mg ($\frac{1}{4}$ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg ($\frac{1}{2}$ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

NOTE: Pyridoxine supplementation is not required with levofloxacin TPT.

If the person with infectious pulmonary TB, the child was in contact with has Pre-XDR-TB or XDR-TB refer or discuss with specialist. Ensure household infection control practices are observed. These children need close, ongoing follow-up for at least two years.

REFERENCES

- ⁱ National Department of Health. Management of Tuberculosis in Children and Adolescents – A Clinical Guideline for diagnosis and treatment of Drug-susceptible TB in Children and Adolescents in South Africa, September 2024. https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-10/Management%20of%20Paeds%20and%20Adol%20Tuberculosis%20Guideline%20%20v6%20202409118%20signed%20WEBview%20%281%29_0.pdf
- ⁱⁱ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022). <https://iris.who.int/server/api/core/bitstreams/6212d328-f45e-4905-ae32-e0161d4f0029/content>
- ⁱⁱⁱ World Health Organization (WHO): WHO Guideline on the prevention and management of wasting and nutritional oedema (acute malnutrition) infants and children under 5 years.
- ^{iv} NEMLC Limited Review: Corticosteroids for the treatment of tuberculous pericarditis. May 2026
- ^v van Toorn R, Springer P, Laubscher JA, Schoeman JF. Value of different staging systems for predicting neurological outcome in childhood tuberculous meningitis. *Int J Tuberc Lung Dis*. 2012 May;16(5):628-32. doi: 10.5588/ijtld.11.0648. Epub 2012 Mar 8. PMID: 22410643.
- ^{vi} NEMLC Limited Review: Corticosteroids for the treatment of tuberculous meningitis (TBM). February 2026
- ^{vii} National Department of Health. Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

SOUTH AFRICAN NATIONAL DEPARTMENT OF HEALTH

NEMLC SUMMARY REPORT ON UPDATES MADE TO THE THE STANDARD TREATMENT GUIDELINES AND ESSENTIAL MEDICINE LIST GUIDANCE PRODUCTS

Paediatric Hospital Chapter 10: Tuberculosis

Document Version

Report Version	Date	Detail
V1.1	September 2026	Ratified for publication
V 1.0	July 2026	Draft for presentation to NEMLC 30 July 2026

Specific guidance products (Tick relevant and specify chapter number)

No	Guidance Product	Tick	Number
1.	Paediatric Hospital Level STGs – Chapter 10: Tuberculosis	✓	Full Chapter Update

Medicine Amendments

Medicine amendment recommendations, with supporting evidence and rationale are listed below. If appropriate can include non-medicine amendments (for example if item has a large impact on how medicine is accessed) and stipulated reference price. Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG). Include updates post initial publication first or mark/highlight appropriately.

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / REMOVED / AMENDED	TI* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
Report Version v1.0							
10.1 Drug Susceptible Tuberculosis							
10.1.1 Tuberculosis, perinatal	✓		✓		BCG vaccine - Administration changed to at birth regardless of TB or HIV exposure. - If TPT or TB treatment is started in first 6 weeks of life, BCG should be repeated one day after completion of TPT or TB treatment. - If HIV positive - should receive repeat BCG after completion of TPT or TB treatment if they are on ART and clinically well (CD4 > 25%).	AMENDED	n/a
	✓		✓		Ethionamide	ADDED	n/a
	✓		✓		Ethambutol	ADDED	n/a
	✓		✓		Pyridoxine For specific indications	ADDED	n/a
	10.1.2 Tuberculosis	✓		✓		Course duration	AMENDED

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / REMOVED / AMENDED	T1* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
in children	✓		✓		Ethambutol	ADDED	n/a
	✓		✓		Rifampicin/Isoniazid 60/60mg formulation	DELETED	n/a
10.1.2 Tuberculosis in children: with intra-thoracic TB lymphadenopathy with significant airway compression and/or TB pericarditis			✓		Corticosteroids	ADDED	n/a
10.1.2.1 Miliary TB in children			✓		Dispersible formulation	ADDED	n/a
			✓		Rifampicin/Isoniazid 60/60mg formulation	DELETED	n/a
			✓		Doses and max doses	AMENDED	n/a
10.1.2.2 Meningitis, Tuberculosis (TBM) in children			✓		Dispersible formulation	ADDED	n/a
			✓		Rifampicin/Isoniazid 60/60mg formulation	DELETED	n/a
			✓		Doses and max doses	AMENDED	n/a
			✓		Corticosteroid – prednisone	RETAINED	n/a
			✓		Acetazolamide	DOSE ALIGNED	n/a
			✓		Furosemide	DOSE ALIGNED	n/a
			✓		Mannitol	REMOVED	n/a
10.2.1 Isoniazid monoresistant tuberculosis (confirmed isoniazid monoresistant TB)	✓		✓		Rifampicin Isoniazid Pyrazinamide Ethambutol	ADDED	n/a
	✓		✓		Pyridoxine	ADDED	
	✓		✓		Levofloxacin	ADDED	n/a
10.2.1 Isoniazid monoresistant tuberculosis (confirmed isoniazid monoresistant TB) AND contraindication to isoniazid	✓		✓		Rifampicin	ADDED	n/a
	✓		✓		Pyrazinamide	ADDED	n/a
	✓		✓		Ethambutol	ADDED	n/a
	✓		✓		Levofloxacin	ADDED	n/a
10.2.2 Rifampicin resistant, Pre-XDR, and XDR	✓		✓		Bedaquiline (BDQ)	ADDED	n/a
	✓		✓		Clofazimine (CFZ)	ADDED	n/a
	✓		✓		Delamanid (DLM)	ADDED	n/a
	✓		✓		Ethionamide (ETO)	ADDED	n/a
	✓		✓		High-dose isoniazid (hdINH)	ADDED	n/a
	✓		✓		Levofloxacin (LFX)	ADDED	n/a
	✓		✓		Linezolid (LZD)	ADDED	n/a
	✓		✓		Para-amino salicylic acid (PAS)	ADDED	n/a
	✓		✓		Terizidone (TRD)	ADDED	n/a

STG/SECTION	GUIDANCE PRODUCTS (Tick relevant)				MEDICINE / MANAGEMENT	ADDED / REMOVED / AMENDED	T1* CONSIDERATIONS (if applicable)
	PHC STGs & EML	AH STG & EML	PaedH STG & EML	TQ EML			
10.3.1 TB Preventative Therapy (TPT) for drug sensitive TB exposure	✓		✓		3RH	ADDED	n/a
	✓		✓		Pyridoxine	ADDED	
10.3.2 TB Preventative Therapy (TPT) for drug resistant TB exposure			✓		Levofloxacin	RETAINED	n/a

*Therapeutic Interchange

General

National Programme Guidelines

Updates were made as far as possible to align with the National Programme Guidelines:

- Management of Tuberculosis in Children and Adolescents – A Clinical Guideline for diagnosis and treatment of Drug-susceptible TB in Children and Adolescents in South Africa, September 2024.¹
- Management of Tuberculosis in Children and Adolescents (0-15 years) – A quick Reference Guide.²
- Clinical Management of Rifampicin-Resistant Tuberculosis – Updated Clinical Reference Guide, September 2023.³
- National Guidelines on the Treatment of Tuberculosis Infection. February 2023.⁴

Dosing tables were aligned with those in the National Programme TB Guidelines to ensure consistency in format and presentation.

Note: Not all recommendations related to TB preventative therapy (TPT) treatment populations and regimens from the NDoH TB Programme are aligned. Only NEMLC approved treatment populations and regimens are included.

The following guiding statement has been added to the start of the chapter:

TB guidelines are updated regularly. This STG should be read in conjunction with the most recent National Tuberculosis Control Programme Guidelines.

¹ National Department of Health. Management of Tuberculosis in Children and Adolescents – A Clinical Guideline for diagnosis and treatment of Drug-susceptible TB in Children and Adolescents in South Africa, September 2024. https://knowledgehub.health.gov.za/system/files/elibdownloads/2024-10/Management%20of%20Paeds%20and%20Adol%20Tuberculosis%20Guideline%20%20v6%20202409118%20signed%20WEBview%20%281%29_0.pdf

² National Department of Health. Management of Tuberculosis in Children and Adolescents (0-15 years) – A quick Reference Guide, 2025. https://tbthinktank.org/wp-content/uploads/2025/09/Paeds-TB-Quick-Ref-Guide_Final_Sept-2025.pdf

³ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis – Updated Clinical Reference Guide, September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

⁴ National Department of Health. National Guidelines on the Treatment of Tuberculosis Infection. February 2023. https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-04/Health_Latent%2520TB%2520Infection_2023_web.pdf

Age cut-offs

Discrepancies with age cut-offs for children with drug-susceptible and drug-resistant TB were noted between the National TB programmatic guidelines and the previously approved NEMLC recommendations. The NEMLC approved age cut-offs are retained. Engagement with the TB programme will however be undertaken to understand age recommendations included in their documents.

- Drug-Susceptible TB (DS-TB): Children eligible < 16 years eligible for treatment shortening. (SHINE Trial)⁶
- Drug-Resistant TB (DR-TB): Children ≥ 14 years eligible for BPAL- (BPAL-L WHO adolescent review)⁵

Following discussion at NEMLC together with TB programme representatives, it was proposed that a common age cut off of 15 years be used for both drug-susceptible, and drug-resistant tuberculosis for pragmatic implementation. Thus, the STGs have aligned as follows:

- Drug-Susceptible TB (DS-TB): Children eligible < 15 years eligible for treatment shortening.
- Drug-Resistant TB (DR-TB): Children ≥ 15 years eligible for BPAL

Terminology

- Following external stakeholder comment, the term 'drug-sensitive' was amended to 'drug-susceptible' throughout the chapter.
- The acronym for rifampicin, isoniazid, pyrazinamide and ethambutol fixed dose combinations was standardised as follows: "RHZE; RHZ; RH".

Infection prevention and control measures

Guidance on basic infection prevention and control measures has been added under the section on general measures as detailed below, in response to external comments received.

Non-severe DS-TB in adolescents – radiological criteria

STG guidance on the radiological criteria that excludes adolescents from treatment shortening for non-severe DS-TB has been retained as lung consolidation ≥ 1 lobe. This aligns with the national TB programme guideline and is informed by the radiological definition included in the SHINE trial.⁷ This contrasts with the WHO guideline⁶ which defines non-severe DS-TB as PTB confined to one lobe.

STG – 10.1.1 Tuberculosis, Perinatal

General Measures

Following external comment, a note was added to ensure that the mother is started on effective anti-TB treatment while breastfeeding is established.

The text was updated as follows:

- » It is not recommended that infants be separated from their mothers after birth, even if the mother is known to still be contagious. Establishing breastfeeding and bonding with the newborn infant is important.
 - The mother should be started on effective anti-TB treatment (refer to Adult Hospital Level STGs and EML, Chapter 26: Tuberculosis) and the infant on TPT or TB treatment, as appropriate.
 - The mother should be advised on infection prevention and control measures, such as wearing a mask when handling

⁵ DR-TB evidence review ratified by NEMLC in Mar 2023. https://www.health.gov.za/wp-content/uploads/2024/07/WHO-Guideline-Adolopment_Drug-Resistant-TB_4May2023_Final.pdf

⁶ WHO operational handbook on tuberculosis. Module 4: treatment and care. Geneva: World Health Organization; 2025.

or feeding the infant until she has been on effective therapy for at least two weeks and/or her sputum is smear-negative for acid-fast bacilli.

- Other measures include sleeping in a separate room if feasible and allowing ventilation in the home.

BCG Vaccine: Amended

BCG vaccine recommendations have been updated in line with the Primary Healthcare STGS and EML; as well as the National TB Guidelines.

The STG was updated from

General and supportive measures

Do not give BCG vaccine at birth but administer BCG after completing TB treatment or prophylaxis.

Medicine Treatment

During prophylaxis, monitor the infant for 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.

TO

General and supportive measures

- » All newborns regardless of HIV status or TB exposure status should receive BCG at discharge from the delivery unit. BCG is a live attenuated *M.bovis* vaccine which is killed by TB medications.
- » If the baby starts TPT or TB treatment in the first 6 weeks of life, the BCG vaccine must be repeated one day after completion of TPT or TB treatment.
- » Babies with HIV should receive the repeat BCG dose after completion of TPT or TB treatment if they are on ART, clinically well, and have a CD4 > 25%.

Ethionamide/Ethambutol: Added

The addition of a fourth drug (ethionamide or ethambutol) and eligibility for treatment shortening for treatment of DS-TB in children was tentatively approved by NEMLC in 2024, based on the results of the SHINE study⁷ (see discussion under Tuberculosis in children below). However, the SHINE study excluded neonates. The inclusion of the fourth agent (ethionamide/ethambutol) in paediatric treatment regimens, including perinatal treatment regimens, is included in the World Health Organization (WHO) Consolidated Guidelines on Tuberculosis. The dosing table was updated to include dosing options for either ethionamide or ethambutol.

The WHO Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022)⁸ make the following recommendation:

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the 6-month treatment regimen (2RHZ(E)/4RH). Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB. (*Strong recommendation, low certainty of evidence*)

The National TB guideline: Management of Tuberculosis in children and adolescents¹, includes the 4-drug regimen intensive phase with either ethambutol or ethionamide as the fourth agent. It is recommended that ethionamide be considered in infants younger than three months or weighing < 3 kg, given the challenges with ethambutol administration and monitoring for ocular toxicity in the very young.

Level of evidence: IIIa: expert opinion and WHO and National TB guidelines

⁷ Turkova A, Wills GH, Wobudeya E, Chabala C, Palmer M, Kinikar A, et.al. Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children (SHINE). The New England Journal of Medicine. 2022, 386 (10): 911-922.

⁸ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022). <https://iris.who.int/server/api/core/bitstreams/6212d328-f45e-4905-ae32-e0161d4f0029/content>

Pyridoxine: Added for TPT and treatment regimens

The National Programme TB Guidelines: Management of Tuberculosis in Children and Adolescents¹ recommends supplemental pyridoxine in the following populations:

- Malnourished children
- CALHIV
- Breastfed infants
- Children or adolescents older than eight years
- Children receiving high-dose INH (as with TBM/miliary TB)

The Quick Reference Guide: Management of Tuberculosis in Children and Adolescents² recommends a dose of pyridoxine 6.25mg for children < 6kg.

Level of evidence: IVb: expert opinion and WHO and National TB guidelines

The following text was added:

AND

In addition, administer pyridoxine to all breastfed infants, malnourished infants, and infants living with HIV (CLHIV). Acute malnutrition refers to wasting, evidenced by a weight-for-length z-score < -2, or bilateral pitting oedema.

- Pyridoxine, oral, once daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (1/4 tablet)

Cross reference m Miliary TB and TB meningitis sections:s

The following cross-reference was added:

For weight-based treatment of infants with perinatal drug-susceptible central nervous system TB, TBM or miliary TB, see Section 10.1.2.1: Miliary TB (Table 5) and Section 10.1.2.2: TBM (Table 6) below.

Perinatal TB preventative Therapy (TPT)

For Perinatal TPT, a cross-reference to the paediatric TPT section has been added.

STG – 10.1.2 Tuberculosis in Children and Adolescents < 15 years

Definition of a significant exposure: Added

The following text was added:

A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). The exposure must have occurred while the source patient was not on TB treatment OR if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment.

Course duration: Amended

For non-severe TB, the course of therapy was amended from a 4-month continuation phase to a 2-month continuation phase. This change was already NEMLC approved and incorporated in the Paediatric Hospital Level STGs and EML 2023 Edition. Additionally, this update is in line with the National TB guidelines: Management of Tuberculosis in children and adolescents, as well as the WHO guidelines.⁶ This change is based on the results from the SHINE trial.⁵

Ethambutol: Added

The treatment regimens for children under the age of 8 years previously recommended a 3-drug intensive phase regimen of rifampicin, isoniazid and pyrazinamide. This has been updated to a 4-drug intensive phase regimen, with ethambutol as the 4th drug. This is in line with the National TB guidelines: Management of Tuberculosis in children and adolescents. The change is based on the results from the SHINE trial⁵, where the majority of patients received ethambutol as 4th drug.

Rifampicin/Isoniazid 60/60mg formulation dosing table: Deleted

The World Health Organization (WHO) dispersible formulations of rifampicin, isoniazid and pyrazinamide (RHZ 75/50/150mg and RH 75/50mg) have been included as the preferential dosing formulation. The historically included RH 60/60mg formulation will no longer be on tender and dosing tables referencing these formulations have therefore been removed.

Pyridoxine: Added

The pyridoxine indication and use was updated in line with the National TB Guidelines for Children and Adolescent.¹ Use was extended to include breastfed infants and children or adolescents > 8 years. Additionally, a definition was provided for malnourished.

Corticosteroids in children with intra-thoracic TB lymphadenopathy with significant airway compression and/or TB pericarditis

Corticosteroids: Added

Intra-thoracic TB lymphadenopathy with significant airway compression

The National TB guidelines: Management of Tuberculosis in children and adolescents¹ recommends corticosteroid use in children with TB with intrathoracic lymphadenopathy with significant airway compression. The WHO Guideline⁷ does not have a recommendation for use of corticosteroids outside of tuberculosis meningitis and tuberculosis pericarditis, however it does indicate that corticosteroids are sometimes used for other complicated forms of TB (e.g. complications of airway obstruction by TB lymph nodes, severely ill children and adolescents with disseminated TB).

There is limited objective evidence for this recommendation, however, locally, it is commonly used for this indication. A study and review evaluating use of corticosteroids for patients with TB with bronchial obstruction or endobronchial TB, see findings below:

- Toppet *et. al.*, 1990⁹, a randomised controlled trial (29 children) evaluated prednisolone use versus control in children with TB hilar adenopathy causing bronchial obstruction. Earlier improvement was seen in the steroid group [both radiologically (p=0.0075) and on bronchoscopy (p=0.003)] with less complications.
- A Systematic Review and Meta-analysis¹⁰ evaluating corticosteroids as an adjunct in the treatment of endobronchial TB (4 trials, 205 patients, 151 children) showed no significant improvement in bronchoscopy findings and all-cause mortality with corticosteroid use; however, the need for repeat bronchoscopy significantly decreased in steroid group (RR 0.13, 95% CI 0.02 to 0.9) and infection rate (adverse event) was less in steroid group (RR 0.53, 95% CI 0.29 to 0.97)(*very low certainty evidence*).

⁹ Toppet M, Malfroot A, Derde MP, Toppet V, Spehl M, Dab I. Corticosteroids in primary tuberculosis with bronchial obstruction. Archives of Disease in Childhood. 1990, 65: 1222-1226.

¹⁰ Mishra N, Panigrahi MK, Bhatt GC, Das RR. Corticosteroid as an adjunct in the treatment of endobronchial tuberculosis: A systematic review and meta-analysis. Current Pediatric Review. 2020, 16: 53-60.

This level of evidence for this recommendation is: **expert opinion**.

Expert comment received from: Dr Karen du Preez, Dr Juaneta Luiz, Prof Simon Schaaf, Prof Helena Rabie, Prof Regan Solomons.

TB pericarditis

See limited review: Corticosteroids for treatment of tuberculous pericarditis – May 2026¹¹

Recommendation:

In children with or without HIV, and with tuberculous pericarditis, we suggest using corticosteroids.
(conditional)

STG – 10.1.2.1 Miliary TB in Children

General

The **Note** was updated to indicate that all children with miliary TB should be considered to have TBM even in the absence of symptoms. The need for lumbar puncture in all these patients was removed based on external comment received.

The text was included as follows:

Note: Children with miliary tuberculosis should all be considered to have meningitis, even if no symptoms or neurological signs are present and even if CSF has a normal result. See Section 10.4: Meningitis, tuberculosis (TBM) in children for relevant special investigations and management considerations.

Doses and max doses: Amended

Dispersible formulation: Added

Rifampicin/Isoniazid 60/60mg formulation dosing table: Deleted

The World Health Organization (WHO) dispersible formulations of rifampicin, isoniazid and pyrazinamide (RHZ 75/50/150mg and RH 75/50mg) have been included as the preferential dosing formulation. The historically included RH 60/60mg formulation will no longer be on tender and dosing tables referencing these formulations have therefore been removed.

The dosing tables for miliary TB were updated in line with the National TB guidelines: Management of Tuberculosis in children and adolescents¹.

Pyridoxine: Amended

Included for all children due to high isoniazid doses.

The text was included as follows:

- Pyridoxine, oral, once daily for 6 – 9 months for all children and adolescents:
 - Body weight < 6 kg: 6.25 mg (1/4 tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (1/2 tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

¹¹ National Department of Health. Limited Review: Corticosteroids for the treatment of tuberculous pericarditis. May 2026.

STG – 10.1.2.2 Meningitis, Tuberculosis (TBM) in children

Note added:

A note specifically indicating that children and adolescents with TBM are not eligible for treatment shortening was added.

Doses and max doses: Amended

Dispersible formulation: Added

Rifampicin/Isoniazid 60/60mg formulation dosing table: Deleted

The World Health Organization (WHO) dispersible formulations of rifampicin, isoniazid and pyrazinamide (RHZ 75/50/150mg and RH 75/50mg) have been included as the preferential dosing formulation. The historically included RH 60/60mg will no longer be on tender and dosing tables referencing these formulations have therefore been removed.

The dosing tables for TBM were updated in line with the National TB guidelines: Management of Tuberculosis in children and adolescents¹.

Pyridoxine: Added

Included for all children due to high isoniazid doses.

The text was included as follows:

- Pyridoxine, oral, once daily for 6–9 months for all children and adolescents:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

Corticosteroids:

Prednisone: Retained

See limited review: Corticosteroids for treatment of tuberculous meningitis –February 2026¹²

Recommendation:

In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids. (Strong)

Acetazolamide: retained

Treatment of communicating hydrocephalus

- The acetazolamide dose listed in the STGs for communicating hydrocephalus is 20mg/kg/dose 8 hourly, whereas the National TB guidelines recommend a dose of 50mg/kg/day 6 hourly.
- However, an 8 hourly dose is more pragmatic than a 6 hourly dose. Thus, the daily dose from the National TB guidelines was included, with an 8 hourly frequency.
- The maximum dose was retained as 1000mg daily and not aligned with the National TB guidelines which indicate 2000 mg daily. No reference was provided for the maximum dose in the National TB guidelines, and this maximum dose is likely derived from idiopathic intracranial hypertension guidelines. In this setting however the 48% of patients using > 1.5g acetazolamide (both adults and children) stop due to adverse effects.¹³

¹² National Department of Health. Limited Review: Corticosteroids for the treatment of tuberculous meningitis – February 2026.

¹³ Mollan SP, Davies B, Silver NC, Shaw S, Mallucci CL, Wakerley BR, et.al. Idiopathic intracranial hypertension: consensus guidelines on management. J Neurosurg Psychiatry. 2018, 89: 1088-1100.

The text was updated as follows:

Acetazolamide, oral, ~~20 mg/kg/dose~~ 50mg/kg/day, divided into 3 doses, given 8 hourly for one month.

- Maximum daily dose: 1000 mg.
- Monitor for metabolic acidosis and serum potassium derangements.

Furosemide: updated

Treatment of communicating hydrocephalus

- The furosemide dose listed in the STGs for communicating hydrocephalus is 0.3mg/kg/dose 8 hourly, whereas the National TB guidelines recommend a dose of 1mg/kg/day in two divided doses.
- The dose used within the National TB guidelines is more pragmatic, and in line with the SAMF¹⁴ dosing of 1-3mg/kg/day.

The dose and maximum dose was updated in line with the National TB guidelines as follows:

Furosemide, oral, ~~0.3 mg/kg/dose 8 hourly~~ 1 mg/kg/day, divided into 2 doses, given 12 hourly for one month ~~for the first month of treatment~~.

- Taper slowly over 2 weeks if the intracranial pressure has normalised, as indicated by clinical response or resolution of hydrocephalus on follow-up scan.
- Do not restrict fluids once on diuretics.

Mannitol: Removed

Where there is sudden deterioration in level of consciousness, mannitol was previously included.

Raised intracranial pressure in paediatric TBM is invariably due to hydrocephalus, thus due to rarity of cerebral oedema as a cause of increased intracranial pressure, the recommendation for use of mannitol is not suitable and is therefore removed.

Drug Resistant TB (DR-TB)

STG – 10.2.1 Isoniazid Monoresistant Tuberculosis

Isoniazid monoresistant Tuberculosis section added to be aligned with recommendations in the Adult Hospital STGs and EML.

Confirmed isoniazid monoresistant TB:

Rifampicin/Isoniazid/Pyrazinamide/Ethambutol: Added

Levofloxacin: Added

Pyridoxine: Added

Confirmed isoniazid monoresistant TB and contraindication to isoniazid

Rifampicin: Added

Ethambutol: Added

Pyrazinamide: Added

Levofloxacin: Added

¹⁴ University of Cape Town, Faculty of Health Sciences, Division of Clinical Pharmacology. (2024). South African Medicines Formulary (SAMF). SAMF website. <https://samf-app.com>

The following text was included:

MEDICINE TREATMENT

Treatment should be given for at least 6 months.

Confirmed isoniazid mono-resistant TB:

- RHZ plus E at standard weight-based dosing, oral, daily.

AND

- Levofloxacin, oral, daily

AND

Breastfed infants, children > 8 years of age, CALHIV, malnourished children, and children with existing neuropathy should receive pyridoxine in addition to TB treatment. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months.
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

Table 9: TB dosing chart for children and adolescents <15 years with confirmed or clinically diagnosed isoniazid mono-resistant pulmonary or extrapulmonary TB (excluding TBM, CNS TB, Miliary TB, bone/joint TB)

	Single phase, 6 months duration Oral, 7 days a week		
Formulation Body Weight (kg)	RHZ 75/50/150mg dispersible tablet (scored) OR 75/50/150mg/4ml suspension*	E 400mg tablet (not scored) OR 400mg/8ml suspension**	Levofloxacin 250 mg tablet OR 500 mg tablet OR 25 mg/ml suspension***
Target dose (range; mg/kg/day)	Isoniazid (H): 10 (7–15) mg Rifampicin (R): 15 (10–20) mg Pyrazinamide (Z): 35 (30–40) mg Ethambutol (E): 20 (15–25) mg Levofloxacin: 15–20 mg		
3–3.9	¾ tab (3 ml)	1.5 ml	2 ml
4–4.9	1 tab	2.5 ml	
5–7.9	1 tab	2.5 ml	5 ml or ½ x 250 mg tablet
8–9.9	2 tabs	½ tab or 4 ml	
10–11.9	2 tabs	½ tab or 4 ml	10 mL or 1 x 250 mg tablet
12–12.9	3 tabs	¾ tab or 6 ml	
13–15.9	3 tabs	¾ tab or 6 ml	15 mL or 1 ½ x 250 mg tablet
16–24.9	4 tabs	1 tab or 8 ml	
≥ 25	RHZE 150/75/400/275 mg tablet		
25–29.9	2 tabs		1 x 500 mg tablet or 2 x 250 mg tablet or 20 mL
30–34.9	3 tabs		1 ½ x 500mg or 3 x 250mg tablets daily
35– < 45.9 kg	4 tabs		
46-65 kg	4 tabs		2 x 500mg or 4 x 250mg tablets daily
≥ 65	5 tabs		

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

* To make an oral suspension, for weight band 3–3.9 kg, for each dose, disperse 1 x RHZ 75/50/150 mg tablet (2 months intensive phase) in 4 ml of water, administer 3 ml, discard unused suspension. For other weight bands, an oral suspension can be made by dispersing the required number of tablets & fractions of tablets in a small amount of water (5–10 ml) and administering all of the suspension to the child orally or via nasogastric tube.

** If oral suspension required, for each dose, crush 1 x ethambutol 400 mg tablet to a fine powder, disperse in 8 ml of water to prepare a concentration of 400 mg/8 ml (50 mg/ml), administer required dose as indicated in above chart, discard unused suspension.

***For levofloxacin 25mg/ml suspension: Crush and disperse 1 x 250mg tablet in 10 mL water.

Confirmed isoniazid mono-resistant TB AND contraindication to isoniazid:

- Rifampicin, oral, 10 mg/kg daily.

AND

- Ethambutol, oral, 15 mg/kg daily.

