PHC Chapter 17: Respiratory conditions

17.1 CONDITIONS WITH PREDOMINANT WHEEZE

17.1.1 ACUTE ASTHMA & ACUTE EXACERBATION OF COPD, ADULTS

J46/J45.0-1/J45.8-9

DESCRIPTION

This is an emergency situation recognised by various combinations of:

- » wheeze
- » tightness of the chest
- » chest indrawing
- » breathlessness
- » respiratory distress
- » cough

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease (COPD) (where the bronchospasm is partially reversible).

The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients > 50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

All PHC facilities must have peak expiratory flow rate (PEFR) meters, as asthma cannot be correctly managed without measuring PEFR.

ASTHMA

Recognition and assessment of severity of asthma attacks in adults

	Mild-Moderate	Severe	Life threatening
Oxygen saturation	>90%	<90%	<90%
Talks in	phrases	words	unable to speak
Alertness	normal	Usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute	often >30 breaths/minute OR feeble effort
Wheeze	present	present	absent
Heart rate	100–120 beats/minute	>120 beats/minute	bradycardia
PEFR	>60% of predicted	<60% of predicted	<33% of expected or unable to blow

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment (see nomogram in Appendix I: Asthma monitoring, to predict PEFR).

LoE:IVb[1]

COPD

Recognition and assessment of severity of COPD attacks in adults

	Moderate	Severe
Talks in	phrases	words
Alertness	usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute
Wheeze	loud	loud or absent
Heart rate	100–120 beats/minute	>120 beats/minute
PEFR after initial nebulisation	±50–75%	<50%; may be too short of breath to blow in PEF meter

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment (see nomogram in Appendix I: Asthma monitoring, to predict PEFR).

MEDICINE TREATMENT

See Appendix II: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Mild to moderate attacks

- Salbutamol 100 mcg metered-dose inhaler (MDI), *LoE:IVb*[2]
  - Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer if required and available. *LoE:IVb*[3]
  - Shake the inhaler between each puff.
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed.

  Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

- Salbutamol 0.5% (5 mg/mL), solution,
  - 1 mL (5 mg) salbutamol 0.5% solution made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed. *LoE:IVb*[4]

PLUS

- Corticosteroids (intermediate-acting), e.g.: *LoE:IVb*[5]
- Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD.
  - Follow with prednisone, oral, 40 mg daily for 7 days.

Severe attacks (while awaiting referral)

- Oxygen to keep oxygen saturation 93-95%.

Note: For adults with COPD:

Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

- Salbutamol 0.5% (5 mg/mL) nebuliser solution,
  - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until PEFR > 60% of predicted.
  - Once PEFR > 60% of predicted, repeat every 2–4 hours if needed.

LoE:IVb[6]

OR

- Salbutamol, inhalation using a MDI,

LoE:IVb[7]

  - Salbutamol 400–1000 mcg (4–10 puffs), up to 20 puffs, using a spacer.
  - Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.
  - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
  - Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

LoE:IVb[8]

If poor response after first salbutamol nebulisation/inhalation:

- Continue salbutamol nebulisation as described in management above and

ADD

- Ipratropium bromide 0.5 mg/2ml; nebuliser solution
  - Ipratroprium bromide, 2 mL (0.5 mg) added to salbutamol 1 mL (5 mg) solution and made up to 4 mL with sodium chloride 0.9%.

LoE:IIb[9]

  - Administer every 20–30 minutes up to a maximum of 3 doses depending on clinical response.

OR

- Ipratroprium bromide, MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

LoE:IIb[10]

AND

- Corticosteroids (intermediate-acting), e.g.:

LoE:IVb[11]

- Prednisone, oral, 40 mg immediately.
  - Follow with prednisone, oral, 40 mg daily for 7 days.

OR

If oral prednisone cannot be taken:

- Hydrocortisone IM/slow IV, 100 mg as a single dose.

LoE:IVb[12]

Followed with:

- Prednisone, oral, 40 mg daily for 7 days.

CAUTION

Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

Life- threatening attacks

- Oxygen, to keep oxygen saturation 93-95%.

Note: For adults with COPD:

- Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

- Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL nebuliser solution.
  - Salbutamol 0.5%, 2 mL (10 mg) plus ipratroprium bromide, 2 mL (0.5 mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
  - Delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

- Parenteral corticosteroids (intermediate-acting) e.g.:
- Hydrocortisone IM/slow IV, 100 mg as a single dose.

LoE:IVb[13]

Followed with:

- Oral corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 40 mg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If response to treatment is adequate and severity improves to become severe but not life threatening, treat as per severe asthma exacerbation above.

Assessment of response in adults

	Response	**No response**
PEFR (if possible)	improvement by >20%	improvement by <20%
Respiratory rate	<20 breaths/ minute	>20 breaths/ minute
Speech	normal	impaired

Patients responding to treatment:

» Routine prescription of antibiotics is not indicated for acute asthma.
» Review current treatment and possible factors causing acute attack, including poor adherence and poor inhaler technique.
» Advise patient/caregiver on further care at home, danger signs and that follow up is required.
» Caution patient on the high chance of further wheezing in the week following an acute attack.
» Patients with a first attack should be fully assessed for maintenance treatment.
» Ask about smoking: if yes, urge patient to stop.

Note: Patients needing repeated courses of oral corticosteroids (more than twice over 6 months) should be assessed by a doctor for maintenance therapy. (See Section 17.1.3: Chronic asthma).

REFERRAL

Urgent (after commencing treatment):

» All patients with severe attack.
» Poor response to initial treatment.
» PEFR < 75% of the predicted normal or of personal best value 15–30 minutes after nebulisation.
» A lower threshold for admission is appropriate in patients when:
  - seen in the afternoon or evening, rather than earlier in the day.
  - recent onset of nocturnal symptoms or aggravation of symptoms.
  - previous severe attacks, especially if the onset was rapid.

17.1.2 ACUTE ASTHMA, CHILDREN

J46/J45.0-1/J45.8-9

DESCRIPTION

Bronchospasm in children is usually associated with asthma or with infections such as bronchiolitis or bronchopneumonia. Consider foreign bodies or obstruction of airways due to tuberculous nodes or congenital malformation, especially if the wheeze is unilateral.

Recognition and assessment of severity of attacks in children

	Mild/Moderate	Severe	Life-threatening
Oxygen saturation	>90%	<90%	<90%
Respiratory rate	<40 breaths/minute	>40 breaths/minute	>60 breaths/minute
Chest indrawing/recession	present	present	present
PEF (if > 5 years of age)	>60% of predicted	<60% of predicted	<33% of expected or unable to blow
Speech	normal	difficult	unable to speak
Feeding	normal	difficulty with feeding	unable to feed
Wheeze	present	present	absent
Consciousness	normal	normal	impaired

MEDICINE TREATMENT

See Appendix II: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Mild to moderate attacks:

- Salbutamol 100 mcg metered-dose inhaler (MDI),

Children ≥ 5 years:

- Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer.
  - Shake the inhaler between each puff
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed.

LoE:IVb[14]

Children < 5 years:

- Salbutamol inhaler 200–600 mcg (2-6 puffs) using a spacer.
  - For children ≥ 3 years, use a spacer with a mouthpiece.
  - If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
  - Inhale one puff at a time. Use a single breath inhalation technique. If single inhalation technique not possible, allow for 6 breaths through the spacer between puffs.
  - If no relief, repeat every 20–30 minutes in the first hour. *LoE:IVb*[15]
  - Thereafter, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

- Salbutamol 0.5% (5 mg/mL), solution,
  - 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes in the first hour.
  - Thereafter, repeat every 2–4 hours if needed. *LoE:IVb*[16]

PLUS

- Corticosteroids (intermediate-acting) e.g.: *LoE:IVb*[17]
- Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight (kg)	**Dose** (mg)	**Tablet** (5 mg)	**Age** (years)
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years

Severe attacks (while awaiting referral)

- Oxygen to keep oxygen saturation 93-95%.

AND

- Salbutamol 0.5% (5mg/mL) nebuliser solution,
  - 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes depending on clinical response.

OR

- Salbutamol, inhalation using an MDI,
  - Salbutamol, 400-1000 mcg (4-10 puffs), using a spacer.
  - For children ≥ 3 years, use a spacer with a mouthpiece.
  - If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
  - Inhale one puff at a time. Use a single breath inhalation technique. If single inhalation technique not possible, allow for 6 breaths through the spacer between puffs.

- If no relief, repeat every 20–30 minutes depending on clinical response.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

If poor response after first salbutamol nebulisation/inhalation:

ADD

LoE:IIb[18]

- Ipratropium bromide 0.25 mg/2ml; nebuliser solution.
  - Ipratropium bromide, 2 mL (0.25 mg) solution, nebulised with salbutamol 0.5 mL (2.5 mg) and made up to 4 mL with sodium chloride 0.9%.
  - Administer every 20–30 minutes depending on clinical response for 4 doses over 2 hours.

OR

- Ipratroprium bromide, MDI, 80–160 mcg (2– 4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

AND

- Corticosteroids (intermediate-acting), e.g.:

LoE:IVb[19]

- Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight (kg)	Dose (mg)	Tablet (5 mg)	Age (years)
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

OR

If oral prednisone cannot be taken:

- Hydrocortisone IM/slow IV, 4 mg/kg (maximum 100 mg) immediately. See dosing table, pg 23.5.

Followed with:

- Prednisone 1–2 mg/kg daily for 7 days as per dosing table above.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

Life- threatening attacks

- Oxygen, to keep oxygen saturation 93-95%.

AND

- Salbutamol 0.5% (5 mg/mL) with ipratropium bromide 0.5 mg/2mL nebuliser solution:
  - Salbutamol 0.5%, 2 mL (10 mg) plus ipratroprium bromide, 2 mL (0.5 mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
  - Delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

- Parenteral corticosteroids (intermediate-acting) e.g.: *LoE:IVb*[20]
- Hydrocortisone IM/slow IV, 4 mg/kg (maximum 100 mg) immediately. See dosing table, pg 23.5.

Followed with:

- Oral corticosteroids (intermediate-acting) e.g.:
- Prednisone 1–2 mg/kg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If response to treatment is adequate and severity improves to become severe but not life threatening, treat as per severe asthma exacerbation above.

Assessment of response in children

	Response	No response
PEFR (if possible)	improvement by >20%	improvement by <20%
Respiratory rate	<40 breaths/minute	>40 breaths/minute
Chest indrawing or recession	absent	present
Speech	normal	impaired
Feeding	normal	impaired

Patients responding to treatment:

» Routine prescription of antibiotics is not indicated for acute asthma.
» Review current treatment and possible factors causing acute attack including poor adherence and poor inhaler technique.
» Advise patient/caregiver on further care at home, danger signs and that follow up is required.
» Caution patient/carer on the high chance of further wheezing in the week following an acute attack.
» Patients with a first attack should be fully assessed for maintenance treatment.

Note: Patients needing repeated courses of oral corticosteroids (more than twice over 6 months) should be assessed by a doctor for maintenance therapy. (See Section 17.1.3: Chronic asthma).

REFERRAL

Urgent (after commencing treatment):

» All patients with severe attack.
» Poor response to initial treatment.
» PEFR < 75% of the predicted normal or of personal best value 15–30 minutes after nebulisation.
» A lower threshold to admission is appropriate in patients when:
  - seen in the afternoon or evening, rather than earlier in the day.
  - recent onset of nocturnal symptoms or aggravation of symptoms.
  - previous severe attacks, especially if the onset was rapid.

17.1.3 CHRONIC ASTHMA

J45.0-1/J45.8-9

DESCRIPTION

A chronic inflammatory disorder with reversible airway obstruction. In susceptible patients, exposure to various environmental triggers, allergens or viral infections results in inflammatory changes, bronchospasm, increased bronchial secretions, mucus plug formation and, if not controlled, eventual bronchial muscle hypertrophy of the smooth muscle in the airways. All these factors contribute to airway obstruction.

Asthma varies in intensity and is characterised by recurrent attacks of:
» wheezing,
» dyspnoea or shortness of breath,
» cough, especially nocturnal, and
» periods of no airway obstruction between attacks.

Acute attacks may be caused by:
» exposure to allergens,
» respiratory viral infections,
» non-specific irritating substances, and
» exercise.

Asthma must be distinguished from COPD, which is often mistaken for asthma. (See Section 17.1.5: Chronic obstructive pulmonary disease (COPD)). The history is valuable in assessing treatment response.

Asthma	COPD
» Young age onset, usually < 20 years.	» Older age onset, usually > 40 years.
» History of hay fever, eczema and/or allergies.	» Symptoms slowly worsen over a long period of time.
» Family history of asthma.	» Long history of daily or frequent cough before the onset of shortness of breath.
» Symptoms are intermittent with periods of normal breathing in between.	» Symptoms are persistent rather than only at night or during the early morning.
» Symptoms are usually worse at night or in the early hours of the morning, during an upper respiratory tract infection, when the weather changes, or when upset.	» History of heavy smoking (>20 cigarettes/day for ≥ 15 years), heavy cannabis use, or previous TB.
» Marked improvement with $ß_2$-agonist.	» Little improvement with $ß_2$-agonist.

Asthma cannot be cured, but it can be controlled with regular treatment.
If symptoms suggest TB (e.g. weight loss, night sweats, etc.), investigate and manage accordingly.
Note: The diagnosis of asthma can be difficult in children < 6 years of age.
Refer the patient if the diagnosis of asthma is uncertain.

ASTHMA DIAGNOSIS AND SEVERITY

Peak Expiratory Flow Rate (PEFR)
See PEFR charts in Appendix I: Asthma monitoring.
The PEFR may provide additional information for diagnosis and assessing response to therapy.
» PEFR is best assessed in the morning and evening.
  - Instruct the patient to blow forcibly into the device after a deep inspiratory effort.

  - The patient must perform three blows at each testing point.
  - Take the highest value as the true value.
» The PEFR can be helpful in confirming a diagnosis of asthma in primary care.
  - An improvement of 60 L/min or ≥ 20% of the pre-bronchodilator PEFR, 10–20 minutes after inhalation of a beta$_2$-agonist e.g. salbutamol, inhalation, 200 mcg, confirms a diagnosis of asthma.
  - A normal PEFR excludes the possibility of moderate and severe COPD.
» PEFR may be useful in assessing response to therapy.
  - Any value > 80% of the personal best before the use of a bronchodilator is regarded as confirmation of adequate control. Ensure that pre-bronchodilator values are measured at follow-up visits.

Note: Initiating and optimising inhalation corticosteroid therapy for step 1 to 3 asthma therapy should always be done with the use of a peak flow meter to assess asthma control and treatment response of asthma.

Starting asthma treatment in children aged 6-11, adolescent > 12 years of age and in adults

STEP 1	STEP 2	STEP 3
Initial asthma treatment in patients with symptoms less than twice a month, and with no exacerbations within the last 12 months.	Asthma symptoms or need for reliever twice a month or more or any exacerbations within the last 12 months.	Troublesome asthma symptoms most days, or waking up from asthma once a week or more.

Figure 17.1 Guidance for assessing asthma treatment in children and adolescents (adapted from the GINA 2023

LoE:IIb[21]

GENERAL MEASURES

» Avoid irritant triggers and relevant allergic triggers.
» Advise patient to stop smoking, and to avoid smoke exposure from others.
» Avoid exposure to known allergens if avoidance measures are feasible and sensitisation has been proven.
» Educate patient and caregiver on:
  - early recognition and management of acute attacks.
  - emphasise the diagnosis and explain the nature and natural course of the condition;
  - Use a spacer for all children and all adults with step 3 therapy and above
  - teach and monitor inhaler technique; and
  - reassure parents and patients of the safety and efficacy of continuous regular controller therapy.

MEDICINE TREATMENT

Medicine treatment is based on severity and control of the asthma and consists of therapy to prevent the inflammation leading to bronchospasm (controller) and to relieve bronchospasm (reliever).

Reliever medicines in asthma:

- Short acting beta$_2$-agonists (SABAs), e.g.:
- Salbutamol
  - Indicated for the immediate relief of the symptoms of acute attacks, i.e. cough, wheeze and shortness of breath.
  - Can be used as needed.
  - Increasing need for reliever medicine indicates poor asthma control.

Controller medicines in asthma:

- Inhaled corticosteroids, e.g.:
- Beclomethasone.
  - Must be used twice daily every day, even when the patient feels well.

Inhalation therapy:

Inhaled therapy is preferable to oral therapy.
See Appendix II: Devices for Respiratory Conditions for guidance on inhaler and spacer device technques

STEP 1

Adults and children > 6 years
As reliever/rescue therapy:

LoE:IIb[22]

- Short acting beta$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, as needed.

AND

- Inhaled corticosteroids, e.g.:
- Budesonide, inhalation, 200 mcg whenever salbutamol is taken.

Note: Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide:

- Beclomethasone, inhalation, 200 mcg whenever salbutamol taken.

STEP 2

Children < 6yrs (wheeze ≥ 3 times a year):

- Inhaled corticosteroids e.g.:
- Beclomethasone, inhalation, 100 mcg 12 hourly.

AND

- Short acting beta$_2$-agonists agonist e.g.:
- Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 6–8 hourly as needed (until symptoms are controlled).

Adults and children ≥ 6yrs

As controller therapy:

- Inhaled corticosteroids, low dose, e.g.:
- Budesonide, inhalation, 200 mcg 12 hourly. *LoE:IIIb*[23]
  - Well and stable after 6 months: can attempt to reduce budesonide dose to 200 mcg daily.
  - Dose adjustments may be required at change of seasons.

Note: Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide.

- Beclomethasone, inhalation, 200 mcg 12 hourly for 6 months; reduced to 200 mcg daily once well and stable.

AND

As reliever/rescue therapy:

- Short acting beta$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, 6 hourly as necessary.

Review treatment every 3 months. Adequate control is defined as:

» ≤ 2 episodes of daytime cough and/or wheeze per week.
» No night-time cough and/or wheeze. *LoE:IIIb*[24]
» No recent (within the last year) admission to hospital for asthma.
» PEFR ≥ 80% predicted between attacks.

If control is inadequate:

» Check adherence and inhaler technique, and
» Exclude ongoing exposure to irritants and allergens.

After excluding those causes, refer to a doctor to confirm the diagnosis of asthma, to exclude other diagnoses.

Once the diagnosis is confirmed, **step-up** treatment to STEP 3 as below:

STEP 3

Children

- Inhaled corticosteroids, e.g.:
- Beclomethasone, inhalation, 200 mcg 12 hourly.

Adults

- Inhaled corticosteroids, e.g.:
- Budesonide, inhalation, 400 mcg 12 hourly

Note: Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide:

- Beclomethasone, inhalation, 400 mcg 12 hourly.

If control is still inadequate in adults, re-evaluate inhaler technique (See Appendix II: Devices for Respiratory Conditions for guidance on inhaler and spacer device technques**) and consider treatment with combination of corticosteroid and long-acting beta agonist (LABA):**

Stop corticosteroid inhaler (e.g. budesonide) and replace controller therapy with:
- Inhaled long-acting beta agonist (LABA)/corticosteroid combination, e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated). *LoE:IVb*[25]

AND

As reliever/rescue therapy:
- Short acting beta$_2$-agonists, e.g.:
- Salbutamol, MDI, 200 mcg, 6 hourly as necessary.

Note: Fluticasone interacts with protease inhibitors. Refer all patients on protease inhibitors requiring inhaled fluticasone for further management. *LoE:IIIb*[26]

Stepping down treatment:
Attempt a reduction in therapy if the patient has not had any acute exacerbation of asthma in the preceding 6 months, and day-time and night-time symptoms are well controlled.
Gradually reduce the dose of inhaled corticosteroid therapy.
If the symptoms are seasonal, corticosteroids may be stopped until the next season.
If symptoms re-appear, increase therapy to the level at which the patient was previously controlled.

REFERRAL TO DOCTOR
» All children < 6 years of age for assessment and confirmation of diagnosis.
» Any patient who has received > 2 courses of oral prednisone within 6 months.
» Brittle asthma (very sudden, very severe attacks).
» All patients without adequate control on step 2 or 3 of treatment.
» Patients on protease inhibitors, requiring inhaled fluticasone.

REFERRAL TO HOSPITAL
Uncontrolled asthma.
Note: In patients with new onset of exercise-related symptoms, consider other diagnoses, particularly if no response to pre-treatment with SABA is noted.

17.1.4 ACUTE BRONCHIOLITIS IN CHILDREN
J20.0-9/J21.0-1/J21.8-9

DESCRIPTION
Acute bronchiolitis is a common cause of wheezing and cough in the first two years of life. It is caused by viral infections and presents with lower airway obstruction due to inflammation and plugging of the small airways. Recurrent episodes can occur, usually during winter.
It can be difficult to distinguish between bronchiolitis and asthma. Bronchiolitis does not respond to salbutamol. If there is a good response to a single dose of salbutamol, asthma is the likely diagnosis. See Section 17.1.1: Acute asthma and acute exacerbation of chronic obstructive pulmonary disease (COPD).
Bronchiolitis is extremely rare in children > 2 years of age. Consider other causes of wheeze in children > 2 years of age. See Section 17.1.1: Acute asthma & acute exacerbation of COPD, adults; and Section 17.3.4.1: Pneumonia in children.

Child presents with:

» rapid breathing
» chest indrawing
» decreased breath sounds
» an audible wheeze or crackles

Risk factors for severe bronchiolitis:

» Infants < 3 months of age
» Chronic lung disease
» Ex-premature babies
» Congenital heart disease

Signs of severe disease:

» Increased respiratory effort: tachypnoea, nasal flaring, severe lower chest wall indrawing, accessory muscle use, grunting.
» Central cyanosis or hypoxia (oxygen saturation < 90% in room air).
» Apnoea.
» Inability to feed.
» Lethargy or decreased level of consciousness.

DIAGNOSTIC CRITERIA

» Prodrome of viral infection: irritability and rhinorrhoea.
» A wheeze that is slowly responsive or non-responsive to bronchodilators.
» Tachypnoea: age dependent:

Age	Respiratory rate
Birth – 2 months	≥ 60 breaths/minute
2–12 months	≥ 50 breaths/minute
1–5 years	≥ 40 breaths/minute

GENERAL MEASURES

» Minimise contact with other children.
» Avoid routine use of antibiotics and corticosteroids.
» Do not sedate child.

MEDICINE TREATMENT

Mild cases, without risk factors may be managed as an outpatient.

Refer severe bronchiolitis or those with risk factors:

- Oxygen, humidified, using nasal prongs or nasal cannula, at 1–2 L/minute.

REFERRAL

» Signs of severe bronchiolitis (respiratory distress, hypoxia, apnoea, inability to feed, lethargy/decreased level of consciousness).
» Bronchiolitis with risk factors for severe disease.
» Previous admission for same problem.

17.1.5 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

J43.0-2/J43.8-9/J44.0-1/J44.8-9

DESCRIPTION

Also referred to as chronic obstructive airways disease (COAD), and comprises chronic bronchitis and emphysema which are characterised by:

» chronic cough with/without sputum production on most days of ≥ 3 months for ≥ 2 consecutive years;
» dyspnoea or shortness of breath; and
» wheezing.

The onset is very gradual with progressively worsening symptoms. Due to the large reserve capacity of the lungs, patients often present when there is considerable permanent damage to the lungs. In addition to the symptoms listed above, patients may present with symptoms or signs of right heart failure. The airways obstruction is not fully reversible (in contrast to asthma).

The main causes of COPD are chronic irritation of the airways caused by smoking, air pollution, previous TB, and previous cannabis (dagga) smoking, although there are many other causes.

If symptoms suggest TB (e.g. weight loss, night sweats, etc.), investigate and manage accordingly (See Section 17.4: Pulmonary Tuberculosis (TB)).

GENERAL MEASURES

» Smoking cessation, including cannabis (dagga), is the mainstay of therapy.
» Chest physiotherapy where available.
» Exercise.

MEDICINE TREATMENT

See Appendix II: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Acute lower airways obstruction:

Treat as for acute asthma but in addition, add antibiotics if patients have increased sputum purulence AND either increased sputum volume or increased dyspnoea.

- Amoxicillin, oral, 500 mg 8 hourly for 5 days. *LoE:IIb*[27]

Severe penicillin allergy:

Z88.0

Azithromycin, oral, 500 mg daily for 3 days.

Chronic management:

» In a stable patient, check PEFR.
» Then give a test dose of salbutamol, i.e. 2 puffs.
» Repeat PEFR 15 minutes later.
» If there is ≥ 20% improvement in peak flow, diagnose asthma and manage patient accordingly. See Section 17.1.3: Chronic asthma.
» Perform spirometry if available. Diagnose COPD if post-bronchodilator $FEV_1/FVC < 70\%$.

- Short acting $beta_2$ agonist, e.g.:

- Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 3–4 times daily via a spacer as needed for relief of wheeze.

If not controlled on SABA alone and diagnosis was confirmed by spirometry (with < 2 exacerbations per year):

- Long-acting beta$_2$ agonist (LABA), e.g.:
- Formoterol, inhaled 12 mcg (1 puff) 12 hourly (Doctor initiated). *LoE:IVb*[28]

If not controlled on SABA alone and spirometry not available:

- Inhaled LABA/corticosteroid combination e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated).

If not controlled on a LABA alone or frequent exacerbations (≥ 2 per year):

Measure blood eosinophil levels.

If eosinophils > 0.1 x10^9 cells/L, replace with:

- Inhaled LABA/corticosteroid combination e.g.:
- Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated). *LoE:IVb*[29]

Note:

» Fluticasone and budesonide interact with protease inhibitors. Refer all patients on protease inhibitors requiring inhaled corticosteroids for further management. *LoE:IIIb*[30]

» Oral corticosteroids may be required for acute exacerbations, but these have severe long-term complications and should only be used long-term if advised by a specialist.

» Do not measure blood eosinophil levels while taking oral corticosteroids, as this may temporarily lower the eosinophil count.

Prophylaxis against respiratory tract infections:

Z25.1

- Influenza vaccination, annually.

REFERRAL

» Poor response to above therapy, for further investigations and adjustment of treatment.

» Patients on protease inhibitors, requiring inhaled corticosteroids.

17.2 STRIDOR (UPPER AIRWAYS OBSTRUCTION)

17.2.1 CROUP (LARYNGOTRACHEO BRONCHITIS) IN CHILDREN

J05.0-1

DESCRIPTION

Croup is a common cause of potentially life-threatening airway obstruction in childhood. It is characterised by inflammation of the larynx, trachea and bronchi. Most common causative pathogens are viruses, including measles.

A clinical diagnosis of viral croup can be made if a previously healthy child develops progressive, inspiratory airway obstruction with stridor and a barking cough, 1–2 days after the onset of an upper respiratory tract infection. A mild fever may be present.
Suspect foreign body aspiration if there is a sudden onset of stridor in an otherwise healthy child.
Suspect epiglottitis if the following are present in addition to stridor:

» very ill child
» high fever
» sitting upright with head held erect
» drooling saliva
» unable to swallow

Assessment of the severity of airway obstruction and management in croup

Grade 1 Inspiratory stridor only	▪ Corticosteroids (intermediate-acting) e.g.: ▪ Prednisone, oral, 1–2 mg/kg, single dose. o Do not give if measles or herpes infection present. » Refer. *LoE:III*[31]
Grade 2 Inspiratory and expiratory stridor	▪ Corticosteroids (intermediate-acting) e.g.: ▪ Prednisone, oral, 1–2 mg/kg, immediately as a single dose. *LoE:III*[32] ▪ Adrenaline, 1:1000 diluted in sodium chloride 0.9%, nebulised, immediately. o Dilute 1 mL of 1:1000 adrenaline with 1 mL sodium chloride 0.9%. o Repeat every 15–30 minutes until expiratory stridor disappears. » Refer.
Grade 3 Inspiratory and expiratory stridor with active expiration, using abdominal muscles	» Treat as above. » If no improvement within one hour, refer **urgently** (intubate before referral if possible).
Grade 4 Cyanosis, apathy, marked retractions, impending apnoea	» Intubate (if not possible give treatment as above). » Refer **urgently**.

GENERAL MEASURES

» Keep child comfortable.
» Continue oral fluids provided that patient is able to swallow.
» Encourage parent or caregiver to remain with the child.

MEDICINE TREATMENT

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 23.8.

Children grade 2 or more stridor- while awaiting transfer:

▪ Corticosteroids (intermediate-acting) e.g.: *LoE:IVb*[33]
- Prednisone, oral, 1–2 mg/kg immediately as a single dose.
- Adrenaline (epinephrine), 1:1000, nebulised, immediately using a nebuliser.
  - If there is no improvement, repeat every 15 minutes until the child is transferred.
  - Dilute 2 mL of 1:1000 adrenaline with 2 mL sodium chloride 0.9%.
  - Nebulise the entire volume with oxygen at a flow rate of 6–8 L/minute.

Weight-based prednisone dosing for children < 18 kg:

Weight (kg)	Dose (mg)	Tablet (5 mg)	Age (years)
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years

If epiglottitis suspected:

- Ceftriaxone, IM,80 mg/kg/dose immediately as a single dose and refer. See dosing table, pg 23.3.
  - Do not inject more than 1 g at one injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.
» Always include the dose and route of administration of ceftriaxone in the referral letter.

Management during transfer:

» Give the child oxygen to keep oxygen saturation levels at 93-95%.
» Continue nebulisations with adrenaline.
» If grade 2-3, contact ambulance or nearest doctor.
» If grade 4, intubate and transfer.

REFERRAL

Urgent

» Children with:
  - Grade 2-4 stridor
  - chest indrawing
  - rapid breathing
  - altered consciousness
  - inability to drink or feed
» For confirmation of diagnosis.
» Suspected foreign body.
» Suspected epiglottitis.

Non Urgent

» All children with grade 1 stridor.

17.3 RESPIRATORY INFECTIONS

17.3.1 INFLUENZA

J09/J10.0-1/J10.8/J11.0-1/J11.8

DESCRIPTION

Influenza is a self-limiting viral condition that presents with headache, muscular pain and fever. It usually begins to clear within 7 days but may last up to 14 days. Malnourished children, the elderly and debilitated patients are at greater risk of developing complications.

CAUTION

Malaria, measles, and HIV seroconversion may present with flu-like symptoms.

Complications:
Secondary bacterial infections, including:
» pneumonia secondary to influenza
» otitis media
» sinusitis

GENERAL MEASURES
» Bed rest, if feverish.
» Ensure adequate hydration.
» Advise patient to return to clinic if earache, tenderness or pain over sinuses develops and/or cough or fever persists for longer than a week.

MEDICINE TREATMENT
Note: Antibiotics are of no value in the treatment of influenza.

Infants
- Sodium chloride 0.9%, instilled into each nostril as required.

Pain and fever with distress:

Children
- Paracetamol, oral, 10–15 mg/kg/dose 4–6 hourly when required. See dosing table, pg 23.8.

Adults
- Paracetamol, oral, 500 mg–1 g 4–6 hourly when required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

REFERRAL
Severe complications.

17.3.2 ACUTE BRONCHITIS IN ADULTS OR ADOLESCENTS
J20.0-9

DESCRIPTION
Acute airway infections, mostly of viral origin, accompanied by cough, sputum production, and sometimes a burning retrosternal chest pain in patients with otherwise healthy lungs.
Clinical features:
» initially: non-productive cough.
» later: productive cough with yellow or greenish sputum.

Viral bronchitis is usually part of an upper respiratory viral infection. It may be accompanied by other manifestations of viral infections. It is important to exclude underlying bronchiectasis or an acute exacerbation of chronic bronchitis in adults.

Antibiotics are not indicated in acute bronchitis in the absence of underlying COPD.

17.3.3 ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

See Sections 17.1.1: Acute asthma and acute exacerbation of COPD, adults, and 17.1.5: Chronic Obstructive Pulmonary Disease.

17.3.4 PNEUMONIA

DESCRIPTION

Acute infection of the lung parenchyma, usually caused by bacteria, especially *Streptococcus pneumonia* (pneumococcus).

Management is guided by:
- » age
- » co-morbidity
- » severity of the pneumonia

Manifestations include:
- » malaise;
- » fever, often with sudden onset and with rigors;
- » cough, which becomes productive of rusty brown or yellow-green sputum;
- » pleuritic type chest pain;
- » shortness of breath;
- » and in severe cases, shock and respiratory failure.

On examination there is:
- » fever
- » tachypnoea
- » crackles or crepitations
- » bronchial breath sounds

A pleural rubbing sound, or signs of a pleural effusion may be present.

Predisposing conditions include:
- » very young or old age
- » malnutrition
- » other concomitant diseases
- » HIV infection

Pneumococcal pneumonia often occurs in previously healthy adults.
Adults with mild to moderately severe pneumonia may be managed at PHC level, depending on the response to initial treatment (see below).

17.3.4.1 PNEUMONIA IN CHILDREN

J18.0-2/J18.8-9

DESCRIPTION

Pneumonia should be distinguished from viral upper respiratory infections. With viral URTIs' the respiratory rate will be normal. A raised respiratory rate indicates an alternate diagnosis such as bronchiolitis or pneumonia.

Assess the child for the severity of the pneumonia

Classify children according to the severity of the illness:

» Pneumonia: fever, cough and rapid breathing, but no chest indrawing (of the lower chest wall) and no flaring of nostrils.

» Severe pneumonia: fever, cough, rapid breathing, chest indrawing and flaring nostrils, or grunting.

Note: Children < 2 months of age with rapid breathing should be classified as having severe pneumonia.

Rapid breathing is defined according to age:

Age	Respiratory rate
Birth – 2 months	≥ 60 breaths/minute
2–12 months	≥ 50 breaths/minute
1–5 years	≥ 40 breaths/minute

Danger signs indicating urgent and immediate referral include:

» oxygen saturation of < 90% in room air
» inability to drink
» impaired consciousness
» cyanosis
» < 2 months of age
» grunting

GENERAL MEASURES

» Ensure adequate hydration.
» Continue feeding.

MEDICINE TREATMENT

Pneumonia (non-severe):

- Amoxicillin, oral, 45 mg/kg/dose, 12 hourly for 5 days. *LoE:IVb*[34]

Weight (kg)	Dose mg	Use one of the following: Syrup (mg/5mL)		Capsule (mg)		Age (Months/years)
		125	250	250	500	
>3.5–5 kg	175 mg	7 mL	3.5 mL	–	–	>1–3 months
>5–7 kg	250 mg	10 mL	5 mL	–	–	>3–6 months
>7–11 kg	375 mg	15 mL	7.5 mL	–	–	>6–18 months
>11–14 kg	500 mg	–	10 mL	2	1	>18 months–3 years
>14–17.5 kg	750 mg	–	15 mL	3	–	>3–5 years
>17.5–25 kg	1000 mg	–	20 mL*	4	2	>5–7 years
>25–30 kg	1250 mg	–	25 mL*	5	–	>7–10 years
>30 kg	1500 mg	–	–	6	3	>10 years

*capsule/tablet preferred

Severe penicillin allergy:

Z88.0

Children

- Macrolide, e.g.:
- Azithromycin, oral, 10 mg/kg/dose daily for 3 days. See dosing table, pg 23.2.

Severe pneumonia:

- Oxygen, using nasal cannula at 1–2 L/minute before and during transfer.

- Ceftriaxone, IM, 80 mg/kg/dose immediately as a single dose. See dosing table, pg 23.3.
  - Do not inject more than 1 g per injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If SUSPECTING SERIOUS BACTERIAL INFECTION in neonate, give ceftriaxone, even if jaundiced.
» Always include the dose and route of administration of ceftriaxone in the referral letter.

REFERRAL

Urgent

» All children with severe pneumonia, i.e. chest indrawing (of the lower chest wall), flaring nostrils or cyanosis.
» All children < 2 months of age.

Non urgent

» Inadequate response to treatment.
» Children coughing for > 3 weeks to exclude other causes such as TB, foreign body aspiration or pertussis.

17.3.4.2 PNEUMONIA IN ADULTS

17.3.4.2.1 UNCOMPLICATED PNEUMONIA

J18.0-2/J18.8-9

DIAGNOSIS

A chest X-ray should ideally be taken in all patients to confirm the diagnosis. Send one sputum specimen for TB DNA PCR (Xpert® MTB/RIF) to exclude pulmonary tuberculosis.

MEDICINE TREATMENT

If not severely ill (see referral criteria below):

- Amoxicillin, oral, 1 g 8 hourly for 5 days.

Severe Penicillin allergy:

Z88.0

- Moxifloxacin, oral, 400 mg daily for 5 days.

A follow-up chest X-ray should ideally be taken to ensure resolution of the pneumonia in patients > 50 years of age. *LoE:IIIb*[35]

REFERRAL

Any of the following:

» Confusion or decreased level of consciousness.
» Cyanosis.
» Respiratory rate of ≥ 30 breaths/minute.
» Systolic BP < 90 mmHg.
» Diastolic BP < 60 mmHg.
» Deterioration at any point.
» No response to treatment after 48 hours.
» Patients with pneumonia:
  - from a poor socio-economic background,

- who are unlikely to comply with treatment,
- who live a considerable distance from health centres,
- who have no access to immediate transport.

17.3.4.2.2 PNEUMONIA IN ADULTS WITH UNDERLYING MEDICAL CONDITIONS OR > 65 YEARS OF AGE

J18.0-2/J18.8-9

A chest X-ray should ideally be taken in all patients to confirm the diagnosis. Send one sputum specimen for TB DNA PCR (Xpert® MTB/RIF) to exclude pulmonary tuberculosis.

Common underlying conditions include:

» Diabetes mellitus.
» HIV infection.
» Cardiac failure.
» COPD.
» Alcoholism.
» Chronic liver disease.
» Chronic kidney disease.

Most of these patients will require referral to a doctor.

MEDICINE TREATMENT

Mild pneumonia:

- Amoxicillin/clavulanic acid 875/125 mg, oral, 12 hourly for 5 days.

Severe Penicillin allergy:

Z88.0

- Moxifloxacin, oral, 400 mg daily for 5 days. *LoE:IIIb*[36]

A follow-up chest X-ray should ideally be taken to ensure resolution of the pneumonia in patients > 50 years of age.

17.3.4.2.3 SEVERE PNEUMONIA

J18.0-2/J18.8-9

DESCRIPTION

Severe pneumonia is defined as ≥ 2 of the following:

» confusion/ decreased level of consciousness
» respiratory rate of ≥ 30 breaths/minute
» > 65 years of age
» systolic BP < 90 mmHg
» diastolic BP < 60 mmHg

MEDICINE TREATMENT

While awaiting transfer:

- Oxygen, to achieve a saturation of 92%.
- Ceftriaxone, IV/IM, 1 g, as a single dose before referral.

CAUTION

Do not administer calcium containing intravenous fluids, e.g. Ringer Lactate, concurrently with IV ceftriaxone.

REFERRAL

Urgent

All patients.

17.3.4.2.4 PNEUMOCYSTIS PNEUMONIA

B20.6

DESCRIPTION

Interstitial pneumonia occurring with advanced HIV infection due to *Pneumocystis jiroveci* (formerly *carinii*). Patients usually present with shortness of breath or dry cough. Chest X-ray may be normal in the early stages, but typically shows bilateral interstitial or ground glass pattern.

GENERAL MEASURES

Ensure adequate hydration.

MEDICINE TREATMENT

Adults

- Cotrimoxazole, oral, 6 hourly for 3 weeks.

Approx. weight	**Use one of the following tablet formulations**	
kg	80/400 mg	160/800 mg
<40 kg	2 tablets	1 tablet
>40–56 kg	3 tablets	1½ tablets
>56 kg	4 tablets	2 tablets

For secondary prophylaxis

- Cotrimoxazole, oral, daily.

Use one of the following tablet formulations	
80/400 mg	160/800 mg
2 tablets	1 tablet

Note: Discontinue cotrimoxazole prophylaxis once the CD4 count increases on ART to > 200 cells/mm^3 for at least 6 months.

REFERRAL

» All children.
» Breathing rate > 24 breaths/minute.
» Shortness of breath with mild effort.
» Cyanosed patients.

17.4 PULMONARY TUBERCULOSIS (TB)

Note: TB is a notifiable disease.

TB guidelines are updated regularly.
Consult the most recent National Tuberculosis Control Programme Guidelines.

DESCRIPTION

Tuberculosis is an infection caused by *Mycobacterium tuberculosis*. The risk of developing TB disease is higher among people living with HIV.