AND

- Pyrazinamide, oral, 25 mg/kg daily.

AND

- Levofloxacin, oral, daily.

REFERRAL

- » Discuss children with isoniazid mono-resistant TB, miliary TB or bone/joint TB with an expert as they may require a different regimen or duration of treatment.
- » Children and adolescents not responding to appropriate TB treatment.
- » If unsure of appropriate treatment regimen – Telephonic consultation with specialist.

Drug Resistant TB (DR-TB)

STG – 10.2.2 Rifampicin resistant, Pre-XDR and XDR TB in Children and Adolescents < 15 years

The previous STG on DR-TB only referred to the TB programme guidelines for the management of DR-TB. For this update the treatment for DR-TB was aligned with the National Department of Health Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis, September 2023¹⁵

Bedaquiline (BDQ): added

Clofazimine (CFZ): added

Delamanid (DLM): added

Ethionamide (ETO): added

High dose isoniazid (hdINH): added

Levofloxacin (LFX): added

Linezolid (LZD): added

Para-amino salicylic acid (PAS): added

Terizidone (TRD): added

Note: Reference to any specific DR-TB regimen in children and adolescents < 15 years was not included. The drugs that may be included in such regimens are simply listed.

For non-pregnant adults and adolescents (≥ 14 years) with pulmonary or non-severe extrapulmonary (e.g. lymphadenopathy or pleural effusion) RR- or Pre-XDR-TB, the BPAL-L regimen is included in the STG in accordance with the NEMLC evidence review: Adolopment of WHO DRTB Guidelines published in May 2023, full review accessible online: <https://www.health.gov.za/wp-content/uploads/2024/07/WHO-Guideline-Adolopment-Drug-Resistant-TB-4May2023-Final.pdf>

NEMLC and the TB programme have aligned on 15 years as a general cut off age for both drug-sensitive and drug-resistant TB.

¹⁵ National Department of Health. Management of Rifampicin-Resistant Tuberculosis. November 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

The National TB Guidelines for Rifampicin-Resistant TB includes the above-mentioned medicines as treatment options for children under 15 years. However, it indicates that there is no standardised treatment regimen for all children under 15 years of age, and the composition and duration of treatment regimens is tailored to each individual children and based on the resistance profile of the organism as well as site and severity of the RR-TB disease.

The WHO DR-TB 2022 guidelines¹⁶ made the following recommendations related to children:

- **Bedaquiline** should be included in longer multidrug-resistant TB (MDR-TB) regimens for patients aged 18 years or more. (*Strong recommendation, moderate certainty of evidence*).
- **Bedaquiline** may also be included in longer MDR-TB regimens for patients aged 6–17 years. (*Conditional recommendation, very low certainty of evidence*) In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used. (*Conditional recommendation, very low certainty of evidence*)
- **Delamanid** may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (*Conditional recommendation, moderate certainty of evidence*) In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. (*Conditional recommendation, very low certainty of evidence*)
- **Group A:** fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated.
- **Group B:** clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice.
- **Group C:** included all other medicines that can be used when a regimen cannot be composed with Group A or Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.

SUMMARY OF SOUTH AFRICAN TB PROGRAMME AND WHO RECOMMENDATIONS FOR DELAMANID

- In March 2022, the World Health Organization (WHO) updated guidelines for management of tuberculosis in children and young adolescents, which recommend that delamanid and bedaquiline be used in all age groups, along with updated dosing guidance for all TB drugs.¹⁷

Recommendation

In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens (*conditional recommendation, very low certainty of evidence*).

- The WHO guidelines on drug resistant TB treatment¹⁸ also published in 2022 include the following recommendations relevant to delamanid.
 - In MDR or RR-TB patients on longer regimens, all three Group A agents (refer table below), and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. (*Conditional recommendation, very low certainty of evidence*).
 - Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer

¹⁶ WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment 2022, IGO. update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0. <https://www.who.int/publications/i/item/9789240063129>.

¹⁷ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022). <https://iris.who.int/server/api/core/bitstreams/6212d328-f45e-4905-ae32-e0161d4f0029/content>

¹⁸ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment (2022). <https://iris.who.int/server/api/core/bitstreams/b4112461-7e9c-403c-808f-055f1dc3a54b/content>

regimens. *(Conditional recommendation, moderate certainty of evidence)*

- In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. *(Conditional recommendation, very low certainty of evidence)*

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx
	Bedaquiline ^{bc}	Bdq
	Linezolid ^d	Lzd
	Clofazimine	Cfz
Group B: Add one or both medicines	Cycloserine or terizidone	Cs Trd
	Ethambutol	E
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Delamanid ^e	Dlm
	Pyrazinamide ^f	Z
	Imipenem–cilastatin or meropenem ^g	Ipm–Cln Mpm
	Amikacin (or streptomycin) ^h	Am (S)
	Ethionamide or prothionamide ⁱ	Eto Pto
	P-aminosalicylic acid ^j	PAS

- The National TB Programme, Updated Clinical Reference Guide: Clinical Management of Rifampicin-Resistant Tuberculosis, September 2023, incorporated delamanid for all for individualised treatment regimens (including in children, adolescents, adults and pregnant or breastfeeding women)
- The 2025 WHO Consolidated guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment (2025) suggested the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid, levofloxacin, and clofazimine in MDR/RR-TB patients with or without fluoroquinolone resistance. *(Conditional recommendation, very low certainty of evidence)*
 - This recommendation applied to people diagnosed with pulmonary TB and extrapulmonary TB (excluding TB of the central nervous system, osteoarticular TB or disseminated forms of TB with multiorgan involvement) of all ages, including children (6 years or older), adolescents, PLWH, and pregnant and breastfeeding women.
 - When resistance to fluoroquinolones is unknown, the full regimen is started and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine is stopped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin. In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine.
 - The rationale for this recommendation is based on the data from an RCT, BEAT Tuberculosis, which showed that the efficacy and safety of the bedaquiline/delamanid/levofloxacin/linezolid/clofazimine regimen was similar to that of the control arm regimen (WHO-recommended 9-month or longer regimens), and offers advantages based on its shorter duration and lower pill burden than the comparators.

Evidence Discussion

Conradie et.al. 2026

The recently published BEAT Tuberculosis trial¹⁹, a phase 3 open-label pragmatic randomised controlled noninferiority trial in South Africa; assessed a 6-month treatment strategy for pulmonary rifampicin-resistant TB. This trial included participants 6 years and older, who were randomly assigned to a regimen consisting of bedaquiline, linezolid, delamanid, and levofloxacin OR clofazimine or both (if fluoroquinolone DST results not

¹⁹ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

obtained) for 6 months; or 9-months South African standard of care. (Note participants included those who were pregnant, breastfeeding or those who had fluoroquinolone-resistant tuberculosis).

- Successful outcome (cure or completion of treatment): 86.1% (174 of 202) in intervention group, and 86% (172 of 200) in control group; adjusted risk difference: -0.2 percent points 95% CI -6.9 to 6.5; p =0.001 for non-inferiority.
- Adverse events (grade 3 or higher): 31.2% (63 of 202) in intervention group and 37% (74 of 200) in control group.

STG – 10.3.1 TB Preventative Therapy (TPT) for Drug Susceptible TB Exposure

Definition of a significant exposure: Added

The following text was added:

A child or adolescent is considered to have had a significant TB exposure if within the 12 months before presentation with presumed TB, they shared an enclosed space with an adult or adolescent with pulmonary TB for ≥ 1 night OR for frequent or extended daytime periods (e.g. at school or creche). The exposure must have occurred while the source patient was not on TB treatment OR if the source patient is on treatment the exposure must have occurred during the three months before the source patient started TB treatment.

In addition, a newborn has had significant exposure to a person with infectious TB if the baby was born to a mother with TB and the mother:

- » started TB treatment within 2 months before delivery OR
- » demonstrates poor clinical response to TB treatment OR
- » is TB smear or acid-fast bacilli (AFB) or culture positive at delivery OR
- » is diagnosed with TB soon after delivery.

Population: aligned to NEMLC recommended population.

The indication was included as follows:

Indications for TB Preventive Therapy (TPT): under 5 years

- » All asymptomatic children < 5 years and CALHIV, i.e. clinically well, normal chest X-ray irrespective of TST, in close contact with someone with infectious pulmonary TB should receive TPT.

Neonatal population: Guidance for this population moved to this section.

Children and adolescents living with HIV, and no TB exposure

TPT guidance for this cohort will be considered for inclusion in the Paediatric hospital level HIV Chapter.

3RH: Added

Rifampicin/isoniazid 75/50 mg daily for 3 months (3RH)

This use of 3RH is already included in the Paediatric Hospital Level STGs and EML for perinatal TB prophylaxis, and thus this would be the extension to all children under 25 kg.

The WHO – Consolidated Guidelines on Tuberculosis: Management of tuberculosis in children and adolescents⁶ indicates a 3-month regimen of daily isoniazid plus rifampicin (3RH), in addition to 6-9 months daily isoniazid; regardless of HIV status. **(strong recommendation, moderate to high certainty in the estimates of effect).**

The WHO – Consolidated Guidelines – Module 1: Prevention indicates rifampicin plus isoniazid daily for 3 months should be offered as an alternative to 6 months of isoniazid monotherapy as preventive treatment for

children and adolescents aged < 15 years in countries with a high TB incidence. **(Strong recommendation, low-quality evidence).**²⁰

The WHO Prevention module¹⁴ indicates that the benefits of 3RH outweigh the harm, given its safer profile, higher completion rate than with isoniazid monotherapy and the availability of child-friendly fixed-dose combinations of rifampicin and isoniazid. Although the quality of the evidence was low, data on adult populations also support the benefits of 3RH. A systematic review of RCTs on preventive treatment options conducted in 2014²¹ showed that the efficacy and the risk for hepatotoxicity are similar for 3RH and isoniazid monotherapy.

Additionally, it was noted that use of 3RH would require fewer resources, given the shorter duration of treatment, which would reduce the number of clinic visits required. The Guideline Development Group agreed that there is no important uncertainty or variation in clients' values and preferences. It also agreed that the acceptability of 3RH is high, given its shorter duration and long use by health-care workers for treatment of active TB disease.

3RH should be prescribed with caution to CALHIV who are on ART because of potential drug–drug interactions; the regimen cannot be co-administered with protease inhibitors or nevirapine.

Pyridoxine: Added

Pyridoxine added for specific indications in line with previous recommendations.

The medicine treatment text was updated as follows to include the 3RH recommendations:

²⁰ WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment, second edition. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.

²¹ Stagg HR, Zenner D, Harris RJ, Muñoz L, Lipman MC, Abubakar I. Treatment of latent tuberculosis infection: a network meta-analysis. *Annals of Internal Medicine*. 2014;161(6):419-428. doi:10.7326/M14-1019.

MEDICINE TREATMENT

- » In HIV-negative children < 25kg, the priority regimen is 3RH (rifampicin plus isoniazid daily for 3 months).
- » In CALHIV, the preferred regimen is 6H (isoniazid daily for 6 months).

If HIV-negative or HIV-exposed not on nevirapine and < 25 kg:

- Rifampicin/isoniazid 75/50 mg daily for 3 months

Weight (kg)	RH (Daily) fixed dose combinations		Duration
	75/50 mg	If crushed and mixed in in water	
2 – 2.9	½ tablet	Mix 1 tablet in 4mL of water. Give only 2mL of this mixture.	3 months
3 – 3.9	¾ tablet	Mix 1 tablet in 4mL of water. Give only 3mL of this mixture.	
4 – 5.9	1 tablet	Mix 1 tablet in 4mL of water and give ALL of this mixture.	
6 – 7.9	1 ½ tablets	Mix 1 ½ tablets in 5-10mL of water and give ALL of this mixture.	
8 – 11.9	2 tablets	Mix 2 tablets in 5-10mL of water and give ALL of this mixture.	
12 – 15.9	3 tablets	Mix 3 tablets in 5-10mL of water and give ALL of this mixture.	
16 – 24.9	4 tablets	Mix 4 tablets in in 5-10mL of water and give ALL of this mixture.	
≥ 25	Use adult formulations and doses		

AND

In addition, administer pyridoxine to all breastfed infants, malnourished children, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 3 months.:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).

If CALHIV or HIV-exposed on nevirapine:

- Isoniazid, oral, 10 mg/kg daily for 6 months.

isoniazid, 600 mg, 10 mg/kg daily for 6 months.		
Weight (kg)	Daily isoniazid 100mg tablet	Duration
2 - 3.4	¼ tablet	6 months
3.5 – 4.9	½ tablet	
5 – 7.4	¾ tablet	
7.5 – 9.9	1 tablet	
10 – 14.9	1 ½ tablets	
15 – 19.9	2 tablets	
20 – 24.9	3 tablets (or one 300 mg tablet)	
≥ 25	Use adult formulations (maximum dose 300 mg per day)	

AND

In addition, administer pyridoxine to all breastfed infants, malnourished children, CALHIV, or those with existing neuropathy. Acute malnutrition refers to wasting (weight-for-length/height z score less than -2); mid upper arm circumference (MUAC) less than 12.5 cm; or bilateral pitting oedema.

- Pyridoxine, oral, daily for 6 months:
 - Body weight < 6 kg: 6.25 mg (¼ tablet).
 - Body weight ≥ 6 kg but age < 5 years: 12.5 mg (½ tablet).
 - Age ≥ 5 years: 25 mg (1 tablet).

STG – 10.3.2 TB Preventative Therapy (TPT) for Resistant Exposure

Isoniazid monoresistance (rifampicin-susceptible)

Rifampicin: Dosing table added

The following dosing table was added for guidance, in line with the NDoH Children and Adolescents (0-15 years) Quick Reference Guide, 2025.²

Daily dose		Dose calculation/preparation (depending on available rifampicin formulation)	Notes
< 10 years old	15 mg/kg daily	<u>15 mg/ml solution</u> • Rifampicin 150mg capsule: open capsule into 10 ml of water. <u>30 mg/ml solution</u> • Rifampicin 300mg capsule: open capsule into 10 ml of water. <u>60 mg/ml solution</u> • Rifampicin 600mg capsule: open capsule into 10 ml of water.	If rifampicin alone is unavailable, discuss alternative with expert.
≥ 10 years old	10 mg/kg daily		

Rifampicin-resistant TB (susceptible for fluoroquinolones):

Levofloxacin: retained

Dosing table added for levofloxacin or isoniazid options as follows:

Dosing table added for Levofloxacin or Isoniazid options as follows:					
Weight	Levofloxacin 250 mg tablet (scored) OR 500 mg tablet (scored)		OR	Isoniazid 100 mg tablet OR 300 mg tablet	
	250 mg tablet	500 mg tablet		100 mg tablet	300 mg tablet
3–4.9 kg	2 mL*		OR	5 mL*	
5–6.9 kg	5 mL* or 0.5 tablet			1 tablet	
7–9.9 kg				1.5 tablets	
10–15.9 kg	1 tablet			2 tablets	
16–23.9 kg	1.5 tablets			3 tablets	1 tablet
24–29.9 kg	2 tablets	1 tablet		4 tablets	1.5 tablets
30–35.9 kg	3 tablets	1.5 tablets		4.5 tablets	
36–45.9 kg					2 tablets
46–55.9 kg	4 tablets				
56–69.9 kg					
≥ 70 kg					
*Dissolution of crushed adult tablets or capsule content in 10 mL of water is required for administering this dose. The number of mL in the table reflects the dose to provide.					

South African National Department of Health
Brief Report of NEMLC Limited Review¹
Corticosteroids for the treatment of tuberculous pericarditis
May 2026

Medicine details:

Medicine Class	Corticosteroids	<i>If applicable Please consider therapeutic interchange policy</i>
Medicine/s name -INN: - South African name (if differs from INN)	Prednisone Prednisolone Dexamethasone	http://www.whocc.no/atc_ddd_in dex/
Medicine/s (ATC5):	H02AB07 H02AB06 H02AB02	http://www.whocc.no/atc_ddd_in dex/
Indication (ICD-10 code):	A18.0	https://www.health.gov.za/icd-10-master-industry-table/
SAHPRA Approved	Yes	SAHPRA registered health products database https://medapps.sahpra.org.za:6006/
Dosage form/s	tablet, suspension, injection	
Route of administration/s	Oral, IV injection	
Patient population	Adults and children with and without HIV with tuberculous pericarditis and/or pericardial effusion	
Prevalence and/or incidence of condition	66% of patients with pulmonary TB have signs of pericardial abnormality on echocardiography at the start of anti-TB treatment.[1] 47% of patients have pericardial effusion at TB diagnosis.[1] 12% of patients with pulmonary TB have features of constrictive pericarditis at diagnosis.[1]	<i>May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.</i>
Level of Care	Hospital level	
Prescriber level	Doctor prescribed	

¹ This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Current Standard of Care

In adults: Antituberculosis drugs for 6 months. No recommendation regarding use of corticosteroids is provided in the Standard Treatment Guidelines (STGs). National Tuberculosis Management guidelines (2014) recommend the use of corticosteroids in adults with extrapulmonary tuberculosis, including pericarditis.

In children: Antituberculosis drugs for 6 months plus corticosteroids in suspected or proven tuberculous pericarditis.

Executive Summary

- ➔ In sub-Saharan Africa, tuberculous pericarditis is associated with all-cause mortality of 9.1 per 100 person-years (Mayosi, 2014).[2]
- ➔ The current Adult Hospital standard treatment guidelines make no recommendation regarding the use of corticosteroids in people with tuberculous pericarditis. However, National Tuberculosis Management guidelines (2014) recommend the use of corticosteroids in adults with tuberculous pericarditis.
- ➔ The current Paediatric Hospital standard treatment guidelines and Management of Tuberculosis in Children and Adolescents: A Clinical Guideline (2024), while acknowledging the limited evidence in children, recommend the use of corticosteroids in children with tuberculous pericarditis.
- ➔ We conducted an updated rapid systematic review of the evidence for the use of corticosteroids in the management of tuberculous pericarditis in HIV-negative children and adults, as well as in children and adults with HIV (PWH). Only guidelines, systematic reviews with meta-analyses, and randomised controlled trials were included.
- ➔ We identified two clinical practice guidelines:
 - Clinical practice guidelines from WHO (2025) and ATS/CDC/ERS/IDSA (2025) included the same primary studies, but did not stratify results by HIV status, and had not updated recommendations since 2016/2017.
 - The WHO (2025) clinical practice guideline recommended that in patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used. (Conditional recommendation, very low certainty of evidence)
 - The ATS/CDC/ERS/IDSA (2025) clinical practice guideline suggested that initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis (Conditional recommendation, very low certainty of evidence).
- ➔ We identified three systematic reviews. The most up-to-date and relevant systematic review which stratified results by HIV-status (Wiysonge, 2017), was considered to be of low-quality on AMSTAR2 assessment. Key findings from this review include:
 - In adults without HIV and with tuberculous pericarditis:
 - Corticosteroids probably reduce deaths from pericarditis (RR 0.39 [95% CI 0.19 to 0.80], moderate certainty evidence) and may reduce all-cause deaths (RR 0.80 [95% CI 0.59 to 1.09], low certainty evidence) and the need for repeat pericardiocentesis (RR 0.85 [95% CI 0.70 to 1.04], low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on the incidence of cancer, hospitalisation, development of constrictive pericarditis, or the need for pericardiectomy (very low certainty evidence).
 - In adult PWH with tuberculous pericarditis:
 - Corticosteroids may reduce constrictive pericarditis (RR 0.55 [95% CI 0.26 to 1.16], low certainty evidence) and hospitalization (RR 0.80 [95% CI 0.59 to 1.09], low certainty evidence).
 - Corticosteroids may make little or no difference to the need for repeat pericardiocentesis (RR 1.02 [95% 0.89 to 1.18], low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on deaths from pericarditis, all-cause deaths, the need for pericardiectomy or the development of cancer (very low certainty evidence).
 - These findings are based largely on data from one RCT, in which the majority of PWH with tuberculous pericarditis were not on ART and had CD4 counts ≤ 350 cells/mm³.
- ➔ Two RCTs were identified in the search, both of which were included in the systematic review. However, since the systematic review included only limited safety outcomes, the safety outcomes from the largest RCT were reviewed (Mayosi, 2014). Key findings include:

- More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant. - Prednisolone, as compared with placebo, was associated with an increased incidence of cancer (1.05 vs. 0.32 cases per 100 person-years; HR 3.27; 95% CI, 1.07 to 10.03; p = 0.03). This increase was due to a higher incidence of HIV-related cancers in the prednisolone group than in the placebo group (0.73 vs. 0.08 per 100 person-years; HR 9.04; 95% CI, 1.14 to 71.33; p = 0.04), particularly Kaposi's sarcoma and non-Hodgkin's lymphoma. This increase may be related to the co-administration of immunotherapy (<i>M. indicus pranii</i>) in this RCT.
➔ Given the important benefits of reducing death in people without HIV, and in reducing hospitalisation and the development of constrictive pericarditis in PWH, we recommend the use of corticosteroids in adults with tuberculous pericarditis while acknowledging the low certainty evidence. - In PWH, a thorough clinical examination should be performed before starting corticosteroids to exclude HIV-related cancers. - In PWH, antiretroviral therapy should be initiated promptly in accordance with standard treatment guidelines.
➔ No data in children with or without HIV and tuberculous pericarditis were identified. Given the important benefits associated with corticosteroids in adults with tuberculous pericarditis, we suggest using corticosteroids in children with tuberculous pericarditis.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		☐		☒ See recommendation 2		☒ See recommendation 1	
High level summary of conclusions	1. In adults with or without HIV, and with tuberculous pericarditis, we recommend using corticosteroids. 2. In children with or without HIV, and with tuberculous pericarditis, we suggest using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	4 June 2026		NEMLC ratified the ERC recommendation as above.					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review	Additional clinical trial data or safety signals.							

*Depending on the review and number of products, an annexure may need to be included

Background and rationale

The standard treatment guidelines (STGs) for tuberculosis are being updated and consolidated into a single chapter to outline the various manifestations of TB disease. Currently, the adult hospital and primary healthcare STGs provide no specific guidance for the management of tuberculous pericarditis. Tuberculous pericarditis is an extrapulmonary manifestation of tuberculosis. It is associated with all-cause mortality of 9.1 per 100 person-years in the IMPI trial conducted in sub-Saharan Africa.[2] The paediatric hospital level STGs Chapter 4 – Cardiovascular system recommends antituberculosis drugs for 6 months plus corticosteroids in suspected or proven tuberculous pericarditis (Figure 1). No differential guidance is provided by HIV status.

CHAPTER 4	CARDIOVASCULAR SYSTEM
MEDICINE TREATMENT	
If suspected or proven TB pericarditis, give antituberculosis drugs for 6 months plus corticosteroids.	
• Prednisone, oral, for 6 weeks: ○ Week 1: 2 mg/kg/day, ○ Week 2: 1.5 mg/kg/day, ○ Week 3: 1 mg/kg/day, ○ Week 4: 1 mg/kg/day, ○ Week 5: 0.5 mg/kg/day, ○ Week 6: 0.25 mg/kg/day.	
LoE III ^{1,14}	

Figure 1. Paediatric Hospital Level Standard Treatment Guidelines. Chapter 4. Cardiovascular system. Pericardial effusion. (The references for this recommendation are the trials by Mayosi, 2014 and Strang, 1987[2,3])

The National Tuberculosis Management Guidelines (2014) recommend the use of corticosteroids in adults with extrapulmonary tuberculosis, including pericarditis (Figure 2). No differential guidance is provided by HIV status.

7.5.2 Steroids The use of corticosteroids is recommended in extra-pulmonary tuberculosis, particularly for TB meningitis and pericarditis. High dose steroid treatment for 2-4 weeks and the taper off gradually over several weeks depending on clinical progress is recommended. The response to treatment is assessed clinically.
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Figure 2. National Tuberculosis Management Guidelines 2014. Page 42 of 120. Adjunctive treatment.

The largest study on the use of corticosteroids in tuberculous pericarditis was published in 2014, subsequent to the 2014 National Tuberculosis Management Guidelines. Recently, data on the differential effect of steroids in people with and without HIV in the setting of other extrapulmonary manifestations of tuberculosis has emerged. Therefore, in order to update and consolidate the tuberculosis STGs a rapid review of use of corticosteroids in tuberculous pericarditis was undertaken.

Purpose/Objective i.e., PICO question:

PICO 1

Population Subgroups	HIV-negative adults and children with tuberculous pericarditis
Intervention(s)	Corticosteroids (prednisone or prednisolone) plus standard anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, constrictive pericarditis, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

PICO 2

Population Subgroups	Adults and children living with HIV and tuberculous pericarditis
Intervention(s)	Corticosteroids (prednisone or prednisolone) plus anti-TB treatment
Comparator(s)	Anti-tuberculosis treatment (ATT) alone or with placebo
Outcome(s)	Mortality, constrictive pericarditis, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

Methods

1. Data Sources

Clinical practice guidelines: We searched for relevant clinical practice guidelines from the American Thoracic Society and World Health Organization.

Systematic reviews and randomised controlled trials: We searched PubMed for guidelines, systematic reviews, and randomised controlled trials.

2. Search Strategy

The following search terms were used:

((TB pericarditis) OR (tuberculous pericarditis)) OR (tuberculosis pericarditis)) AND (corticosteroids)
PubMed searches were filtered by guideline, systematic review, meta-analysis and randomised controlled trials.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The study screening, selection and data extraction, analysis and evidence was conducted by 1 reviewer. Evidence was synthesised narratively.

4. Assessment of methodological quality

The most recent and up-to-date systematic review was appraised by one reviewer using AMSTAR.[4]

5. GRADE assessment

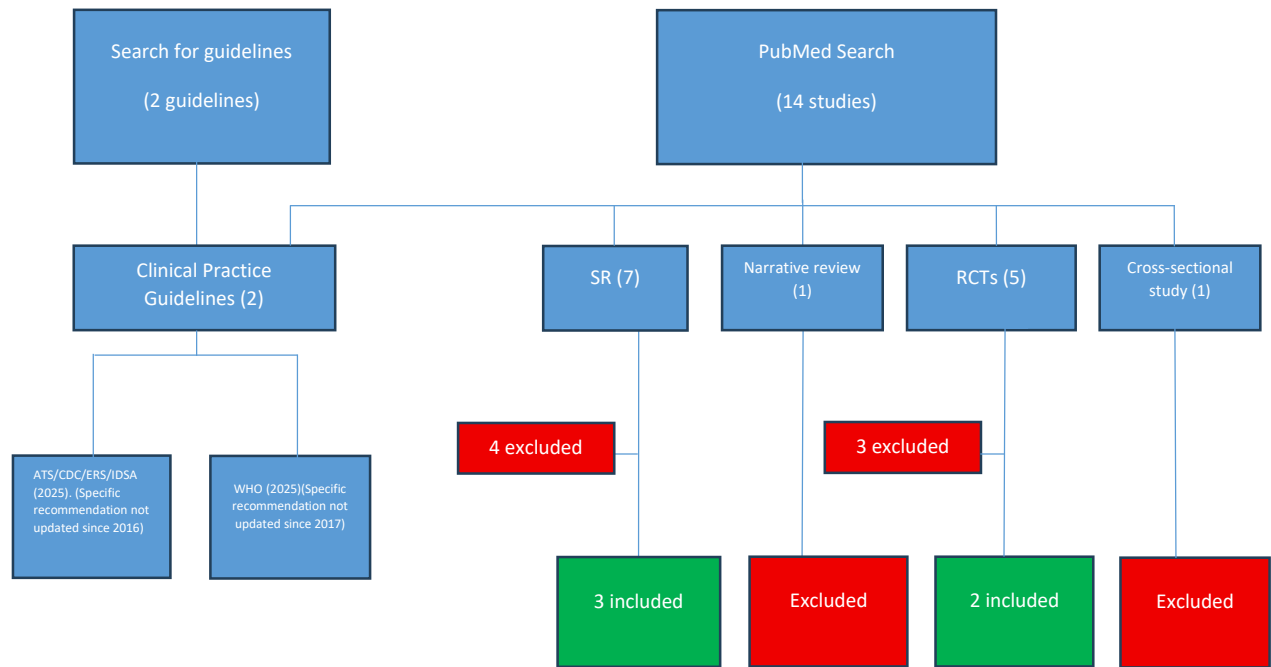
We adopted the GRADE (Grading of Recommendations Assessment, Development and Evaluation) assessment in the systematic review.