17.4.1 PULMONARY TUBERCULOSIS (TB) IN ADULTS

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-9 + (B20.0)

DIAGNOSIS

Pulmonary TB is diagnosed on sputum by TB nucleic acid amplification tests (TB-NAAT) such as Xpert® MTB/RIF Ultra, sputum smear, or culture.

» Send 1 sputum specimen for TB-NAAT.
- If TB-NAAT is unsuccessful: collect another sample and repeat TB-NAAT.
- If TB-NAAT is trace (only applies to Xpert® MTB/RIFUltra): If the clinical presentation and chest X-ray are suggestive of TB, treat for drug-sensitive TB (DS-TB), and collect sputum specimen for TB culture and drug sensitivity testing (DST). If the patient is asymptomatic, with no abnormalities on chest X-ray, continue routine care with close follow-up for features of TB.
- If TB-NAAT is positive and susceptible to rifampicin: treat for DS-TB and send a sputum specimen for baseline smear microscopy (the smear is used for reporting, not for diagnosis).
- If TB-NAAT is positive, susceptible to rifampicin and resistant to isoniazid: treat for isoniazid monoresistant TB (See Section 17.4.4.1: Isoniazid mono-resistant tuberculosis in adults). Collect sputum sample for reflex testing of fluoroquinolone susceptibility.
- If TB-NAAT is positive and rifampicin unsuccessful: start DS-TB treatment and collect another sputum sample for smear, culture and drug sensitivity testing (DST). Follow-up culture and DST results.
- If TB-NAAT is positive and resistant to rifampicin (with or without isoniazid resistance): treat for rifampicin resistant TB and send sputum sample for further reflex testing and DST.
- If TB-NAAT is negative and patient is living with HIV: send sputum for TB culture and perform chest X-ray. If CD4 < 200 within the last 6 months and they have signs and symptoms of TB (pulmonary or extrapulmonary), the patient has advanced HIV disease or the patient is currently seriously ill and requiring hospitalization, perform urine LAM (U-LAM) test. *LoE:I*[37]
- If TB-NAAT is negative and patient is HIV negative: treat with antibiotics and consider further investigation only if symptoms persist.

Note: Patients with a history of TB can remain TB-NAAT positive for several years after completion of appropriate anti-TB treatment. To diagnose a new episode of TB in previously treated patients, send sputum for smear microscopy and culture instead.

GENERAL MEASURES

» Counsel patients about the disease and infection control in the home. Explain the importance of completing treatment.
» Advise against the use of tobacco and excessive alcohol.
» If more than two doses of treatment are missed, extra effort should be made to identify and manage any problems the patient might have.

MEDICINE TREATMENT

Administer total daily amount of each medicine in one dose and not as divided doses.

Important medicine interactions

Rifampicin may reduce the efficacy of low dose combined oral contraceptives and progestin-only implants, resulting in possible unplanned pregnancies (See PHC Chapter 7: Family planning).

» Use of alternative contraceptive methods, such as IUD or DMPA, should be advised.
OR
» Women choosing to use a progestin-only subdermal implant should be advised to use additional contraception for the duration of TB therapy. See Section: 11.1 Antiretroviral therapy, adults.

CAUTION
Antiretroviral medicines frequently interact with TB medicines.
Consult the National Department of Health antiretroviral treatment guidelines.

Dose adjustment in renal impairment (eGFR < 30 mL/min)

- Ethambutol 15 – 25mg/kg three times weekly
- Pyrazinamide 20 – 30 mg/kg three times weekly
- Rifampicin and isoniazid do not require dose adjustment.

Intensive phase of treatment:

- Alternate day dosing of RH and RHZE
  - Administer standard weight-based dosing of RH on Tuesday, Thursday, Saturday, Sunday.

  AND
  - Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday.

Continuation phase of treatment:

- Rifampicin and isoniazid — *LoE:IVb*
  - Do not require dose adjustment. Continue daily weight-based dosing of RH.

Adverse effects of TB medicines include:

» Nausea:
- Taking medicines with meals can minimise nausea.
- Hepatitis must be excluded, if there is new onset nausea. Request serum alanine aminotransferase test urgently in these patients.

» Hepatitis (drug induced liver injury):
- Rifampicin, isoniazid and pyrazinamide may cause hepatitis. Cotrimoxazole and antiretrovirals (efavirenz, nevirapine, lopinavir + ritonavir) can also cause hepatitis.
- Patient may present with jaundice and/or complaining of hepatitis symptoms (e.g. nausea, malaise, abdominal pain).
- Refer to hospital for urgent (same day) ALT and further management.
- If jaundiced, stop TB treatment and medicines known to cause hepatitis before referring. See Section: 11.1: Antiretroviral therapy, adults (Rifampicin-based TB treatment).

» New onset skin rash:
  - Refer if suspected drug rash.
» Neuropathy:
  - Can be prevented by taking pyridoxine.
» Arthralgia:
  - Exclude gout, and treat symptomatically.

17.4.1.1 TB CHEMOPROPHYLAXIS/ISONIAZID PREVENTIVE THERAPY (IPT) IN ADULTS

See Section 11.2.2: Tuberculosis preventive therapy (TPT).

17.4.1.2 TB CONTROL PROGRAMME: MEDICINE REGIMENS IN ADULTS

A15.0-3/A15.7-8/A16.0-2/ A16.4/A16.7-8 + (B20.0)

Treatment should be given once daily, **seven days per week**, in both the intensive and continuation phases.

R – Rifampicin
H – Isoniazid
Z or PZA– Pyrazinamide
E or EMB – Ethambutol

Pre-treatment body weight kg	**Two months initial phase**	**Four months continuation phase**	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
30–37 kg	2 tablets	2 tablets	
38–54 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
≥71kg	5 tablets		2 tablets

» Adhere to the correct dose and the duration of treatment.
» Weigh patient frequently and adjust the dose according to current weight.

17.4.2 PULMONARY TUBERCULOSIS (TB) IN CHILDREN

A15.0-3/A15.7-8/A16.0-2/A16.4/A16.7-8 + B20.0

Most children acquire tuberculosis from infected adults by inhalation. Malnourished, immunosuppressed (HIV and AIDS) children, and children < 5 years of age, are at increased risk for pulmonary tuberculosis.

DIAGNOSIS

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

» A chest X-ray suggestive of TB,

AND/OR

» History of exposure to an infectious TB case and/or positive tuberculin skin test (TST) e.g. Mantoux.

A positive TB-NAAT and/or smear microscopy and/or culture, on early morning gastric aspirate or induced sputum, confirms TB disease.

Signs and symptoms include:
» unexplained weight loss or failure to thrive,
» unexplained fever for ≥ 2 weeks,
» chronic unremitting cough for > 14 days,
» lymphadenopathy (especially cervical, often matted),
» hepatosplenomegaly,
» consolidation and pleural effusion.

Tuberculin skin test (TST), e.g. Mantoux:
» A positive test: TST induration ≥ 10 mm.
» A TST may be falsely negative in the presence of:
  - Malnutrition,
  - immunodeficiency, e.g. HIV and AIDS,
  - immunosuppression, e.g. steroid therapy, cancer chemotherapy,
  - following overwhelming viral infection, e.g. measles or post vaccination.

  In these circumstances a TST induration ≥ 5 mm may be regarded as positive. Frequently, the TST will be non-reactive in these cases. TB treatment should be considered, despite a negative TST.

The following may be evident on chest X-ray:
» Direct or indirect evidence of hilar or mediastinal adenopathy, with or without parenchymal opacification, and/or bronchopneumonia.

GENERAL MEASURES
» Identify and treat the source case.
» Screen all contacts for TB infection.
» Monitor the nutritional status of the child to assess response to treatment.

17.4.2.1 TB CHEMOPROPHYLAXIS/ISONIAZID PREVENTIVE THERAPY (IPT) IN CHILDREN

Z20.1

Consider TB chemoprophylaxis/isoniazid preventive therapy (IPT) in all children younger than 5 years, or who are living with HIV, and exposed to a pulmonary TB contact.

Exclude active TB (i.e. no signs or symptoms suggestive of TB):
» Refer to Section 17.4.2: Pulmonary tuberculosis (TB) in children.
» If any signs or symptoms of pulmonary TB are present, refer for chest X-ray.
» Never give TPT to children with active TB.

TB chemoprophylaxis/ IPT is only used in:
» Children < 5 years of age.

OR

» Children of any age, who are living with HIV.

WITH EITHER

- Close contact with an infectious pulmonary TB case. If child is re-exposed to a close contact, TB chemoprophylaxis must be repeated (Previous IPT does not protect the child against subsequent TB exposure/ infection).
- Positive TST (only applicable on the first occasion of a positive TST).

MEDICINE TREATMENT

Preventive therapy in case of drug-sensitive TB contact:

- Isoniazid, oral, 10 mg/kg daily for 6 months.
    - Maximum dose: 300 mg daily.

Weight kg	**Daily isoniazid (INH)** 100 mg tablet
>2–3.4 kg	¼ tablet
>3.5–6.9 kg	½ tablet
>7–9.9 kg	1 tablet
>10–14.9 kg	1½ tablets
>15–19.9 kg	2 tablets
>20–24.9 kg	2½ tablets
>25 kg	3 tablets

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight > 30 kg) plus rifapentine (900mg if weight > 30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

LoE:IIb[38]

Preventive therapy in case of drug-resistant TB contact:

Isoniazid mono-resistant contact:

- Rifampicin, oral, 15 mg/kg daily for 4 months.

Rifampicin mono-resistant contact: *LoE:IVb*[39]

- Isoniazid, oral, 10 mg/kg daily for 6 months (see table above). *LoE:IVb*[40]

Children living with HIV or malnutrition or existing neuropathy taking isoniazid:

ADD

- Pyridoxine, oral, daily for duration of prophylaxis:
    - Child < 5 years old: 12.5 mg.
    - Child ≥ 5 years old: 25 mg. *LoE:IVb*[41]

REFERRAL

Children with drug resistant TB contacts for expert advice.

17.4.2.2 TB CONTROL PROGRAMME: MEDICINE REGIMENS IN CHILDREN

A15.0-3/A15.7-8/A16.0-2/ A16.4/A16.7-8 + (B20.0)

The employment of directly observed therapy (DOT) with short-course, fixed medicine combinations are recommended. Treatment should be given daily in both the intensive (initial) and continuation phases.

Recommended dose ranges		
	Daily (mg/kg)	**Maximum daily dose**
H	10–15	300 mg
R	10–20	600 mg
Z/ PZA	30–40	2 g
E/EMB	15–25	1 200 mg

UNCOMPLICATED PULMONARY TB

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

Children ≤ 8 years of age or < 25 kg):

	2 months intensive phase given daily			**4 months continuation phase given daily**
Weight (kg)	**RH**	**PZA**		**RH**
	60/60 mg	150 mg* **OR** 150 mg/3 mL	500 mg	60/60 mg
2–2.9 kg	½ tablet	1.5 mL	expert advice on dose	½ tablet
3–3.9 kg	¾ tablet	2.5 mL	¼ tablet	¾ tablet
4–5.9 kg	1 tablet	3 mL	¼ tablet	1 tablet
6–7.9 kg	1½ tablets		½ tablet	1½ tablets
8–11.9 kg	2 tablets		½ tablet	2 tablets
12–14.9 kg	3 tablets		1 tablet	3 tablets
15–19.9 kg	3½ tablets		1 tablet	3½ tablets
20–24.9 kg	4½ tablets		1½ tablet	4½ tablets
25–29.9 kg	5 tablets		2 tablets	5 tablets

* For each dose, dissolve 150 mg dispersible (1 tablet) in 3 mL of water to prepare a concentration of 50 mg/mL (150 mg/3 mL)
Note: Give PZA 150 mg **or** 500 mg, and not both.

LoE:IVb[42]

Dosing recommendations for dispersible fixed dose combinations tablets:

Weight kg	**2 months intensive phase given daily**	**4 months continuation phase given daily**
	RHZ (75/50/150 mg)	**RH** (75/50 mg)
4–7.9 kg	1 tablet	1 tablet
8–11.9 kg	2 tablets	2 tablets
12–15.9 kg	3 tablets	3 tablets
16–24.9 kg	4 tablets	4 tablets
≥25 kg	Adult dosages recommended	

ADD

- Pyridoxine, oral, daily for 6 months if living with HIV, malnourished, or has existing neuropathy:
  - Child < 5 years old: 12.5 mg.
  - Child ≥ 5 years old: 25 mg.

LoE:IVb[43]

Children ≥ 8 years and adolescents (and ≥ 25 kg)

Pre-treatment body weight kg	2 months intensive phase given daily	4 months continuation phase given daily	
	RHZE (150/75/400/275)	RH (150/75)	RH (300/150)
25–37.9 kg	2 tablets	2 tablets	
38–54.9 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
>71 kg	5 tablets		2 tablets

AND

If living with HIV, malnourished or has existing neuropathy:

- Pyridoxine, oral, daily for 6 months.
  - Child ≥ 5 years old: 25 mg.

LoE:IVb[44]

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

COMPLICATED PULMONARY TB

» Includes all other forms of pulmonary TB, such as smear positive TB, cavitating pulmonary TB, bronchopneumonic TB, large lesion pulmonary TB, and tuberculous empyema.
» Refer all cases of miliary TB for exclusion of TB meningitis.

Children ≤ 8 years of age (or < 25 kg):

» Intensive phase: Standard dose 4-drug therapy daily (RHZE) for 2 months.

THEN

» Continuation phase: Standard dose 2-drug therapy daily for 4–7 months.

	Intensive phase: 2 months				Continuation phase:4–7 months***
Weight kg	**RH**	**PZA**		**EMB**	**RH**
	60/60	150 mg* **OR** 150 mg/3 mL	500 mg	400 mg tablet **OR** 400 mg/8 mL** solution	60/60
2–2.9 kg	½ tablet	1.5 mL	Expert advice on dose	1 mL	½ tablet
3–3.9 kg	¾ tablet	2.5 mL	¼ tablet	1.5 mL	¾ tablet
4–5.9 kg	1 tablet	3 mL	¼ tablet	2 mL	1 tablet
6–7.9 kg	1½ tablet		½ tablet	3 mL	1½ tablets
8–11.9 kg	2 tablets		½ tablet	½ tablet	2 tablets
12–14.9 kg	3 tablets		1 tablet	¾ tablet	3 tablets
15–19.9 kg	3½ tablets		1 tablet	1 tablet	3½ tablets
20–24.9 kg	4½ tablets		1½ tablet	1 tablet	4½ tablets
25–29.9 kg	5 tablets		2 tablets	1½ tablets	5 tablets

* PZA: For each dose, dissolve 150 mg dispersible (1 tablet) in 3 mL of water to prepare a concentration of 50 mg/mL (150 mg/3mL).
** EMB: For each dose, crush 400 mg (1 tablet) to a fine powder and dissolve in 8 mL of water to prepare a concentration of 400mg/8mL. Discard unused solution.
Note: Give PZA 150 mg or 500 mg, and not both.
*** Continuation phase may be prolonged to 7 months in slow responders and children with HIV.

AND

If living with HIV, malnourished or has existing neuropathy:

- Pyridoxine, oral, daily for 6–9 months. *LoE:IVb*[45]
    - Child < 5 years old: 12.5 mg.
    - Child ≥ 5 years old: 25 mg.

Children ≥ 8 years and adolescents (and > 25 kg)

	2 months intensive phase given daily	**4 months continuation phase given daily**	
Weight kg	**RHZE (150/75/400/275)** mg	**RH (150/75)** mg	**RH (300/150)** mg
25–37.9 kg	2 tablets	2 tablets	
38–54.9 kg	3 tablets	3 tablets	
55–70 kg	4 tablets		2 tablets
>71 kg	5 tablets		2 tablets

AND

If living with HIV, malnourished, or has existing neuropathy:

- Pyridoxine, oral, daily for 6–9 months. *LoE:IVb*[46]
    - Child ≥ 5 years old: 25 mg.

» Weigh at each visit and adjust treatment dosages to body weight. If calculating dosages, rather give ½ tablet more than ½ tablet less.
» Ensure that the correct dose and duration of treatment are adhered to.

REFERRAL

Disseminated forms of TB.
All patients who cannot be managed on an ambulatory basis.
Children < 12 years of age for a chest X-ray for diagnostic purposes.
Children with previously treated TB requiring re-treatment.
Children who are contacts of patients with drug resistant TB.

17.4.3 TB, HIV AND AIDS

B20.0

People living with HIV (PLHIV) with suspected TB should have one negative sputum TB-NAAT test or two negative sputum smears, before sputum is sent for culture.

Advise PLHIV to present to a clinic if they develop common TB symptoms:

» active cough (any duration)
» fever
» night sweats
» loss of weight

PLHIV with concomitant TB should be treated according to the standard TB treatment protocol.

Medicine interactions may occur with ART (See Sections 11.1: Antiretroviral therapy, adults and adolescents; 11.7.8: Opportunistic infections, treatment in children.

17.4.4 DRUG-RESISTANT TUBERCULOSIS (MDR TB)

Drug-resistant TB (DR-TB) guidelines are updated regularly.
Consult the most recent National DR-TB Programme Guidelines.

DESCRIPTION

Isoniazid monoresistant TB is TB disease caused by *M.tuberculosis* that is resistant to isoniazid, but susceptible to rifampicin.

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 a strain of *M. tuberculosis* that is resistant to rifampicin and at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Extensively drug-resistant TB (XDR-TB) is TB disease caused by a strain of *M. tuberculosis* that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid. *LoE:IVb*[47]

17.4.4.1 ISONIAZID MONO-RESISTANT TUBERCULOSIS IN ADULTS

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

MEDICINE TREATMENT

Confirmed isoniazid mono-resistant TB:

- RHZE at standard doses (See Section 17.4.1: Pulmonary Tuberculosis (TB) in adults).

AND

- Levofloxacin, oral, daily
  - 30–45 kg: 750 mg.
  - ≥ 46 kg: 1 000 mg.

Confirmed isoniazid monoresistant 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.
  - 30–45 kg: 750 mg
  - > 46 kg: 1 000 mg

LoE:IIb[48]

Treatment should be given for at least 6 months.

REFERRAL

All drug resistant TB patients to medical officer at primary care level for initiation of therapy.

17.4.4.2 RIFAMPICIN-RESISTANT TUBERCULOSIS (RR TB), IN ADULTS

A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0)

Never treat for drug resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.

GENERAL MEASURES

Counsel and educate patients about the disease and its treatment, including treatment duration.

Screen all close contacts for signs and symptoms of drug-resistant TB and by sputum sampling to detect early disease.

Infection control and cough etiquette is important to limit spread.

MEDICINE TREATMENT

Drug resistant TB prophylaxis

The effectiveness of preventive therapy in adults exposed to drug resistant TB bacteria is not currently known. Consult a specialist for management.

RR-TB and Pre-XDR TB treatment

Consult the most recent national drug resistant TB programme guidelines.
Treatment for 6–18 months is required.

Management of drug resistant TB should be conducted in dedicated drug resistant TB clinics and hospitals with appropriate infection control measures.

XDR-TB treatment

Patients with XDR-TB should be discussed with the National Clinical Advisory Committee (NCAC - NCAC@witshealth.co.za) and referred to a TB hospital for an individualised regimen of at least 4 effective medicines, based on susceptibility tests and treatment history. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.

REFERRAL

All drug resistant TB patients to medical officer at primary care level for initiation of therapy.

17.4.4.3 RIFAMPICIN-RESISTANT (RR), PRE-XDR AND XDR TUBERCULOSIS, IN CHILDREN

A15.0-3/A15.7-8/A16.0-2/A16.7-8 + (U50.00-01+U50.20-21) + (B20.0)

Never treat for drug resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.
All cases should be discussed with a designated specialist drug resistant TB centre.

GENERAL MEASURES

Suspect drug-resistant TB when any of the features listed below is present:

» A known source case (or contact) with drug resistant TB or high-risk source case, e.g. on TB therapy who was recently released from prison.
» A patient with confirmed treatment adherence that remains smear positive after 2 months of 1st line TB treatment.
» Any severely ill child with TB who failed to improve, or got worse on TB treatment.
» Patients who defaulted TB treatment (> 2 months).
» History of treatment interruption (< 1 month) or relapse at some point during their TB therapy.
» With recurrent TB disease after completion of TB treatment (re-treatment case).

Management of drug resistant TB should be conducted in dedicated drug resistant TB clinics and hospitals with appropriate infection control measures. Initiate treatment in consultation with a designated expert. An uninterrupted medicine supply, direct supervision with proper education and counselling is necessary.

REFERRAL

All children with suspected drug resistant TB to a medical officer at primary care level for initiation of therapy.

References:

[1] D'Amato G, Vitale C, Lanza M, et al. Near fatal asthma: treatment and prevention. *Eur Ann Allergy Clin Immunol. 2016;48(4):116-122*

[2] Salbutamol MDI (adults): Rodrigo C, Rodrigo G. Salbutamol treatment of acute severe asthma in the ED: MDI versus hand-held nebulizer. Am J Emerg Med. 1998 Nov16(7):637-42. https://www.ncbi.nlm.nih.gov/pubmed/9827736

Salbutamol MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[3] Salbutamol MDI (dose in adults and children): SAMF 14th Edition

[4] Salbutamol nebulisation (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[5] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[6] Salbutamol nebulisation (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[7] Salbutamol MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[8] Salbutamol MDI (adults): Rodrigo C, Rodrigo G. Salbutamol treatment of acute severe asthma in the ED: MDI versus hand-held nebulizer. Am J Emerg Med. 1998 Nov16(7):637-42. https://www.ncbi.nlm.nih.gov/pubmed/9827736

Salbutamol MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[9] Ipratropium bromide 0.5 mg nebulisation (adults): Global initiative for asthma (GINA) Guidelines, 2018. http://ginasthma.org/

[10] Ipratropium bromide MDI (adults): Global initiative for asthma (GINA) Guidelines, 2018. http://ginasthma.org/

[11] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[12] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[13] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[14] Salbutamol MDI (dose in adults and children): SAMF 14th Edition

[15] 6 breaths: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30

[16] Salbutamol nebulisation (paediatrics): National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[17] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[18] Ipratropium bromide nebulisation (paediatrics): Kling S, Zar HJ, Levin ME, Green RJ, Jeena PM, Risenga SM, Thula SA ,Goussard P, Gie RP, for the South African Childhood Asthma Working Group (SACAWG)S Afr Med J 2013;103(3):199-207. http://www.samj.org.za/index.php/samj/article/view/6658

[19] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[20] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[21] Step-wise assessment: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Available from: www.ginasthma.org

[22] Low-dose ICS with SABA MDI (Rescue use): Global Initiative for Asthma. Global Strategy for asthma management and prevention, 2019. http://www.ginasthma.org/

Low-dose ICS with SABA MDI (Rescue use): Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet LP. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019 Jun 27;53(6). https://www.ncbi.nlm.nih.gov/pubmed/31249014

Low-dose ICS with SABA MDI (Rescue use): Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM; BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007 May 17;356(20):2040-52. https://www.ncbi.nlm.nih.gov/pubmed/17507703

Low-dose ICS with SABA MDI (Rescue use): Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423

Low-dose ICS with SABA MDI (Rescue use): Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002 Oct;57(10):880-4. https://www.ncbi.nlm.nih.gov/pubmed/12324675

Low-dose ICS with SABA MDI (Rescue use):Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003 Mar 29;361(9363):1071-6. https://www.ncbi.nlm.nih.gov/pubmed/12672309

Low-dose ICS with SABA MDI (Rescue use): Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982

[23] Inh Inhaled corticosteroids: Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423.

Inhaled corticosteroids: Busse WW, Pedersen S, Pauwels RA, Tan WC, Chen YZ, Lamm CJ, O'Byrne PM; START Investigators Group. The Inhaled Steroid Treatment As Regular Therapy in Early Asthma (START) study 5-year follow-up: effectiveness of early intervention with budesonide in mild persistent asthma. J Allergy ClinImmunol. 2008May;121(5):1167-74.http://www.ncbi.nlm.nih.gov/pubmed/18405951

Inhaled corticosteroids: Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982

Inhaled corticosteroids: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/

[24] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-*Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527*

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

LABA/ICS (Salmeterol/fluticasone) MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2015. http://www.health.gov.za/

[26] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[27] Antibiotics – lower airway obstruction: 2023 *Global Strategy for Asthma Management and Prevention (GINA 2023)*, pg 142.

[28] LABA (Formoterol) MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[29] LABA/ICS (Salmeterol/fluticasone) MDI (adults): National Department of Health, Essential Drugs Programme: Adult Hospital Level STGs and EML, 2019. http://www.health.gov.za/

[30] Inhaled corticosteroids (Patients on protease inhibitors): Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496

Inhaled corticosteroids (Patients on protease inhibitors): Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486

Inhaled corticosteroids (Patients on protease inhibitors): Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527

Inhaled corticosteroids (Patients on protease inhibitors): Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010

[31] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[32] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[33] Corticosteroids (intermediate-acting): National Department of Health, Essential Drugs Programme: Adult Hospital level STGs and EML, 2019. http://www.health.gov.za/

Corticosteroids (intermediate-acting): South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[34] Amoxicillin: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[35] Chest x-ray diagnosis (follow-up for community acquired pneumonia): Tang KL, Eurich DT,Minhas-Sandhu JK,Marrie TJ,Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med 2011;171:1193–1198. https://www.ncbi.nlm.nih.gov/pubmed/21518934

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Mortensen EM, Copeland LA, Pugh MJ, Fine MJ, Nakashima B, Restrepo MI, de Molina RM, Anzueto A. Diagnosis of pulmonary malignancy after hospitalization for pneumonia. Am J Med. 2010 Jan;123(1):66-71. https://www.ncbi.nlm.nih.gov/pubmed/20102994

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55. https://www.ncbi.nlm.nih.gov/pubmed/19783532

[36] Chest x-ray diagnosis (follow-up for community acquired pneumonia): Tang KL, Eurich DT,Minhas-Sandhu JK,Marrie TJ,Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med 2011;171:1193–1198. https://www.ncbi.nlm.nih.gov/pubmed/21518934

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Mortensen EM, Copeland LA, Pugh MJ, Fine MJ, Nakashima B, Restrepo MI, de Molina RM, Anzueto A. Diagnosis of pulmonary malignancy after hospitalization for pneumonia. Am J Med. 2010 Jan;123(1):66-71. https://www.ncbi.nlm.nih.gov/pubmed/20102994

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

Chest x-ray diagnosis (follow-up for community acquired pneumonia): Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55. https://www.ncbi.nlm.nih.gov/pubmed/19783532

[37] LAM urine testing (DS-TB): National Department of Health. Guidance on the use of the lipoarabinomannan lateral flow assay (LF-LAM) for the diagnosis of tuberculosis in people living with HIV, Update February 2021. http://www.health.gov.za/

LAM urine testing (DS-TB): Bjerrum S, Schiller I, Dendukuri N, Kohli M, Nathavitharana RR, Zwerling AA, Denkinger CM, Steingart KR, Shah M. Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in people living with HIV. Cochrane Database Syst Rev. 2019 Oct 21;10:CD011420. https://www.ncbi.nlm.nih.gov/pubmed/31633805

[38] Rifapentine-containing regimen (3HP): Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

Rifapentine-containing regimen (3HP): Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Rifapentine (3HP) as TPT in PLHIV on DTG-regimens, November 2019. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list

[39] Rifampicin, oral - Isoniazid mono-resistant contact: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[40] Isoniazid, oral - Rifampicin mono-resistant contact: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[41] Pyridoxine, oral: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[42] Dispersible paediatric FDC TB formulations (dosing): National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[43] Pyridoxine, oral: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[44] Pyridoxine, oral: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[45] Pyridoxine, oral: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[46] Pyridoxine, oral: National Department of Health, Essential Drugs Programme: Paediatric Hospital Level STGs and EML, 2017. http://www.health.gov.za/

[47] Definitions of DR-TB: WHO announces updated definitions of extensively drug-resistant tuberculosis https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis

[48] Levofloxacin, oral (with rifampicin, ethambutamol, pyrazinamide): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Levofloxacin, oral (in addition to rifampicin, pyrazinamide, and ethambutol) for isoniazid-resistant tuberculosis, September 2019. http://www.health.gov.za/

Levofloxacin, oral (with rifampicin, ethambutamol, pyrazinamide): Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2018;6(4):265-75. https://www.ncbi.nlm.nih.gov/pubmed/29595509

Levofloxacin, oral (with rifampicin, ethambutamol, pyrazinamide): World Health Organization. WHO Consolidated Guidelines on Drug-resistant Tuberculosis Treatment 2019.Available from: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
PRIMARY HEALTHCARE CHAPTER 17: RESPIRATORY CONDITIONS
NEMLC RECOMMEDATIONS FOR MEDICINE AMENDMENTS (2020-4 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/

This chapter has been subject to clinical editorial review. All editorial changes may not be reflected in this report.

A: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
17.1 Conditions with predominant wheeze		
17.1.1 Acute asthma & acute exacerbations of COPD, Adults	Description	Amended
	Appendix II: Devices for Respiratory conditions	Cross reference to Appendix added
	Medicine Treatment – mild-moderate attacks	Guidance amended
	Medicine Treatment – severe attacks (while awaiting referral	Guidance amended
	Medicine treatment – life-threatening asthma:	New guidance added
17.1.1 Acute asthma, children	Description	Amended
	Appendix II: Devices for Respiratory conditions	Cross reference to Appendix added
	Medicine Treatment – mild-moderate attacks	Guidance amended
	Medicine Treatment – severe attacks (while awaiting referral	Guidance amended
	Medicine treatment – life-threatening asthma:	New guidance added
17.1.2 Chronic asthma	Asthma diagnosis and severity:	Guidance amended
	General measures:	Editorial amendments
	Medicine treatment – technique for spacer devices	Guidance amended and transferred to new Appendix II
	Medicine treatment – technique for dry powder inhalers (DPIs):	Guidance added to new Appendix II
	Budesonide	Added for Step 1
	Beclomethasone	Added for Step 1
	Budesonide for children	Not added for Step 2
	Beclomethasone in patients on protease inhibitors	Guidance clarified
	Formoterol/ICS combination	Not added
	Referral for rehabilitation	Not added
17.1.4 Acute bronchiolitis in children	Description	Editorial amendment
	Referral for rehabilitation	Not added
17.1.5 Chronic obstructive pulmonary disease (COPD)	Acute lower airways obstruction in patients with severe penicillin allergy – doxycycline	Deleted
	Acute lower airways obstruction in patients with severe penicillin allergy – azithromycin	Added
	Eosinophil monitoring	Added
	LAMAs	Not added
	Severe penicillin allergy	Not amended
	Acute infective exacerbations of chronic bronchiolitis	Editorial amendments
	Referral for rehabilitation	Not added
17.2 Stridor (upper airway obstruction)		
17.2.1 Croup (laryngotracheo bronchitis) in children	Description - adrenaline	Editorial amendments
	General measures	Editorial amendments
	Medicine management - adrenaline	Dose amended
	Caution - ceftriaxone	Editorial amendments
	Management during transfer	Amended

	Referral	Amended
17.3 Respiratory Infections	Referral for rehabilitation	Not added
17.3.1 Influenza	Influenza STG	Retained
	Medicine - paracetamol	Amended
17.3.4.1 Pneumonia in children	Description	Editorial amendments
	Caution - ceftriaxone	Editorial amendments
	Referral for rehabilitation	Not added
17.3.4.2.3 Severe pneumonia	Caution - ceftriaxone	Guidance clarified
17.4 Pulmonary TB	Description	Editorial amendments
17.4.1 Pulmonary TB in adults	Diagnosis - testing: (TB-NAAT)	Added
	Xpert MTB/RIF	Deleted
	Medicine treatment – important medicine interaction	Aligned
	Medicine treatment – renal impairment: Ethambutol	Deleted
	Medicine treatment – renal impairment: RHZE FDC	Added
17.4.2.1 TB Chemoprophylaxis/isoniazid preventative therapy (IPT) in children	IPT: eligibility criteria	Retained and clarified
	Patients initiating DTG-containing ART:	Isoniazid daily for 12 months added
	Virally suppressed patients on DTG-containing ART: Isoniazid plus rifapentine	Added
17.4.2.2 TB Control programme: Medicine regimens in children	Weight threshold	Added
	Uncomplicated pulmonary TB in children – 4 month TB regimen	Not added
17.4.4 Drug-resistant TB (DR TB)	Description	Amended
	Fluoroquinolones for MDR-TB chemoprophylaxis in household contacts:	Not added
17.4.4.1 Isoniazid mono-resistant TB in adults	RHZE	Added
17.4.4.2 Rifampicin-resistant TB in adults	BPaL 6 month regimen	Added
17.4.4.3 Rifampicin-resistant (RR), Pre-XDR and XDR TB in children	General measures	Amended
Appendix I	Asthma monitoring	New guidance added
Appendix II	Devices for Respiratory conditions	New guidance added

17.1 CONDITIONS WITH PREDOMINANT WHEEZE

In response to external comments received, the historic STG Section 17.1.1 Acute asthma & acute exacerbation of COPD, has been separated out for adults and children for ease of understanding and improved clarity, as follows:
Section 17.1.1 Acute asthma & acute exacerbation of COPD, adults
Section 17.1.2 Acute asthma, children

17.1.1 ACUTE ASTHMA & ACUTE EXACERBATIONS OF COPD, ADULTS

Description: *Amended*

Guidance on the recognition and assessment of the severity of acute asthma attacks in adults has been revised to include potentially life-threatening presentations[1]. This revised guidance is intended to assist PHC staff to recognize and manage life threatening presentations of acute exacerbations of asthma until patients can be transferred to an acute facility for further management. Guidance on the recognition and assessment of severity of COPD attacks in adults has been retained[2]. The revised asthma guidance is as tabulated below:

AMENDED FROM:

DESCRIPTION

This is an emergency situation recognised by various combinations of:

- wheeze
- tightness of the chest
- breathlessness
- respiratory distress

[1] D'Amato G, Vitale C, Lanza M, et al. Near fatal asthma: treatment and prevention. *Eur Ann Allergy Clin Immunol. 2016;48(4):116-122*

[2] NDoH Internal Communication Records – confidential on file.

- chest indrawing in children
- cough

use of accessory muscles of respiration

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease (COPD) (where the bronchospasm is partially reversible).

- The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients >50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

Bronchospasm in children is usually associated with asthma or with infections such as bronchiolitis or bronchopneumonia. Consider foreign bodies or obstruction of airways due to tuberculous nodes or congenital malformation, especially if the wheeze is unilateral.

- All PHC facilities must have peak expiratory flow rate (PEFR) meters, as asthma cannot be correctly managed without measuring PEFR.

Recognition and assessment of severity of attacks in <u>adults</u>

	Moderate	**Severe**
Talks in	phrases	words
Alertness	usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute
Wheeze	loud	loud or absent
Heart rate	100–120 beats/minute	>120 beats/minute
PEFR after initial nebulisation	±50–75%	<50%; may be too short of breath to blow in PEF meter

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment.

AMENDED TO:

DESCRIPTION

This is an emergency situation recognised by various combinations of:

- wheeze
- tightness of the chest
- chest indrawing
- breathlessness
- respiratory distress
- cough

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease (COPD) (where the bronchospasm is partially reversible).

The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients >50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

All PHC facilities must have peak expiratory flow rate (PEFR) meters, as asthma cannot be correctly managed without measuring PEFR.

ASTHMA

Recognition and assessment of severity of asthma attacks in adults

	Mild-Moderate	**Severe**	**Life threatening**
Oxygen saturation	>90%	<90%	<90%
Talks in	phrases	words	Unable to speak
Alertness	normal	Usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute	often >30 breaths/minute OR feeble effort
Wheeze	present	present	absent
Heart rate	100–120 beats/minute	>120 beats/minute	bradycardia
PEFR	>60% of predicted	<60% of predicted	<33% of expected or unable to blow

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment.

COPD

Recognition and assessment of severity of COPD attacks in <u>adults</u>

	Moderate	**Severe**
Talks in	phrases	words
Alertness	usually agitated	agitated, drowsy or confused
Respiratory rate	20–30 breaths/minute	often >30 breaths/minute
Wheeze	loud	loud or absent
Heart rate	100–120 beats/minute	>120 beats/minute

PEFR after initial nebulisation	±50–75%	<50%; may be too short of breath to blow in PEF meter

Note: PEFR is expressed as a percentage of the predicted normal value for the individual, or of the patient's personal best value obtained previously when on optimal treatment.

Appendix II: Devices for Respiratory conditions: *Cross reference to Appendix added*

Guidance on the use of inhaler devices and nebulisers included in the newly developed Appendix II: Devices for respiratory conditions. The Appendix can be found at the end of this report or on the NHI webpage.

Medicine Treatment – mild-moderate attacks: *Guidance amended*

Administration of bronchodilators via metered dose inhaled with/without spacer recommended as first line treatment due to increased efficacy and lower cost. When using beta$_2$ agonists with MDI and spacer, the doses for emergency management differ from the doses recommended for ambulatory use. Doses of up to 1mg have been used without side effects, and are still lower than the doses given by nebulizer but with better effect due to the smaller particle size and better drug delivery. Furthermore, the use of corticosteroids should be administered immediately and not only if reversal of bronchodilation is incomplete with use of nebulized bronchodilators. Doses of salbutamol metered dose inhaler (MDI) have been aligned to the SAMF 14th Edition.

AMENDED FROM:	**AMENDED TO:**
MEDICINE TREATMENT **Adults with mild and moderate attacks** Salbutamol, inhalation using a metered-dose inhaler (MDI), 400–800 mcg (4–8 puffs), using a spacer. ○ Inhale one puff at a time. Allow for 4 breaths through the spacer between puffs. ○ If no relief, repeat every 20–30 minutes in the first hour. ○ Thereafter, repeat every 2–4 hours if needed. **Note:** Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser. **OR** Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 8 L/min with oxygen. ○ 1 mL (5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%. ○ If no relief, repeat every 20–30 minutes in the first hour. ○ Thereafter, repeat every 2–4 hours if needed. **AND** Corticosteroids (intermediate-acting) e.g.: Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD. Follow with prednisone, oral, 40 mg daily for 7 days **Children with mild and moderate attacks** Salbutamol, inhalation, using a MDI, 200–400 mcg (2–4 puffs), using a spacer. Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs. If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer. If no relief, repeat every 20–30 minutes in the first hour. Thereafter, repeat every 2–4 hours if needed. **Note:** Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser. **OR** Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 5 L/min with oxygen.	**MEDICINE TREATMENT** **Mild and moderate attacks** Salbutamol 100mcg metered-dose inhaler (MDI), ○ Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer if required and available. ○ Shake the inhaler between each puff ○ If no relief, repeat every 20–30 minutes in the first hour. ○ Thereafter, repeat every 2–4 hours if needed. **Note:** Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser. **OR** Salbutamol 0.5% (5mg/mL), nebuliser solution, ○ 1 mL (5 mg) salbutamol 0.5% solution made up to 4 mL with sodium chloride 0.9%. preferably delivered at a flow rate of 8 L/min with oxygen. ○ If no relief, repeat every 20–30 minutes in the first hour. ○ Thereafter, repeat every 2–4 hours if needed. **PLUS** Corticosteroids (intermediate-acting) e.g.: • Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD. ○ Follow with prednisone, oral, 40 mg daily for 7 days.

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

If reversal of bronchospasm is incomplete after the first nebulisation/inhalation:

ADD

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

Medicine Treatment – severe attacks (while awaiting referral): *Guidance amended*

External comments received that for patients with severe attacks awaiting transfer, administration of oxygen should preferably be titrated according to the oxygen saturation, with the aim of keeping the oxygen saturation 93-95% rather than the recommendation to use oxygen, 40% or higher. Amendments to the STG as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

Adults with severe attacks (while awaiting referral)

Oxygen, 40% or higher, using highest concentration facemask.

Note: In COPD:

Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 8 L/min with oxygen.

- 1 mL (5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
- Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

OR

Salbutamol, inhalation using a MDI, 400–800 mcg (4–8 puffs), up to 20 puffs, using a spacer.

- Inhale 1 puff at a time. Allow for 4 breaths through the spacer between puffs.
- If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
- Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg immediately.

- Follow with prednisone, oral, 40 mg daily for 7 days.

OR

If oral prednisone cannot be taken:

Hydrocortisone IM/slow IV, 100 mg as a single dose.