Results

1. Result of the search

The search results are illustrated in **Figure 3. Search Flow Chart**. Specific reasons for inclusion or exclusion of studies identified in the search are listed in **Appendix 1**.

Figure 3. Search Flow Chart



Abbreviations: ATS, American Thoracic Society; CDC, Centers for Disease Control and Prevention; ERS, European Respiratory Society; IDSA, Infectious Diseases Society of America; WHO, World Health Organisation; SR, systematic review; RCTs, randomised controlled trials

2. Description of included studies

2.1. Clinical Practice Guidelines

Two clinical practice guidelines were identified. Both clinical practice guidelines had not updated specific recommendations related to corticosteroid use in tuberculous pericarditis since 2016-2017. These guidelines with their respective recommendations are summarised in **Table 1**. Importantly, effect estimates by HIV status are not provided in either guideline's summary of findings tables. Summary of findings tables from the guidelines are included in **Appendix 2**.

Table 1. Summary of the recommendations from clinical practice guidelines identified

Guideline	Recommendation	Justification	Subgroup considerations	Studies included in the systematic review	Outcomes considered
WHO Consolidated guidelines on tuberculosis. Module 4: Treatment and care. 2025.	In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy <u>may be</u> used. (Conditional recommendation, very low certainty of evidence) This recommendation was first put forward in the guidelines update of 2017. They are copied without modification into this consolidated document and appear exactly as in the 2017 guidelines.	In patients with tuberculous pericarditis, evidence from studies in the systematic review showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the IMPI study – showed no benefit with steroids. However, a complicating factor in these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative people or persons living with HIV who are on ART. In the IMPI study, a supplemental analysis was done of the HIV-negative patients only and a small mortality benefit was shown with steroid treatment. However, the relationship between HIV infection and steroids is complex. In another smaller study of 58 subjects, all of whom were HIV-positive, steroids were found to reduce mortality. It is of note that the other studies in the review did not address HIV and mortality. The panel considered that the benefit in preventing constrictive pericarditis outweighed the potential harms of corticosteroid therapy.	With regard to the use of steroids in tuberculous pericarditis, in one study an increase in HIV-related cancers (non-Hodgkins' lymphoma and Kaposi sarcoma) was observed. However, this increase appears to be caused by co-administration of immunotherapy (<i>M. indicus pranii</i>).	Strang et al. 1987 Strang et al. 1988 Hakim Et Al. 2000 Mayosi et al. 2014 Reuter et al. 2006	Mortality (5 studies) Treatment adherence (2 studies) Constrictive pericarditis (3 studies)
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, 2016. Update on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis. An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline, 2025.	We suggest initial adjuvant corticosteroid therapy <u>not be</u> routinely used in patients with tuberculous pericarditis (Conditional recommendation; very low certainty of evidence).	Based on small studies that have shown mortality and morbidity benefits, corticosteroids have previously been universally recommended in combination with a standard 6-month regimen for treating tuberculous pericarditis; however, a recent placebo-controlled randomized clinical trial with 1400 participants did not find a difference in the combined primary endpoint of the trial, which included mortality, cardiac tamponade, or constrictive pericarditis, between patients treated with adjuvant corticosteroids vs placebo. A subgroup analysis, however, did suggest a benefit in preventing constrictive pericarditis. Similarly, a systematic review conducted to obtain evidence in support of this guideline did not find a statistically significant benefit in terms of mortality or constrictive pericarditis from the use of corticosteroids. Therefore, we suggest that adjuvant corticosteroids should not be used routinely in the treatment of patients with pericardial tuberculosis.	However, selective use of corticosteroids in patients who are at the highest risk for inflammatory complications might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction.	Strang et al. 1987 Strang et al. 1988 Hakim Et Al. 2000 Mayosi et al. 2014 Reuter et al. 2006	Mortality (5 studies) Treatment adherence (2 studies) Constrictive pericarditis (3 studies)

2.2. Systematic reviews

Three systematic reviews were identified in the search (**Table 2**). The Cochrane systematic review by Wiysonge, 2017 was considered to be the most up-to-date and relevant as analyses presented are stratified by HIV status.

Table 2. Characteristics of systematic reviews identified

Systematic review	Year Published	Studies included	Subgroup analysis by HIV status	Comment
George et al.[5]	2018	Strang, 1987 Strang, 1988 Hakim, 2000 Mayosi, 2014 Reuter, 2006	No	
Wiysonge et al.[6]	2017 (reviewed in 2019 and considered up-to-date with respect to intervention of corticosteroids)	Schrire, 1959 Hakim, 2000 Strang, 2004a (10-year follow-up study of Strang 1987) Strang, 2004b (10-year follow-up study of Strang 1988) Reuter, 2006 Mayosi, 2014	Yes	Most up-to-date and relevant AMSTAR quality appraisal: Low-quality (Appendix 3)
Ntsekhe et al. [7]	2003	Schrire, 1959 Strang, 1987 Strang, 1988 Hakim, 2000	Yes	

2.2.1. Wiysonge, 2017[6]

This is an update of an earlier Cochrane systematic review published in 2002. This systematic review included seven randomised controlled trials (RCTs) or quasi-RCTs, all from sub-Saharan Africa, including the largest RCT conducted to date. Six trials comprising 1926 participants evaluated corticosteroids in tuberculous pericarditis.[2,8-11] Characteristics of these studies are summarised in **Table 3**. Four trials, comprising 1841 participants, were considered to be at low risk of bias. Three trials, comprising 118 participants, were considered to be at high risk of bias (**Figure 4**). Five trials enrolled participants with tuberculous pericardial effusion and one trial enrolled participants with tuberculous pericardial constriction. The corticosteroids evaluated included cortisone (1 trial), prednisone and triamcinolone hexacetonide (1 trial), and prednisolone (4 trials). The length of follow-up across trials ranged from 1 to 10 years. Only 2 trials included adults and children, with only 7 participants < 15 years included in the systematic review.[8]

In the systematic review, analyses were stratified by HIV status. Data on HIV status were not available in three trials that were conducted in South Africa before the onset of the HIV epidemic.[8,9] The participants in these trials were assumed to be HIV negative for the purposes of the systematic review. One trial enrolled only people with HIV (PWH).[10] Two trials enrolled both PWH and HIV-negative people. [2,11] More than half of all participants included in the systematic review were PWH (1018/1926, 52.9%), however only 19.9% were on antiretroviral therapy at enrolment. In the largest trial included in the systematic review, which comprised 939 PWH, baseline CD4 was available for 633 of 939 participants (67.4%). In these participants, the median CD4 count was 144 cells/mm³; 103 participants (16.3%) had a CD4 count < 50 cells/mm³; 295 participants (46.6%) had a CD4 count between 50 and 199 cells/mm³, 144 participants (22.7%) had a CD4 count between 200 to 350 cells/mm³, and 91 participants (14.4%) had CD4 cell counts > 350 cells/mm³. [12]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Hakim 2000	+	+	+	+	+	?	+
Liebenberg 2016	+	+	?	+	-	?	+
Mayosi 2014	+	+	+	+	+	+	+
Reuter 2006	?	-	+	?	-	?	+
Schrire 1959	-	-	-	-	?	?	+
Strang 2004a	+	+	+	+	+	?	+
Strang 2004b	+	+	+	+	+	?	+

Figure 4. Risk of bias summary from systematic review

(Note: The study by Liebenberg 2016 included in Figure 4 below is relevant to a different research question with colchicine as the intervention)

Table 3. Summary of studies included in Wiysonge, 2017

Study and Location	Methods	Participants	Interventions	Outcomes
Schire 1959 Cape Town, South Africa	Alternate allocation of 28 participants to adjuvant steroids or no steroids	28 adult participants with pericardial effusion who were on antituberculous chemotherapy for suspected tuberculous pericarditis. The trial authors did not provide the characteristics of the included participants, and did not specify the antituberculous drugs used. No participants with HIV. Definite TB: Not reported	Intervention • Cortisone with a loading dose of 300 mg and maintenance dose of 100 mg daily for several weeks was prescribed for 14 participants. - At a later date, prednisolone 60 mg/day with a maintenance dose of 20 mg was substituted. Control • No corticosteroids. The trial authors did not specify the length of follow-up.	Constriction requiring pericardiectomy
Hakim 2000 Harare, Zimbabwe	Computer-generated randomization list Double blind placebo controlled trial	58 HIV-positive adults with pericardial effusion who were on antituberculous chemotherapy for suspected tuberculous pericarditis. Inclusion criteria: (a) age 18 to 55 years; (b) residence in Harare city to ensure good follow up; (c) HIV seropositive; (d) no diagnosis of tuberculosis within the past two years; (e) large pericardial effusion on echocardiography (> 1 cm anteriorly and > 1 cm posteriorly; and (f) pericardial aspirate with > 50% lymphocytes and protein content > 30 g/L. Exclusion criteria: (a) antituberculous treatment started more than 48 hours before recruitment; (b) corticosteroid treatment within previous one month; (c) presence of Kaposi's sarcoma or any other malignancy; (d) coexisting life threatening disease; (e) bacterial pneumonia; (f) pregnancy; (g) cavitating pulmonary tuberculosis; and (h) other causes of pericardial effusion. All patients received a standard short course anti tuberculous regimen in accordance with national guidelines. This included rifampicin, isoniazid, pyrazinamide, and ethambutol for two months, followed by rifampicin and isoniazid for a further four months in standard doses. 0 participants on ART Definite TB: 38%	Intervention • Prednisolone for the first 6 weeks of antituberculous chemotherapy. • Dose for adults: 60 mg for the first week and tapering by 10 mg every week. Control • Placebo.	Primary outcomes • Death. • Resolution of pericardial effusion. Secondary outcomes • Resolution of pretreatment symptoms and signs, and ECG changes. • Corticosteroid-related adverse effects.

Study and Location	Methods	Participants	Interventions	Outcomes
Strang 2004a Umtata, South Africa (Follow-up of Strang, 1987)	Central randomization Double blind placebo- controlled study	143 participants with suspected tuberculous constrictive pericarditis aged 5 years and older. Only 2 participants were younger than 15 years of age. The participants in the treatment and control groups were well-matched in terms of clinical characteristics and completion of antituberculous chemotherapy. Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months. Assumed no participants with HIV. Definite TB: 10%	Intervention • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. Control • Matching placebo.	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Pericardiectomy.
Strang 2004b Umtata, South Africa (Follow-up of Strang, 1988)	Central randomization Double blind placebo- controlled study Factorial design	240 participants aged 5 years or more diagnosed as having active tuberculous pericardial effusion. Only 5 participants were younger than 15 years of age. The participants in the treatment and control groups were well-matched in terms of their clinical characteristics and completion of antituberculous chemotherapy. Those consenting to take part were all prescribed the same 6-month standard antituberculosis regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide daily for 14 weeks as an in-patient, followed by isoniazid and rifampicin daily up to 6 months. Assumed no participants with HIV. Definite TB: 60%	Intervention 1 • Complete open surgical drainage on admission. Control 1 • No open drainage. Intervention 2 • Prednisolone for the first 11 weeks of antituberculous chemotherapy. The dose for children aged 5 to 9 years was 30 mg daily for weeks 1 to 4; 15 mg daily for weeks 5 to 8; 7.5 mg daily for weeks 9 to 10; and 2.5 mg daily for week 11. Regarding children aged 10 to 14 years, the dose was 45 mg for weeks 1 to 4; 22.5 mg for weeks 5 to 8; 7.5 mg for weeks 9 to 10; and 2.5 mg for week 11. The dose for adults was 60 mg for the first 4 weeks; 30 mg for weeks 5 to 8; 15 mg for weeks 9 to 10; and 5 mg for week 1. Control 2 • Matching placebo.	• Death. • Death from pericarditis. • Favourable clinical status at 24 months. • Tamponade requiring pericardiocentesis. • Constriction. • Pericardiectomy.

Study and Location	Methods	Participants	Interventions	Outcomes
Reuter 2006 Cape Town, South Africa	Computer-generated randomization list Double-blind placebo-controlled study	57 participants, aged 17 to 66 years, with large pericardial effusions on echocardiography, pericardial aspirate with protein content > 30 g/L, and pericardial fluid adenosine deaminase (ADA) activity > 35 U/L; 23 females and 34 males; 40 had microbiological or histological evidence of TB or both, and 17 patients were diagnosed by clinical and supportive laboratory data. 21 (37.0%) were HIV-positive. No PWH were on ART. A standard short-course anti-tuberculous regimen was initiated according to national guidelines, namely a combination of rifampicin, isoniazid, pyrazinamide and ethambutol for two months, followed by rifampicin and isoniazid for a further four months. Patients were discharged on anti-tuberculous therapy and pyridoxine, with or without adjunctive prednisone. HIV-positive patients also received daily oral cotrimoxazole; due to the prevailing national policy at the time of this study, none of these patients received antiretroviral therapy. Definite TB: not reported	Intervention 1 • 200 mg (5 mL) intrapericardial triamcinolone hexacetonide. Triamcinolone was injected directly into the pericardium just prior to the removal of the indwelling catheter. Due to limited resources, an oral placebo was not used in conjunction with the intrapericardial triamcinolone. 17 participants were in this arm, 6 (35%) were HIV-positive. Intervention 2 • Oral prednisone plus intrapericardial placebo (5 mL 0.9% saline solution). Oral prednisone was started at 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks and 5 mg/day for 1 week. There were 16 participants in this arm, 9 (56%) were HIV-positive. Control • Placebo (5 mL intrapericardial 0.9% saline). 24 participants were included in this arm, and 6 (25%) were HIV-positive. We excluded data from the intrapericardial triamcinolone arm from this review.	Primary outcome • All-cause mortality. Secondary outcomes • Death attributed to pericarditis. • Disability related to pericardial disease at 1 year (defined as a history of restricted physical activity using New York Heart Association functional classification.) • Effusive constriction. • Fibrous constrictive pericarditis requiring pericardiectomy.

Study and Location	Methods	Participants	Interventions	Outcomes
Mayosi 2014 Multiple sites in South Africa, Mozambique, Malawi, Uganda, Sierra Leone, Zimbabwe, Kenya, and Nigeria	Computer-generated randomization list Double-blind placebo-controlled 2x2 factorial study	1400 participants (67% HIV-positive) 18 years of age or older, evidence of definite or probable tuberculous pericarditis, and had begun antituberculous treatment less than 1 week before enrolment. 83% of participants had pericardial effusion. 17% had constriction. 22% of PWH were on ART. Trial participants received antimicrobial treatment for tuberculosis and antiretroviral treatment for HIV according to World Health Organization (WHO) guidelines; management during the trial was revised as recommended treatment practices evolved. Definite TB: 17%	Intervention 1 • Prednisolone for 6 weeks at a dose of 120 mg per day in the first week, 90 mg per day in the second week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week. Control 1 • Identical placebo for 6 weeks at a dose of 120 mg per day in the 1st week, 90 mg per day in the 2nd week, 60 mg per day in the 3rd week, 30 mg per day in the 4th week, 15 mg per day in the 5th week, and 5 mg per day in the 6th week Intervention 2 • M. indicus pranii preparation (CADI-Mw injection, Cadila Pharmaceuticals) in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL (containing 0.5 Å~ 109 organisms) in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL. Control 2 • Identical placebo in 5 doses: at the time of enrolment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The 1st dose was given as 2 injections of 0.1 mL in each deltoid region of the upper arm; the 4 subsequent doses were given as a single injection of 0.1 mL.	Primary outcome • Composite of death or 1st occurrence of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. Secondary outcomes • Individual components of the primary outcome. • Hospitalization. Safety outcomes • Opportunistic infections. • Cancer. • CD4+ T-lymphocyte cell count (measure of immunosuppression) and immune reconstitution inflammatory syndrome (in HIV-positive).

2.3 Randomised controlled trials (RCTs)

Two RCTs were identified in the search.[2,8] Both studies were included in the Wiysonge(2017) systematic review and the effectiveness results for these two studies are not discussed further. Since the identified systematic review included only limited safety outcomes, the safety outcomes from the largest RCT are included.

The largest RCT was the IMPI trial, which utilised a 2 x 2 factorial double-blind design and was conducted in multiple centres across Sub-Saharan Africa.[2] The study enrolled 1400 adults with definite or probable tuberculous pericarditis to receive either prednisolone (n = 706) or placebo (n = 694) for 6 weeks, and either *M.indicus prannii* immunotherapy or placebo, in addition to standard anti-tuberculous therapy. The primary outcome was a composite of death or the first episode of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. Two thirds of participants were PWH, and across study arms <15% of PWH were on antiretroviral medication at randomisation. In the Wiysonge (2017) systematic review the IMPI trial was assessed to be at low risk of bias.

3. Effectiveness and/or safety results

3.1 PICO 1: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in HIV-negative adults with tuberculous pericarditis

Table 4. Summary of findings table for HIV-negative people from Wiysonge, 2017

Summary of findings for the main comparison. Corticosteroids for tuberculous pericarditis in HIV-negative people						
Population: HIV-negative people with tuberculous pericarditis Settings: any setting Intervention: corticosteroids Comparison: placebo						
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Steroids				
Death from all causes	22 per 100	18 per 100 (13 to 24)	RR 0.80 (0.59 to 1.09)	660 (4 trials)	⊕⊕⊕⊕ low ^{1,2}	Steroids may reduce the risk of deaths from all causes among HIV-negative people.
Death from pericarditis	8 per 100	3 per 100 (1 to 6)	RR 0.39 (0.19 to 0.80)	660 (4 trials)	⊕⊕⊕⊕ moderate ²	Steroids probably reduce the risk of deaths from pericarditis among HIV-negative people.
Constrictive pericarditis	10 per 100	7 per 100 (3 to 15)	RR 0.72 (0.34 to 1.55)	281 (2 trials)	⊕⊕⊕⊕ very low ^{2,3,4}	It is uncertain whether steroids have an effect on the risk of constriction among HIV-negative people.
Repeat pericardiocentesis	40 per 100	34 per 100 (28 to 41)	RR 0.85 (0.70 to 1.04)	492 (2 trials)	⊕⊕⊕⊕ low ^{1,4}	Steroids may reduce the risk of repeat drainage of the pericardium among HIV-negative people.
Cancer	1 per 100	1 per 100 (0 to 12)	RR 0.85 (0.05 to 13.80)	256 (1 trial)	⊕⊕⊕⊕ very low ^{3,5}	It is uncertain whether steroids have an effect on the risk of cancer among HIV-negative people.
Abbreviations: CI: confidence interval; RR: risk ratio.						
GRADE Working Group grades of evidence High certainty: further research is very unlikely to change our confidence in the estimate of effect. Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low certainty: we are very uncertain about the estimate.						

¹We downgraded by 1 for imprecision: the CI ranges from a large clinical benefit to a small increase in harm.

²We downgraded by 1 for study limitations: one trial was at high risk of bias.

³We downgraded by 2 for imprecision: the CI ranges from clinically important benefits to a large increase in harm.

⁴We downgraded by 1 for selective reporting: data were only reported by 2 of the 4 trials that recruited HIV-negative people.

⁵We downgraded by 1 for selective reporting: data were only reported by 1 of the 4 trials that recruited HIV-negative people.

In addition, only 1 trial reported on hospitalisation. It is uncertain whether corticosteroids reduced the risk of hospitalisation in people without HIV (RR 0.98, 95% CI 0.57 to 1.70, 256 participants, 1 trial, very low certainty evidence).

The effects of corticosteroids on risk of pericardiectomy in people without HIV is also uncertain (RR 0.91, 95% CI 0.58 to 1.41; 432 participants; 4 trials; very low certainty evidence).

3.2 PICO 2: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in adults with HIV and tuberculous pericarditis

Table 5. Summary of findings table for PWH from Wiysonge, 2017

Summary of findings 2. Corticosteroids for tuberculous pericarditis in HIV-positive people

Population: HIV-positive people with tuberculous pericarditis. Most patients (80%) not on antiretroviral drugs

Settings: any setting

Intervention: corticosteroids

Comparison: placebo

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Placebo	Corticosteroids				
Death from all causes	17 per 100	15 per 100 (6 to 40)	RR 0.91 (0.34 to 2.42)	575 (3 trials)	⊕⊕⊕⊕ very low ^{1,2}	It is uncertain whether steroids have an effect on the risk of deaths from all causes among people living with HIV.
Death from pericarditis	4 per 100	4 per 100 (2 to 10)	RR 1.07 (0.46 to 2.54)	517 (2 trials)	⊕⊕⊕⊕ very low ^{1,3}	It is uncertain whether steroids have an effect on the risk of deaths from pericarditis among people living with HIV.
Constrictive pericarditis	6 per 100	4 per 100 (2 to 7)	RR 0.55 (0.26 to 1.16)	575 (3 trials)	⊕⊕⊕⊕ low ¹	Steroids may reduce the risk of developing constriction among people living with HIV.
Repeat pericardiocentesis	60 per 100	61 per 100 (53 to 71)	RR 1.02 (0.89 to 1.18)	517 (2 trials)	⊕⊕⊕⊕ low ^{3,5}	Steroids may have little or no effect on the risk of repeat pericardiocentesis among people living with HIV.
Cancer	1 per 100	1 per 100 (0 to 8)	RR 1.62 (0.27 to 9.77)	502 (1 trial)	⊕⊕⊕⊕ very low ^{1,3}	It is uncertain whether steroids have an effect on the risk of cancer among people living with HIV.

Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence

High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low certainty: we are very uncertain about the estimate.

¹We downgraded by 2 for imprecision: the CI ranges from substantial clinical benefits to substantial harm.

²We downgraded by 1 for unexplained heterogeneity ($\text{Chi}^2 = 3.82$, $\text{df} = 1$ ($P = 0.05$); I^2 statistic = 74%).

³We downgraded by 1 for selective reporting: only 2 of the 3 studies that recruited HIV-positive people reported data.

⁴We downgraded by 1 for study limitations: 1 study had a high risk of bias.

⁵We downgraded by 1 for imprecision: the CI ranges from a small beneficial effect to clinically important harms.

Corticosteroids may reduce the risk of hospitalisation in PWH (RR 0.80, 95% CI 0.59 to 1.09; 502 participants, 1 trial, low certainty evidence).

It is uncertain whether corticosteroids have an effect on risk of pericardiectomy in PWH (RR 2.10, 95% CI 0.10 to 44.40; 15 participants, 1 trial, very low certainty evidence)

It is uncertain whether corticosteroids have an effect on the risk of opportunistic infections in PWH (RR 0.95, 95% CI 0.61 to 1.48; 517 participants, 2 trials, very low certainty evidence).

The IMPI trial, which contributed to the majority of participants with HIV in the Wiysonge 2017 systematic review, included a subgroup analyses of the effect of prednisolone on the primary composite outcome by CD4 count (**Figure 5**).

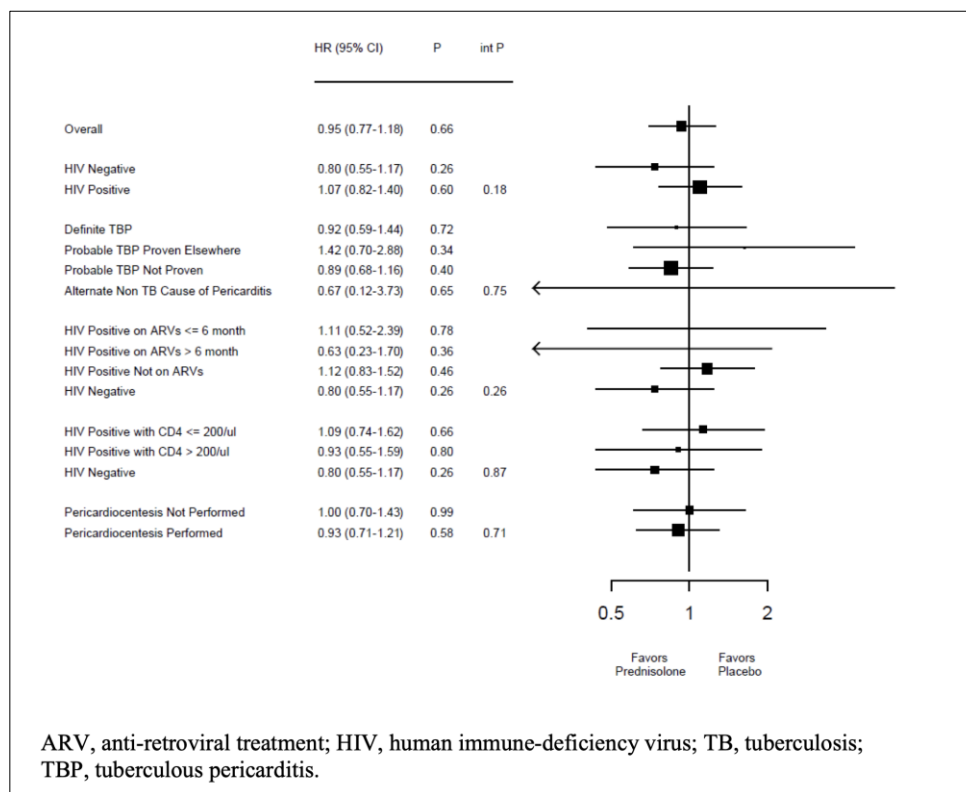


Figure 5. Forest Plot of Effect on Primary Composite Outcome by Key Subgroups for the Prednisolone Comparison from Mayosi, 2014

3.3 Safety Outcomes from Mayosi, 2014[2]

Table 6. Effects of prednisolone on Safety Outcomes from Mayosi, 2014

Outcome	Prednisolone (N = 706)		Placebo (N = 694)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	no. of events/100 person-yr	no. of patients (%)	no. of events/100 person-yr		
Opportunistic infection	78 (11.0)	6.89	68 (9.8)	5.91	1.16 (0.84–1.61)	0.36
Candida infection	54 (7.6)	4.68	36 (5.2)	3.01	1.52 (1.00–2.32)	0.05
Cancer	13 (1.8)	1.05	4 (0.6)	0.32	3.27 (1.07–10.03)	0.03
HIV-related cancer	9 (1.3)	0.73	1 (0.1)	0.08	9.04 (1.14–71.33)	0.04
Immune reconstitution disease	2 (0.3)	0.16	1 (0.1)	0.08	2.02 (0.18–22.28)	0.56

More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant. There were very few cases of immune reconstitution inflammatory syndrome (IRIS) in the trial overall, 2 cases of IRIS occurred in the prednisolone group and 1 in the placebo group. Prednisolone, as compared with placebo, was associated with an increased incidence of cancer (1.05 vs. 0.32 cases per 100 person-years; HR 3.27; 95% CI, 1.07 to 10.03; $p = 0.03$). This increase was due to a higher incidence of HIV-related cancers in the prednisolone group than in the placebo group (0.73 vs. 0.08 per 100 person-years; HR 9.04; 95% CI, 1.14 to 71.33; $p = 0.04$). The various cancers are summarised in **Table 7**. Nine of

the 13 cases of cancer in the prednisolone group occurred in participants who also received *M. indicus pranii*. Kaplan-Meier estimates of time to cancer occurrence for all four comparisons in the trial are shown in **Figure 6**. It should be noted that based on the suggestion of a clinical interaction between prednisolone and *M. indicus pranii* on cancer incidence, in the Wiysonge 2017 systematic review for the outcome of cancer, only data from the group that took 1 active intervention (i.e. prednisolone and placebo) were included, and data from the group that received both interventions was excluded.