Follow with:

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg daily for 7 days.

ADD

If poor response after first salbutamol nebulisation/inhalation:

AMENDED TO:

MEDICINE TREATMENT

Severe attacks (while awaiting referral)

- Oxygen, to keep oxygen saturation 93-95%

Note: **For adults with COPD**:

Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

- Salbutamol 0.5% (5mg/mL) nebuliser solution,
  - 1 mL (5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%,.preferably delivered at a flow rate of 8 L/min with oxygen.%.
  - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
  - Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

OR

- Salbutamol, inhalation using a MDI,
  - Salbutamol 400–1000 mcg (4–10 puffs), up to 20 puffs, using a spacer.
  - Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.
  - If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
  - Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

If poor response after first salbutamol nebulisation/inhalation:

- Continue salbutamol nebulisation as described in management above and

ADD

- Ipratropium bromide 0.5mg/2ml; nebuliser solution
  - Ipratroprium bromide, 2 mL (0.5 mg) added to salbutamol 1mL (5mg) solution and made up to 4mL with sodium chloride 0.9%.

Ipratropium bromide solution, 0.5 mg nebulised, 2 mL (0.5 mg) added to salbutamol solution every 20–30 minutes for 3 doses depending on clinical response.

OR

Ipratropium bromide, using MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

Children with severe attacks (while awaiting referral)

Oxygen, 100%, at least 4-6 L/minute by facemask or 1-2 L/minute by nasal cannula.

AND

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 5 L/min with oxygen.

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes depending on clinical response.

OR

Salbutamol, inhalation using a metered-dose inhaler (MDI), 400–600 mcg (4–6 puffs) up to 10 puffs, using a spacer.

- Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.
- If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
- If no relief, repeat every 20–30 minutes depending on clinical response.

Note: Administering salbutamol via a spacer is as effective as and cheaper than using a nebuliser.

AND

Ipratropium bromide, 0.25 mg solution, nebulised with salbutamol and sodium chloride.

- 0.25 mg (2 mL) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

OR if oral prednisone cannot be taken:

Hydrocortisone IM/slow IV, 4–6 mg/kg immediately. See dosing table, pg 23.5.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently

- Administer every 20–30 minutes up to a maximum of 3 doses depending on clinical response.

OR

- Ipratropium bromide, MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg immediately.

- Follow with prednisone, oral, 40 mg daily for 7 days.

OR

If oral prednisone cannot be taken:

Hydrocortisone IM/slow IV, 100 mg as a single dose.

Followed with:

- Prednisone, oral, 40 mg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

Medicine treatment – life-threatening asthma: *New guidance added*

Guidance has been added to the STG for the management of patients presenting with life-threatening asthma at Primary Healthcare facilities, until such time that patients can be transferred to acute facilities. Treatment with standard guidelines for asthma exacerbations are not suitable for those with life threatening attacks in which minimal airflow results in inadequate deposition of medication to the lungs, and in which anticholinergic therapy should not be delayed. In addition the hypoxemia requires immediate commencement of nebulized therapy (along with nasal

prongs or facemask when not being nebulized), precluding the use of MDI and spacer therapy. In such patients the deposited dose is a minute fraction of the prescribed dose and thus far higher doses than usual can be given without any risk of side effects. The risks of poor drug delivery far outweigh any risks from overdosage. The guideline recommends reassessment prior to each medication administration and when the patient improves to become severe, but not life threatening, normal doses are then recommended. For life threatening attacks, (and similar to the guidance for severe attacks), the aim should be to keep the oxygen saturation 93-95% rather than the recommendation to use oxygen, 40% or higher.

NEW GUIDANCE ADDED:

Life- threatening attacks

- Oxygen, to keep oxygen saturation 93-95%.

Note: For adults with COPD:

- Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

Salbutamol 0.5% (5mg/mL) with ipratropium bromide 0.5mg/2mL nebuliser solution

- Salbutamol 0.5%, 2 mL (10 mg) plus Ipratroprium bromide, 2 mL (0.5mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
- Delivered at a flow rate of 8 L/min with oxygen.
- If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

Parenteral corticosteroids (intermediate-acting) e.g.:

- Hydrocortisone IM/slow IV, 100 mg as a single dose.

Followed with:

Oral corticosteroids (intermediate-acting) e.g.:

- Prednisone, oral, 40 mg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If response to treatment is adequate and severity improves to become severe but not life threatening, treat as per severe asthma exacerbation above.

. **Assessment of response in adults**

	Response	**No response**
PEFR (if possible)	improvement by >20%	improvement by <20%
Respiratory rate	<20 breaths/ minute	>20 breaths/ minute
Speech	normal	impaired

17.1.2 ACUTE ASTHMA, CHILDREN

In response to external comments received, the historic STG Section 17.1.1 Acute asthma & acute exacerbation of COPD, has been separated out for adults and children for ease of understanding and improved clarity. Amendments to the EML are as tabulated below:

Description: *Amended*

Guidance on the recognition and assessment of the severity of acute asthma attacks in children has been revised to include potentially life-threatening presentations[3]. This revised guidance is intended to assist PHC staff to recognize and manage life threatening presentations of acute exacerbations of asthma until patients can be transferred to an acute facility for further management. The revised asthma guidance for children is as tabulated below:

AMENDED FROM:

[3] D'Amato G, Vitale C, Lanza M, et al. Near fatal asthma: treatment and prevention. *Eur Ann Allergy Clin Immunol. 2016;48(4):116-122*

DESCRIPTION

This is an emergency situation recognised by various combinations of:

wheeze	breathlessness
tightness of the chest	respiratory distress
chest indrawing in children	cough
use of accessory muscles of respiration	

In adults, bronchospasm is usually associated with asthma (where the bronchospasm is usually completely reversible) or chronic obstructive pulmonary disease (COPD) (where the bronchospasm is partially reversible).

- The clinical picture of pulmonary oedema due to left ventricular heart failure may be similar to that of asthma. If patients >50 years of age present with asthma for the first time, consider pulmonary oedema due to left ventricular heart failure.

Bronchospasm in children is usually associated with asthma or with infections such as bronchiolitis or bronchopneumonia. Consider foreign bodies or obstruction of airways due to tuberculous nodes or congenital malformation, especially if the wheeze is unilateral.

- All PHC facilities must have peak expiratory flow rate (PEFR) meters, as asthma cannot be correctly managed without measuring PEFR.

Recognition and assessment of severity of attacks in children

	Moderate	**Severe**
Respiratory rate	>40 breaths/minute	>40 breaths/minute
Chest indrawing/recession	present	present
PEF (if > 5 years of age)	50–70% of predicted	<50% of predicted
Speech	normal or difficult	unable to speak
Feeding	difficulty with feeding	unable to feed
Wheeze	present	absent
Consciousness	normal	impaired

AMENDED TO:

DESCRIPTION

Bronchospasm in children is usually associated with asthma or with infections such as bronchiolitis or bronchopneumonia. Consider foreign bodies or obstruction of airways due to tuberculous nodes or congenital malformation, especially if the wheeze is unilateral.

Recognition and assessment of severity of attacks in children

	Mild/Moderate	**Severe**	**Life-threatening**
Oxygen saturation	>90%	<90%	<90%
Respiratory rate	<40 breaths/minute	>40 breaths/minute	>60 breaths/minute
Chest indrawing/recession	present	present	present
PEF (if > 5 years of age)	>60% of predicted	<60% of predicted	<33% of expected or unable to blow
Speech	normal	difficult	unable to speak
Feeding	normal	difficulty with feeding	unable to feed
Wheeze	present	present	absent
Consciousness	normal	normal	impaired

Appendix II: Devices for Respiratory conditions: *Cross reference to Appendix added*

Guidance on the use of inhaler devices and nebulisers included in the newly developed Appendix II: Devices for respiratory conditions. The Appendix can be found at the end of this report or on the NHI webpage.

Medicine Treatment – mild-moderate attacks: *Guidance amended*

Amendments to the STG as tabulated below: Administration of bronchodilators via metered dose inhaler and spacer recommended as first line treatment due to increased efficacy and lower cost. When using beta 2 agonists with MDI and spacer, the doses for emergency management differ from the doses recommended for ambulatory use. Doses of up to 1mg have been used without side effects, and are still lower than the doses given by nebulizer but with better effect due to the smaller particle size and better drug delivery. Furthermore, the use of corticosteroids should be administered immediately and not only if reversal of bronchodilation is incomplete with use of nebulized bronchodilators. Instructions on spacer selection and use updated. Doses of salbutamol metered dose inhaler (MDI) in children have been aligned to the SAMF 14th Edition.

AMENDED FROM	**AMENDED TO**

MEDICINE TREATMENT

Adults with mild and moderate attacks

Salbutamol, inhalation using a metered-dose inhaler (MDI), 400–800 mcg (4–8 puffs), using a spacer.

- Inhale one puff at a time. Allow for 4 breaths through the spacer between puffs.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 8 L/min with oxygen.

- 1 mL (5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg immediately if patient known to have asthma/COPD.

Follow with prednisone, oral, 40 mg daily for 7 days

Children with mild and moderate attacks

Salbutamol, inhalation, using a MDI, 200–400 mcg (2–4 puffs), using a spacer.

Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.

If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.

If no relief, repeat every 20–30 minutes in the first hour.

Thereafter, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 5 L/min with oxygen.

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

<u>If reversal of bronchospasm is incomplete after the first nebulisation/inhalation:</u>

ADD

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

MEDICINE TREATMENT

Mild to moderate attacks

Salbutamol 100mcg metered-dose inhaler (MDI),

<u>Children >/= 5years</u>

- Salbutamol inhaler 400–1000 mcg (4-10 puffs) using a spacer if required and available.
- Shake the inhaler between each puff
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

<u>Children < 5 years</u>

- Salbutamol inhaler 200–600 mcg (2-6 puffs) using a spacer.
- For children =/> 3 years, use a spacer with a mouthpiece.
- If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
- Inhale one puff at a time. Use a single breath inhalation technique. If single inhalation technique not possible, allow for 6 breaths through the spacer between puffs.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

OR

Salbutamol 0.5% (5mg/mL), nebuliser solution,

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%, preferably delivered at a flow rate of 8 L/min with oxygen.
- If no relief, repeat every 20–30 minutes in the first hour.
- Thereafter, repeat every 2–4 hours if needed

PLUS

Corticosteroids (intermediate-acting) e.g.:

- Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

<u>Medicine Treatment – severe attacks (while awaiting referral):</u> *Guidance amended*

External comments received that for patients with severe attacks awaiting transfer, administration of oxygen should preferably be titrated according to the oxygen saturation, with the aim of keeping the oxygen saturation 93-95% rather than the recommendation to use oxygen, 40% or higher. The dose of hydrocortisone IV for children, has been amended from 4-6mg/kg to 4mg/kg (maximum 100mg) in line with recommendations in the BNF for children[4]. Amendments to the STG as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

Adults with severe attacks (while awaiting referral)

Oxygen, 40% or higher, using highest concentration facemask.

Note: In COPD:

Give oxygen with care (preferably by 24% or 28% facemask, if available). Observe patients closely, as a small number of patients' condition may deteriorate.

AND

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 8 L/min with oxygen.

- 1 mL (5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
- Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

OR

Salbutamol, inhalation using a MDI, 400–800 mcg (4–8 puffs), up to 20 puffs, using a spacer.

- Inhale 1 puff at a time. Allow for 4 breaths through the spacer between puffs.
- If no relief, repeat every 20–30 minutes until PEF > 60% of predicted.
- Once PEF > 60% of predicted, repeat every 2–4 hours if needed.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg immediately.

- Follow with prednisone, oral, 40 mg daily for 7 days.

OR

If oral prednisone cannot be taken:

Hydrocortisone IM/slow IV, 100 mg as a single dose.

Follow with:

Corticosteroids (intermediate-acting) e.g.:

Prednisone, oral, 40 mg daily for 7 days.

ADD

If poor response after first salbutamol nebulisation/inhalation:

Ipratropium bromide solution, 0.5 mg nebulised, 2 mL (0.5 mg) added to salbutamol solution every 20–30 minutes for 3 doses depending on clinical response.

OR

Ipratroprium bromide, using MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

AMENDED TO:

MEDICINE TREATMENT

Severe attacks (while awaiting referral)

- Oxygen, to keep oxygen saturation 93-95%

AND

Salbutamol 0.5% (5mg/mL) nebuliser solution,

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, made up to 4 mL with sodium chloride 0.9%., preferably delivered at a flow rate of 8 L/min with oxygen.
- If no relief, repeat every 20–30 minutes depending on clinical response

OR

Salbutamol, inhalation using a MDI,

- Salbutamol 400-1000 mcg (4-10 puffs), using a spacer.
- For children >/= 3 years, use a spacer with a mouthpiece.
- If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
- Inhale one puff at a time. Use a single breath inhalation technique. If single inhalation technique not possible, allow for 6 breaths through the spacer between puffs.
- If no relief, repeat every 20–30 minutes depending on clinical response.

Note: Administering salbutamol via a spacer is as effective as, and cheaper than, using a nebuliser.

If poor response after first salbutamol nebulisation/inhalation:

ADD

- Ipratropium bromide 0.25mg/2ml; nebuliser solution
  - Ipratropium bromide, 2mL (0.25 mg) solution, nebulised with salbutamol 0.5mL (2.5mg) and made up to 4mL with sodium chloride 0.9%.
  - Administer every 20–30 minutes depending on clinical response for 4 doses over 2 hours.

OR

- Ipratroprium bromide, using MDI
  - Ipratroprium bromide, MDI, 80–160 mcg (2–4 puffs), using a spacer every 20–30 minutes as needed for up to 3 hours.

AND

Corticosteroids (intermediate-acting) e.g.:

- Prednisone, oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

OR

[4] British National Formulary for Children (BNF-C). 2020 Edition

Children with severe attacks (while awaiting referral)

Oxygen, 100%, at least 4-6 L/minute by facemask or 1-2 L/minute by nasal cannula.

AND

Salbutamol 0.5%, solution, nebulised, preferably delivered at a flow rate of 5 L/min with oxygen.

- 0.5–1 mL (2.5–5 mg) salbutamol 0.5% solution, in 4 mL of sodium chloride 0.9%.
- If no relief, repeat every 20–30 minutes depending on clinical response.

OR

Salbutamol, inhalation using a metered-dose inhaler (MDI), 400–600 mcg (4–6 puffs) up to 10 puffs, using a spacer.

- Inhale 1 puff at a time. Allow for 6 breaths through the spacer between puffs.
- If child < 3 years of age, use a mask attached to the spacer. Apply the mask to the face to create a seal so that the child breathes through the spacer.
- If no relief, repeat every 20–30 minutes depending on clinical response.

Note: Administering salbutamol via a spacer is as effective as and cheaper than using a nebuliser.

AND

Ipratropium bromide, 0.25 mg solution, nebulised with salbutamol and sodium chloride.

- 0.25 mg (2 mL) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.

AND

Corticosteroids (intermediate-acting) e.g.:

Prednisone oral, 1–2 mg/kg immediately and follow with same dose for 7 days:

Weight kg	**Dose** mg	**Tablet** 5 mg	**Age** months/years
>11–14 kg	20 mg	4 tablets	>2–3 years
>14–17.5 kg	30 mg	6 tablets	>3–5 years
>17.5 kg	40 mg	8 tablets	>5 years and adult

OR if oral prednisone cannot be taken:

Hydrocortisone IM/slow IV, 4–6 mg/kg immediately. See dosing table, pg 23.5.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently

If oral prednisone cannot be taken:

- Hydrocortisone IM/slow IV, 4 mg/kg (maximum 100 mg) immediately. See dosing table, pg 23.5.

Followed with:

- Prednisone 1–2 mg/kg daily for 7 days as per dosing table above.

CAUTION
Avoid sedation of any kind.

Note: If poor response to treatment, consider alternate diagnosis and refer urgently.

Medicine treatment – life-threatening asthma: *New guidance added*

Guidance has been added to the STG for the management of children presenting with life-threatening asthma at Primary Healthcare facilities, until such time that patients can be transferred to acute facilities. Treatment with standard guidelines for asthma exacerbations are not suitable for those with life threatening attacks in which minimal airflow results in inadequate deposition of medication to the lungs, and in which anticholinergic therapy should not be delayed. In addition the hypoxemia requires immediate commencement of nebulized therapy (along with nasal prongs or facemask when not being nebulized), precluding the use of MDI and spacer therapy. In such patients the deposited dose is a minute fraction of the prescribed dose and thus far higher doses than usual can be given without any risk of side effects. The risks of poor drug delivery far outweigh any risks from overdosage. The guideline recommends reassessment prior to each medication administration and when the patient improves to become severe,

but not life threatening, normal doses are then recommended. For life threatening attacks, (and similar to the guidance for severe attacks), the aim should be to keep the oxygen saturation 93-95% rather than the recommendation to use oxygen, 40% or higher.

NEW GUIDANCE ADDED

Life- threatening attacks

- Oxygen, to keep oxygen saturation 93-95%.

AND

- Salbutamol 0.5% (5mg/mL) with ipratropium bromide 0.5mg/2mL nebuliser solution
  - Salbutamol 0.5%, 2 mL (10 mg) plus Ipratroprium bromide, 2 mL (0.5mg) every 20–30 minutes depending on clinical response for 4 doses over 2 hours.
  - Delivered at a flow rate of 8 L/min with oxygen.
  - If no relief, repeat every 20–30 minutes until asthma severity category moves from life-threatening to severe.

AND

Parenteral corticosteroids (intermediate-acting) e.g.:

- Hydrocortisone IM/slow IV, 4 mg/kg (maximum 100 mg) immediately. See dosing table, pg 23.5.

Follow with:

Oral corticosteroids (intermediate-acting) e.g.:

- Prednisone 1–2 mg/kg daily for 7 days.

CAUTION
Avoid sedation of any kind.

Note: If response to treatment is adequate and severity improves to become severe but not life threatening, treat as per severe asthma exacerbation above.

Assessment of response in children

	Response	**No response**
PEFR (if possible)	improvement by >20%	improvement by <20%
Respiratory rate	<40 breaths/ minute	>40 breaths/ minute
Chest indrawing or recession	absent	present
Speech	normal	impaired
Feeding	normal	impaired

Patients responding to treatment:

- Routine prescription of antibiotics is not indicated for acute asthma.
- Review current treatment and possible factors causing acute attack including poor adherence and poor inhaler technique.
- Advise patient/caregiver on further care at home, danger signs and that follow up is required.
- Caution patient/carer on the high chance of further wheezing in the week following an acute attack.
- Patients with a first attack should be fully assessed for maintenance treatment.
- **Note:** Patients needing repeated courses of oral corticosteroids (more than twice over 6 months) should be assessed by a doctor for maintenance therapy. (See Section 17.1.2: Chronic asthma

REFERRAL

Urgent (after commencing treatment):

- All patients with severe attack.
- Poor response to initial treatment.
- PEFR < 75% of the predicted normal or of personal best value 15–30 minutes after nebulisation.
- A lower threshold to admission is appropriate in patients when:
  - seen in the afternoon or evening, rather than earlier in the day
  - recent onset of nocturnal symptoms or aggravation of symptoms
  - previous severe attacks, especially if the onset was rapid

17.1.3 CHRONIC ASTHMA

Asthma diagnosis and severity: *Guidance amended*

Guidance for assessing asthma treatment in children and adults has been adapted from the updated GINA 2023 guidelines[5]. The STG for the assessment and management of chronic asthma now refers to a 3 step management plan as tabulated below. Guidance is limited to a 3 step management plan rather than the 5 step plan included in the GINA

[5] Step-wise assessment: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2022. Available from: www.ginasthma.org

GINA 2023 guidelines,[6] as a 3 step plan is appropriate for primary health care level of care. Patients with more severe disease should be referred to the next level of care.

AMENDED FROM:

Place patient in a severity category based on frequency of daytime symptoms, frequency of night-time symptoms, PEFR, and history of admission for asthma exacerbation. Note that an admission in the 12 months' prior means that the patient requires treatment for persistent asthma, including inhaled corticosteroids.