Table 7. Causes of Malignancy Prednisolone vs. Placebo

Cause of malignancy	Prednisolone 706/1400		Placebo 649/1400		P value*
	n	%	n	%	
All malignancies (Patient could have multiple malignancies)	13	1.8	4	0.6	0.05
Kaposi	7	1.0	1	0.1	0.07
Non Hodgkin's lymphoma	2	0.3	0	0.0	0.50
Gastric / colon cancer	1	0.1	0	0.0	>0.99
Progression of pre-existing malignancy	1	0.1	1	0.1	>0.99
Other	2	0.3	2	0.3	>0.99

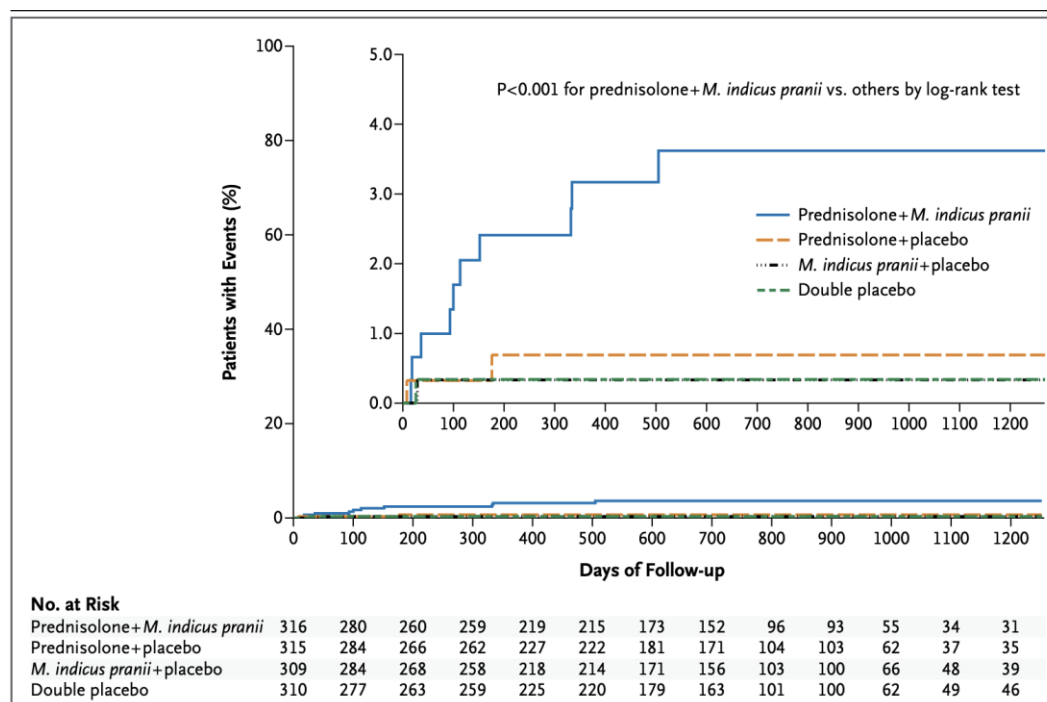


Figure 6. Time to cancer occurrence by study arm from Mayosi, 2014

Costs

The management of TB pericarditis will be a new STG addition to the Adult Hospital publication. As the national TB guidelines recommend the use of corticosteroids in TB pericarditis, we anticipate a minimal incremental budget impact with this recommendation. Costs have been calculated using the oral prednisone dose regimen from Mayosi (2014) RCT as this includes the largest patient cohort. Equivalent doses of dexamethasone IV for patients unable to take oral therapy, were obtained using the online steroid conversion calculator: https://www.mdcalc.com/calc/2040/steroid-conversion-calculator?drug_dosage=90

Table 8. Direct cost of corticosteroids in the treatment of tuberculous pericarditis in adults

TB PERICARDITIS - cost of corticosteroids as adjunctive therapy (ADULTS)					
Dexamethasone IV					
STG dosing guidance		Formulation	Price per ampoule (Rands)	Equivalent number of amps per week	Cost per week (Rands)
Week 1	18mg	4mg/mL as 1mL inj	6,83	35	239,05
Week 2	13,5mg			28	191,24
Week 3	9mg			21	143,43
Week 4	4,5mg			14	95,62
Week 5	2,3mg			7	47,81
Week 6	0,8mg			7	47,81
Cost per course					R764,96
Prednisone oral					
STG dosing guidance		Formulation	Price per tablet (Rands)	Equivalent number of tablets per day	Cost per week (Rands)
Week 1	120mg/day	5mg tablet	0,19	24	31,92
Week 2	90mg/day			18	23,94
Week 3	60mg/day			12	15,96
Week 4	30mg/day			6	7,98
Week 5	15mg/day			3	3,99
Week 6	5mg/day			1	1,33
Cost per course					R85,12
Notes:					
1. Dexamethasone dose conversion based on equivalent dose of oral prednisone using Mayosi 2014 regimen https://www.mdcalc.com/calc/2040/steroid-conversion-					
2. Doses rounded to nearest ampoule/tablet					
3. Prices based on MHPL (Feb 2026)					
4. Where dose ranges recommended - max dose applied for costing					
5. For prednisone, ave price per tablet applied as multiple products on tender					

As the use of adjunctive corticosteroids is already included in the paediatric STGs as standard of care, there is no anticipated incremental budget impact associated with this recommendation (**Table 9**).

Table 9. Direct cost of corticosteroids in the treatment of tuberculous pericarditis in children by weight band (based on current dosing guidance in Paediatric STG)

Assumed weight per patient				10kg			20kg			30kg					
Formulation	Price per pack (Rands)	STG dosing guidance		Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)	Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)	Dose per week (mg)	Equivalent number of bottles per patient	Cost per course (Rands)			
15mg/5mL solution (50mL pack) = 150mg per bottle	95,21	Week 1	2mg/kg/day	140	3		280	6		420	9				
		Week 2	1.5mg/kg/day	105			210			315					
		Week 3	1mg/kg/day	70			140			210					
		Week 4	1mg/kg/day	70			140			210					
		Week 5	0.5mg/kg/day	35			70			105					
		Week 6	0.25mg/kg/day	17,5			35			52,5					
				437,5			R285,63		875			R571,26	1312,5		R856,89
Notes:															
1. Based on 3 weight bands (10kg, 20kg and >/=30kg)															
2. Total dose per course rounded to nearest full pack															
3. Prices based on MHPL (Feb 2026)															

Key findings

- In adults without HIV and with tuberculous pericarditis:
 - Corticosteroids probably result in a reduction in deaths from pericarditis (moderate certainty evidence) and may reduce deaths from all causes and the need for repeat pericardiocentesis (low certainty evidence).
 - It is uncertain whether corticosteroids have any effect on the incidence of cancer, hospitalisation, development of constrictive pericarditis, or the need for pericardiectomy.
- In adult PWH not on ART with CD4 counts ≤ 350 cells/mm³ with tuberculous pericarditis:
 - Corticosteroids may reduce constrictive pericarditis and hospitalization (low certainty evidence).
 - Corticosteroids may make little or no difference to the need for repeat pericardiocentesis (low certainty evidence)
 - It is uncertain whether corticosteroids have any effect on deaths from pericarditis, deaths from all causes, the need for pericardiectomy or the development of cancer (very low certainty evidence).
- In the largest RCT conducted to date, key findings relevant to safety outcomes include:
 - More participants in the prednisolone group developed candida and other opportunistic infections than in the placebo group, though this was not statistically significant.
 - Prednisolone, as compared with placebo, was associated with an increased incidence of cancer, particularly HIV-related cancers (Kaposi's sarcoma and non-Hodgkin's lymphoma). This increase may be related to co-administration of immunotherapy (*M. indicus pranii*) in this RCT.
- No data in adult PWH on ART or with higher CD4 cell counts was identified and in these patients the results from adults without HIV may be more applicable.
- No data in children with or without HIV and tuberculous pericarditis was identified.

Conclusion and Recommendation

Given the important benefits of corticosteroids in reducing deaths in adults without HIV, and in reducing hospitalisations and the development of constrictive pericarditis in PWH, we recommend the use of corticosteroids in tuberculous pericarditis, acknowledging the low certainty evidence. In PWH, a thorough clinical examination should be performed before starting corticosteroids to exclude HIV-related cancers and antiretroviral therapy should be initiated promptly in accordance with standard treatment guidelines to mitigate the potential signal of harm observed in the largest RCT.

While no data in children with or without HIV and tuberculous pericarditis was identified, given the important benefits associated with the use of corticosteroids in adults with tuberculous pericarditis, we suggest using corticosteroids in children with tuberculous pericarditis.

Review Team

The following people were involved in this review (alphabetical by surname):

Name	Affiliation(s)	Role and Contribution	Interest declaration
Jessica Taylor (Lead author)	University of Cape Town	Literature search, quality appraisal, data synthesis, drafting report	None
Zahiera Adam	Clinton Health Access Initiative (CHAI) and NDoH	Costing, QA and recommendation	None
Prof Karen Cohen	Division of Clinical Pharmacology, University of Cape Town	QA, expert guidance and recommendation	None
Dr Halima Dawood	Infectious Diseases Unit, Greys Hospital	Expert guidance	None
Dr Jeremy Nel	Division of Infectious Diseases, Department of Medicine, University of the Witwatersrand	QA, expert guidance and recommendation	None

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References

- [1] Samim D, Muula G, Banholzer N, et al. Cardiovascular Involvement in Tuberculosis Patients Treated in Southern Africa. *JACC: Advances*. 2025;4(1):101427.
- [2] Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371(12):1121–30.
- [3] Strang JJ, Kakaza HH, Gibson DG, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet*. 1987;2(8573):1418–22.
- [4] Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- [5] George IA, Thomas B, Sadhu JS. Systematic review and meta-analysis of adjunctive corticosteroids in the treatment of tuberculous pericarditis. *Int J Tuberc Lung Dis*. 2018;22(5):551–556.
- [6] Wiysonge CS, Ntsekhe M, Thabane L, et al. Interventions for treating tuberculous pericarditis. *Cochrane Database Syst Rev*. 2017;9(9):Cd000526.
- [7] Ntsekhe M, Wiysonge C, Volmink JA, et al. Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven. *Qjm*. 2003;96(8):593–9.
- [8] Strang JJ, Nunn AJ, Johnson DA, et al. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. *Qjm*. 2004;97(8):525–35.
- [9] Schrire V. Experience with pericarditis at Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases studied over a six-year period. *S Afr Med J*. 1959;33:810–7.
- [10] Hakim JG, Ternouth I, Mushangi E, et al. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart*. 2000;84(2):183–8.
- [11] Reuter H, Burgess LJ, Louw VJ, et al. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. *Cardiovasc J S Afr*. 2006;17(5):233–8.
- [12] Gumede F, Pandie S, Nachega J, et al. The impact of HIV co-infection on presentation and outcome in adults with tuberculous pericarditis: Findings from the IMPI trial. *SAMJ: South African Medical Journal*. 2023;113(3B):1109–1115.

Appendix 1: Search results and reasons for exclusion

	Reference	Study Type	Included/Excluded	Reason
1.	Imazio M, Gaita F, LeWinter M. Evaluation and Treatment of Pericarditis: A Systematic Review. JAMA. 2015 Oct 13;314(14):1498-506. doi: 10.1001/jama.2015.12763. Erratum in: JAMA. 2015 Nov 10;314(18):1978. doi: 10.1001/jama.2015.14947. Erratum in: JAMA. 2016 Jan 5;315(1):90. doi: 10.1001/jama.2015.16998. Dosage error in article text. PMID: 26461998.	Systematic review	Excluded	Incorrect population - Not specific to tuberculous pericarditis
2.	López-López JP, Posada-Martínez EL, Saldarriaga C, Wyss F, Ponte-Negretti CI, Alexander B, Miranda-Arboleda AF, Martínez-Sellés M, Baranchuk A; Neglected Tropical Diseases, Other Infectious Diseases Affecting the Heart (the NET-Heart Project). Tuberculosis and the Heart. J Am Heart Assoc. 2021 Apr 6;10(7):e019435. doi: 10.1161/JAHA.120.019435. Epub 2021 Mar 18. PMID: 33733808; PMCID: PMC8174360.	Narrative review	Excluded	Incorrect study type
3.	George IA, Thomas B, Sadhu JS. Systematic review and meta-analysis of adjunctive corticosteroids in the treatment of tuberculous pericarditis. Int J Tuberc Lung Dis. 2018 May 1;22(5):551-556. doi: 10.5588/ijtld.17.0341. PMID: 29663961.	Systematic review	Included	
4.	Wiyongse CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, Pandie S, Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2017 Sep 13;9(9):CD000526. doi: 10.1002/14651858.CD000526.pub2. PMID: 28902412; PMCID: PMC5618454.	Systematic review	Included	
5.	Diallo A, Diallo BD, Diallo OH, Carlos-Bolumbu M, Camara M, Sidikiba S. Corticosteroids for reducing tuberculosis mortality in persons living with HIV: a systematic review and meta-analysis using reconstructed individual patient data. BMJ Glob Health. 2025 Aug 14;10(8):e017923. doi: 10.1136/bmjgh-2024-017923. PMID: 40813100; PMCID: PMC12352167	Systematic review	Excluded	Incorrect population – pericardial, meningeal and pleural tuberculosis
6.	Ntsekhe M, Wiyongse C, Volmink JA, Commerford PJ, Mayosi BM. Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven. QJM. 2003 Aug;96(8):593-9. doi: 10.1093/qjmed/hcg100. PMID: 12897345.	Systematic review	Included	
7.	Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2002;(4):CD000526. doi: 10.1002/14651858.CD000526. Update in: Cochrane Database Syst Rev. 2017 Sep 13;9:CD000526. doi: 10.1002/14651858.CD000526.pub2. PMID: 12519546.	Systematic review	Excluded	2017 update included (Wiyongse et al.)
8.	Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2000;(2):CD000526. doi: 10.1002/14651858.CD000526. Update in: Cochrane Database Syst Rev. 2002;(4):CD000526. doi: 10.1002/14651858.CD000526. PMID: 10796550.	Systematic Review	Excluded	2017 update included (Wiyongse et al.)
9.	Reuter H, Burgess LJ, Louw VJ, Doubell AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovasc J S Afr. 2006 Sep-Oct;17(5):233-8. PMID: 17117227.	Randomised controlled trial	Excluded	Incorrect intervention/comparison – intrapericardial corticosteroid therapy vs. oral corticosteroid vs. intrapericardial placebo
10.	Strang JI, Nunn AJ, Johnson DA, Casbard A, Gibson DG, Girdling DJ. Management of tuberculous constrictive pericarditis and tuberculous pericardial effusion in Transkei: results at 10 years follow-up. QJM. 2004 Aug;97(8):525-35. doi: 10.1093/qjmed/hch086. PMID: 15256610.	10-year follow-up of 2 randomised controlled trials	Included	.
11.	Mayosi BM, Ntsekhe M, Bosch J, Pogue J, Gumedze F, Badri M, Jung H, Pandie S, Smieja M, Thabane L, Francis V, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Banda AC, Mutyaba A, Brown B, Ntuli P, Mntla P, Ntintyane L, Ramjee R, Manga P, Kirenga B, Mondo C, Russell JB, Tsitsi JM, Peters F, Essop MR, Barasa AF, Mijinyawa MS, Sani MU, Olunuga T, Ogah O, Adebiyi A, Aje A, Ansa V, Ojji D, Danbauchi S, Hakim J, Matenga J, Yusuf S. Rationale and design of the Investigation of the Management of Pericarditis (IMPI) trial: a 2 × 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and Mycobacterium m immunotherapy in tuberculous pericarditis. Am Heart J. 2013 Feb;165(2):109-15.e3. doi: 10.1016/j.ahj.2012.08.006. Epub 2012 Dec 13. PMID: 23351812.	Randomised controlled trial protocol	Excluded	Incorrect study design - protocol
12.	Liebenberg JJ, Dold CJ, Olivier LR. A prospective investigation into the effect of colchicine on tuberculous pericarditis. Cardiovasc J Afr. 2016 Nov/Dec;27(6):350-355. doi: 10.5830/CVJA-2016-035. PMID: 27965998; PMCID: PMC5412665.	Randomised controlled trial	Excluded	Incorrect comparator - colchicine
13.	Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, Pogue J, Thabane L, Smieja M, Francis V, Joldersma L, Thomas KM, Thomas B, Awotedu AA, Magula NP, Naidoo DP, Damasceno A, Chitsa Banda A, Brown B, Manga P, Kirenga B, Mondo C, Mntla P, Tsitsi JM, Peters F, Essop MR, Russell JB, Hakim J, Matenga J, Barasa AF, Sani MU, Olunuga T, Ogah O, Ansa V, Aje A, Danbauchi S, Ojji D, Yusuf S; IMPI Trial Investigators. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014 Sep 18;371(12):1121-30. doi: 10.1056/NEJMoa1407380. Epub 2014 Sep 1. PMID: 25178809; PMCID: PMC4912834.	Randomised controlled trial	Included	Primary study included in systematic review
14.	Wiyongse CS, Ntsekhe M, Gumedze F, Siwa K, Blackett KN, Commerford PJ, Volmink JA, Mayosi BM. Contemporary use of adjunctive corticosteroids in tuberculous pericarditis. Int J Cardiol. 2008 Mar 14;124(3):388-90. doi: 10.1016/j.ijcard.2006.12.060. Epub 2007 Apr 18. PMID: 17445921.	Cross-sectional study	Excluded	Incorrect study type

Appendix 2.

Summary of findings table from WHO Guideline WHO Consolidated guidelines on tuberculosis. Module 4: Treatment and care.

PICO 7

Author(s): Lelia Chaisson

Question: Adjuvant corticosteroids compared with TB treatment without corticosteroids for tuberculous pericarditis

Bibliography: Strang JI et al. Lancet 1987; Strang JI et al. Lancet 1988; Hakim JG et al. Heart 2000; Mayosi BM et al. N Engl J Med 2014; Reuter H et al. Cardiovasc J S Afr. 2006

Quality assessment							Number of patients		Effect			Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvant corticosteroids	TB treatment without corticosteroids	Relative (95% CI)	Absolute (95% CI)			
Death													
5	randomized trials	not serious	serious ¹	serious ²	serious ³	none ⁴	142/897 (15.8%)	142/882 (16.1%)	RR 0.54 (0.23 to 1.26)	74 fewer per 1000 (from 42 more to 124 fewer)	⊕○○○ VERY LOW		CRITICAL
Treatment adherence													
2	randomized trials	serious ⁵	very serious ¹	serious ⁵	not serious	none	744/888 (83.8%)	785/907 (86.5%)	RR 0.91 (0.75 to 1.12)	78 fewer per 1000 (from 104 more to 216 fewer)	⊕○○○ VERY LOW		IMPORTANT
Constrictive pericarditis													
3	randomized trials	not serious	not serious	not serious	very serious ³	none	36/768 (4.7%)	56/747 (7.5%)	RR 0.72 (0.32 to 1.58)	21 fewer per 1000 (from 43 more to 51 fewer)	⊕⊕○○ LOW		IMPORTANT

CI: confidence interval; RR: risk ratio.

1. Inconsistent findings between studies. Death $I^2 = 70\%$; adherence $I^2 = 89\%$. Older studies show larger effects.
2. Although not alone a reason for downgrading (only in context of the concern for publication bias), we considered the older studies not necessarily reflecting the populations seen in practice today.
3. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
4. Publication bias is possible – small studies show a large effect. However, these studies are also older, and the enrolled populations may differ, accounting for the difference in the effects.
5. Different definitions of adherence were used by different studies.

Summary of findings table from the *Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis, 2016*.

Evidence profile 14

Date: 05/16/2014

PICO Question 7: Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Comparison: systemic corticosteroid therapy versus placebo.

Quality assessment							N of patients		Effect		Certainty in the Evidence	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroids	placebo	Relative (95% CI)	Absolute (95% CI)		
Death												
5 studies	randomized trials	not serious	very serious ¹	not serious	serious ²	none	142/897 (15.8%)	142/882 (16.1%)	RR 0.54 (0.23 to 1.26)	74 fewer per 1000 (from 42 more to 124 fewer)	 VERY LOW	CRITICAL
Adherence												
2 studies	randomized trials	serious ³	very serious ¹	serious ¹	not serious	none	744/888 (83.8%)	785/907 (86.5%)	RR 0.91 (0.75 to 1.12)	78 fewer per 1000 (from 104 more to 216 fewer)	 VERY LOW	IMPORTANT
Constrictive pericarditis												
3 studies	randomized trials	not serious	not serious	not serious	very serious ²	none	36/768 (4.7%)	56/747 (7.5%)	RR 0.72 (0.32 to 1.58)	21 fewer per 1000 (from 43 more to 51 fewer)	 LOW	IMPORTANT

MD – mean difference, RR – relative risk

Events:

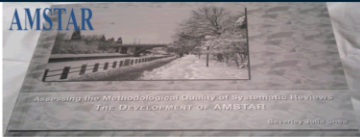
1. Inconsistent findings between studies. Death $I^2 = 70\%$; Adherence $I^2 = 89\%$.
2. The effects at the ends of the confidence interval would lead to different clinical decisions; in addition, the sample sizes are smaller than the optimal information size.
3. Different definitions of adherence were used by different studies.

Evidence Profile References:

- Strang JI, Kakaza HH, Gibson DG, Girding DJ, Nunn AJ, Fox W. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987; 2(8573): 1418-22.
- Strang JI, Kakaza HH, Gibson DG, et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988; 2(8614): 759-64.
- Hakim JG, Temouth I, Mushang E, Sizya S, Robertson V, Malin A. Double blind randomized placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; 84(2): 183-8.
- Mayosi BM, Ntsokhe M, Smeja M. Immunotherapy for tuberculous pericarditis. *N Engl J Med* 2014; 371(26): 2534.
- Reuter H, Burgess LJ, Lowe VJ, Doull AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. *Cardiovasc J S Afr*. 2006 Sep-Oct;17(5):233-8.

Appendix 3: AMSTAR assessment

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AMSTAR 2 Results

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Article Name:

Interventions for treating tuberculous pericarditis (Cochrane Review). 2017 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes Yes Yes Yes Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Yes Yes Yes Yes Yes Yes Yes Yes
5. Did the review authors perform study selection in duplicate?	Yes Yes
6. Did the review authors perform data extraction in duplicate?	Yes Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes Yes Yes
8. Did the review authors describe the included studies in adequate detail?	Partial Yes Yes Yes Yes Yes Yes Yes Yes Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
RCT	
NRSI	0 Yes Yes Yes Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
RCT	
NRSI	Yes Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes Yes
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes Yes Yes

To cite this tool: Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

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South African National Department of Health

Brief Report of NEMLC Limited Review¹

Corticosteroids for the treatment of tuberculous meningitis (TBM)

February 2026

Medicine details:

Medicine Class	Corticosteroids	<i>If applicable Please consider therapeutic interchange policy</i>
Medicine/s name -INN: - South African name (if differs from INN)	Prednisone Prednisolone Dexamethasone	http://www.whocc.no/atc_ddd_index/
Medicine/s (ATC5):	H02AB07 H02AB06 H02AB02	http://www.whocc.no/atc_ddd_index/
Indication (ICD-10 code):	A17.0	https://www.health.gov.za/icd-10-master-industry-table/
SAHPRA Approved	Yes	SAHPRA registered health products database https://medapps.sahpra.org.za:6006/
Dosage form/s	tablet, suspension, solution for injection	
Route of administration/s	oral, intravenous	
Patient population	Adults and children with and without HIV	
Prevalence and/or incidence of condition	Overall, in 2012, 6.8 cases per 100 000 persons. In people living with HIV 34.9 cases per 100 000 persons. (Britz et al. PloS One. 2016)	<i>May refer to estimates or routine data (DHIS, StatsSA), not necessarily published data.</i>
Level of Care	Hospital level (initiation) Primary Healthcare (continuation)	
Prescriber level	Doctor initiated	

¹ This template was informed by examples of previous NEMLC limited reviews, input from the Essential Drug Programme Oversight Group and the NEMLC Medicine Review Template which was updated with support through the Evidence-to-Decision (E2D) project which is a collaboration between National Department of Health, the South African Medical Research Council and the University of Stellenbosch.

Current Standard of Care

In adults: Combination anti-tuberculosis treatment for 9 months duration. In people without HIV, with grade II to III TBM, adjunctive corticosteroids are recommended. No recommendation is currently made for corticosteroid use in people living with HIV (PWH) and TBM.

In children: Combination anti-tuberculosis treatment for 6 to 9 months duration. In all children, irrespective of HIV status or TBM grade, adjunctive corticosteroids are recommended.

Executive Summary

- TB meningitis (TBM) is associated with significant mortality, with a pooled case fatality rate of 53% in people with HIV (PWH) and 22% in HIV-negative people.[1]
- The current standard treatment guidelines recommend the use of corticosteroids in HIV-negative adults with Grade II² or III TBM, and in children with TBM, only. These recommendations are based on a 2008 Cochrane systematic review [2]
- We conducted an updated rapid systematic review of the evidence for the use of corticosteroids in the management of TBM in HIV-negative children and adults, as well as in children and adults with HIV. Only guidelines, systematic reviews with meta-analyses, and randomised controlled trials published subsequent to 2008 (and not included in the previous reference) were included.
- We identified three clinical practice guidelines:
 - Clinical practice guidelines from WHO (2025) and ATS/CDC/ERS/IDSA³ (2025) recommend using corticosteroids in people with TBM, irrespective of TBM grade, and without any differential recommendation based on HIV status. These recommendations had not been updated since 2016-2017.[3,4]
 - The Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) was identified as the most up-to-date clinical practice guideline for the management of TBM. [5] This guideline recommends using adjunctive corticosteroid therapy for TBM in people without HIV (strong recommendation, high certainty of evidence). In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and based on the safety and potential effectiveness of corticosteroids, they recommend using corticosteroids on a case-by-case basis in PWH (weak recommendation, high certainty of evidence).
- We identified one updated Cochrane systematic review and meta-analysis of adjunctive corticosteroids in predominantly HIV-negative adults and children with TBM.[6] Key findings include:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence).
 - This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
 - Therefore, we recommend using corticosteroids in HIV-negative adults, and children, with any grade of TBM.

² British Medical Research Council Staging. Grade I TBM: No focal neurological signs, Glasgow Coma Scale (GCS) 15; Grade II TBM: GCS 11 to 14 or GCS 15 with focal neurological deficits; Grade III TBM: GCS ≤ 10.

³ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

- We identified one systematic review and meta-analysis from the Tuberculous Meningitis International Research Consortium clinical practice guideline (2026) and one randomised controlled trial (RCT) of adjunctive corticosteroids in adult PWH with TBM.[5,7] The methods and GRADE assessment underpinning the systematic review and meta-analysis from the clinical practice guideline were poorly reported. Key findings include:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).
 - Corticosteroids did not increase serious adverse events.
 - These findings are based largely on data from the one RCT identified, in which the majority of PWH and TBM had a CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit specifically in PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.
 - We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³.
 - In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified.
 - There is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.
 - In children, with or without HIV, with TB meningitis, we recommend using corticosteroids.

Key Recommendations *(if more appropriate, describe in narrative form)*

Type of ERC recommendation	We recommend against the option and for the alternative (strong)		We suggest not to use the option or to use the alternative (conditional)		We suggest using the option (conditional)		We recommend the option (strong)	
	☐		✓ See recommendation 2		✓ See recommendation 3		✓ See recommendation 1 and 4	
High level summary of conclusions	1. In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids. 2. In adults with HIV and TB meningitis of any grade, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids. 3. In adults with HIV and TB meningitis of any grade, with CD4 count >200 cells/mm³, we suggest using corticosteroids. 4. In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.							
NEMLC Ratification	Date		Comments/Recommendation					
	26 Mar 2026		NEMLC ratified the ERCs recommendation as detailed above, pending agreement with the national TB and HIV programs. (Program confirmation received by email communication April 2026).					
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval		If NO, tick box	
							✓	
Trigger for review								

Background and rationale

The current Adult Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in adults with grade II to III tuberculous meningitis (TBM) **(Figure 1)**. This recommendation (level of evidence IIa) is based on evidence from Prasad et al.'s 2008 Cochrane review which demonstrate that corticosteroids can reduce the risk of neurological deficits and death in adults with TBM.[2] However, in adults living with HIV co-infected with TBM, the standard treatment guidelines highlight ongoing uncertainty regarding the benefits of corticosteroids therapy (level of evidence IIa, Prasad et al. Cochrane. 2008).[2] The 2008 Cochrane systematic review on which these recommendations are based was subsequently updated in 2016 and more recent studies in people living with HIV (PWH) have emerged as of 2023. [6,7]

The current Paediatric Hospital standard treatment guidelines recommend the use of adjunctive corticosteroids alongside standard anti-tuberculosis therapy in all children irrespective of HIV status or grade of TBM. No reference or level of evidence for this recommendation is provided (Figure 2).

This rapid review aims to evaluate the most up to date evidence for adjunctive corticosteroid therapy in people with TBM, and to inform a more refined and specific recommendation in PWH.

MEDICINE TREATMENT	
Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See Section 16.9: Tuberculosis, Pulmonary for details.	
In HIV-negative individuals:	
Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less).	
Dexamethasone, IV, dosing as follows:	
Weeks	Dosing regimen
Initial dose	0.3-0.4 mg/kg/day for 2 weeks.
Week 3	0.2 mg/kg daily.
Week 4	0.1 mg/kg daily.
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week.
OR	
- Corticosteroids (intermediate-acting) e.g.: LoE:IIa^{vi} - Prednisone, oral, 60 mg daily for 2 weeks. - Then taper gradually over the next 6 weeks (see Appendix II for an example of a dose reduction regimen). LoE:IVb^{vi}	
In people with HIV:	
Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM. LoE:IIa^{ix}	
LoE:IIa^{ix}	

Figure 1. Adult Hospital. Chapter 14 Neurological Disorders. 14.8.1.1 TB meningitis

CHAPTER 10	TUBERCULOSIS
Steroid therapy:	
- Prednisone, oral, 2 mg/kg as a single daily dose for 4 weeks. - Maximum daily dose: 60 mg. - Taper to stop over further 2 weeks.	

Figure 2. Paediatric Hospital. Chapter 10 Tuberculosis. Section 10.4: Meningitis, tuberculosis (TBM) in children

Purpose/Objective i.e., PICO question (if relevant):

PICO 1

Population Subgroups	HIV-negative adults and children with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus standard anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

PICO 2

Population Subgroups	Adults and children living with HIV co-infected with TBM
Intervention(s)	Corticosteroids (prednisone, prednisolone or dexamethasone) plus anti-TB treatment
Comparator(s)	Anti-tuberculous treatment (ATT) alone or with placebo
Outcome(s)	Mortality, severe disability, adverse events
Study types	Guidelines, systematic reviews with meta-analysis, randomised controlled trials

Methods

1. Data Sources

Clinical practice guidelines: We searched for relevant clinical practice guidelines from the American Thoracic Society and World Health Organization.

Systematic reviews and randomised controlled trials: We searched PubMed for guidelines, systematic reviews, and randomised controlled trials.

2. Search Strategy

The following search terms were used:

((TB meningitis) OR (tuberculous meningitis)) OR (tuberculosis meningitis) AND (corticosteroids)

We restricted our search to studies published from 2004, since the most recent study included in the 2008 Prasad et al. Cochrane review referenced in the current standard treatment guidelines was from 2004. PubMed searches were filtered by year (from 2004), guideline, systematic review, meta-analysis and randomised controlled trials.

3. Study selection and eligibility criteria, data extraction and analysis, and evidence synthesis

The study screening, selection and data extraction, analysis and evidence was conducted by 1 reviewer. Evidence was synthesised narratively.

Results

1. Result of the search

Three clinical practice guidelines were identified: the ATS/CDC/ERS/IDSA⁴ Clinical Practice Guideline (2025), the World Health Organisation (WHO) consolidated guidelines on tuberculosis. Module 4: Treatment and care (2025), and the Tuberculous Meningitis International Research Consortium guideline (2026).[3-5] In both the ATS/CDC/ERS/IDSA and WHO guidelines, specific recommendations relating to corticosteroids use in TBM have not been updated since 2016 – 2017.

The PubMed search identified 23 studies and 1 clinical practice guideline from the European Respiratory Society 2009. Of the 23 studies identified, there were 9 systematic reviews, 13 randomised controlled trials (RCTs) and 1 retrospective cohort study. Of the 9 systematic reviews, only 1 (Prasad (2016)) was eligible for inclusion.[6] Of the 13 RCTs, 3 were eligible for inclusion: Thwaites (2004); Malhotra (2009); Donovan, (2023).[7-9]

The WHO and ATS/CDC/ERS/IDSA clinical practice guidelines were based on systematic reviews of the same 5 primary studies.[8-12] The Tuberculous Meningitis International Research Consortium guideline included all 5 of these studies, 8 of 9 primary studies included in the Prasad (2016) systematic review, and the most recent RCT identified by Donovan (2023).[7] This clinical practice guideline was therefore the most up-to-date guideline and selected for inclusion.

The search results are illustrated in **Figure 3. Search Flow Chart**. Specific reasons for inclusion or exclusion of studies identified in the search are listed in **Appendix 1**. **Appendix 2** includes a comparison of the specific recommendations and primary studies included in the WHO, ATS/CDX/ERS/IDSA and Tuberculous Meningitis International Research Consortium guidelines.

⁴ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

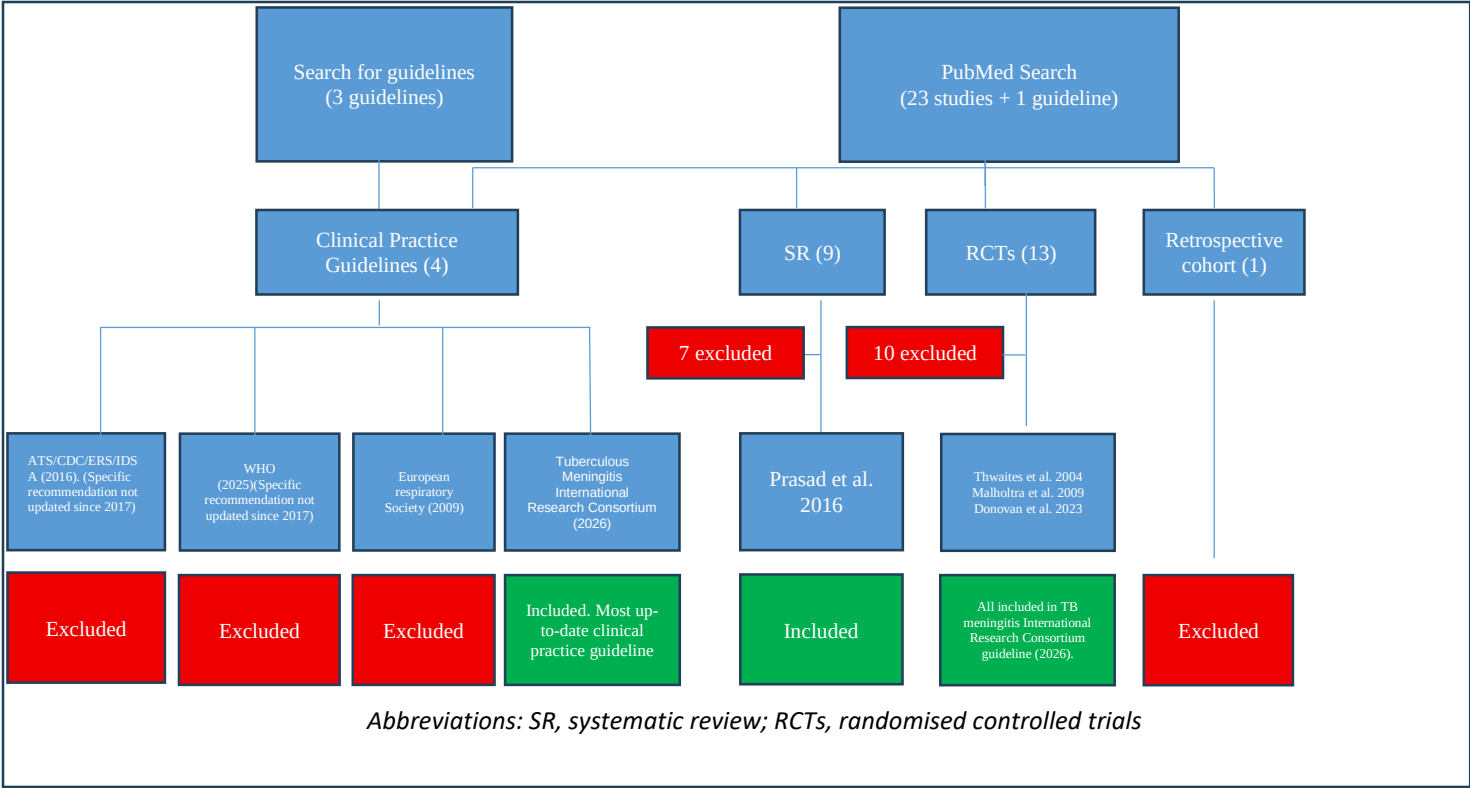


Figure 3. Search Flow Chart

2. Description of included studies

2.1. Clinical Practice Guidelines

The Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026) was considered the most up-to-date clinical practice guideline which included subgroup considerations by HIV status. The recommendations from this guideline are summarised in **Table 1**. Insufficient detail was provided in the clinical practice guideline concerning the underlying systematic review methodology and GRADE assessment, therefore, the quality of the underlying systematic review was not assessed. The results of the systematic review and meta-analyses are reported in **Results Section 3**.

Table 1. Summary of the recommendation from the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Recommendation	Justification	Subgroup considerations	Studies included in the systematic review (9)	Outcomes considered	AGREE II
In people without HIV, we recommend the use of adjunctive corticosteroid therapy. (strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence).	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole (1969)[7] Girgis (1991)[13] Kumaravelu (1994)[10] Chotmongkol (1996)[11] Schoeman (1997)[12] Lardizabal (1998)[14] Malhotra (2009)[9] Thwaites (2004)[8] Donovan (2023)[7]	Mortality Morbidity	Overall: 60 % Domain 1- Scope and Purpose: 90% Domain 2 – Stakeholder involvement: 57% Domain 3 - Rigour of development: 61% Domain 4 – Clarity of presentation: 67% Domain 5 - Applicability: 32% Domain 6 – Editorial independence: 64%

2.2. Systematic reviews

One systematic review was eligible for inclusion, Prasad (2016).[6] This systematic review is the update of the Prasad (2008) Cochrane systematic review.[2]

This systematic review evaluated the effects of adjunctive corticosteroids on death and severe disability in people with tuberculous meningitis. It included only RCTs that compared corticosteroids plus ATT with ATT treatment alone, and which included death or disability as an outcome.

Nine RCTs with 1337 participants were included. The 9 RCTs were: O'Toole (1969); Girgis (1991); Kumaravelu (1994); Chotmongkol (1996); Schoeman (1997); Lardizabal (1998); Thwaites (2004); Prasad (2006 (unpublished data only); Malhotra (2009).[8-15] The characteristics of these RCTs are summarised in **Table 2**. All but one of the RCTs included in the Prasad (2016) systematic review are included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). The Prasad (2006) trial (unpublished data) is not included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline,

One RCT included only young children.[12] Two RCTs included adults and children.[13,15] Six RCTs included only adults or adults and adolescents ≥ 14 years of age. Only one RCT reported on HIV-co-infection.[8] One RCT included prolonged follow-up to 5 years. At least 5 RCTs were considered to be at high risk of bias (including the unpublished data from the Prasad (2006) RCT).[9,10,13,14] Three RCTs had unclear risk of bias.[11,12,15] One RCT was considered to be at low risk of bias (**Figure 4**).[8]

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (death)	Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Chotmongkol 1996	?	+	+	+	?	?	?
Girgis 1991	+	?	?	?	-	?	?
Kumarvelu 1994	+	-	?	+	-	-	?
Lardizabal 1998	?	?	?	+	-	+	+
Malhotra 2009	+	?	?	+	-	+	+
O'Toole 1969	?	+	+	+	+	+	?
Prasad 2006	+	+	+	+	?	?	-
Schoeman 1997	?	?	?	+	+	?	+
Thwaites 2004	+	+	+	+	+	+	+

Figure 4. Risk of bias summary from Prasad (2016) systematic review

Table 2. Summary of studies included in Prasad (2016) systematic review

Study	Methods	Participants	Interventions	Outcomes
O'Toole 1969	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: unclear.	Setting: Infectious Diseases Hospital, Calcutta, India - tertiary referral centre. Number of participants: 23 participants in total, 11 females, 12 males; 11 received dexamethasone, 12 received no steroid. Inclusion criteria: not explicitly specified, but the trial authors state that due to the trial institution's admissions policy only participants with a short history or acute signs and symptoms of meningitis were selected; due to limited bed availability only moderate to severely unwell participants were included (MRC Stage II and III). All age groups were included. Treatment allocation was stratified for age and disease severity. HIV status: not reported.	1. ATT plus dexamethasone given for up to 4 weeks in an adult dose of 9 mg/day during the first week, 6 mg/day during the second week, 3 mg/day during the third week, and 1.5 mg/day during the 4th week; dose for children was calculated according to their body surface area (no more details available). 2. ATT alone. ATT: isoniazid intramuscular or oral (10 mg/kg/day, except in children < 2 years of age who received 20 mg/kg/day) and streptomycin (20 mg/kg/day, maximum 1 g), duration not specified	1. Death at the end of follow-up (duration unclear). 2. Number with elevated CSF opening pressure on days 1, 4, 7, and 14. 3. CSF sugar, protein, and cell count on days 1, 4, 7, 14, 21, and 28 in decreasing number of participants, depending apparently on the surviving number. Number with residual deficits not given. Surviving participants all been described as "significantly improved". 4. Adverse events recorded: upper gastrointestinal bleed, invasive bacterial infection, hypoglycaemia, and hypothermia. 5. Resolution of CSF findings
Girgis 1991	Randomized parallel group, 2-arm study with allocation ratio: 1:1. Length of follow-up: 24 months.	Setting: Abbassia Fever Hospital, Cairo, Egypt - tertiary referral centre. Number of participants: 280 participants; 158 males, 122 females; 145 received dexamethasone, 135 received no steroid. Age: all ages included, 37% aged 0 to 5 years, 22% aged 5 to 16 years. Inclusion criteria: clinically diagnosed tuberculous meningitis based on history and examination (duration of illness > 30 days, consisting of fever, headache, vomiting, altered sensorium, generalized weakness or cranial nerve deficits); comparison of first and second CSF findings; and a poor response to antibacterial therapy for 48 hrs. Exclusion criteria: not reported. HIV status: not reported.	1. ATT plus dexamethasone given intramuscularly (12 mg/day to adults and 8 mg/day to children weighing < 25 kg) for 3 weeks and then tapered during the next 3 weeks). 2. ATT alone. ATT: isoniazid (10 mg/kg/day, maximum 600 mg) intramuscularly for 2 weeks then orally for 2 years, streptomycin intramuscular (25 mg/kg/day, maximum 1000 mg) for 6 weeks, and ethambutol oral (25 mg/kg/day, maximum 1200 mg) for 6 weeks, then 15 mg/kg/day for 2 years.	1. Death during 2-year follow-up. 2. Residual neurological sequelae. 3. Neurological complications developing during therapy. 4. CSF leucocytes, glucose, and protein on day 15 and day 30 after initiation of treatment. Trial authors reported case-fatality rate, which by definition includes all deaths caused by tuberculous meningitis, but not deaths attributed to other causes. They did not report whether any death during the follow-up period was considered to be due to any cause other than tuberculous meningitis.
Kumarvelu 1994	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 3 months.	Setting: all India Institute of Medical Sciences (AIIMS), New Delhi, India - tertiary referral centre. Number of participants: 47 participants; 22 females, 25 males; 24 received dexamethasone, 23 received no steroid. Inclusion criteria: aged over 10 years; clinically diagnosed tuberculous meningitis (meeting any 3 of the following criteria). 1. Fever, headache, neck stiffness for 2 weeks. 2. CSF profile of > 20 cells/mm predominantly lymphocytes, protein > 1 g/L, and sugar < 2/3 of corresponding blood sugar with no malignant cells on cytological examination and bacteria/fungi on culture. 3. Head contrast-enhanced CT showing basal exudates or hydrocephalus. 4. Clinical, radiological, or histological evidence of extracranial TB). All stages of severity and any duration of disease included. Exclusion criteria: aged < 10 years, received ATT for more than 4 weeks prior to admission, received corticosteroids before admission. HIV status: not reported.	1. ATT plus dexamethasone (intravenous 16 mg/day in 4 divided doses for 7 days, then oral tablet 8 mg/ day for 21 doses, and in children 0.6 mg/kg/day for 7 days, reducing to 0.3 mg/kg/day for 21 days). 2. ATT alone. ATT: rifampicin (450 mg), isoniazid (300 mg), and pyrazinamide (1500 mg) all oral daily; for those weighing < 30 kg 15 mg/kg, 10 mg/kg, and 30 mg/kg respectively. Duration of treatment: 1 year.	1. Death at 3 months. 2. Major sequelae (totally dependent for activities of daily living) at 3 months. 3. Minor sequelae (activities of daily living with no or minimal assistance) at 3 months. 4. Adverse effects. 5. Time to recover from altered sensorium, from fever, and from headache.
Chotmongkol 1996	Randomized parallel group study. Length of follow-up: 6 months but post-study follow-up continued for 16 to 45 months (mean = 30 months).	Setting: Sringerind Hospital, Khon Kaen, Thailand - tertiary referral centre. Number of participants: 59 participants; 27 females, 32 males; 29 received prednisolone, 30 received no steroid. Inclusion criteria: age > 15 years; clinically diagnosed tuberculous meningitis (characteristic clinical features with typical CSF profile consisting of lymphocytic meningitis with low glucose level and elevated protein), all stages of disease included. Exclusion criteria: children <15 years old, HIV-positive, VDRL positive for syphilis, cryptococcal antigen positive, CSF positive for bacterial or fungal infection on latex agglutination or culture, malignant cells in CSF. HIV status: HIV-positive participants excluded.	1. ATT plus prednisolone orally on tapering dosage for 5 weeks (week 1 =60 mg, week 2 = 45 mg, week 3 = 30 mg; week 4 = 20 mg, week 5 = 10 mg). 2. ATT alone. ATT: isoniazid oral (300 mg), rifampicin oral (600 mg, 450 mg for those weighing < 50 kg), pyrazinamide oral (1500 mg), and streptomycin intramuscular (750 mg) for the first 2 months; followed by isoniazid and rifampicin in above dosage for 4 months.	1. Death at the end of 6 months. 2. Residual neurological deficits at the end of 6 months. 3. Time until resolution of fever. 4. Time until disappearance of headache. Adverse events recorded were gastrointestinal bleeding and hyperglycaemia.
Schoeman 1997	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 6 months.	Setting: Tygerberg Hospital, Tygerberg, South Africa. Number of participants: 141 randomized (gender balance not specified); 70 received prednisolone and 71 received no steroid. Inclusion criteria: children (age limit not specified); diagnosis of tuberculous meningitis based on history and "typical CSF changes" with at least 2 of the following: strongly positive (> 15 mm) Mantoux test, chest x-ray suggesting TB or CT head showing basal enhancement and acute hydrocephalus. Only MRC Stage II and III included. HIV status: not reported.	1. ATT plus prednisolone (given to first 16 participants in a dose of 2 mg/kg/day and to the remaining 54 participants in a dose of 4 mg/kg/day (once in the morning); decision to double the dose after the first 16 participants). 2. ATT alone. ATT: isoniazid (20 mg/kg/day), rifampicin (20 mg/kg/day), ethionamide (20 mg/kg/day), and pyrazinamide (40 mg/kg/day) for 6 months.	1. Deaths at 6 months. 2. Disability (mild and severe) at 6 months. 3. Serious side effects.++ 4. Baseline and pulse pressure of lumbar CSF. 5. Changes in ventricular size in CT. 6. Proportion of participants with successful treatment of raised intracranial pressure. 7. Proportion of participants with basal ganglia infarcts, tuberculomas, meningeal enhancement, and enlarged subarachnoid spaces.

Study	Methods	Participants	Interventions	Outcomes
Lardizabal 1998	Randomized parallel group, 2-arm study with allocation ratio 1:1 Length of follow-up: 2 months	Setting: University of the Philippines College of Medicine, tertiary care facility, single centre Number of participants: 58 participants; 31 males and 27 females; 29 received dexamethasone, 29 received no steroid. Inclusion criteria: aged 18 years and above; probable tuberculous meningitis diagnosed using ASEAN Neurological Association criteria based on the following. 1. Insidious onset fever for at least 1 week, headache and vomiting, with or without nuchal rigidity followed by altered consciousness, cranial nerve palsies, or long tract signs. 2. CSF profile of lymphocyte predominance, elevated protein and reduced glucose. 3. CSF negative for cryptococcal antigen plus 1 or more of the following: basilar/meningeal enhancement on contrast CT scanning, active pulmonary disease, positive purified protein derivative (PPD), history of contact with TB; confirmed tuberculous meningitis based on positive CSF culture or microscopy, or both. 4. British MRC stages II and III disease. Exclusion criteria 1. Aged under 18. 2. British MRC stage I TB meningitis, or bacterial or fungal meningitis diagnosed on CSF culture. 3. Pregnancy or lactation. 4. History of diabetes mellitus or hypertension. 5. Upper gastrointestinal bleeding, or history of peptic ulcer disease in the previous month. 6. Raised bilirubin, SGPT or serum creatinine.	1. ATT plus dexamethasone (16 mg/day for 3 weeks (first 5 days intravenous thereafter orally or via nasogastric tube); after 3 weeks corticosteroid was tapered by 4 mg decrements every 5 days). 2. ATT alone. ATT: rifampicin (10 to 15 mg/kg/day), isoniazid (5 to 10 mg/kg/day), pyrazinamide (15 to 30 mg/kg/day), and ethambutol (15 to 20 mg/kg/day) for the first 2 months; thereafter, rifampicin and isoniazid only for 10 months; total treatment duration 12 months; route of administration was not stated. An H2-antagonist (famotidine or ranitidine) was given during the period of corticosteroid administration.	1. Death on days 15, 30, and 60 post-randomization. 2. Functional independence assessed by attending doctor on admission and 60 days after randomization: Functional Independence Measure (FIM) used assesses self-care, sphincter control, mobility, locomotion, and social cognition on a 7-point scale. 3. Potential adverse reactions to corticosteroids including weakness, oedema, hypertension, euphoria, psychosis, epigastric discomfort, Cushingoid facies, hirsutism, acne, insomnia, and increased appetite.
Thwaites 2004	Randomized parallel group 2-arm study with allocation ratio 1:1. Length of follow-up: 9 months (initial report), followed by a 5-year follow-up trial.	Setting: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam - two tertiary referral centres. Number of participants: 545 randomized, 331 males, 214 females; 274 received dexamethasone, 271 received placebo. Inclusion criteria: aged over 14 years, clinical meningitis (defined as combination of nuchal rigidity and CSF abnormalities). Tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if at least 1 of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness more than 5 days, ratio of CSF to plasma glucose less than 0.5, altered consciousness, yellow CSF, focal neurological signs. Exclusion criteria: contraindication to corticosteroids; received more than 1 dose of any corticosteroid, or more than 30 days of ATT immediately before the trial. HIV status: 98/545 HIV-positive, 44/274 (16.1%) in dexamethasone group, 54/271 (19.9%) in placebo group. Three participants in the dexamethasone group, and eight participants in the placebo group were not tested for HIV.	1. ATT plus dexamethasone, dose stratified by disease severity*. 2. ATT plus placebo. ATT: For previously untreated participants: oral isoniazid (5 mg/kg), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg, maximum, 2 g/day), and intramuscular streptomycin (20 mg/kg, maximum 1 g/day) for 3 months followed by 6 months of isoniazid, rifampicin, and pyrazinamide at the same daily doses; ethambutol (20 mg/kg; maximum 1.2/day) substituted for streptomycin in HIV-positive participants and was added to the regimen for 3 months for participants previously treated for TB. *Grade II and III disease: intravenous dexamethasone sodium phosphate given 0.4 mg/kg/day for week 1, 0.3 mg/kg/d for week 2, 0.2 mg/kg/d for week 3, and 0.1 mg/kg/day for week 4, and then oral dexamethasone for 4 weeks decreasing by 1 mg each week. Grade I disease: intravenous dexamethasone sodium phosphate 0.3 mg/kg/day for week 1 and 0.2 mg/kg/day for week 2 followed by 4 weeks of oral dexamethasone (0.1 mg/kg/day for week 3 then a total of 3 mg/day, decreasing by 1 mg each week).	Assessed at 9 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; gastrointestinal bleeding, bacterial sepsis, septic shock, brain herniation syndrome, decreased visual acuity, hyponatraemia, hyperglycaemia, hypertension, vertigo, deafness, Cushingoid features, pruritis, polyarthralgia, streptomycin reaction, rifampicin flu, rash, and others. 3. Coma clearance time. 4. Fever clearance time. 5. Time to discharge. 6. Time to relapse. 7. Presence of focal neurological deficit (9 months post-randomization). Assessed during 5-year follow-up study (9 months to 5 years post-randomization). 1. Death. 2. Disability status. 3. TB relapse.
Prasad 2006	Double-blind, randomized, concurrent placebo-controlled parallel group trial. Length of follow-up: 18 months. A 10-year follow-up was planned but not completed.	Setting: All India Institute of Medical Sciences, New Delhi, India - tertiary referral centre. Number of participants: 87 participants; 39 females, 48 males; 41 received dexamethasone, 46 received placebo. Inclusion criteria: clinically diagnosed tuberculous meningitis based on meeting these 3 criteria. 1. Gradual onset of any 2 of fever, progressive headache, or impaired consciousness with at least 1 symptom of 3 weeks duration. 2. At least 1 sign of meningeal irritation for example, neck stiffness, Kernig's sign, Brudzinski's sign (except in deeply comatose cases). 3. CSF profile characteristic of tuberculous meningitis (containing more than 0.02 Å~ 109 cells per litre with predominant lymphocytes , protein more than 1 g/Pl, sugar less than two-thirds of simultaneous blood sugar). Exclusion criteria: 1. Alternative diagnosis (including non-tubercular infection, malignancy) made on CSF testing or imaging. 2. Treatment with steroids regularly for more than 10 days used during the current illness. 3. Liver disease or gout. 4. History of gastric or duodenal ulcer, gastrointestinal haemorrhage, malignant hypertension. 5. Pregnant women. HIV status: not specified.	1. ATT plus dexamethasone 0.15 mg per kg body weight (up to a maximum of 4 mg) every 6 hours for 3 weeks then tapered gradually. 2. ATT plus placebo (0.9% saline). ATT: oral (through nasogastric tube in unconscious participants) administration of isoniazid 10 mg/kg up to 300 mg, rifampicin 15 mg/kg up to 450 mg, and pyrazinamide 30 mg/kg for participants less than 30 kg and 1500 mg for participants over 30 kg daily, plus pyridoxine 50 mg daily. Total duration was 9 months	Outcomes identified in trial protocol 1. Treatment success, defined as resolution of meningitic symptoms and achievement of good neurologic function and stability of this state for 3 consecutive months. 2. All-cause death in the first 3 months. 3. Secondary treatment failure. 4. Adverse events related to ATT or dexamethasone, for example deranged liver function tests, hypertension, hyperglycaemia, secondary infection, rash, gastrointestinal bleeding. Outcomes reported in results 1. Death. 2. Non-disabling neurological deficit. 3. Disabling neurological deficit. 4. Bad outcome (death plus disabling neurological deficit). 5. Any deficit (non-disabling neurological deficit plus disabling neurological deficit).

Study	Methods	Participants	Interventions	Outcomes
Malhotra 2009	Randomized parallel group 3-arm study with allocation ratio 1:1:1. Length of follow-up: 10 months.	Setting: Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow, India - tertiary referral centre. Number of participants: 91 participants; 48 males, 43 females (6 participants randomized but lost to follow-up); 32 randomized to dexamethasone (1 lost to follow-up), 33 randomized to methylprednisolone (3 lost to follow-up), 32 randomized to no steroid (2 lost to follow-up). Inclusion criteria: age > 14 years; meningitis syndrome; tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if one or more than one of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness > 5 days, ratio of CSF to plasma glucose < 0.5, altered consciousness, yellow CSF, or focal neurological signs. Exclusion criteria: age < 14 years; HIV-positive; contraindication to corticosteroids; received corticosteroid or ATT before presentation at the CSMMU, evidence of space occupying lesion on CT brain, refused consent.	1. ATT + dexamethasone (intravenous for 4 weeks as (at 0.4, 0.3, 0.2 and 0.1 mg/kg/day during weeks 1, 2, 3, 4 respectively); daily oral dose for following 4 weeks as 4, 3, 2, 1 mg/day on weeks 5, 6, 7, 8 respectively). 2. ATT + methylprednisolone (intravenous for 5 days (1 g/day for participants weighing > 50kg and 20 mg/kg/day for participant weighing < 50 kg). 3. ATT alone. ATT: rifampicin (15 mg/kg/day), isoniazid (10 mg/kg/day), pyrazinamide (30 mg/kg/day) and either ethambutol (20 mg/kg/day) or streptomycin (15 mg/kg/day) for 2 months and isoniazid (10 mg/kg/day) for 7 months.	Assessed at 6 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; anti-epileptic toxicity, gastro-intestinal bleeding, paradoxical tuberculoma. 3. Deterioration in vision, development of new focal neurological deficit and new-onset seizures.