	Mild intermittent asthma	Mild persistent asthma	Moderate persistent asthma	Severe persistent asthma
Daytime symptoms	≤2 episodes of daytime cough and/or wheeze per week	2-4 episodes of day time wheeze, tightness or cough per week	>4 episodes of day time wheeze, tightness or cough per week	continuous day time wheeze, tightness or cough
Night-time symptoms	≤1 night-time cough and/or wheeze per month	2–4 episodes of night time wheeze or cough per month	>4 episodes of night time wheeze or cough per month	frequent night time awakenings
PEFR	PEFR ≥80% predicted between attacks	PEFR ≥80% predicted between attacks	PEFR 60-80% predicted between attacks	PEFR < 60% predicted
Admissions for exacerbation	no admission to hospital for asthma within last 12 months	-	-	-

AMENDED TO:

Starting asthma treatment in children aged 6-11, adolescent > 12 years of age and in adults

STEP 1	STEP 2	STEP 3
Initial asthma treatment in patients with symptoms less than twice a month, and with no exacerbations within the last 12 months.	Asthma symptoms or need for reliever twice a month or more or any exacerbations within the last 12 months.	Troublesome asthma symptoms most days, or waking up from asthma once a week or more,

Figure 17.1 Guidance for assessing asthma treatment in children and adolescents (adapted from the GINA 2023

General measures: *Editorial amendments*

Editorial amendments were made to the STG as tabulated below:

GENERAL MEASURES

Avoid irritant triggers and relevant allergic triggers
Advise patient to stop smoking, and to avoid smoke exposure from others.
Avoid exposure to known allergens if avoidance measures are feasible and sensitisation has been proven
Educate patient and caregiver on:

- early recognition and management of acute attacks.
- emphasise the diagnosis and explain the nature and natural course of the condition;
- Use a spacer for all children and all adults with step 3 therapy and above
- teach and monitor inhaler technique; and
- reassure parents and patients of the safety and efficacy of continuous regular controller therapy.

Medicine treatment – technique for spacer devices: *Guidance amended and transferred to new Appendix II*

Medicine treatment – technique for dry powder inhalers (DPIs): *Guidance added to new Appendix II*

Guidance on the use of spacer and inhaler devices used for respiratory conditions, have been reviewed and transferred to a separate Appendix in the PHC EML – see Appendix II: Devices for Respiratory Conditions. Refer to the end of this report or the NHI webpage for further details.

[6] Step-wise assessment: Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Available from: www.ginasthma.org

Medicine treatment – budesonide:- *Added for STEP 1*

Medicine treatment – beclomethasone:- *Added for STEP 1*

Guidance on the management of chronic asthma has been aligned to the AH Respiratory chapter which was amended in the 2019 review cycle[7]. For the management of STEP 1 chronic asthma (previously described as mild intermittent asthma), inhaled corticosteroids (ICS) has been added in addition to short-acting beta agonist rescue therapy, as use of beta$_2$ agonists alone is associated with significant adverse outcomes. Budesonide has been added as the first line ICS as it is more cost effective per dose than beclomethasone. Beclomethasone is included for patients receiving concomitant treatment with protease inhibitors.

Medicine treatment – budesonide:- *Not added for STEP 2*

For STEP 2, external comment was received to include budesonide on the EML as an alternative to beclomethasone in children under 6 years of age, specifically for children requiring combination nasal beclomethasone due to the potential of negative growth effects as reported in the Cochrane review by Axelsson I et al[8]. The Committee did not support the inclusion of budesonide as an alternative to beclomethasone for children less than 6 years, as the certainty of evidence was rated by Axelsson I et al. to be of low certainty due to the small study sizes and number of trials, as well as the low quality of evidence of some the included trials. The authors also noted concerns of possible influence of industry funding on the reporting of trial results.

Beclomethasone in patients on protease inhibitors: *Guidance clarified*

External comment received to clarify guidance on the use of beclomethasone as the preferred inhaled corticosteroid (ICS) in asthmatic patients who are on concomitant treatment with protease inhibitors. The Committee supported the proposed amendment as tabulated below. This has been amended throughout the text where beclomethasone can appropriately be substituted for budesonide for asthma management at PHC level of care.

In patients on protease inhibitors, beclomethasone is the preferred ICS as there are drug interactions between protease inhibitors and budesonide.

Updates to the STG are as tabulated below:

AMENDED FROM:	**AMENDED TO:**
MILD INTERMITTENT ASTHMA Adults and children SABA, e.g.: Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 6–8 hourly as needed (until symptoms are controlled).	**STEP 1** Adults and children > 6 years *As reliever/rescue therapy:* ▪ Short acting ß$_2$-agonists, e.g.: • Salbutamol, MDI, 200 mcg, as needed. **AND** ▪ ICS, e.g.: • Budesonide, inhalation, 200 mcg whenever salbutamol is taken. **Note:** Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide: • Beclomethasone, inhalation, 200 mcg whenever salbutamol taken.
PERSISTENT ASTHMA Children Inhaled corticosteroids e.g.: Beclomethasone, inhalation, 100 mcg 12 hourly. **AND** Short acting beta2 agonist e.g.: Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 6–8 hourly as needed (until symptoms are controlled) Adults Inhaled corticosteroids e.g.: Beclomethasone, inhalation, 200 mcg 12 hourly.	**STEP 2** Children < 6yrs (wheeze >= 3x a year) Inhaled corticosteroids e.g.: Beclomethasone, inhalation, 100 mcg 12 hourly. **AND** Short acting ß$_2$-agonists agonist e.g.: Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 6–8 hourly as needed (until symptoms are controlled) Adults and children >/= 6yrs *As controller therapy:*

[7] NDoH AH Chp 18 NEMLC Report 2019 Review Cycle

[8] Axelsson I, Naumburg E, Prietsch SO, Zhang L. Inhaled corticosteroids in children with persistent asthma: effects of different drugs and delivery devices on growth. Cochrane Database Syst Rev. 2019 Jun 10;6(6):CD010126. doi: 10.1002/14651858.CD010126.pub2. PMID: 31194879; PMCID: PMC6564081.

AND SABA e.g.: Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 6–8 hourly as needed (until symptoms are controlled). **Note:** Fluticasone and budesonide interacts with protease inhibitors. Refer all patients on protease inhibitors requiring inhaled corticosteroids for further management. Review treatment every 3 months. Adequate control is defined as: ≤ 2 episodes of daytime cough and/or wheeze per week. No night-time cough and/or wheeze. No recent (within the last year) admission to hospital for asthma. PEFR≥ 80% predicted between attacks. **If control is inadequate:** check adherence and inhaler technique, and exclude on-going exposure to allergens. After excluding those causes, refer to a doctor to confirm the diagnosis of asthma, and to exclude TB and heart failure. Once the diagnosis is confirmed, step-up treatment as follows: <u>Children</u> Inhaled corticosteroids, e.g.: Beclomethasone, inhalation, 200 mcg 12 hourly. <u>Adults</u> Inhaled corticosteroids, e.g.: Beclomethasone, inhalation, 400 mcg 12 hourly. **If control is still inadequate in adults, treat with combination of corticosteroid and long-acting beta agonist (LABA)** Stop inhaled corticosteroid (e.g. beclomethasone) and replace with: Inhaled long-acting beta agonist (LABA)/corticosteroid combination, e.g.: • Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated). **Note:** Fluticasone and budesonide interacts with protease inhibitors. Refer all patients on protease inhibitors requiring inhaled corticosteroids for further management.	▪ ICS, low dose, e.g.: • Budesonide, inhalation, 200 mcg 12 hourly. ○ Well and stable after 6 months: can attempt to reduce budesonide dose to 200 mcg daily. ○ Dose adjustments may be required at change of seasons. **Note:** Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide. • Beclomethasone, inhalation, 200 mcg 12 hourly for 6 months; reduced to 200 mcg daily once well and stable. **AND** *As reliever/rescue therapy:* ▪ Short acting ß2-agonists, e.g.: Salbutamol, MDI, 200 mcg, 6 hourly as necessary Review treatment every 3 months. Adequate control is defined as: ≤ 2 episodes of daytime cough and/or wheeze per week. No night-time cough and/or wheeze. No recent (within the last year) admission to hospital for asthma. PEFR≥ 80% predicted between attacks. **If control is inadequate:** check adherence and inhaler technique, and exclude on-going exposure to irritants and allergens. After excluding those causes, refer to a doctor to confirm the diagnosis of asthma, to exclude other diagnoses. Once the diagnosis is confirmed, **step-up** treatment **to STEP 3** as below: **STEP 3** <u>Children</u> Inhaled corticosteroids, e.g.: Beclomethasone, inhalation, 200 mcg 12 hourly. <u>Adults</u> Inhaled corticosteroids, e.g.: Budesonide, inhalation, 400 mcg 12 hourly **Note:** Beclomethasone is the preferred ICS in patients on protease inhibitors due to drug interactions between protease inhibitors and budesonide: Beclomethasone, inhalation, 400 mcg 12 hourly. **If control is still inadequate in adults, re-evaluate inhaler technique (refer to Appendix II: Devices for Respiratory Conditions and consider treatment with combination of corticosteroid and long-acting beta agonist (LABA):** Stop corticosteroid inhaler (e.g. budesonide) and replace controller therapy with: Inhaled long-acting beta agonist (LABA)/corticosteroid combination, e.g.: • Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated). **AND** *As reliever/rescue therapy:* ▪ Short acting beta2-agonists, e.g.: Salbutamol, MDI, 200 mcg, 6 hourly as necessary

<u>Medicine treatment – formoterol/ICS combination:</u> *Not added*

An evidence review was undertaken on the use of formoterol/ICS taken as needed compared with daily low-dose ICS and a short-acting beta$_2$ agonist (SABA) reliever in adults and adolescents with mild persistent asthma. The Committee supported a conditional recommendation for the use Formoterol/inhaled corticosteroid (ICS) combination taken as needed, however as a decision to implement would require full costing data demonstrating affordability and a comprehensive management strategy (i.e. SABA versus ICS/LABA to relieve symptoms) for all degrees of asthma severity, the formoterol/ICS combination has not been added to the EML. The NEMLC has established an Asthma Sub-committee which has been tasked with completing evidence reviews in other degrees of asthma severity, which in turn will inform the future strategy for the management of asthma. Evidence reviews will be published once the work of the Asthma Sub-Committee has been finalized.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: The majority of the Committee supported a conditional recommendation to use Formoterol/inhaled corticosteroid (ICS) combination taken as needed in adolescents and adults, aged 12 years and older with mild persistent asthma (GINA Step 2) in preference to daily low-dose ICS and a short-acting beta$_2$ agonist (SABA) reliever. However, a number of uncertainties remain as the evidence reviews for populations in other asthma severity categories (i.e. moderate and severe asthma) are yet to be reviewed.

To note:

A decision to implement would require full costing data demonstrating affordability and a comprehensive management strategy (i.e. SABA versus ICS/LABA to relieve symptoms) for all degrees of asthma severity.

There was dissent among some members of the Committee with putting a recommendation forward at this time in view of the uncertainties that remain.

Rationale: Slight reduction in asthma exacerbations resulting in ED visits, little to no difference in harms and possibly cheaper.

Level of Evidence: Moderate certainty evidence

Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECOMMENDATION 14 March 2024:

- The Committee acknowledged the value of the preliminary work presented which has demonstrated some value in an alternative strategy for the management of asthma.
- The Committee supported that work be continued on the 2 remaining PICOs, however, acknowledging that the Term of Office of the PHC/Adult Hospital ERC is near complete. Final recommendations on the asthma management strategy will only be made once this work is finalised.
- No amendments to be made to the STG on asthma for the PHC and Adult Hospital Level Respiratory chapters which are due to be circulated for external comment. A note to be included with the respective chapters and NEMLC reports that the STGs on the management of asthma are currently under review.

Referral for rehabilitation: *Not added*

The request from RuRehab to refer patients for rehabilitation (as per list detailed below), was not supported by the Committee as they were either deemed as inappropriate for PHC level of care, or concerns with equity of care were noted, particularly in rural settings where rehabilitation services were not readily accessible:

- *Patients with unexplained (idiopathic/refractory) chronic cough to rehabilitation to reduce cough symptoms and improve wellbeing*
- *Asthma patients with hyperventilation symptoms should be referred to rehabilitation for cardiorespiratory assessment and management.*
- *Refer patients with poor exercise capacity to rehabilitation to improve exercise tolerance and physical function.*
- *Screen asthma patients for mental health and refer patients with symptoms of anxiety or depression associated with chronic disease for cognitive rehabilitation to improve mental health and wellbeing.*

17.1.4 ACUTE BRONCHIOLITIS IN CHILDREN

Description: *Editorial amendment*
The following editorial amendment was made in response to a suggestion from an external commentator as an aid to diagnosis:

Child presents with:

- rapid breathing
- chest indrawing
- decreased breath sounds
- an audible wheeze or crackles

Referral for rehabilitation: *Not added*
The request from RuRehab to refer *"children with acute bronchiolitis to physiotherapy for slow passive expiratory chest physiotherapy to relieve immediate symptoms,"* was not supported by the Committee due to equity concerns. Furthermore, the GRADE recommendation of the supporting evidence provided with this request was rated as low certainty evidence.

17.1.5 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Medicine treatment – acute lower airways obstruction in patients with severe penicillin allergy – doxycycline: *Deleted*
Medicine treatment – acute lower airways obstruction in patients with severe penicillin allergy – azithromycin: *Added*
Guidance on the use of antibiotic therapy for acute exacerbations of COPD has been amended to align with the GOLD guidelines 2023,[9] and in alignment with the AH EML Section 16.4 Chronic Obstructive Pulmonary disease (COPD).

AMENDED FROM:
Severe penicillin allergy:
Z88.0

- Doxycycline, oral, 100 mg 12 hourly for 5 days.

AMENDED TO:
Severe penicillin allergy:
Z88.0

- Azithromycin, oral, 500 mg daily for 3 days.

Treatment for patients not controlled on LABA alone or frequent exacerbations (>/= 2 per year) - Eosinophil monitoring *Added*
Evidence from both post-hoc analyses and pre-specified analyses of RCT data have shown that blood eosinophil counts predict the magnitude of the effect of inhaled corticosteroids (ICS) in COPD. ICS-containing regimens appear to have little or no effect at a blood eosinophil count <0.1 $x10^9$ cells/L. In addition, observational data suggests that lower blood eosinophil counts are associated with increased risk of bacterial pneumonia, a known-side effect of ICS therapies. Therefore patients with COPD and a blood eosinophil count <0.1 $x10^9$ cells/L appear to have little or no benefit from ICS and simultaneously possibly a higher risk of harm. Since 2019, the GOLD guidelines have recommended that a blood eosinophil level be performed to select which COPD patients are likely to benefit from ICS.

Medicine treatment – LAMAs: *Not added*
The use of long-acting muscarinic antagonists (LAMAs) was not added to the Adult Hospital EML – an evidence review by the Tertiary and Quaternary (T&Q) Committee has been deferred to the next review cycle.

Severe penicillin allergy: *Not amended*
External comment was received to consider referring to 'penicillin allergy' rather than 'severe penicillin allergy' across both the PHC and AH Respiratory chapters. The Committee noted that the reference to '*severe* penicillin allergy' was deliberate mechanism to manage the high rate of false positive reporting of penicillin allergy and to limit the use of

[9] Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. Eur Respir J. 2023 Apr 1;61(4):2300239. doi: 10.1183/13993003.00239-2023. pg 142-143

second and third line antibiotics under these circumstances. There is also the common misconception among patients to report well recognised side effects (e.g. diarrhoea with co-amoxiclav) as penicillin allergy. Limiting guidance to patients with severe penicillin allergy e.g. severe anaphylaxis, is aligned to improved antimicrobial stewardship.

Acute infective exacerbations of chronic bronchitis: *Editorial amendments*

Guidance included on the monitoring of eosinophils for patients not controlled on LABA monotherapy or for patients with frequent exacerbations as detailed below. Editorial amendments also made to remove repetitive text for the management of acute infective exacerbation of chronic bronchitis as tabulated below:

MEDICINE TREATMENT

See Appendix II: Devices for Respiratory Conditions for guidance on inhaler, spacer and nebuliser device techniques.

Acute lower airways obstruction:
Treat as for acute asthma but in addition, add antibiotics if patients have increased sputum purulence AND either increased sputum volume or increased dyspnoea.

Amoxicillin, oral, 500 mg 8 hourly for 5 days.

Severe penicillin allergy:
Z88.0
Doxycycline, oral, 100 mg 12 hourly for 5 days.

Chronic management:
In a stable patient, check PEFR.
Then give a test dose of salbutamol, i.e. 2 puffs.
Repeat PEFR 15 minutes later.
If there is ≥ 20% improvement in peak flow, diagnose asthma and manage patient accordingly. See Section 17.1.2: Chronic asthma.
Perform spirometry if available. Diagnose COPD if FEV1/FVC < 70%.
SABA e.g.:
Salbutamol, inhalation, 100–200 mcg (1–2 puffs), 3–4 times daily via a spacer as needed for relief of wheeze.

If not controlled on SABA alone and diagnosis was confirmed by spirometry (with < 2 exacerbations per year):
Long-acting β2-agonist (LABA), e.g.:
Formoterol, inhaled 12 mcg (1 puff) 12 hourly (Doctor initiated).

If not controlled on SABA alone and spirometry not available:
Inhaled LABA/corticosteroid combination e.g.:
Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated).
If not controlled on a LABA alone or frequent exacerbations (≥ 2 per year):
Measure blood eosinophil levels
If eosinophils >0.1 x10^9 cells/L, replace with:
Inhaled LABA/corticosteroid combination e.g.:
Salmeterol/fluticasone, inhalation, 50/250 mcg (1 puff) 12 hourly (Doctor initiated).

~~**Acute infective exacerbation of chronic bronchitis:**~~
~~Amoxicillin, oral, 500 mg 8 hourly for 5 days.~~

~~**Severe penicillin allergy:**~~
~~Z88.0~~
~~Doxycycline, oral, 100 mg 12 hourly for 5 days.~~

Note:

- Fluticasone and budesonide interact with protease inhibitors. Refer all patients on protease inhibitors requiring inhaled corticosteroids for further management.
- Oral corticosteroids may be required for acute exacerbations, but these have severe long-term complications and should only be used long-term ~~benefit has been proven by lung function testing.~~if advised by a specialist.
- Do not measure blood eosinophil levels while taking oral corticosteroids, as this may temporarily lower the eosinophil count.

Referral for rehabilitation: *Not added*

The request from RuRehab to refer patients for rehabilitation (as per list detailed below), was not supported by the Committee. While the Committee acknowledged that pulmonary rehabilaition may be reasonable for patients with COPD, the recommendations as listed, were either deemed as inappropriate for PHC level of care, or concerns with resources and equity of care were noted.

- Patients with COPD should be referred to rehabilitation following exacerbations for cardiopulmonary assessment and management as part of a multidisciplinary approach.

- Refer patients with pulmonary hypertension to rehabilitation to improve physical function and performance
- Refer patients with cystic fibrosis to rehabilitation in addition to standard care to reduce pulmonary exacerbations and improve cardiorespiratory function.

17.2 STRIDOR (UPPER AIRWAY OBSTRUCTION)

17.2.1 CROUP (LARYNGOTRACHEO BRONCHITIS) IN CHILDREN

Description – adrenaline: *Editorial amendment*

The text has been amended to refer to adrenaline 1:1000 which is more readily applied and recognised in local clinical practice, rather than epinephrine 1:1000 which is the international nonproprietary name (rINN).

General measures: *Editorial amendment*

The statement as tabulated below was amended:

GENERAL MEASURES

- Keep child comfortable.
- Continue oral fluids provided that patient is able to swallow.
- Encourage parent or caregiver to remain with the child.

Medicine treatment – adrenaline: *Dose amended*

The dose of adrenaline 1:1000 has been amended to allow for a minimum volume of 4mL to be added to the nebuliser's reservoir to accommodate for the 'dead volume' (residual drug solution that cannot be nebulised which results in wastage of the drug). The STG has been amended as follows:

AMENDED FROM:

- Adrenaline (epinephrine), 1:1000, nebulised, immediately using a nebuliser.
  If there is no improvement, repeat every 15 minutes, until the child is transferred.
  Dilute 1 mL of 1:1000 adrenaline with 1 mL sodium chloride 0.9%.

AMENDED TO:

- Adrenaline (epinephrine), 1:1000, nebulised, immediately using a nebuliser.
  - If there is no improvement, repeat every 15 minutes, until the child is transferred.
  - Dilute 2 mL of 1:1000 adrenaline with 2 mL sodium chloride 0.9%.

Caution – ceftriaxone: *Editorial amendment*

The interaction between calcium-containing IV fluids and ceftriaxone when administered via the same IV line is not relevant to the management of croup at PHC level of care. The EML guidance for managing croup in children includes a stat dose of ceftriaxone IM before the child is transferred. Amendments to the STG are tabulated below:

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.

~~Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:~~

- ~~If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.~~
- ~~If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.~~
- ~~Preferably administer IV fluids without calcium contents.~~

Always include the dose and route of administration of ceftriaxone in the referral letter.

Management during transfer: *Amended*

The STG has been amended to include contacting an ambulance or the nearest doctor for *both* grade 2 and 3 croup from the previous recommendation to contact an ambulance or nearest doctor for grade 3 group. Amendments are as tabulated below:

AMENDED FROM:

Management during transfer:
Give the child oxygen.
Continue nebulisations with epinephrine (adrenaline).
If grade 3, contact ambulance or nearest doctor.
If grade 4, intubate and transfer.

AMENDED TO:

Management during transfer:
- Give the child oxygen to keep oxygen saturation levels at 93-95%.
- Continue nebulisations with adrenaline.
- If grade 2-3, contact ambulance or nearest doctor.
- If grade 4, intubate and transfer.

Referral: *Amended*

Amendments were made to the referral criteria as tabulated below:

REFERRAL

Urgent

Children with:
- Grade 2-4 stridor
- chest indrawing
- rapid breathing
- altered consciousness
- inability to drink or feed

For confirmation of diagnosis.
Suspected foreign body.
Suspected epiglottitis.

Non Urgent

All children grade1 ~~or 2~~ stridor.

17.3 RESPIRATORY INFECTIONS

Referral for rehabilitation: *Not added*

The request from RuRehab to refer patients *'with bronchiectasis for pulmonary rehabilitation to manage fatigue, improve lung clearance and reduce exacerbations,'* was not supported by the Committee as the management of bronchiectasis is not covered in the PHC EML.

17.3.1 INFLUENZA

Influenza STG: *Retained*

External comment was received to move the influenza STG Section 17.3.1 to Section 17.1.3 Acute Bronchiolitis in children, as a definitive diagnosis of influenza is unlikely to be made at the local PHC level of care. This suggestion was not accepted by the Committee as the management of influenza is relevant to both adults and children while bronchiolitis is limited to just paediatrics.

Medicine treatment – paracetamol dose: *Amended*

The dose of paracetamol was amended to align with guidance in the PHC Chp 20 Pain chapter.

17.3.4.1 PNEUMONIA IN CHILDREN

Description: *Editorial amendment*

Editorial amendments were made to the description as detailed below:

AMENDED FROM:

DESCRIPTION
Pneumonia should be distinguished from viral upper respiratory infections. The most valuable sign in pneumonia is the presence of rapid breathing.

AMENDED TO:

DESCRIPTION
Pneumonia should be distinguished from viral upper respiratory infections. With viral URTIs' the respiratory rate will be normal. A raised respiratory rate indicates an alternate diagnosis such as bronchiolitis or pneumonia.

Caution – ceftriaxone: *Editorial amendment*
The caution against the co-administration of IV ceftriaxone and calcium-containing IV fluids has been removed similar to Section 17.2.1 Croup above, as not relevant to s stat dose of IM ceftriaxone.

Referral for rehabilitation: *Not added*
The request from RuRehab to *refer 'adults and children with pneumonia to rehabilitation improve mobility and treatment outcomes,'* was not supported by the Committee this recommendation was not deemed appropriate for PHC level of care.

17.3.4.2.3 SEVERE PENUMONIA

Caution – ceftriaxone: *Guidance clarified*
The caution to avoid co-administration of ceftriaxone IV and calcium-containing IV fluid via the same IV line has been clarified as below:

CAUTION
Do not administer calcium containing intravenous fluids, e.g.
Ringer-Lactate, concurrently with IV ceftriaxone.

17.4 PULMONARY TB

Description: *Editorial amendments*
Editorial amendments as tabulated below:

AMENDED FROM:

DESCRIPTION
Tuberculosis is an infection caused by Mycobacterium tuberculosis. It is exacerbated and complicated by HIV, AIDS, and multi drug-resistant mycobacteria.

AMENDED TO:

DESCRIPTION
Tuberculosis is an infection caused by Mycobacterium tuberculosis. The risk of developing TB disease is higher among people living with HIV.

17.4.1 PULMONARY TUBERCULOSIS (TB) IN ADULTS

Diagnosis - testing:-TB nucleic acid amplification tests (TB-NAAT): *Added*
Diagnosis – testing - Xpert MTB/RIF*: Deleted*

Diagnostic tests for TB have been aligned throughout the chapter to include TB nucleic acid amplification tests (TB-NAAT) in line with the NDoH National Rifampicin-resistant TB guidelines[10] and which are now readily available at PHC level of care. Guidance on TB-LAM testing has been aligned to the NDoH LAM guidelines 2021[11].

STG amendments are as tabulated below:

AMENDED FROM:	**AMENDED TO:**
DIAGNOSIS Pulmonary TB is diagnosed on Xpert MTB/RIF testing, sputum smear or culture. Send 1 sputum specimen for Xpert MTB/RIF. - If Xpert MTB/RIF is positive: treat for TB and send a sputum specimen for smear microscopy. (The smear is used for reporting, not for diagnosis). - If Xpert MTB/RIF is positive and susceptible to RIF: treat for TB. - If Xpert MTB/RIF is positive and resistant to RIF: commence MDR treatment and send sputum for drug susceptibility testing to confirm MDR TB. - If Xpert MTB/RIF is negative and patient is HIV-infected: send sputum for culture and chest X-ray, if available. - If Xpert MTB/RIF is negative and patient is HIV negative: treat with antibiotics and consider further investigation only if symptoms persist.	**DIAGNOSIS** Pulmonary TB is diagnosed on sputum by TB nucleic acid amplification tests (TB-NAAT), such as Xpert® MTB/RIF Ultra, sputum smear or culture. Send 1 sputum specimen for TB-NAAT. - If TB-NAAT is unsuccessful: collect another sample and repeat TB-NAAT - If TB-NAAT is trace (only applies to Xpert® MTB/RIFUltra): If the clinical presentation and chest X-ray are suggestive of TB treat for drug-sensitive TB (DS-TB), and collect sputum specimen for TB culture and drug sensitivity testing (DST). If the patient is asymptomatic, with no abnormalities on chest X-ray, continue routine care with close follow-up for features of TB. - If TB-NAAT is positive and susceptible to rifampicin: treat for DS-TB and send a sputum specimen for baseline smear microscopy (the smear is used for reporting, not for diagnosis). - If TB-NAAT is positive, susceptible to rifampicin and resistant to isoniazid: treat for isoniazid monoresistant TB. Collect sputum sample for reflex testing of fluoroquinolone susceptibility. - If TB-NAAT is positive and rifampicin unsuccessful: start DS-TB treatment and collect another sputum sample for smear, culture and drug sensitivity testing (DST). Follow-up culture and DST results - If TB-NAAT is positive and resistant to rifampicin (with or without isoniazid resistance): treat for rifampicin resistant TB and send sputum sample for further reflex testing and DST. - If TB-NAAT is negative and patient is living with HIV: send sputum for TB culture and perform chest X-ray. If CD4 < 200 within the last 6 months and they have signs and symptoms of TB (pulmonary or extrapulmonary), perform urine LAM (U-LAM) test. - If TB-NAAT is negative and patient is HIV negative: treat with antibiotics and consider further investigation only if symptoms persist. **Note:** Patients with a history of TB can remain TB-NAAT positive for several years after completion of appropriate anti-TB treatment. To diagnose a new episode of TB in previously treated patients, send sputum for smear microscopy and culture instead.

Medicine treatment – important medicine interactions: *Aligned*

Guidance on managing medicine interactions between TB medicines and contraceptives was amended to align with guidance in the PHC Chp 7: Family planning chapter Section 7.2 Contraception, hormonal. Amendments are as tabulated below:

AMENDED FROM:

10 NDoH: Clinical Management of Rifampicin-resistant tuberculosis – updated clinical reference guide. September 2023

[11] NDoH Guideline: Guidance on the use of the Lateral flow urine lipoarabinomannan assay for the diagnosis of active tuberculosis in people living with HIV. Update February 2021.

Important medicine interactions
Rifampicin may reduce the efficacy of low dose combined oral contraceptives, resulting in possible unplanned pregnancies (See Chapter 7: Family planning).
Alter the oral contraceptive to a high dose preparation for the duration of TB treatment or use an injectable contraception or IUD.
Use additional contraception in patients using a progestin-only subdermal implant for the duration of TB therapy. See Section: 11.1 Antiretroviral therapy, adults.

AMENDED TO:

Important medicine interactions
Rifampicin may reduce the efficacy of low dose combined oral contraceptives and progestin-only implants, resulting in possible unplanned pregnancies (See PHC Chapter 7: Family planning).

- Use of alternative contraceptive methods, such as IUD or DMPA, should be advised.
  OR
- Women choosing to use a progestin-only subdermal implant should be advised to use additional contraception for the duration of TB therapy. See Section: 11.1 Antiretroviral therapy, adults.

Medicine treatment – renal impairment- Ethambutol*: Deleted*
Medicine treatment – renal impairment: RHZE FDC*: Added*
Guidance on dose adjustments in renal impairment has been amended as tabulated below. The fixed dose combination RHZE (rifampicin 150mg/isoniazid 75mg/pyrazinamide 400mg/ethambutol 275mg) tablet will be more convenient for patients due to the lower pill burden, and will be more readily be available at PHC level of care i.e. individual doses of ethambutol and pyrazinamide may not be readily available at PHC level of care.

AMENDED FROM:	**AMENDED TO:**
Dose adjustment Ethambutol should be given on alternative days in patients with impaired renal function (eGFR < 10 mL/min).	**Dose adjustment in renal impairment (eGFR < 30 mL/min)** • Ethambutol 15 – 25mg/kg three times weekly • Pyrazinamide 20 – 30 mg/kg three times weekly • Rifampicin and isoniazid do not require dose adjustment. Intensive phase of treatment: • Alternate day dosing of RH and RHZE o Administer standard weight-based dosing of RH on Tuesday, Thursday, Saturday, Sunday **AND** o Administer standard weight-based dosing with RHZE on Monday, Wednesday, Friday Continuation phase of treatment: • Rifampicin and isoniazid o Do not require dose adjustment. Continue daily weight-based dosing of RH.

17.4.2.1 TB CHEMOPROPHYLAXIS/ISONIAZID PREVENTATIVE THERAPY (IPT) IN CHILDREN

IPT: eligibility criteria: R*etained and clarified*
The NEMLC recommended that TPT not be used for household contacts beyond the current national policy. Refer to the evidence summary below or alternatively source online from the Knowledge Hub or the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: Based on this review, the PHC/Adult Hospital Level Committee suggests not to use TB preventive therapy for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST). *Rationale:* The absolute reduction in active TB cases with TB preventive therapy to household contacts is small. TB preventive therapy may cause serious adverse reactions such as drug-induced liver injury. There are substantial logistical challenges to implementation, and this may divert resources from other aspects of the TB control programme. In addition, it is unclear whether TPT implementation for all household contacts would be acceptable and there may be substantial barriers to acceptability for patients and healthcare providers. The cost of offering TPT to household contacts of all ages will be much higher than current costs incurred due to a larger eligible patient population (more than eight-fold increase). There are concerns regarding implementation and uncertainties on the overall impact of scaling up TPT to all household contacts on the health system. **Level of Evidence: Moderate certainty clinical evidence, low certainty costing information** **Review indicators:** New high-quality evidence of a clinical and community-wide relevant benefit. Reduction in cost of short course TPT regimens					
NEMLC RECOMMENDATION (23 JUNE 2022): The NEMLC accepted the recommendation proposed by the PHC/Adult Hospital Level Committee. NEMLC suggested that TB preventive therapy not be used for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST). Some members indicated that while they did not question the quality of the review, they did not support the recommendation against the use of TPT for all household contacts, and preferred the following recommendation, "*We suggest using either the option or the alternative*".					
Monitoring and evaluation considerations:					
Research priorities: Local AST resistance evaluations for various TB preventive therapies; Impact of TB responses to measure the effect for each action					

All children younger than 5 years or who are HIV infected and exposed to a pulmonary TB contact would be eligible for IPT. The STG has been clarified as tabulated below:

Consider TB chemoprophylaxis/isoniazid preventive therapy (IPT) in all children younger than 5 years, or who are HIV-infected, and exposed to a pulmonary TB contact.

Patients initiating DTG-containing ART: *Isoniazid daily for 12 months added*
Virally suppressed patients on DTG-containing ART: *Isoniazid plus rifapentine added*
The EML has been updated as follows:

Note: For adults and adolescents initiating a DTG-containing ART regimen, isoniazid daily for 12 months is the preferred regimen. For patients who are already virally suppressed on a DTG-based regimen, a weekly combination of isoniazid (900mg if weight >30 kg) plus rifapentine (900mg if weight >30 kg) for three months may be preferred. Do not use rifapentine-containing TPT in patients on protease inhibitor-based ART, or in women on hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

17.4.2.2 TB CONTROL PROGRAMME: MEDICINE REGIMENS IN CHILDREN

Weight threshold: *Added*
In addition to the age threshold of either less than or greater than 8 years of age, a weight threshold of less than or greater than 25kg respectively, has been added as a guide for the treatment of uncomplicated pulmonary TB including the use of pyridoxine. Weight banded dosing tables have been amended to include children weighing 25kg and upward in alignment with the Paediatric EML.

Uncomplicated pulmonary TB in children – 4 month TB regimen: *Not added*

External comment received to include a 3RH TB treatment regimen for children with uncomplicated TB, was not supported by the Committee as such a change in regimen would require an evidence review to support the motivation. The Committee recommended that this request be considered for prioritsation during the next review cycle.

17.4.4 DRUG-RESISTANT TUBERCULOSIS (DR TB)

Description: *Amended*

Descriptions for the different categories of drug-resistant TB have been added to the STG in line with WHO approved definitions. The amendments to the STG as tabulated below:

AMENDED FROM:

MDR TB guidelines are updated regularly. Consult the most recent National MDR TB Programme Guidelines.

DESCRIPTION

Isoniazid mono-resistant TB is diagnosed when there is resistance to isoniazid only.
MDR TB is diagnosed when there is resistance to rifampicin **and** isoniazid.
XDR TB is diagnosed when there is resistance to rifampicin and isoniazid **plus** resistance to fluoroquinolones and an injectable medicine e.g. kanamycin.

AMENDED TO:

Drug-resistant TB (DR-TB) guidelines are updated regularly. Consult the most recent National DR TB Programme Guidelines.

DESCRIPTION

Isoniazid monoresistant TB is TB disease caused by *M.tuberculosis* that is resistant to isoniazid, but susceptible to rifampicin.

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 a strain of *M. tuberculosis* that is resistant to rifampicin and at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Extensively drug-resistant TB (XDR TB) is TB disease caused by a strain of *M. tuberculosis* that is resistant to rifampicin AND at least one fluoroquinolone (levofloxacin or moxifloxacin) AND either bedaquiline or linezolid.

Fluoroquinolones for MDR-TB chemoprophylaxis in household contacts: *Not added*

The recommendation from an evidence review undertaken to assess the efficacy and safety of fluoroquinolones as prophylaxis for household contacts exposed to an index case of MDR-TB did not support inclusion on the EML. For a copy of the complete review, refer to the report below or alternatively source online from the Knowledge Hub or the NHI webpage.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: Based on this evidence review, the PHC/Adult Hospital Level Committee suggests not to use fluoroquinolones as prophylaxis for high risk contacts of cases of active MDR TB (conditional recommendation). *Rationale:* Very low quality evidence based on small observational studies with substantial methodological problems. In addition the need to establish latent TB status by tuberculin skin testing was felt not to be feasible; and side-effect profile of longterm fluoroquinolone use and its possible impact on the development of drug resistance were concerns **Level of Evidence:** Low certainty evidence **Review indicator:** Randomised controlled trial evidence showing benefit.					
NEMLC RECOMMENDATION (9 DECEMBER 2021): The NEMLC accepted the review and the proposed recommendation made by the PHC-AH ERC. The Committee added its concerns regarding the side-effect profile of longterm fluoroquinolone use and the possible inpact on the development of drug resistance.					
Monitoring and evaluation considerations					
Research priorities					

17.4.4.1 ISONIAZID MONO-RESISTANT TUBERUCLOSIS IN ADULTS

Medicine treatment – RHZE *Added*

STG guidance has been amended to include treatment regimens for patients with isoniazid mono-resistant TB as well patients with a contraindication to isoniazid. Updates to the STG are as tabulated below:

AMENDED FROM:

MEDICINE TREATMENT

Confirmed INH mono-resistant TB:
Rifampicin, oral, 10 mg/kg daily.
AND
Ethambutol, oral, 15 mg/kg daily.
AND
Pyrazinamide, oral, 25 mg/kg daily.
AND
Levofloxacin, oral, daily.
30–50 kg: 750 mg
>50 kg: 1000 mg

Where single medicines are not available or the pill burden is too high a FDC of RHZE dosed as per weight may be used, and levofloxacin added to this.

Treatment should be given for at least 6 months.

AMENDED TO:

MEDICINE TREATMENT

Confirmed isoniazid mono-resistant TB:
- RHZE at standard dosage

AND
- Levofloxacin, oral, daily
  - 30 – 45kg: 750 mg
  - ≥ 46kg: 1000 mg

Confirmed isoniazid monoresistant 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.
30–45 kg: 750 mg
>46 kg: 1000 mg
Treatment should be given for at least 6 months.

REFERRAL
All drug resistant TB patients to medical officer at primary care level for initiation of therapy.

17.4.4.2 RIFAMPICIN-RESISTANT TUBERUCLOSIS (RR TB) IN ADULTS

Medicine treatment - BPaL 6 month regimen: *Added*

An adolopment of the WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment 2022[12] was undertaken to assess whether a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen in adults with RR-TB. The NEMLC suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Levofloxacin to be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen. Refer to the enclosed review document for further details. This recommendation has been incorporated in the updated national program guideline on the clinical management of rifampicin-resistant TB[13].

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE 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: The PHC/Adult hospital ERC suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) **Although WHO recommend moxifloxacin for inclusion in their updated regimen (BPaLM), the PHC/Adult hospital level committee suggest that levofloxacin to be used as fluoroquinolone of choice.** ***Rationale:*** The recommended regimen is shorter in duration, less complex and may be cost-saving, particularly for those patients requiring treatment with current South African long regimens. Additionally, the recommended regimen was judged to probably be feasible and acceptable and to improve equity. However, the committee noted the very low quality of evidence on which WHO recommendations are based. In view of the paucity of evidence, the committee felt that the implementation of operational research and enhanced pharmacovigilance to detect safety signals is essential. **Level of Evidence:** Very low quality evidence **Review indicator:** New high quality evidence					
NEMLC RECOMMENDATION (30 March 2023): **The committee supports the ERC's adapted recommendation as follows:** We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Levofloxacin to be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.					
Monitoring and evaluation considerations Operational research and enhanced pharmacovigilance essential.					
Research priorities Shortened regimens for paediatric and pregnant populations					

[12] 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.

[13] NDoH: Clinical Management of Rifampicin-resistant tuberculosis – updated clinical reference guide. September 2023

STG guidance has been amended as tabulated below. Reference is made to the national drug resistant TB programme guidelines[14] where appropriate. Patients may now be managed at the primary healthcare level of care, with treatment being initiated by a medical officer.

AMENDED FROM:

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR TB), IN ADULTS

A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Never treat for MDR TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results. All cases should be discussed with a designated specialist centre and MDR TB medicines accessed from the designated centres.

GENERAL MEASURES

Counsel and educate patients about the disease and its treatment, including treatment duration.
Screen all close contacts for signs and symptoms of MDR TB and by sputum sampling to detect early disease.
Infection control and cough etiquette is important to limit spread.

REFERRAL

All MDR patients.
All XDR patients.

AMENDED TO:

RIFAMPICIN-RESISTANT TUBERCULOSIS (RR TB), IN ADULTS

A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Never treat for drug resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.