2.3 Randomised controlled trials (RCTs)

Only one additional RCT published subsequent to the Prasad (2016) systematic review was identified.[7] This RCT is included in the Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

This RCT was a double-blind, placebo-controlled trial that included only adults living with HIV and TBM. Participants were recruited from the Hospital for Tropical Diseases and Pham Ngo Thach Hospital for Tuberculosis and Lung Disease in Ho Chi Minh City, Vietnam and from Dr Cipto Mangunkusumo National Reference Hospital and Persahabatan National Respiratory Referral Hospital in Jakarta, Indonesia. Eligible participants were 18 years or older, living with HIV, had been clinically diagnosed with TBM based on ≥ 5 days of meningitis symptoms and cerebrospinal fluid abnormalities, and had started ATT. Participants were further classified as having definite, probable, and possible TBM.

Enrolled participants were randomly assigned in a 1:1 ratio to receive a 6- to 8-week tapering course of dexamethasone or placebo in addition to 12 months of standard ATT and antiretroviral therapy (ART). Randomisation was computer-generated using randomly permuted block sizes of 4 and 6. Randomisation was stratified by participating site and modified Medical Research Council tuberculous meningitis severity grade⁵.

First-line ATT followed Vietnamese and Indonesian national guidelines. Rifampin (10mg/kg/24 hrs; maximum 600mg), isoniazid (5mg/kg/24hrs; maximum 300mg), pyrazinamide (25mg/kg/24hrs; maximum 2g) and ethambutol (20mg/kg/24 hrs; maximum 1.2g) were given the first 2 months of treatment, provided drug resistance was not suspected or proven. Pyrazinamide was then stopped and rifampin, isoniazid and ethambutol were continued until at least 12 months of ATT in total had been completed. In ART naïve participants, ART was started 6 to 8 weeks after initiation of ATT according to national guidelines.

Participants with grade II or III TBM randomised to the intervention arm received intravenous dexamethasone for 4 weeks (0.4 mg per kilogram of body weight per day for the first week, 0.3 mg per kilogram per day for the second week, 0.2 mg per kilogram per day for the third week, and 0.1 mg per kilogram per day for the fourth week) and then oral dexamethasone for 4 weeks, starting at 4 mg per day and decreasing by 1 mg each week. Participants with grade I TBM randomised to the intervention arm received intravenous dexamethasone for 3 weeks (0.3 mg per kilogram per day for the first week, 0.2 mg per kilogram per day for the second week, and 0.1 mg per kilogram per day for the third week) and then oral dexamethasone for 3 weeks, starting at 3 mg per day and decreasing by 1 mg each week.

The primary endpoint was death from any cause during the 12 months after randomisation. Secondary endpoints included neurological disability (defined as a modified Rankin scale score of 3-5) at 12 months after randomisation and neurological immune reconstitution inflammatory syndrome (IRIS) during the first 6 months. Additional secondary endpoints assessed at 12 months after randomisation included first new neurologic event or death, HIV-associated cancer, use of open-label glucocorticoid treatment for any reason, shunt surgery, and serious adverse events.

The study sample size calculation assumed a 9-month mortality of 40% in the dexamethasone arm and a hazard ratio of death for the dexamethasone arm compared to the placebo arm of 0.69. An estimated 520 PWH with TBM were required for 80% power, allowing 5% loss to follow-up.

Between 25 May 2017 and 29 April 2021, 520 participants were enrolled, with 263 participants randomly assigned to the dexamethasone arm and 257 participants randomly assigned to placebo arm. Almost half (49%) of participants were ART naïve. In participants with a baseline CD4 count ($n = 484$), 51.9% ($n = 251$) had a baseline

⁵ Modified Medical Research Council tuberculous meningitis severity grade: Grade I, Glasgow coma scale (GCS) of 15 with no focal neurological deficit; Grade II, GCS 11 to 14 OR GCS 15 with focal neurological deficit; Grade III, GCS ≤ 10 with or without focal neurological deficit.

CD4 count ≤ 50 cells per cubic millimetre. The median age of participants was 36 years. Overall, 40.8% of participants had definite TBM, 48.7% had probable TBM and 10% had possible TBM. The majority of participants (86%) had grade I or II disease. In total, 16 participants (10 in the dexamethasone arm and 6 in the placebo arm) had multidrug-resistant TBM.

Overall this RCT was assessed to be at low risk of bias (**Appendix 3**)

3. Results: Effectiveness and/or safety

3.1 PICO 1: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in HIV-negative adults and children with TBM

3.1.1 Outcome 1: Mortality and Outcome 2: Severe disability

3.1.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline, 2026.

Clinical Practice Guideline (2026). Corticosteroids be used as an adjunctive agent for TBM irrespective of HIV status.

Certainty assessment							No of patients		Effect	
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
9	Randomised trials, ¹⁰⁵⁻¹¹³	Not serious	Not serious	Not serious	Not serious	None	316/910 (34.7%)	367/860 (42.7%)	RR 0.81 (0.72-0.92)	79 fewer per 1,000 (from 34 fewer to 125 fewer)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
8	Randomised trials, ¹⁰⁵⁻¹¹²	Not serious	Serious	Not serious	Not serious	None	102/589 (17.3%)	100/490 (20.4%)	RR 0.85 (0.66-1.09)	31 fewer per 1,000 survivors (from 78 fewer to 16 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: these estimates are based on ALL RCTs including 2 RCTs that enrolled 614 PWH.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited, as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. Consequently, the certainty of evidence ratings are not presented here.

3.1.1.2 Systematic review: Prasad (2016)

Table 4. Summary of findings table from Prasad (2016) systematic review

Summary of findings for the main comparison. Any corticosteroid compared to control for tuberculous meningitis					
Any corticosteroid compared to control for tuberculous meningitis					
Participant or population: adults or children with tuberculous meningitis on tuberculosis (TB) chemotherapy					
Settings: hospital care					
Intervention: any corticosteroid					
Comparison: placebo or no corticosteroid					
Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk*	Corresponding risk			
	Control	Corticosteroid			
Follow-up to 2 to 24 months					
Death	41 per 100	31 per 100 (27 to 36)	RR 0.75 (0.65 to 0.87)	1337 (9 trials)	⊕⊕⊕⊕ high 1,2,3,4,5
Disabling neurological deficit	8 per 100	7 per 100 (6 to 10)	RR 0.92 (0.71 to 1.20)	1314 (8 trials)	⊕⊕⊕⊕ low 6,7,8
Follow-up to 5 years					
Death	47 per 100	44 per 100 (37 to 53)	RR 0.93 (0.78 to 1.12)	545 participants (1 trial)	⊕⊕⊕⊕ moderate 9,10
Disabling neurological deficit	15 per 100	14 per 100 (7 to 25)	RR 0.91 (0.49 to 1.69)	244 (1 trial)	⊕⊕⊕⊕ very low 10,11,12
*The assumed risk is from the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio; TB: tuberculosis.					
1	Not downgraded for risk of bias. There are few uncertainties regarding allocation concealment or sequence generation in one of the two largest studies, but the largest trial was high quality and effects between these two trials were consistent.				
2	Not downgraded for inconsistency: low statistical heterogeneity, and the forest plot shows a consistent benefit.				
3	Not downgraded for indirectness in relation to age: all the participants in Schoeman 1997 and 59% of the participants in Girgis 1991 were children, and the effect is consistent with the other large trial, Thwaites 2004, which included participants aged 14 and over.				
4	Not downgraded for indirectness for HIV status: one trial included 98 HIV-positive participants, with no obvious qualitative heterogeneity when compared to HIV-negative participants (Thwaites 2004). If making recommendations for HIV-positive participants only, a guidelines panel may wish to downgrade on indirectness.				
5	Not downgraded for serious imprecision: the overall meta-analysis is adequately powered to detect this effect but is only adequately powered when the trials at unclear or high risk of bias are included. The effect is clinically important.				
6	Downgraded by one for risk of bias: four of the eight trials were at high risk of bias due to lack of blinding of outcome assessors, which could impact on the interpretation of assessments of disability.				
7	Not downgraded for indirectness: trials included children, adults, some HIV-positive people, and people from different continents.				
8	Downgraded by one for imprecision: effects range from clinically important benefits of 29% reduction to 20% increase in disability.				
9	Not downgraded on risk of bias or imprecision: number of participants followed up was high: 91% at five years.				
10	Downgraded by one for indirectness. This was a single trial conducted in a high-quality health care unit in a population with high levels of infectious diseases endemicity and poverty. The attenuation of the effect may be less marked in populations with lower exposure to infectious diseases and other causes of reduced life expectancy associated with poverty. The authors were not able to establish the cause of death in most of the people who died after 9 months follow-up, and so it is not possible to assess whether these deaths were related to tuberculous meningitis or to other causes.				
11	Not downgraded on risk of bias. Although the assessors were not blind to the allocation, and some assessments were conducted by telephone, the numbers of disabled participants in the two groups were the same, and it is unlikely that systematic bias in the observers is present.				
12	Downgraded by two for imprecision. There were few events, and the confidence interval ranges from substantive harms to substantive benefits.				

The effect of corticosteroids appeared to be consistent across all grades of the disease although this analysis is underpowered (Grade I TBM RR 0.50, 95% CI 0.29 to 0.85; six trials, 305 participants); Grade II (RR 0.72, 95% CI 0.56 to 0.93; seven trials, 581 participants); and Grade III (RR 0.69, 95% CI 0.54 to 0.88; eight trials, 651 participants).

3.1.2 Outcome 3: Adverse events

3.1.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026).

No summary of findings table for adverse events was included in the publication.

3.1.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events was included in the publication. There was no difference in incidence of hyperglycaemia/glycosuria, hepatitis, gastrointestinal bleeding, or invasive bacterial infection (Figure 5).

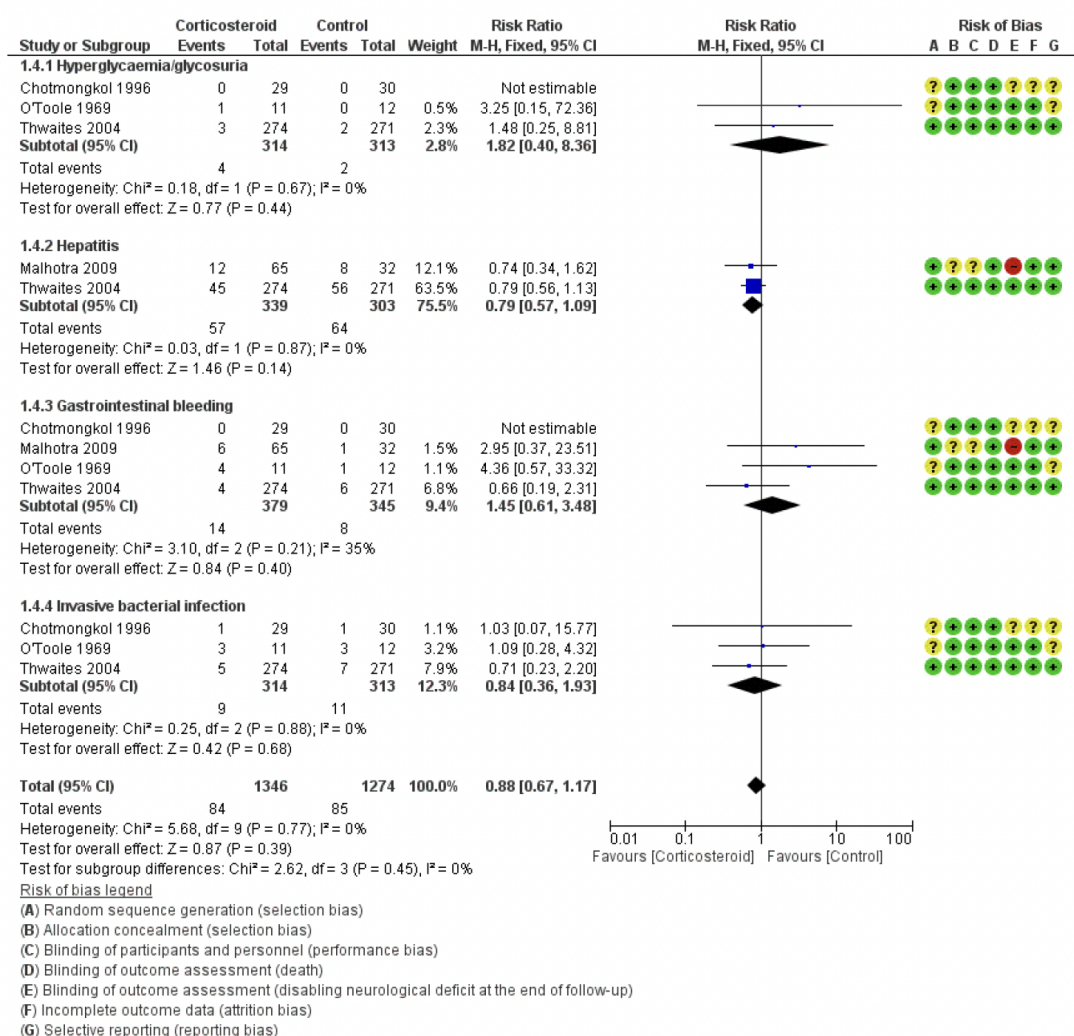


Figure 5. Forest plot of comparison any corticosteroid versus control, outcome adverse events from Prasad (2016)

3.2 PICO 2: Corticosteroids plus standard anti-tuberculous treatment compared to anti-tuberculous treatment alone or with placebo in adults and children living with HIV and co-infected with TBM

3.2.1 Outcome 1 and 2: Mortality and severe disability

3.2.1.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

Table 5. Summary of findings table from Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026). Corticosteroids used as an adjunctive agent for TBM with HIV co-infection.

Certainty assessment							№ of patients		Effect	
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	no corticosteroids	Relative (95% CI)	Absolute (95% CI)
Mortality (follow-up: range 9 months to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	143/307 (46·6%)	163/311 (52·4%)	RR 0·90 (0·77 to 1·05)	52 fewer per 1,000 (from 121 fewer to 26 more)
Morbidity as defined by modified Rankin Scale 3-5 (compared to 0-2) amongst survivors with follow-up from 9 to 12 months)										
2	Randomised trials ^{111,112}	Not serious	Not serious	Not serious	Not serious	None	15/147 (10·2%)	10/131 (7·6%)	RR 1·34 (0·62 to 2·87)	25 more per 1,000 (from 41 fewer to 93 more)

CI=confidence interval. OR=odds ratio. RR=risk ratio. TBM=tuberculous meningitis.

Note: The two RCTs included in the systematic review and meta-analysis are Thwaites (2004) which included 98 PWH and Donovan (2023) which included 520 PWH. [7,8] Neither of these RCTs enrolled children < 14 years of age.

Insufficient methodological detail was provided in the clinical practice guideline to allow appraisal of the underpinning systematic review. The transparency of the guideline's GRADE assessment was limited as explicit justifications for decisions to downgrade (or not downgrade) the certainty of evidence were not reported. For example, despite a low event rate and wide confidence interval for the morbidity outcome, the certainty of evidence was not downgraded for imprecision. Consequently, the reported certainty of evidence ratings are not presented here.

3.2.1.2 Systematic review: Prasad (2016)

No summary of findings table for PWH specifically was included in the publication. In a subgroup analysis by HIV status, only one RCT specifically mentioned that 98 participants were PWH. Analyses stratifying the outcomes of death and disabling neurological deficit in PWH did not detect any large differences and showed no apparent effect of HIV status on the effect estimates, but the analysis is underpowered.

Table 6. Any corticosteroid versus control stratified by HIV status from Prasad (2016)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
1.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.20]
1.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
2 Disabling neurological deficit	1	534	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.79]
2.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.08, 19.07]
2.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.73, 1.80]
3 Death or disabling residual neurological deficit	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
3.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.20]
3.2 HIV-negative	1	447	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]

3.2.1.3 Randomised controlled trial: Donovan (2023)

Death occurred in 116 of 263 participants (44.1%) in the dexamethasone group and in 126 of 257 participants (49.0%) in the placebo group (HR 0.85; 95% CI 0.66 to 1.10; $p = 0.22$) (RR 0.90; 95% CI 0.75 to 1.08; $p = 0.26$; 49 fewer per 1000 (122 fewer to 39 more per 1000)). No benefit associated with dexamethasone was observed in any prespecified subgroup in the intention-to-treat population, including modified MRC disease-severity grade, or CD4 cell count at enrolment. However, in subgroup analyses by diagnostic category, the apparent benefit of corticosteroids appeared to be driven by participants classified as having possible tuberculous meningitis, although the small size of this subgroup and the issue of multiple testing limit the interpretability of this finding (Table 7).

Table 7. Death from any cause in pre-specified subgroups of PWH in the intention-to-treat population adapted from Donovan (2023)

Subgroup	Dexamethasone (n = 263)	Placebo (n = 257)	Hazard Ratio (95% CI)
Overall	116/263	126/257	0.85 (0.66–1.10)
Modified MRC disease-severity grade			
I	22/99	28/97	0.72 (0.41–1.25)
II	60/125	68/126	0.82 (0.58–1.16)
III	34/39	30/34	1.03 (0.63–1.69)
Diagnostic category			
Definite tuberculous meningitis	48/108	49/104	0.90 (0.61–1.35)
Probable tuberculous meningitis	61/129	61/124	0.91 (0.64–1.30)
Possible tuberculous meningitis	5/24	15/28	0.34 (0.12–0.94)
ART status at enrolment			
No previous ART	64/133	64/122	0.85 (0.60–1.21)
>3 months of ART	20/46	26/58	0.96 (0.54–1.72)
ART of undetermined duration	19/58	19/48	0.80 (0.42–1.51)
CD4 cell count at enrolment (1)			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
51–100 per cubic millimetre	12/45	19/44	0.52 (0.25–1.06)
101–200 per cubic millimetre	14/36	13/35	1.04 (0.49–2.22)
>200 per cubic millimetre	11/37	15/36	0.70 (0.32–1.52)
CD4 cell count at enrolment (2)*			
≤ 50 per cubic millimetre	67/126	67/125	0.96 (0.69–1.35)
>50 per cubic millimetre	37/118	47/118	0.79 (0.56–1.11)

*Note: the effect estimates for CD4 cell count at enrolment (2) were conducted post-hoc by the reviewer.

3.2.2 Outcome 2: Adverse events

3.2.2.1 Guideline: Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)

No summary of findings table for adverse events was included in the publication.

3.2.2.2 Systematic review: Prasad (2016)

No summary of findings table for adverse events in PWH was included in the publication.

3.2.2.3 Randomised controlled trial: Donovan (2023)

The numbers of participants with at least one serious adverse event were similar between the dexamethasone group compared to the placebo group (73% vs. 75.5%, $p = 0.52$). Fewer participants had serious neurologic adverse events in the dexamethasone group than in the placebo group (36.1% vs. 44.7%). These serious neurologic adverse events included depressed consciousness and new focal neurologic signs.

Gastrointestinal bleeding events and other adverse events possibly, probably, or definitely related to glucocorticoids occurred with a similar incidence in the two trial groups. The incidence of clinical grade 3 or 4 adverse events (including hyperglycaemia and psychiatric disorders), adverse events leading to interruptions in ATT or ART (including sepsis), and grade 3 or 4 laboratory abnormalities was similar in the two groups, except for elevated ALT levels, which occurred more often in the dexamethasone arm than in the placebo arm (13.7% versus 7.8%).

Table 8. Serious adverse events from Donovan (2023)

Event	Dexamethasone (N=263)		Placebo (N=257)	
	no. of participants (%)	no. of events	no. of participants (%)	no. of events
Any selected serious adverse event	192 (73.0)	486	194 (75.5)	442
Nervous system disorder	95 (36.1)	128	115 (44.7)	147
Infection or infestation	60 (22.8)	79	50 (19.5)	63
Metabolism or nutrition disorder	51 (19.4)	66	59 (23.0)	68
Respiratory, thoracic, or mediastinal disorder	39 (14.8)	40	37 (14.4)	39
Hepatobiliary disorder	38 (14.4)	44	29 (11.3)	29
Gastrointestinal disorder	32 (12.2)	33	21 (8.2)	25
Blood or lymphatic system disorder	20 (7.6)	23	17 (6.6)	17
Investigation†	14 (5.3)	14	9 (3.5)	9
General disorder or administration-site condition	14 (5.3)	15	7 (2.7)	7
Vascular disorder	10 (3.8)	10	11 (4.3)	11
Skin or subcutaneous-tissue disorder	12 (4.6)	13	5 (1.9)	6
Cardiac disorder	7 (2.7)	7	4 (1.6)	4
Renal or urinary disorder	4 (1.5)	4	6 (2.3)	6
Musculoskeletal or connective-tissue disorder	4 (1.5)	4	2 (0.8)	2
Psychiatric disorder	3 (1.1)	3	1 (0.4)	1
Eye disorder	0	0	3 (1.2)	3
Endocrine disorder	1 (0.4)	1	2 (0.8)	2
Ear or labyrinth disorder	1 (0.4)	1	1 (0.4)	1
Injury, poisoning, or procedural complication	1 (0.4)	1	1 (0.4)	1
Immune system disorder	0	0	1 (0.4)	1

* Events were summarized according to the system organ class of the *Medical Dictionary for Regulatory Activities* hierarchy. The number of participants with any adverse events and specific events were summarized and compared between the two trial groups on the basis of chi-square tests or (if the expected number in one of the table cells was <1) Fisher's exact test.

† Abnormal results of investigations were reported.

Costs

As the use of adjunctive corticosteroids is already included in the paediatric STG as standard of care, there is no change in recommendation and no resultant incremental budget impact. The historic absence of a definitive recommendation for the use of corticosteroids for the treatment of TBM in PLWH is likely to have resulted in discretionary clinical judgement being applied in clinical practice. An accurate assessment of any budget impact is not possible, however, we do not anticipate any significant incremental budget impact with the CD4 stratified treatment approach included in our recommendation above.

TBM - cost of corticosteroids as adjunctive therapy (PAEDIATRICS)								
Prednisolone oral								
Formulation	Price per pack (Rands)	STG dosing guidance		Assumed weight per patient (kg)	Dose per day (mg)	Dose per course (mg)	Equivalent number of bottles per patient	Cost per course (Rands)
15mg/5mL solution (50mL pack) = 150mg per bottle	95,21	Weeks 1 -4	2mg/kg/day	10	20	560	5	R444,31
		Weeks 5-6	1mg/kg/day		10	140		
		Weeks 1 -4	2mg/kg/day	20	40	1120	10	R952,10
		Weeks 5-6	1mg/kg/day		20	280		
		Weeks 1 -4	2mg/kg/day	>30	60	1680	14	R1 332,94
		Weeks 5-6	1mg/kg/day		30	420		
Notes: 1. Based on 3 weight bands (10kg, 20kg and >/=30kg) 2. Total dose per course rounded to nearest full pack 3. Prices based on MHPL (Feb 2026) 4. Weeks 5-6 dose taper calculated at 50% of treatment dose for pragmatic reasons								
TBM - cost of corticosteroids as adjunctive therapy (ADULTS)								
Dexamethasone IV								
STG dosing guidance		Formulation	Price per ampoule (Rands)	Daily dose for 70kg (mg)	Equivalent number of amps per day	Cost per week (Rands)		
Week 1	0.3-0.4mg/kg/day	4mg/mL as 1mL inj	6,83	28	7	334,67		
Week 2	0.3-0.4mg/kg/day			28	7	334,67		
Week 3	0.2mg/kg/day			14	4	191,24		
Week 4	0.1mg/kg/day			7	2	95,62		
Week 5	4mg/day			4	1	47,81		
Week 6	3mg/day			3	1	47,81		
Week 7	2mg/day			2	1	47,81		
Week 8	1mg/day			1	1	47,81		
Cost per course						R1 147,44		

Prednisone oral (ADULTS)					
STG dosing guidance		Formulation	Price per tablet (Rands)	Equivalent number of tablets per day	Cost per week (Rands)
Week 1	60mg/day	5mg tablet	0,19	12	15,96
Week 2	60mg/day			12	15,96
Week 3	40mg/day			8	10,64
Week 4	25mg/day			5	6,65
Week 5	20mg/day			4	5,32
Week 6	15mg/day			3	3,99
Week 7	10mg/day			2	2,66
Week 8	5mg/day			1	1,33
Cost per course					R62,51
Notes: 1. Based on 70kg adult for weight-based dosing 2. Doses rounded to nearest ampoule/tablet 3. Prices based on MHPL (Feb 2026) 4. Where dose ranges recommended - max dose applied for costing 5. For prednisone, ave price per tablet applied as multiple products on tender					

Key findings and discussion

- In adults and children with TBM who are HIV-negative[6]:
 - Corticosteroids reduce mortality moderately (RR 0.75, 95% CI 0.65 to 0.87, high certainty of evidence). This reduction in mortality is consistent across all grades of the disease.
 - Corticosteroids may reduce severe disability (RR 0.92, 95% CI 0.71 to 1.20, low certainty of evidence).
 - Corticosteroids result in little to no difference in serious adverse events (RR 0.88, 95% CI 0.67 to 1.17).
- In adult PWH and TBM:
 - Corticosteroids may result in lower mortality (RR 0.90, 95% CI 0.77 to 1.05).[5]
 - Corticosteroids may increase severe disability, but the confidence interval is very wide (RR 1.34, 95% 0.65 to 2.87).[5]
 - Corticosteroids did not increase serious adverse events (73% vs. 75.5%, $p = 0.52$).[7]
 - These findings are predominantly based on data from one RCT in which the majority of PWH and TBM had CD4 cell count ≤ 200 cell/mm³.
 - It is biologically plausible that in PWH with TBM and relatively preserved CD4 counts, the mortality benefit of adjunctive corticosteroids would approximate that observed in HIV-negative patients.
 - The exact CD4 count at which this mortality benefit would approximate that observed in HIV-negative individuals has not been established, and there is insufficient data to define this threshold.
 - Given the high mortality of TBM, the absence of demonstrated harm associated with corticosteroids, and the potential for a small mortality benefit, specifically in those PWH with higher CD4 counts, withholding corticosteroids from all PWH may not be appropriate.

- We pragmatically suggest, based on expert opinion and aligned with the National Department of Health programmatic definitions of advanced HIV disease (AHD), that corticosteroids be used in PWH with TBM and CD4 cell counts > 200 cells/mm³. In PWH with TBM and CD4 cell counts ≤ 200 cells/mm³ we suggest not using corticosteroids.
- In children with HIV and TBM
 - No randomized controlled trials evaluating corticosteroids in children with HIV and TBM were identified. Consequently, there is currently no direct evidence to indicate that children with HIV and TBM fail to derive a mortality benefit comparable to that observed in HIV-negative children with TBM.

Recommendations

- In HIV-negative adults with TB meningitis of any grade, we recommend using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count ≤ 200 cells/mm³, we suggest not using corticosteroids.
- In adults with HIV and TB meningitis, with CD4 count >200 cells/mm³, we suggest using corticosteroids.
- In children, with or without HIV, with TB meningitis of any grade, we recommend using corticosteroids.

Review Team

The following people were involved in this review:

Name	Affiliation	Role and Contribution	Interest declaration
Jessica Taylor	University of Cape Town	PICO; Title, abstract and full text screening; Write-up, referencing and appendices; Quality appraisal, Clinical expertise; Formulation of recommendations; Quality assurance	None
Zahiera Adam	CHAI, Affordable Medicines Directorate, NDoH	Costing; Quality assurance; Formulation of recommendations	None
Gayle Tatz	University of Cape Town	Clinical expertise; Formulation of Recommendations	None
Halima Dawood	Infectious diseases specialist, Greys Hospital, KZN	Clinical expertise; Formulation of recommendations	None
Jeremy Nel	Infectious diseases specialist, Helen Joseph Hospital and the University of the Witwatersrand.	Clinical expertise; Formulation of recommendations	None
Karen Cohen	University of Cape Town	Clinical expertise; Formulation of recommendations	None

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References

- [1] Seid G, Alemu A, Dagne B, et al. Microbiological diagnosis and mortality of tuberculosis meningitis: Systematic review and meta-analysis. *PLOS ONE*. 2023;18(2):e0279203.
- [2] Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2008(1):Cd002244.
- [3] WHO Guidelines Approved by the Guidelines Review Committee. WHO consolidated guidelines on tuberculosis: Module 4: Treatment and care. Geneva: World Health Organization © World Health Organization 2025.; 2025.
- [4] Saukkonen JJ, Duarte R, Munsiff SS, et al. Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis: An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2025;211(1):15-33.
- [5] Donovan J, Cresswell FV, Tucker EW, et al. A clinical practice guideline for tuberculous meningitis. *Lancet Infect Dis*. 2026;26(2):e96-e111.
- [6] Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4(4):Cd002244.
- [7] Donovan J, Bang ND, Imran D, et al. Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults. *N Engl J Med*. 2023;389(15):1357-1367.
- [8] Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741-51.
- [9] Malhotra HS, Garg RK, Singh MK, et al. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. *Ann Trop Med Parasitol*. 2009;103(7):625-34.
- [10] Kumarvelu S, Prasad K, Khosla A, et al. Randomized controlled trial of dexamethasone in tuberculous meningitis. *Tuber Lung Dis*. 1994;75(3):203-7.
- [11] Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. *J Med Assoc Thai*. 1996;79(2):83-90.
- [12] Schoeman JF, Van Zyl LE, Laubscher JA, et al. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics*. 1997;99(2):226-31.
- [13] Girgis NI, Farid Z, Kilpatrick ME, et al. Dexamethasone adjunctive treatment for tuberculous meningitis. *Pediatr Infect Dis J*. 1991;10(3):179-83.
- [14] Lardizabal DV, Roxas AA, Jr. Dexamethasone as adjunctive therapy in adult patients with probable tuberculous meningitis stage II and III: An open randomized controlled trial. *Philippine Journal of Neurology*. 1998.
- [15] O'Toole RD, Thornton GF, Mukherjee MK, et al. Dexamethasone in tuberculous meningitis. Relationship of cerebrospinal fluid effects to therapeutic efficacy. *Ann Intern Med*. 1969;70(1):39-48.

Appendix 1: Search results and reasons for exclusion

	Reference	Study Type	Included/Excluded	Reason
1.	Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2016 Apr 28;4(4):CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 27121755; PMCID: PMC4916936.	Systematic review	Included	
2.	Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TT, Nguyen TC, Nguyen QH, Nguyen TT, Nguyen NH, Nguyen TN, Nguyen NL, Nguyen HD, Vu NT, Cao HH, Tran TH, Pham PM, Nguyen TD, Stepniowska K, White NJ, Tran TH, Farrar JJ. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004 Oct 21;351(17):1741-51. doi: 10.1056/NEJMoa040573. PMID: 15496623.	Randomised controlled trial	Included	
3.	Donovan J, Bang ND, Imran D, Nghia HDT, Burhan E, Huong DTT, Hiep NTT, Ngoc LHB, Thanh DV, Thanh NT, Wardhani ALS, Maharani K, Gasmara CP, Hanh NHH, Oanh PKN, Estiasari R, Thu DDA, Kusumaningrum A, Dung LT, Giang DC, Ha DTM, Lan NH, Chau NVV, Nguyet NTM, Gekus RB, Thuong NTT, Kestelyn E, Hamers RL, Phu NH, Thwaites GE; ACT HIV Investigators. Adjunctive Dexamethasone for Tuberculous Meningitis in HIV-Positive Adults. N Engl J Med. 2023 Oct 12;389(15):1357-1367. doi: 10.1056/NEJMoa2216218. PMID: 37819954; PMCID: PMC7615197.	Randomised controlled trial	Included	
4.	Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J; British Infection Society. British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. J Infect. 2009 Sep;59(3):167-87. doi: 10.1016/j.jinf.2009.06.011. Epub 2009 Jul 4. PMID: 19643501.	Guideline	Excluded	Never updated. More up-to-date clinical practice guidelines available.
5.	Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. Update in: Cochrane Database Syst Rev. 2016 Apr 28;4:CD002244. doi: 10.1002/14651858.CD002244.pub4. PMID: 18254003.	Systematic review	Excluded	2016 update included.
6.	Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013 Mar;13(3):223-37. doi: 10.1016/S1473-3099(12)70321-3. Epub 2013 Jan 29. PMID: 23369413.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
7.	Thuong NTT, Heemskerk D, Tram TTB, Thao LTP, Ramakrishnan L, Ha VTN, Bang ND, Chau TTH, Lan NH, Caws M, Dunstan SJ, Chau NVV, Wolbers M, Mai NTH, Thwaites GE. Leukotriene A4 Hydrolase Genotype and HIV Infection Influence Intracerebral Inflammation and Survival From Tuberculous Meningitis. J Infect Dis. 2017 Apr 1;215(7):1020-1028. doi: 10.1093/infdis/jix050. PMID: 28419368; PMCID: PMC5426373.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within randomised controlled trial.
8.	Saluja A, Vibha D, Pandit AK, Shukla G, Srivastava AK, Tripathi M, Srivastava MVP, Prasad K, Dwivedi SN. Comparison of dexamethasone regimens in tubercular meningitis (TBM): a randomized open label clinical trial. J Infect Dev Ctries. 2023 Dec 31;17(12):1769-1774. doi: 10.3855/jidc.17563. PMID: 38252729.	Randomized controlled trial	Excluded	Incorrect intervention and comparator – oral and intravenous dexamethasone.
9.	Diallo A, Diallo BD, Diallo OH, Carlos-Bolumbu M, Camara M, Sidikba S. Corticosteroids for reducing tuberculosis mortality in persons living with HIV: a systematic review and meta-analysis using reconstructed individual patient data. BMJ Glob Health. 2025 Aug 14;10(8):e017923. doi: 10.1136/bmjgh-2024-017923. PMID: 40813100; PMCID: PMC12352167.	Systematic review	Excluded	Incorrect population – includes any TB diagnosis, not specifically TBM.
10.	Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol. 2009 Oct;103(7):625-34. doi: 10.1179/000349809X12502035776315. PMID: 19825284.	Randomised controlled trial	Included	
11.	Prasad K, Volmink J, Menon GR. WITHDRAWN: Steroids for treating tuberculous meningitis. Cochrane Database Syst Rev. 2007 Jul 18;(1):CD002244. doi: 10.1002/14651858.CD002244.pub2. Update in: Cochrane Database Syst Rev. 2008 Jan 23;(1):CD002244. doi: 10.1002/14651858.CD002244.pub3. PMID: 17836701.	Systematic review	Excluded	Study withdrawn
12.	Madani N, Dendane T, Zekraoui A, Abidi K, Zegwagh AA, Aboual R. Effects of corticosteroids on adults with tuberculous meningitis admitted to intensive care unit: a propensity score analysis. Rev Med Interne. 2009 Jan;30(1):12-9. French. doi:10.1016/j.revmed.2008.06.023. Epub 2008 Aug 15. PMID: 18706739.	Retrospective cohort study	Excluded	Incorrect study type
13.	Rustami R, Ganien AR, Dian S, Apriani L, Achmad TH, van der Ven AJ, Born G, Aarnoutse RE, van Crevel R. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 2013 Jan;13(1):27-35. doi: 10.1016/S1473-3099(12)70264-5. Epub 2012 Oct 25. PMID: 23103177.	Randomised controlled trial	Excluded	Incorrect intervention – moxifloxacin and rifampicin.
14.	Kalita J, Misra UK, Prasad S, Bhoi SK. Safety and efficacy of levofloxacin versus rifampicin in tuberculous meningitis: an open-label randomized controlled trial. J Antimicrob Chemother. 2014 Aug;69(8):2246-51. doi:10.1093/jac/dku103. Epub 2014 Apr 20. PMID: 24752957.	Randomised controlled trial	Excluded	Incorrect intervention – levofloxacin.
15.	Moloughgi K, Sheybani F, Naderi H, Mirfeizi Z, Morovatdar N, Baradaran A. Central nervous system infections in patients with systemic lupus erythematosus: a systematic review and meta-analysis. Lupus Sci Med. 2022 Jan;9(1):e000560. doi: 10.1136/lupus-2021-000560. PMID: 34980679; PMCID: PMC8724813.	Systematic review	Excluded	Incorrect population – systemic lupus erythematosus.
16.	Verma R, Chakraborty R. A Clinico-Immunological Perspective of Paradoxical Reaction in HIV-ve Tuberculous Meningitis with Therapeutic Possibilities. Neurol India. 2025 Jul 1;73(4):678-691. doi: 10.4103/neuro-india.Neurol-India-D-24-00443. Epub 2025 Jul 24. PMID: 40705281.	Systematic review	Excluded	Incorrect population - people with TBM with paradoxical reactions
17.	Green JA, Tran CT, Farrar JJ, Nguyen MT, Nguyen PH, Dinh SX, Ho ND, Ly CV, Tran HT, Friedland JS, Thwaites GE. Dexamethasone, cerebrospinal fluid matrix metalloproteinase concentrations and clinical outcomes in tuberculous meningitis. PLoS One. 2009 Sep 30;4(9):e7277. doi: 10.1371/journal.pone.0007277. PMID: 19789647; PMCID: PMC2748711.	Randomised controlled trial	Excluded	Non-interventional, mechanistic study nested within Thwaites, 2008 randomised controlled trial.
18.	Simmons CP, Thwaites GE, Quyen NT, Chau TT, Mai PP, Dung NT, Stepniowska K, White NJ, Hien TT, Farrar J. The clinical benefit of adjunctive dexamethasone in tuberculous meningitis is not associated with measurable attenuation of peripheral or local immune responses. J Immunol. 2005 Jul 1;175(1):579-90. doi:10.4049/jimmunol.175.1.579. PMID: 15972695.	Randomised controlled trial	Excluded	Mechanistic study nested within Thwaites, 2008 randomised controlled trial
19.	Contopoulos-Ioannidis DG, Ioannidis JP. Claims for improved survival from systemic corticosteroids in diverse conditions: an umbrella review. Eur J Clin Invest. 2012 Mar;42(3):233-44. doi: 10.1111/j.1365-2362.2011.02584.x. Epub 2011. Aug 31. PMID: 21880039.	Systematic review	Excluded	Incorrect population – any indication for corticosteroids
20.	Misra UK, Kalita J, Nair PP. Role of aspirin in tuberculous meningitis: a randomized open label placebo controlled trial. J Neurol Sci. 2010 Jun 15;293(1-2):12-7. doi: 10.1016/j.jns.2010.03.025. Epub 2010 Apr 24. PMID: 20421121.	Randomised controlled trial	Excluded	Incorrect intervention – aspirin.
21.	Schoeman JF, Springer P, van Rensburg AJ, Swanevelder S, Hanekom WA, Haslett PA, Kaplan G. Adjunctive thalidomide therapy for childhood tuberculous meningitis: results of a randomized study. J Child Neurol. 2004 Apr;19(4):250-7. doi: 10.1177/088307380401900402. PMID: 15163089.	Randomised controlled trial	Excluded	Incorrect intervention – thalidomide.
22.	Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, Dang QT, Nguyen DP, Nguyen HP, To SD, Nguyen vV, Nguyen MD, Campbell J, Schultz C, Parry C, Torok ME, White N, Nguyen TC, Tran TH, Stepniowska K, Farrar JJ. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. N Engl J Med. 2007 Dec 13;357(24):2431-40. doi: 10.1056/NEJMoa070852. PMID: 18077808.	Randomised controlled trial	Excluded	Incorrect population – bacterial meningitis.
23.	Garg RK, Pandey S, Mahdi RA, Singhal S. Movement Disorders in Central Nervous System Tuberculosis: A Systematic Review. Can J Neurol Sci. 2025 Sep 29;1-10. doi: 10.1017/cjn.2025.10436. Epub ahead of print. PMID: 41017616.	Systematic review	Excluded	Incorrect population – people with TBM and with movement disorders
24.	Beardsley J, Hoang NLT, Kibengo FM, Tung NLN, Binh TQ, Hung LQ, Chieraku W, Thwaites GE, Chau NVV, Nguyen TTT, Gekus RB, Day JN. Do Intracerebral Cytokine Responses Explain the Harmful Effects of Dexamethasone in Human Immunodeficiency Virus-associated Cryptococcal Meningitis? Clin Infect Dis. 2019 Apr 24;68(9):1494-1501. doi: 10.1093/cid/ciy725. PMID: 30169607; PMCID: PMC6481995.	Randomised controlled trial	Excluded	Incorrect population – cryptococcal meningitis

Appendix 2. Summary of clinical practice guidelines and recommendations

Clinical Practice Guideline	Recommendation	Justification	Subgroup considerations	Studies included in the systematic review	Outcomes considered
Tuberculous Meningitis International Research Consortium Clinical Practice Guideline (2026)	In people without HIV, we recommend the use of adjunctive corticosteroid therapy, (Strong recommendation, high certainty of evidence) In the absence of an effective alternative adjunctive therapy for HIV-associated tuberculous meningitis, and the safety and potential effectiveness of corticosteroids, we recommend their use on a case-by-case basis in people living with HIV (weak recommendation, high certainty evidence)	Corticosteroids reduced case fatality, especially in children and adults without HIV. There is no signal for a change in disability among survivors in these groups. In people living with HIV and tuberculous meningitis, the benefits of corticosteroids are uncertain.	Separate recommendations for those with and without HIV.	O'Toole RD et al. Ann Intern Med 1969 Girgis N et al. Pediatr Infect Dis J 1991 Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Lardizabal DV et al. Philippine Journal of Neurology 1998 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004 Donovan J et al. N Engl J Med 2023	Mortality Morbidity
WHO consolidated guidelines on tuberculosis. Module 4: Treatment and care. (2025). (Note: specific recommendation not updated since 2017)	4.1 In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks should be used. (Strong recommendation, moderate certainty of evidence) This recommendation was first put forward in the 2017 guideline update and are copied without modification into the 2025 guideline update.	In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The benefits in terms of mortality increased with the increasing TB meningitis stage (i.e. increasing severity of disease).	Steroids should be given regardless of the severity of meningitis. No subgroup consideration by HIV status.	Kumarvelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

		Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.			
ATS/CDC/ERS/IDSA ⁶ Clinical Practice Guideline (2025) (Note: specific recommendation not updated since 2016)	Recommendation 8. We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6 – 8 weeks for patients with tuberculous meningitis (strong recommendation, moderate certainty in evidence)	Our updated systematic review found a mortality benefit from the use of adjuvant corticosteroids.	No subgroup consideration by severity of TB meningitis or HIV status.	Kumaravelu S et al. Tuber Lung Dis 1994 Chotmongkol V et al. J Med Assoc Thai 1996 Schoeman JF et al. Pediatrics 1997 Malhotra HS et al. Ann Trop Med Parasitol 2009 Thwaites GE et al. N Engl J Med 2004	Mortality Death or severe disability Relapse Adverse events

⁶ American Thoracic Society/United States Centers for Disease Control and Prevention/Infectious Diseases Society of America, the European Respiratory Society.

Appendix 3. Risk of bias assessment Donovan (2023)

Unique ID	Donovan et. al. 2023	Study ID	DOI:10.1056/NEJMoa2216218	Assessor	JT
Ref or Label		Aim	assignment to intervention (the 'intention-to-treat' effect)		
Experimental	Adjunctive dexamethasone	Comparator	Placebo	Source	Journal article(s)
Outcome	Mortality	Results	HR 0.85	Weight	1
Domain	Signalling question		Response		Comments
Bias arising from the randomization process	1.1 Was the allocation sequence random?		Y	Randomization computer-generated using randomly permuted blocks of 4 and 6. Randomization of participants performed using trained clinical staff, with 24-hour availability using Web-based software.	
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y		
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N		
	Risk of bias judgement		Low		
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?		N		
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N		
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA		
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA		
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA		
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y		
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA		

	Risk of bias judgement	Low	
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	
	Risk of bias judgement	Low	
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Death of any cause - objective
	4.3 Were outcome assessors aware of the intervention received by study participants?	NI	Not specifically stated
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	N	Death of any cause - objective
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	
	Risk of bias judgement	Low	
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	
	5.2 ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	
	5.3 ... multiple eligible analyses of the data?	N	
	Risk of bias judgement	Low	
Overall bias	Risk of bias judgement	Low	

South African National Department of Health

NATIONAL ESSENTIAL MEDICINES LIST COMMITTEE

DELAMANID – MDR/RR-TB

Medicine details

Medicine Class	No
Medicine/s name INN:	Delamanid
Medicine/s (ATC5):	J04AK06
Indication (ICD-10 code):	U50.0, U50.2, U50.20, U50.21, U50.5
SAHPRA Approved	Yes
Dosage form/s	Tablet
Route of administration/s	Oral
Patient population	Children, adolescents and adults (including pregnant or breastfeeding women) with multidrug-resistant/rifampicin-resistant tuberculosis (RR-MDR/RR-TB)
Prevalence and/or incidence of condition	In 2024, the estimated prevalence of MDR/RR-TB among TB cases in South Africa was 3.6% in new cases and 17% in previously treated cases. The estimated burden of MDR/RR-TB was 14,000 incident cases, corresponding to an incidence of 21 per 100,000 population per year. ¹
Level of Care	Primary Healthcare
Prescriber level	Doctor prescribed

Current Standard of Care

Delamanid is included in the National TB Programme guidelines for the management of MDR/RR-TB.¹ Delamanid, in combination with other anti-TB medicines, is used as part of individualised treatment regimens for MDR/RR-TB in children, adolescents, adults and pregnant or breastfeeding women not eligible for BPAL-L. Delamanid, in combination with other anti-TB medicines, is used as part of individualised rescue regimens for bedaquiline-resistant TB in children, adolescents, adults and pregnant or breastfeeding women.

Executive Summary

- Delamanid is included in the National TB Programme Guidelines and is used, in combination with other appropriate anti-TB medicines, as part of individualised or rescue regimens for children, adolescents, adults, and pregnant or breastfeeding women with MDR/RR-TB not eligible for BPAL-L or with bedaquiline-resistant TB.
- Delamanid has not been formally evaluated by the NEMLC. The development of updated Tuberculosis Standard Treatment Guidelines (STGs) in 2025/2026 required consideration of its inclusion in the Essential Medicines List (EML).
- Given the widespread programmatic use of delamanid in South Africa since 2019, it was not considered an efficient use of resources to undertake a full de novo evidence review to support inclusion in the EML. Instead, a limited review was conducted to evaluate current international guideline recommendations and supporting evidence for the use of delamanid in the treatment of MDR/RR-TB.

¹ World Health Organization. *Global tuberculosis report 2025*. Geneva: World Health Organization; 2025.

- The World Health Organisation (WHO) consolidated guidelines on tuberculosis, Module 4: Treatment and Care,^{2,3} which were considered to be of high-quality by AGREE-II assessment, and a recently published randomised control trial, the BEAT TB study, were reviewed.
- WHO Consolidated guideline recommendations relevant to delamanid include:
 - Recommendation 1.2. WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. (*Conditional recommendation, very low certainty of evidence*)
 - This recommendation applies to people with diagnosed pulmonary TB of all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women.
 - Recommendation 3.1. In MDR or RR-TB patients on longer regimens, all three Group A agents (refer table below), and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents (including delamanid) are added to complete it. (*Conditional recommendation, very low certainty of evidence*).
 - Recommendation 3.8. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. (*Conditional recommendation, moderate certainty of evidence*). In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. (*Conditional recommendation, very low certainty of evidence*)
 - Although the WHO recommendations are conditional and based on very low to moderate certainty evidence, they reflect the limited treatment options available for drug-resistant TB and the need to maximise the number of likely effective medicines in an individualised regimen.
- The BEAT Tuberculosis trial, which enrolled pregnant and breastfeeding women and children ≥ 6 years, showed that the efficacy of the 6- month bedaquiline, linezolid, delamanid, clofazimine and/or levofloxacin regimen was non-inferior to a 9-month or longer regimen to treat RR-TB, including fluoroquinolone-resistant TB. Safety outcomes were also similar.
 - Of the 170 female participants (42.2%), 9 (5.3%) were pregnant at baseline: one was in the first trimester, six were in the second trimester, and two were in the third trimester. One participant became pregnant during the trial. All pregnancies resulted in singleton live births, with one premature delivery. Among the pregnant participants, two serious adverse events occurred which were not related to treatment. One pregnant participant in the trial-strategy group had a recurrence of tuberculosis disease.
 - Thirty participants (7.4%) were 8 to 17 years of age. All participants younger than 18 years of age had a successful outcome at the end of treatment and the end of follow-up. Delamanid was discontinued in one child because of neuropsychiatric adverse reactions.
 - The BEAT Tuberculosis provides evidence for a shorter treatment option of comparable duration to BPAL-L for these vulnerable populations.
- Inclusion of delamanid on the Essential Medicines List aligns with current evidence-based WHO recommendations and will ensure availability of an important treatment option for patients requiring individualised management of drug-resistant tuberculosis.

Key Recommendations

Type of ERC recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)		
	☐	☐	X	☐		
High level summary of conclusions	It is recommended that delamanid be included on the EML for people with DR-TB requiring individualised treatment regimens, including in children, adolescents, adults and pregnant or breastfeeding women.					
NEMLC Ratification	Date	Comments/Recommendation				
EML Status	EML	Non-EML – contingent on stated reference price threshold in Rand Value	Non-EML			
	X	☐	☐			
Therapeutic Interchange Considerations (if applicable)*	If YES:	Alternative medicine/s name (INN)	Alternative/s SAHPRA registered?	Formulation/s	Equipotent dose/ Dose range and dosing interval	If NO, tick box
						X
Trigger for review	New evidence for safety or efficacy					

REVIEW TEAM

Review contributors as detailed below:

Name & Affiliation	Declaration of Interests	Defining the PICO	Protocol development	Literature search	Study selection	Data extraction & characteristics of	Quality appraisal	Data analysis	GRADE assessment	Write up and referencing	Clinical Expertise &	Quality assurance
Jessica Taylor	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X	X	X
Zahiera Adam	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X		X
Jane Riddin	None to declare	n/a	n/a	n/a	X	n/a	n/a	n/a	n/a	X		X

Background and rationale

Delamanid is a first-in-class bicyclic nitroimidazole that was first approved by the European Medicines Agency in 2014. In 2019, the South African Health Products Regulatory Authority (SAHPRA) registered delamanid for use, in combination with other anti-tuberculosis medicines, for the treatment of adults with pulmonary multidrug-resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot be constructed because of drug resistance or intolerance. Since then, delamanid has been included in various treatment regimens recommended by the South African National Tuberculosis Programme. Delamanid is listed on the Master Health Product List as a non-EML medicine and is available for procurement in the public sector. It has not previously undergone formal evaluation by the National Essential Medicines List Committee (NEMLC) for inclusion in the National Essential Medicines List (EML). Current South African programmatic guidelines for the management of RR-TB recommend delamanid in combination with other anti-TB medicines, as part of individualised treatment regimens for people with RR-TB not eligible for a 6-month BPaL-L² regimen. People not eligible for BPaL-L include pregnant women, children and adolescents < 15 years, and adults with severe extrapulmonary DR-TB. In addition, individualised regimens containing delamanid may be required by some adults with limited treatment options due to drug resistance, such as bedaquiline-resistance, or toxicity.

In 2025/2026, the development of dedicated tuberculosis chapters for the Primary Healthcare, Adult Hospital, as well as update of the Paediatric Hospital Standard Treatment Guidelines (STGs) was undertaken. The objective was to update treatment recommendations and ensure alignment, as far as possible, with national tuberculosis programme guidance. This process necessitated consideration of the inclusion of delamanid in the EML for the management of drug-resistant tuberculosis. Given the widespread programmatic use of delamanid in South Africa since 2019, it was not considered an efficient use of resources to undertake a full de novo evidence review to support inclusion in the EML. Instead, this limited review was conducted to evaluate current international guideline recommendations and the supporting evidence for the use of delamanid in the treatment of drug-resistant tuberculosis.

Methods

1. Data Sources

The World Health Organization (WHO) consolidated guidelines for the treatment of tuberculosis were identified and recommendations relevant to delamanid were extracted. Additionally, the recently published BEAT TB study (Conradie et.al. 2026) was identified.⁴

Results

Description of included studies

1.1. Clinical Practice Guidelines

- World Health Organization: Consolidated Guidelines on Tuberculosis:
 - WHO 2025. Consolidated Guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment.
 - This guideline was appraised as being of high quality using the AGREE II tool (overall quality of this guideline score of 6)

²A 6-month regimen of bedaquiline, linezolid, pretomanid with or without levofloxacin.

Domain	
Scope and purpose	21 (100%)
Stakeholder involvement	17 (77.8%)
Rigour of development	49 (85.4%)
Clarity of presentation	17 (77.8%)
Applicability	23(79.2%)
Editorial Independence	12 (83.3%)

1.2. RCTs

Conradie et.al. 2026⁴

Study ID	Country	Type of study	Primary outcome	Study Duration	Intervention	Comparison	Age Median (IQR)	Sample Size
Conradie, et.al. 2026	South Africa: Durban Gqeberha	Phase 3, open-label, pragmatic, randomised, controlled non-inferiority trial.	The primary efficacy end point was a successful outcome (cure or completion of treatment) at the end of treatment and 76 weeks after randomisation. The primary safety end point was adverse events of grade 3 or higher.	76 weeks	Bedaquiline, linezolid, delamanid, and levofloxacin OR clofazimine OR both for 6 months.	9-month South African standard-of-care treatment for rifampicin-resistant tuberculosis*	35 (28.0 – 43.0) < 18 years: 30 (7.4%)	Intervention: 203 Control: 200 61% susceptible to fluoroquinolones

*At study start and throughout, the South African standard treatment for RR-TB was a 9-month, all-oral regimen consisting of bedaquiline (used for 6 months), linezolid (used for first 2 months), levofloxacin, ethambutol, high-dose isoniazid (for 4 months, extended to 6 months if the patient remains sputum smear positive at the end of 4 months), pyrazinamide and clofazimine, followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). If fluoroquinolone resistance was diagnosed, then an 18-month regimen of bedaquiline, linezolid, clofazimine, terizidone and delamanid was given.

Effectiveness and/or safety

WHO Consolidated guidelines on Tuberculosis: Module 4: Treatment. Guideline Recommendations:

RECOMMENDATION	ADDITIONAL COMMENTS
Recommendation 1.2. WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC) in MDR/RR-TB patients with or without fluoroquinolone resistance. <i>(Conditional recommendation, very low certainty of evidence)</i>	- Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB. Although it should not delay the initiation of the BDLLfxC, the test results should guide the decision on whether levofloxacin or clofazimine should be retained. - This recommendation applies to the following: - People with MDR/RR-TB or pre-XDR-TB (i.e. MDR/RR-TB and resistance to fluoroquinolones). - Patients with less than 1 month of previous exposure to bedaquiline, linezolid, delamanid or clofazimine. When exposure is greater than 1 month, these patients may still receive the regimen if resistance to

	the specific medicines involved in such exposure has been ruled out. ○ People with diagnosed pulmonary TB of <u>all ages, including children, adolescents, PLHIV, and pregnant and breastfeeding women.</u> ○ People with all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular TB, or disseminated forms of TB with multiorgan involvement. ○ Children and adolescents who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB). ● When resistance to fluoroquinolones is unknown, the regimen should be started as BDLLfxC and then adjusted based on the DST results. In cases of quinolone susceptibility, clofazimine should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and levofloxacin (BDLLfx). In cases of resistance to fluoroquinolones, levofloxacin should be dropped and the regimen started or continued as bedaquiline, delamanid, linezolid and clofazimine (BDLC). The rationale for this recommendation is based on the evidence and considerations described in detail in the following two subsections. Data from an RCT (BEAT Tuberculosis trial: NCT04062201) showed that the efficacy and safety of the BDLLfxC regimen was similar to that of the control arm regimen (WHO-recommended 9-month or longer regimens), and offers advantages based on its shorter duration and lower pill burden than the comparators. It was judged that implementing this regimen was probably feasible and acceptable, with equity probably improved, and that implementing this regimen was probably suitable for most population groups, including pregnant and breastfeeding women, children and PLHIV.
Recommendation 3.1. In MDR or RR-TB patients on longer regimens, all three Group A agents (refer table), and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only	Group A: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated. Group B: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice. Group C: included all other medicines that can be used when a regimen cannot be composed with Group A or

one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. <i>(Conditional recommendation, very low certainty of evidence).</i>	Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each. Anti-TB medicine grouping <table><tr><th>Groups and steps</th><th>Medicine</th><th>Abbreviation</th></tr><tr><td rowspan="4">Group A: Include all three medicines</td><td>Levofloxacin or moxifloxacin</td><td>Lfx Mfx</td></tr><tr><td>Bedaquiline^{bc}</td><td>Bdq</td></tr><tr><td>Linezolid^d</td><td>Lzd</td></tr><tr><td></td><td></td></tr><tr><td rowspan="2">Group B: Add one or both medicines</td><td>Clofazimine</td><td>Cfz</td></tr><tr><td>Cycloserine or terizidone</td><td>Cs Trd</td></tr><tr><td rowspan="8">Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used</td><td>Ethambutol</td><td>E</td></tr><tr><td>Delamanid^e</td><td>Dlm</td></tr><tr><td>Pyrazinamide^f</td><td>Z</td></tr><tr><td>Imipenem–cilastatin or meropenem^g</td><td>Ipm–Cln Mpm</td></tr><tr><td>Amikacin (or streptomycin)^h</td><td>Am (S)</td></tr><tr><td>Ethionamide or prothionamideⁱ</td><td>Eto Pto</td></tr><tr><td>P-aminosalicylic acid^j</td><td>PAS</td></tr><tr><td></td><td></td></tr></table> Group A: fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid were considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated. Group B: clofazimine and cycloserine or terizidone were conditionally recommended as agents of second choice. Group C: included all other medicines that can be used when a regimen cannot be composed with Group A or Group B agents. The medicines in Group C are ranked by the relative balance of benefit to harm usually expected of each.	Groups and steps	Medicine	Abbreviation	Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx	Bedaquiline ^{bc}	Bdq	Linezolid ^d	Lzd			Group B: Add one or both medicines	Clofazimine	Cfz	Cycloserine or terizidone	Cs Trd	Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E	Delamanid ^e	Dlm	Pyrazinamide ^f	Z	Imipenem–cilastatin or meropenem ^g	Ipm–Cln Mpm	Amikacin (or streptomycin) ^h	Am (S)	Ethionamide or prothionamide ⁱ	Eto Pto	P-aminosalicylic acid ^j	PAS		
Groups and steps	Medicine	Abbreviation																																	
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx																																	
	Bedaquiline ^{bc}	Bdq																																	
	Linezolid ^d	Lzd																																	
Group B: Add one or both medicines	Clofazimine	Cfz																																	
	Cycloserine or terizidone	Cs Trd																																	
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E																																	
	Delamanid ^e	Dlm																																	
	Pyrazinamide ^f	Z																																	
	Imipenem–cilastatin or meropenem ^g	Ipm–Cln Mpm																																	
	Amikacin (or streptomycin) ^h	Am (S)																																	
	Ethionamide or prothionamide ⁱ	Eto Pto																																	
	P-aminosalicylic acid ^j	PAS																																	
Recommendation 3.8. Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens. <i>(Conditional recommendation, moderate certainty of evidence)</i> In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens. <i>(Conditional recommendation, very low certainty of evidence)</i>	To answer the PICO question on the use of delamanid in children aged below 3 years, data were reviewed by the guideline development group 2021 from a Phase 1, open-label, age de-escalation trial designed to assess the pharmacokinetics, safety and tolerability of delamanid administered twice daily for 10 days in children with MDR/RR-TB on treatment with an optimized background regimen (protocol 242–12–232) and from the corresponding open-label extension study (protocol 242–12–233). Data from cohorts 1 (age 12–17 years), 2 (age 6–11 years), 3 (age 3–5 years) and 4 (age 0–2 years) for both protocols were reviewed. Exposures in the 0–2-year age group were lower than those of children aged 3 years and older, necessitating a modelling or simulation approach to dosing. No cardiac safety signals distinct from those reported in adults were observed in children aged 0–2 years. However, consideration of these																																		

	findings should take into account that children had lower drug exposures than adults. Pharmacodynamic simulations suggested that clinically meaningful changes in QT (i.e. prolongation) would be unlikely in children aged below 3 years, even if higher doses were used to reach drug exposures comparable to those achieved in adults. CNS effects (paraesthesia, tremors, anxiety, depression and insomnia) were included in the delamanid label for both adults and children as important potential safety concerns for the drug. In March 2021, the study sponsor released a statement of intent to modify the labelling to include hallucinations as an adverse reaction. This new safety signal has been more prevalent among children than adults, with 15 reports in 14 children aged 2 – 16 years in India, the Phillippines, South Africa, Tajikistan and Ukraine. Children experiencing this safety signal included some with extensively resistant forms of TB (MDR/XDR-TB) treated with delamanid under programmatic conditions (12 reports) and children enrolled in a clinical trial studying delamanid for TB prevention (3 reports). Seven of the 15 reports were for children also receiving cycloserine (under programmatic conditions). The guideline development group noted the importance of side-effects involving the CNS in young children, considering their dynamic brain development. In addition to data from the trials, data from a paediatric DR-TB individual participant data were analysed descriptively (24 231 records from all six WHO regions, the majority from India and South Africa). The search was conducted in April 2020. Just under 20 000 of these records were used for a matched analysis of treatment outcomes in children being treated for DR-TB. The paediatric DR-TB IPD included only seven children aged below 3 years treated with delamanid, 14 children aged 3–6 years and 69 children aged 6–12 years. All 21 children aged below 6 years were successfully treated. The number of children was insufficient for a matched analysis.
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Conradie et.al. 2026

The BEAT Tuberculosis trial³, a phase 3 open-label pragmatic randomised controlled non-inferiority trial in South Africa, assessed a 6-month treatment strategy for pulmonary RR-TB. Eligible participants had pulmonary tuberculosis with resistance to rifampicin with or without resistance to isoniazid or fluoroquinolones (or both). Children ≥ 6 years, and pregnant or breastfeeding women were eligible. Participants were randomly assigned to a regimen consisting of bedaquiline, linezolid, delamanid, and levofloxacin or clofazimine or both for 6 months (the trial strategy); or 9-months of South African standard of care at the time (control strategy). In the trial-strategy group, when the results of fluoroquinolone susceptibility testing were available either levofloxacin (if the results showed fluoroquinolone resistance) or clofazimine (if the results showed fluoroquinolone susceptibility) was discontinued. If the susceptibility results were available at the time of randomization, either levofloxacin or clofazimine was not initiated. At study start and throughout, the South African standard treatment for RR-TB was a 9-month, all-oral regimen consisting of bedaquiline (used for 6 months), linezolid (used for first 2 months), levofloxacin, ethambutol, high-dose isoniazid (for 4 months, extended to 6 months if the patient remains sputum smear positive at the end of 4 months), pyrazinamide and clofazimine, followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). If fluoroquinolone resistance was diagnosed in the control strategy arm, then an 18-month regimen of bedaquiline, linezolid, clofazimine, terizidone and delamanid was given. The primary efficacy outcome was successful treatment outcome (cure or completion of treatment) at the end of treatment and at 76 weeks after randomisation. Cure was defined as adequate treatment adherence ($\geq 80\%$ of doses taken) and two negative sputum specimens obtained before the end of treatment, at least 14 days apart. Completion of treatment was defined as adequate adherence without evidence of treatment failure (defined as lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects) but no record of two or more consecutive negative sputum specimens obtained at least 14 days apart. The primary safety endpoint was an adverse event of grade 3 or higher. The composite efficacy-safety end point was a successful outcome at end of follow-up and no adverse events of grade 3 or higher during treatment. The primary efficacy analysis was performed in the intention-to-treat population. For the primary analysis, the between group difference (risk difference) in the percentage of participants who met criteria for the primary end point (a successful outcome) at the end of treatment and at 76 weeks after randomisation was compared. Non-inferiority was determined if the upper boundary of the 95% confidence interval for the risk difference was less than 10 percentage points. A total sample size of 400 patients would provide 87.3% power to show non-inferiority assuming a proportion cure of 0.60 in the control strategy and 0.65 in the study strategy (an absolute increase of 0.05) or 89.4% assuming a proportion cure of 0.65 in the control strategy and 0.7 in the study strategy. Between August 2019 and October 2022, 403 participants were randomised. The median age was 35 years, and 30 participants (7.4%) were 8 to 17 years of age. A total of 205 participants (50.9%) were PLHIV, with a median CD4 count of 194 cells/mm³.

Outcome – Successful outcome (Cure or completion of treatment):

Successful outcome at the end of treatment and at 76 weeks: 86.1% (174 of 202) in trial-strategy group, and 86% (172 of 200) in control group; adjusted risk difference: -0.2 percent points 95% CI -6.9 to 6.5; $p=0.001$ for non-inferiority.

Treatment effects did not appear to vary by age, sex, HIV status, status of sputum smear at baseline (positive vs. negative), presence of cavities on chest radiography, or fluoroquinolone resistance although the trial was not powered to rule out differences across subgroups. All participants younger than 18 years of age had a successful

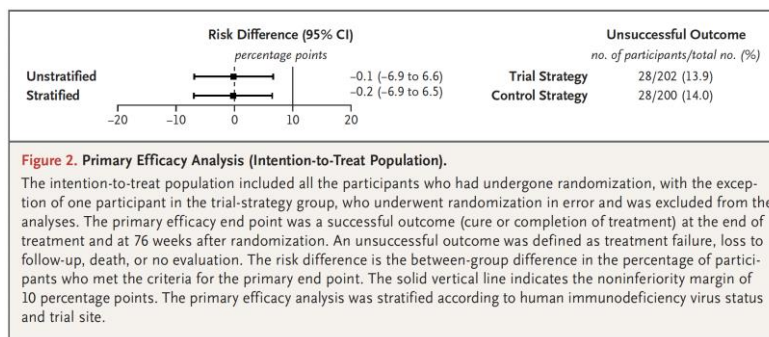
³ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

outcome at the end of treatment and the end of follow-up. One pregnant participant in the trial-strategy group had a recurrence of tuberculosis disease.

Table 2. Primary Efficacy Analysis (Intention-to-Treat Population).*

Variable	Trial Strategy (N = 202)	Control Strategy (N = 200)	Total (N = 402)
	<i>number (percent)</i>		
Primary end point: successful outcome at end of treatment and at end of follow-up	174 (86.1)	172 (86.0)	346 (86.1)
Cure at end of treatment and at end of follow-up	160 (79.2)	162 (81.0)	322 (80.1)
Cure at end of treatment and negative culture at last visit	14 (6.9)	10 (5.0)	24 (6.0)
Unsuccessful outcome at end of treatment	14 (6.9)	22 (11.0)	36 (9.0)
Treatment failure	7 (3.5)	10 (5.0)	17 (4.2)
Lost to follow-up during treatment	2 (1.0)	4 (2.0)	6 (1.5)
Died during treatment	4 (2.0)	7 (3.5)	11 (2.7)
Not evaluated because of withdrawn consent	1 (0.5)	1 (0.5)	2 (0.5)
Unsuccessful outcome at end of follow-up	14 (6.9)	6 (3.0)	20 (5.0)
Recurrence after cure at end of treatment	10 (5.0)	4 (2.0)	14 (3.5)
Died after cure at end of treatment	4 (2.0)	2 (1.0)	6 (1.5)

* The intention-to-treat population included all the participants who had undergone randomization, with the exception of one participant in the trial-strategy group, who underwent randomization in error and was excluded from the analyses. Participants were followed for 76 weeks after randomization. A successful outcome was defined as cure or completion of treatment. An unsuccessful outcome was defined as treatment failure (lack of sputum culture conversion, bacteriologic reversion, or substitution of two or more drugs because of adverse effects), loss to follow-up, death, or no evaluation.



Outcome – Adverse events:

Adverse events (grade 3 or higher) that occurred during treatment: 31.2% (63 of 202) in trial-strategy group and 37% (74 of 200) in control group. Among the pregnant participants, two serious adverse events occurred which were not related to treatment. Delamanid was discontinued in one child because of neuropsychiatric adverse reactions.

Table 3. Safety (Safety Population).^a

Adverse Event	Trial Strategy (N = 202)	Control Strategy (N = 200)	Total (N = 402)	Risk Difference (95% CI) [†]
Grade ≥3 event	69 (34.2)	76 (38.0)	145 (36.1)	3.8 (-5.5 to 13.2)
Grade ≥3 event during treatment	63 (31.2)	74 (37.0)	137 (34.1)	5.8 (-3.4 to 15.1)
Treatment-related grade ≥3 event [‡]	52 (25.7)	56 (28.0)	108 (26.9)	2.3 (-6.4 to 10.9)
Serious adverse event at any time	45 (22.3)	44 (22.0)	89 (22.1)	-0.3 (-8.4 to 7.8)
Serious adverse event during treatment	38 (18.8)	42 (21.0)	80 (19.9)	2.2 (-5.6 to 10.0)
Notable event [§]	36 (17.8)	31 (15.5)	67 (16.7)	-2.3 (-9.6 to 5.0)
Death at any time	10 (5.0)	10 (5.0)	20 (5.0)	0.0 (-4.2 to 4.3)
Death during treatment	6 (3.0)	8 (4.0)	14 (3.5)	1.0 (-2.6 to 4.6)
Death after treatment	4 (2.0)	2 (1.0)	6 (1.5)	-1.0 (-3.3 to 1.4)
Anemia leading to treatment discontinuation	10 (5.0)	8 (4.0)	18 (4.5)	-1.0 (-5.0 to 3.1)
Anemia leading to blood transfusion	20 (9.9)	11 (5.5)	31 (7.7)	-4.4 (-9.6 to 0.8)
Grade ≥3 liver abnormality	4 (2.0)	9 (4.5)	13 (3.2)	2.5 (-0.9 to 6.0)
Peripheral neuropathy leading to treatment discontinuation	10 (5.0)	7 (3.5)	17 (4.2)	-1.5 (-5.4 to 2.5)
Optic neuropathy leading to treatment discontinuation	7 (3.5)	2 (1.0)	9 (2.2)	-2.5 (-5.3 to 0.4)
QTcF ≥480 msec	12 (5.9)	19 (9.5)	31 (7.7)	3.6 (-1.7 to 8.8)
QTcF ≥500 msec	5 (2.5)	7 (3.5)	12 (3.0)	1.0 (-2.3 to 4.4)
Treatment-related serious adverse events [‡]				
Related to linezolid	20 (9.9)	16 (8.0)	36 (9.0)	-1.9 (-7.5 to 3.7)
Related to bedaquiline	4 (2.0)	7 (3.5)	11 (2.7)	1.5 (-1.7 to 4.7)
Related to levofloxacin	3 (1.5)	4 (2.0)	7 (1.7)	0.5 (-2.0 to 3.1)
Related to clofazimine	6 (3.0)	7 (3.5)	13 (3.2)	0.5 (-2.9 to 4.0)
Related to delamanid	2 (1.0)	2 (1.0)	4 (1.0)	0.0 (-1.9 to 2.0)

^a The safety population included all the participants who had undergone randomization and received at least one dose of the assigned treatment. QTcF denotes corrected QT interval calculated with the use of Fridericia's formula.

[†] The risk difference is the difference in percentage points.

[‡] Included are events that were at least possibly related to treatment.

[§] Notable events included grade 3 or 4 cardiotoxic effects, increase in aspartate aminotransferase or alanine aminotransferase level, pregnancy, and peripheral neuropathy.

Outcomes – pregnancy outcomes

Of the 170 female participants (42.2%), 9 (5.3%) were pregnant at baseline: one was in the first trimester, six were in the second trimester, and two were in the third trimester. One participant became pregnant during the trial. All pregnancies resulted in singleton live births, with one premature delivery.

Costs

Delamanid is currently procured as a non-EML medicine for use in the public sector.

Product	Brand As Per Contract	Supplier Name	Price*
Delamanid; 50mg; Tablet; 48 Tablets	DELTIBA	Viatrix Healthcare (Pty) Ltd	R1498.4

MHPL (Jul 2026)

As delamanid is already being used for select MDR/RR-TB regimens in the public sector in accordance with the National RR-TB guideline, we do not anticipate any incremental budget impact through its listing on the EML.

Discussion and Conclusion

Current South African National TB programme guidelines for the management of RR-TB recommend delamanid, in combination with other appropriate anti-TB medicines, as part of individualised or rescue regimens for children, adolescents, adults, and pregnant or breastfeeding women with MDR/RR-TB not eligible for BPAL-L, or when drug resistance or toxicity, necessitate an individualised approach.

The WHO classifies delamanid as a Group C medicine and recommend using it to construct effective longer individualised MDR/RR-TB regimens when Group A and Group B medicines are insufficient due to resistance or toxicity. Although the WHO recommendations are conditional and based on very low to moderate certainty

evidence, they reflect the limited treatment options available for drug-resistant TB and the need to maximise the number of likely effective medicines in an individualised regimen.

The recently published BEAT-Tuberculosis trial provides additional evidence supporting the inclusion of delamanid in a shorter, all-oral regimen for RR-TB. Importantly, the trial enrolled patient groups who are not eligible for the current South African standard-of-care BPAL-L regimen, including pregnant and breastfeeding women and children under 15 years of age, thereby providing evidence for a shorter treatment option of comparable duration to BPAL-L for these vulnerable populations.

Inclusion of delamanid on the Essential Medicines List aligns with current evidence-based WHO recommendations and will ensure availability of an important treatment option for patients requiring individualised management of drug-resistant tuberculosis.

References

¹ National Department of Health. Management of Rifampicin-Resistant Tuberculosis. November 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

² The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 4: Treatment – Drug-resistant tuberculosis treatment (2022). <https://iris.who.int/server/api/core/bitstreams/b4112461-7e9c-403c-808f-055f1dc3a54b/content>

³ The World Health Organization (WHO) Consolidated Guidelines on Tuberculosis: Module 5 – Management of tuberculosis in children and adolescents (2022). <https://iris.who.int/server/api/core/bitstreams/6212d328-f45e-4905-ae32-e0161d4f0029/content>

⁴ Conradie F, Badat T, Poswa A, Rajaram S, Kooverjee S, et.al. A Pragmatic Trial of a 6-month strategy for rifampicin-resistant tuberculosis. NEJM. 2026; 394: 2429-2439.

South African National Department of Health

HISTORICALLY ACCEPTED USE REVIEW: Para-aminosalicylic acid (PAS)

Executive Summary

Date: July 2026

Medicine(s) (INN): Para-aminosalicylic acid (PAS) (4-aminosalicylic acid)

Medicine(s) (ATC): J04AA01

Indication/s (ICD10 code/s): Drug-resistant TB (DR-TB) (U50, U50.9, U50.91)

Patient population/s: Children and adults with DR-TB with limited treatment options requiring individualised and/or rescue regimens.

Prevalence of condition/s:

Level of Care: individualised regimens as advised by the National clinical advisory committee (NCAC), then down referred to PHC for ongoing care

Prescriber Level: Doctor initiated

Current Standard(s) of Care: PAS is included in the NDoH TB guidelines for use in individualised DR-TB regimens when other medicines are unlikely to be effective because of resistance and/or are not tolerated.

Background:

The Tuberculosis (TB) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML) are being updated, with a focus to align with the National Department of Health (NDoH) TB Guidelines and Recommendations.

Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023).¹ PAS is classified as a Group C medication by the World Health organisation². The Group C medications are medications added to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective because of resistance and/or are not tolerated.

Group A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
Group B	Clofazimine
	Cycloserine or terizidone
Group C	Ethambutol
	Delamanid
	Pyrazinamide
	Imipenem-cilastatin or meropenem
	Amikacin (or streptomycin)
	Ethionamide or prothionamide
	P-aminosalicylic acid

PAS has historically been used in the management of TB since the 1940s.³ PAS is listed on the Current Master Health Product list as non-EML, although it has never been considered for EML inclusion.

Methods:

The WHO Drug-Resistant TB (DR-TB) Guidelines will be evaluated to understand the evidence supporting the use of PAS in individualised DR-TB regimens.

Summary of Evidence:

Specific indications for PAS have been included in WHO TB guidelines for management of DR-TB since 1997.⁴

Clinical Practice Guideline (CPG) recommendations:

Guideline	Recommendations	AGREE II assessment
World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025	Recommendation 3.1. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. <i>(Conditional recommendation, very low certainty of evidence)</i>	97% <i>See annexure 1</i>
	Recommendation 3.13. P-aminosalicylic acid may be included in the treatment of MDR/RR-TB patients on longer regimens only if bedaquiline, linezolid, clofazimine or delamanid are not used, or if better options to compose a regimen are not possible. <i>(Conditional recommendation against use, very low certainty of evidence)</i> This recommendation has been in place since 2019 <i>(PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible)</i>	

Historically accepted use Criteria

SECTION A		
	Criteria	Comment
1	The medicine is included in the World Health Organization (WHO) Model Essential Medicines List, either as a core or complementary item, for the indication requested.	YES NO ☒ ☐
2	The medicine is currently registered by South African Health Products Regulatory Authority (SAHPRA).	YES NO ☒ ☐

3	A documented rapid literature review identified no new safety concerns or new evidence of lack of efficacy.	YES NO X <i>PAS is associated with <u>known</u> higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (iPD) found that 12.2% of patients had adverse effects attributed to PAS.⁵</i> Use of PAS remains limited to exceptional individualised regimens where safer alternatives are not clinically appropriate.
4	The anticipated costs and usage are not likely to result in a substantial impact on the budget.	YES NO X <i>Comment:</i> <i>PAS 4g sachets (30s); R1250*</i> <i>*MHPL July 2026</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁶ and already being used to manage patients with DR-TB and limited treatment options requiring individualised regimens. We therefore do not anticipate any incremental budget impact.
SECTION B		
1	There is evidence prior to 2007* of safety and efficacy for the recognised indication (a systematic review/meta-analysis, or at least one critically appraised controlled trial.) <i>Information after 2007 would need to be subject to standard review processes for a new inclusion.</i>	YES NO X <i>See above: Used to treat TB since 1940s.</i>
OR		
2	It is included as part of standard of care in a critically appraised clinical practice guideline (CPGs) of adequate quality, for the particular indication.	YES NO X <i>See above: CPG recommendations</i>
AND		
3	It is currently use in practice for this indication.	YES NO X <i>Comment:</i> Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)

Modified Evidence to Decision Framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	What is the size of the effect for beneficial outcomes? Large ☐ Moderate ☐ Small ☒ None ☐	
EVIDENCE OF HARMS	What is the size of the effect for harmful outcomes? Large ☐ Moderate ☒ Small ☐ None ☐	PAS is associated with known higher incidence of adverse reactions. Data from the Individual Patient Data Meta-Analysis (pIPD) found that 12.2% of patients had adverse effects attributed to PAS. ⁵
QUALITY OF EVIDENCE	What is the certainty/quality of evidence? High ☐ Moderate ☐ Low ☐ Very low ☒ <i>High quality:</i> confident in the evidence <i>Moderate quality:</i> mostly confident, but further research may change the effect <i>Low quality:</i> some confidence, further research likely to change the effect <i>Very low quality:</i> findings indicate uncertain effect	Limited evidence in the DR-TB setting
BENEFITS & HARMS	Do the desirable effects outweigh the undesirable harms? Favours intervention ☒ Favours control ☐ Intervention = Control <i>or</i> Uncertain ☒	PAS showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and is thus proposed only when better options to compose a regimen are not possible. In these situations, desirable effects outweigh the undesirable harm.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes ☐ No ☒	
FEASIBILITY	Is implementation of this recommendation feasible? Yes ☒ No ☐ Uncertain ☐	Currently being used for individualised regimens only.
RESOURCE USE	How large are the resource requirements? More intensive ☐ Less intensive ☐ No impact ☒	Currently being used for individualised regimens only.. No incremental budget impact is anticipated.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	Is there important uncertainty or variability about how much people value the options? Minor ☐ Major ☐ Uncertain ☒ Is the option acceptable to key stakeholders? Yes ☒ No ☐ Uncertain ☐	Request from TB programme to list PAS in STGs to improve access. PAS is already being used for individualised regimens only by the local TB programme.
EQUITY	Would there be an impact on health inequity? Yes ☒ No ☐ Uncertain ☐	Formally updating the EML status in line with National TB guidelines will aid in facilitating equitable access.

RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative (strong)	We suggest not to use the option (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
				X	
Recommendation: It is recommended that para-aminosalicylic acid be included on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated. Rationale: Para-aminosalicylic acid (PAS) is included in the National Department of Health Clinical Management of Rifampicin-Resistant Tuberculosis – updated Clinical Reference Guide (2023)⁷, recommended by the WHO, and already being used to manage patients with DR-TB and limited treatment options. Use is limited to individualised DR-TB regimens where other EML alternatives are not clinically appropriate. Level of Evidence: Very low certainty evidence Review indicator: New efficacy or safety data					
NEMLC RECOMMENDATION: NEMLC recommended the inclusion of PAS on the EML to complete individualised DR-TB regimens, where medicines from Group A and B cannot be used because they are unlikely to be effective due to resistance and/or are not tolerated.					
Monitoring and evaluation considerations:					
Research priorities:					

Annexure 1:

• World Health Organisation: Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care - 2025²

		Appraiser 1	Rationale	Domain total	Domain score
Scope & Purpose	Q1	7	Objectives clearly stated.	21	100%
	Q2	7	Clinical questions defined using PICO.		
	Q3	7	Target population clearly described.		
Stakeholder Involvement	Q4	7	Multidisciplinary GDG.	20	94%
	Q5	6	Patient values considered; direct involvement less explicit.		
	Q6	7	Target users identified.		
Rigour of Development	Q7	7	Systematic searches described.	55	98%
	Q8	7	Selection criteria predefined.		
	Q9	7	GRADE used to assess certainty.		
	Q10	7	EtD framework used.		
	Q11	7	Benefits and harms balanced.		
	Q12	7	Recommendations linked to evidence.		
	Q13	7	External review documented.		
	Q14	6	Updating described but interval not explicit.		
Clarity of Presentation	Q15	7	Recommendations specific.	21	100%
	Q16	7	Management options presented.		
	Q17	7	Key recommendations identifiable.		
Applicability	Q18	6	Implementation barriers partly addressed.	26	92%
	Q19	7	Implementation tools provided.		
	Q20	7	Resource implications considered.		
	Q21	6	Monitoring guidance limited in core guideline.		
Editorial Independence	Q22	7	Funding independent.	14	100%
	Q23	7	Conflicts managed transparently.		
Overall Assessment					97%

References

¹ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

² World Health Organization. WHO Consolidated Guidelines on Tuberculosis. Module 4: Treatment and Care. Updated 2025. <https://iris.who.int/server/api/core/bitstreams/f663f086-5d97-4355-beea-0635d47f1227/content>

³ Lehmann J. Para-aminosalicylic acid in the treatment of tuberculosis. *Lancet*. 1946, 1(6384):15.

⁴ Crofton J, Chaulet P, Maher D, et.al. Guidelines for the Management of Drug-Resistant Tuberculosis. World Health Organization. 1997. <https://iris.who.int/server/api/core/bitstreams/a0cb51ce-893e-425a-b62f-cadd522bd397/content>

⁵ Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, Baghaei P, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821–834. doi:10.1016/S0140-6736(18)31644-1.

⁶ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>

⁷ National Department of Health. Clinical Management of Rifampicin-Resistant Tuberculosis: Updated Clinical Reference Guide. September 2023. <https://www.health.gov.za/wp-content/uploads/2023/10/Updated-RR-TB-Clinical-Guidelines-September-2023.pdf>