GENERAL MEASURES

Counsel and educate patients about the disease and its treatment, including treatment duration.
Screen all close contacts for signs and symptoms of drug-resistant TB and by sputum sampling to detect early disease.
Infection control and cough etiquette is important to limit spread.

MEDICINE TREATMENT

Drug resistant TB prophylaxis

The effectiveness of preventive therapy in adults exposed to drug resistant TB bacteria is not currently known. Consult a specialist for management.

RR TB and Pre-XDR TB treatment

Consult the most recent national drug resistant TB programme guidelines.
Treatment for 6–18 months is required.

Management of drug resistant TB should be conducted in dedicated drug resistant TB clinics and hospitals with appropriate infection control measures.

XDR TB treatment

Patients with XDR TB should be discussed with the National Clinical Advisory Committee (NCAC - NCAC@witshealth.co.za) and referred to a TB hospital for an individualised regimen of at least 4 effective medicines, based on susceptibility tests and treatment history. Infection control to prevent airborne transmission is essential to prevent nosocomial transmission.

REFERRAL

All drug resistant TB patients to medical officer at primary care level for initiation of therapy.

17.4.4.3 RIFAMPICIN-RESISTANT (RR) , PRE-XDR AND XDR TUBERUCLOSIS IN CHILDREN

General Measures: *Amended*

The STG has been editorially amended as not all children with drug-resistant TB require hospital admission. All cases, must however be discussed with a specialist drug-resistant TB centre and where treatment can be initiated at primary

[14] NDoH: Clinical Management of Rifampicin-resistant tuberculosis – updated clinical reference guide. September 2023

healthcare level of care, treatment must be initiated by a medical officer. Editorial amendments to the STG are as tabulated below:

AMENDED FROM:

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR TB), IN CHILDREN

A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Never treat for MDR TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results. All cases should be discussed with a designated specialist centre and MDR TB medicines accessed from the designated centres.

GENERAL MEASURES

Suspect DR-TB when any of the features listed below is present:

- A known source case (or contact) with drug resistant TB or high-risk source case, e.g. on TB therapy who was recently released from prison.
- A smear positive case after 2 months of TB treatment who failed (or deteriorated on) 1st line antituberculosis treatment to which they were adherent (treatment failure or relapse within 6 months of treatment).
- Any severely ill child with TB who failed or got worse on TB treatment.
- Patients who defaulted TB treatment (> 2 months).
- Treatment interruptions (< 1 month) or who relapsed while on TB treatment or at the end of treatment.
- With recurrent TB disease after completion of TB treatment (retreatment case).

Manage confirmed DR-TB in a dedicated MDR-TB centre with appropriate infection control measures to prevent nosocomial transmission. Initiate treatment in consultation with a designated expert while awaiting referral to the designated MDR-TB centre. An uninterrupted medicine supply, direct supervision with proper education and counselling is necessary.

REFERRAL

All children

AMENDED TO:

RIFAMPICIN-RESISTANT (RR), PRE-XDR AND XDR TUBERCULOSIS , IN CHILDREN

A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Never treat for drug resistant TB without laboratory confirmation, either by molecular or phenotypic (culture and sensitivity) results.
All cases should be discussed with a designated specialist drug resistant TB centre.

GENERAL MEASURES

Suspect drug-resistant TB when any of the features listed below is present:

- A known source case (or contact) with drug resistant TB or high-risk source case, e.g. on TB therapy who was recently released from prison.
- A patient with confirmed treatment adherence that remains smear positive after 2 months of 1st line TB treatment.
- Any severely ill child with TB who failed to improve, or got worse on TB treatment.
- Patients who defaulted TB treatment (> 2 months).
- History of treatment interruption (< 1 month) or relapse at some point during their TB therapy.
- With recurrent TB disease after completion of TB treatment (re-treatment case).

Management of drug resistant TB should be conducted in dedicated drug resistant TB clinics and hospitals with appropriate infection control measures. Initiate treatment in consultation with a designated expert. An uninterrupted medicine supply, direct supervision with proper education and counselling is necessary.

REFERRAL

All children with suspected drug resistant TB to a medical officer at primary care level for initiation of therapy.

APPENDIX I: ASTHMA MONITORING

New appendix added to the PHC EML. Appendix I detailing guidance on asthma monitoring may be found at the end of this report or alternatively online on the NHI webpage.

APPENDIX II: DEVICES FOR RESPIRATORY CONDITIONS

New appendix added to the PHC EML. Appendix II detailing guidance on device techniques which may be found at the end of this report or alternatively online on the NHI webpage.

PEAK EXPIRATORY FLOW RATES

Suggested reference peak expiratory flow (PEF) values for children:

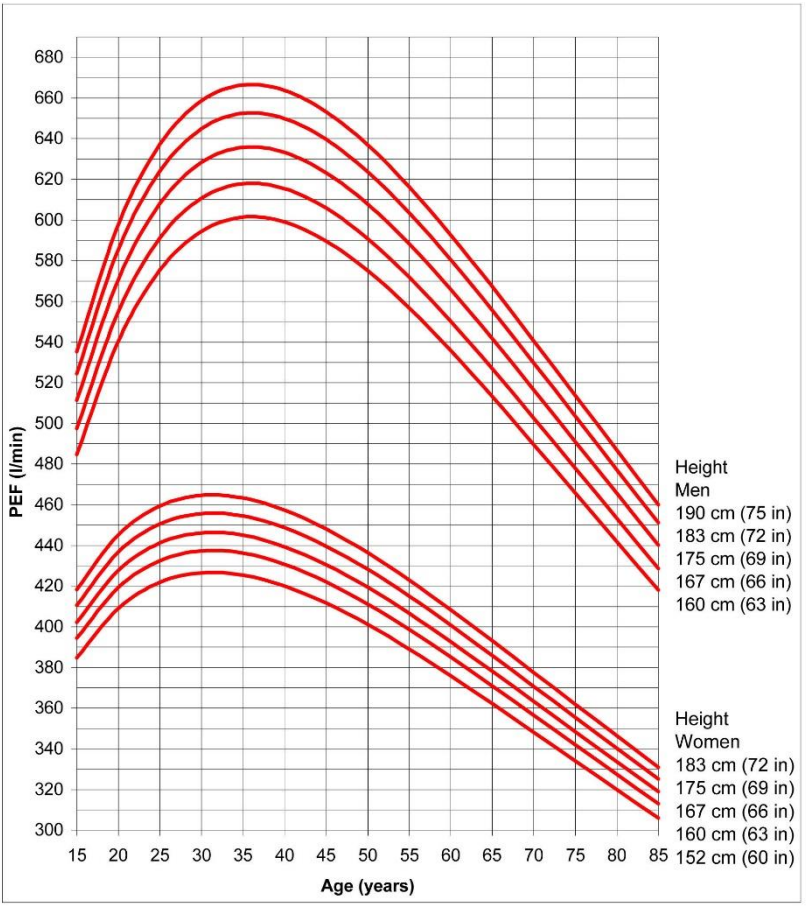
Height (cm)	PEF		PEF	
	Caucasian		African*	
	Male	Female	Male	Female
100	127	142	120	126
101	131	145	124	130
102	135	149	128	133
103	138	152	131	137
104	142	156	135	140
105	146	159	139	144
106	150	163	143	148
107	154	166	147	151
108	158	170	151	155
109	162	174	155	159
110	166	178	159	163
111	170	182	163	167
112	175	185	168	171
113	179	189	172	175
114	184	193	176	179
115	188	197	181	184
116	193	202	186	188
117	197	206	190	192
118	202	210	195	197
119	207	214	200	201
120	212	218	205	206
121	217	223	210	210
122	222	227	215	215
123	227	232	220	220
124	232	236	226	225
125	237	241	231	230
126	243	245	236	235
127	248	250	242	240
128	254	255	248	245
129	259	259	253	250
130	265	264	259	255
131	271	269	265	260
132	276	274	271	266
133	282	279	277	271
134	288	284	283	277
135	294	289	289	282
136	300	294	295	288
137	307	299	302	293
138	313	304	308	299
139	319	309	315	305
140	326	315	322	311
141	332	320	328	317

Height (cm)	PEF		PEF	
	Caucasian		African*	
	Male	Female	Male	Female
142	339	325	335	323
143	345	331	342	329
144	352	336	349	335
145	359	342	356	342
146	366	348	363	348
147	373	353	371	354
148	380	354	378	361
149	387	365	386	368
150	395	371	392	374
151	402	377	401	381
152	410	382	409	388
153	417	388	417	395
154	425	394	425	402
155	433	401	433	409
156	440	409	441	416
157	448	413	442	423
158	456	419	458	430
159	464	426	466	437
160	473	432	475	445
161	481	438	484	452
162	489	445	492	460
163	498	451	501	468
164	506	458	510	475
165	515	465	520	483
166	524	471	529	491
167	533	478	538	499
168	542	485	548	507
169	551	492	557	515
170	560	499	567	523
171	569	506	577	532
172	578	513	587	540
173	588	520	597	548
174	597	527	607	557
175	607	534	617	566
176	617	541	627	574
177	626	549	638	583
178	636	556	648	592
179	646	563	659	601
180	657	571	670	610

**Based on African American data.*

For optimal control, 80% of the predicted peak flow is required.

Peak expiratory flow in normal adult subjects



Adapted with permission from Nunn AJ Gregg I, Br Med J 1989:298;1068-70 and Clement Clarke International.

CALCULATING % PREDICTED PEAK FLOW RATE

- Take the best of 3 of the patient's observed peak flow rates (l/min): e.g. 200, 180, 190 performed – so take 200.
- Find the patient's sex, age and height predicted value from the nomogram. e.g. 440 l/min for a woman of age 25 years and height 167 cm
- Divide patient's observed peak flow rate over their predicted peak flow rate: e.g. 200/440 = 0.45
- Multiply by 100: e.g. 0.45 X 100 = 45%

So, in this example, the patient's observed peak flow rate is 45% of their predicted.

CALCULATING BRONCHODILATOR RESPONSIVENESS USING PEAK FLOW IN ADULTS

Perform peak flow testing and select the best of the 3 values to use as the pre-bronchodilator peak flow.

- Administer salbutamol 400 µg using a metered dose inhaler and spacer without a mask.
- Wait 15 minutes before repeating peak flow
- Repeat peak flow testing to obtain a post-bronchodilator peak flow.
- Subtract the pre-bronchodilator reading from the post-bronchodilator reading.
- Divide the difference by the pre-bronchodilator reading.
- Multiply by 100.

For example, a patient with readings that improve from 300 to 400, has reversibility of 33%. Measurements that improve by >20% strongly suggest a diagnosis of asthma. (See Sections 16.1: Asthma, acute and 16.2: Asthma, chronic persistent).

CALCULATING PEAK FLOW VARIABILITY IN CHILDREN AND ADULTS

- Perform peak flow measurements 4 times per day spread over the course of the day.
- Subtract the lowest reading of each day from the highest reading.
- Calculate the mean/average reading by adding all 4 readings from that day and dividing total by 4.
- Calculate PEF variability:

$$\text{PEF variability} = \frac{(\text{Highest PEF} - \text{Lowest PEF})}{\text{Mean PEF}} \times 100.$$

Determine this value on each day over two weeks, and average the results. Excessive diurnal PEF variability defined as >10% in adults and >12% in children strongly supports a diagnosis of asthma.

ASTHMA CONTROL TEST™

This is a validated measure of clinical asthma control that can be completed by the patient (after initial instruction) at each visit to the clinic prior to consultation. A value of ≥19 suggests adequate asthma control.

Online version of the test is accessible at: https://www.asthmacontroltest.com/

Reference: Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, Murray JJ, Pendergraft TB. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004 Jan;113(1):59-65. http://www.ncbi.nlm.nih.gov/pubmed/14713908

INHALER DEVICES

SPACER DEVICES

» Spacers are vital for an adequate therapeutic effect of inhaled therapy.
» Spacer devices should be used for all inhaled medications in all age groups to improve efficacy of medicine delivery and limit adverse effects.
» Use a spacer that is appropriate for the patient's age.

	Spacer volume	Valve	Delivery	Technique
Infants <3 years	150–250 mL	Required	Face mask	Deep tidal breathing
Children 3 to 6 years	500 mL	Required	Mouthpiece	Deep tidal breathing
Children >7 and adults	500 mL	Optional	Mouthpiece	Single inhalation and breath-hold

» Inhalation spacer devices enable optimal aerosol delivery.
» Children < 3 years of age should have a spacer with a face mask, while older children and adults should use the spacer with a mouth piece directly.
» Demonstrate the relevant inhaler technique more than once to ensure the correct procedure (see below). *LoE:IVb*[1]

Patient and caregiver education on inhaler and spacer techniques:
» If patients are switched between different types of devices (e.g. from MDI to DPI), patients need to be re-educated on inhaler technique.
» If changing from a DPI to MDI, consider if a spacer is required, and the optimal technique for inhalation.
» Doses may not be equivalent between different inhaler devices – ensure that patients are prescribed the correct dose when switching between devices.

METERED DOSE INHALERS (MDIs)

» A mask attachment must be used with the spacer for children < 3 years of age and be removed as soon as the child is able to use the mouthpiece.

A. Inhalation therapy without a spacer in adults: Single breath inhalation technique

1. Remove the cap from the mouthpiece.
2. Shake the inhaler well.
3. While standing or sitting upright, breathe out as much air as possible.
4. Immediately place the mouth piece of the inhaler between the lips and gently close the lips around it.
5. Start breathing in slowly.

6. Immediately press down the canister of the metered dose inhaler once to release one puff while simultaneously breathing in as deeply as possible.
7. Hold breath for 5 to 10 seconds, if possible.
8. Breathe out slowly through the nose and rest for a few breaths (30–60 seconds).
9. Repeat steps 2–8 for each puff prescribed.
10. Rinse mouth after inhalation of corticosteroids.

LoE:IVb[2]

B. Inhalation therapy with a spacer in adults and older children: Single breath inhalation technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the metered dose inhaler into the back of the spacer.
4. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
5. Exhale fully into the spacer.
6. Start inhalation and immediately press down the canister of the metered dose inhaler once to release one puff into the spacer.
7. Breathe in slowly to full inhalation and hold the breath for 5 to 10 seconds.
8. Breathe out through the nose.
9. Repeat steps 2–8 for each puff prescribed, waiting at least 30 seconds between puffs.
10. Rinse mouth after inhalation of corticosteroids.

C. Inhalation therapy with the spacer alone in younger children or in adolescent and adults unable to do single inhalation: Deep tidal breathing technique

1. Remove the caps from the inhaler and the spacer.
2. Shake the inhaler well.
3. Insert the mouthpiece of the spacer into the mouth and close the lips around the mouthpiece.
4. Press down the canister of the metered dose inhaler once to release one puff into the spacer.
5. Breathe slowly and deeply in and out of the spacer continuously for at least 6 breaths
6. If breathing through the nose as well as the mouth, pinch the nose gently while breathing from the spacer.

D. Inhalation therapy with a spacer and mask for infants and children < 3 years:

1. Remove the caps from the inhaler and the spacer.
2. Infants may be preferably placed on the caregiver's lap or alternatively laid on a bed while administering the medication.
3. Shake the inhaler well.
4. Apply the mask to the face, ensuring that the mouth and nose are well covered.

5. With the mask held firmly onto the face, press down the canister of the metered dose inhaler once to release one puff into the spacer.
6. Keep the mask in place for at least six breaths, then remove.
7. Repeat steps 3–6 for each puff prescribed, waiting at least 30 seconds between puffs.

DRY POWDER INHALERS (DPIs)

E. Inhalation therapy with a dry powder inhaler (DPI) for adults and children over 6 years of age:

1. There is no need to shake a DPI.
2. Open, twist or click the device to load the medication dose.
3. Stand or sit up straight and breathe out completely (away from the device, not into the mouthpiece).
4. Immediately place the mouthpiece into the mouth, close lips tightly around it and breathe in quickly and forcefully to full inhalation.
5. Remove the DPI from the mouth, hold breath for 5-10 seconds, then exhale slowly.
6. Optimise positioning and repeat steps 2–5 for each puff prescribed, waiting at least 30 seconds between puffs.
7. Rinse mouth with water after inhalation of corticosteroids.

NEBULISERS

NEBULISERS

The guidance below is tailored to the use of jet nebulisers which are primarily used in the public sector.

1. Ensure the nebuliser cup is filled sufficiently to allow effective nebulisation (approx. 4L minimum volume). Volume must be more than the equipment dead space to be sufficient. The dead space in a nebuliser refers to the volume of the nebulizer chamber and tubing that remains filled with medication after treatment. This volume is not delivered to the patient and can vary depending on the nebulizer design. Typical dead space volumes in jet nebulizers is 2-3 mL.
2. Hold the nebuliser upright.
3. Select a flow rate of oxygen of 6 to 8 L/min for jet nebulisers.
4. Use a mouthpiece rather than a facemask in adults and in any child able to hold a mouthpiece between their lips and breathe via their mouths.
   Better medication delivery: The T-piece allows for more direct delivery of medication to the lungs, reduced medication loss, improved patient comfort, enhanced cooperation, reduced risk of skin irritation and easier observation of the patient's mouth and nose.

5. Place the mouthpiece in the patient's mouth. Advise the patient to keep their lips firmly around the mouthpiece. If using a facemask, place it over the mouth and nose.
6. Ensure patient is calm and relaxed.
7. Advise patient to breathe slowly and deeply through the mouth as far in and as far out as possible until all the medication is used.

The following should be avoided when using nebulisers:

» Rapid or forceful inhalation (including crying)
» Nebulising whilst sleeping
» Using a facemask when a mouthpiece is possible
» A loose-fitting facemask or placing the nebuliser near a child's nose and mouth rather than securing a facemask

LoE:IVb[3]

[1] Spacers: Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.
Berlinski A. Pediatric Aerosol Therapy. Respir Care. 2017 Jun;62(6):662-677. doi: 10.4187/respcare.05298. PMID: 28546371.
Patient education: Inhaler techniques in adults (Beyond the Basics) . https://www.uptodate.com/contents/inhaler-techniques-in-adults-beyond-the-basics/print
[2] Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30
Rubin BK Fink JB. Optimizing aerosol delivery by pressurized metered-dose inhalers. Respir Care 2005; 50 (9): 1191-1200.
Devadason SG. Recent advances in aerosol therapy for children with asthma. J Aerosol Med. 2006 Spring;19(1):61-6. doi: 10.1089/jam.2006.19.61. PMID: 16551216.
Everard ML, Clark AR, Milner AD. Drug delivery from holding chambers with attached facemask. Archives of Disease in Childhood. 1992 May;67(5):580-585. DOI: 10.1136/adc.67.5.580. PMID: 1599292; PMCID: PMC1793709.
Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.
Esposito-Festen JE, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. J Aerosol Med. 2004 Spring;17(1):1-6. doi: 10.1089/089426804322994406. PMID: 15120007.
[3] Optimal aerosol delivery: Levin ME. Optimal aerosol delivery. Current Allergy & Clinical Immunology. 2011; 24(1):27-30

South African National Essential Medicine List
Primary Level Medication Review Process
Component: Respiratory conditions

MEDICINE REVIEW

Question: What is the efficacy and safety of TB preventive therapy for reducing the incidence of TB amongst TB household contacts?

Date: 21 June 2022

Key findings

- Tuberculosis (TB) is a communicable disease and one of the top ten causes of death worldwide. Providing TB preventive therapy (TPT) to those at highest risk of developing active TB disease may decrease TB related morbidity and mortality.
- We conducted a review of clinical studies to assess the efficacy and safety of different TB preventive therapy options for reducing the incidence of TB in household contacts of people diagnosed with drug-susceptible TB.
- We searched for WHO guidelines, systematic reviews and randomized controlled trials related to TB preventive therapy up to 19 May 2021. We included three TB preventive regimens: daily isoniazid (INH) for six or more months, weekly rifapentine plus isoniazid for three months (3HP) and daily rifapentine plus isoniazid for one month (1HP). We looked for comparisons of the regimens compared to placebo/no treatment, and for comparisons between INH and either 3HP or 1HP.
- We included one recent WHO guideline, three systematic reviews of randomised controlled trials and three primary randomised controlled trials.
- Compared to placebo, INH probably reduces active TB by 60%, risk ratio (RR) 0.40 (95% CI 0.31 to 0.52), 11 trials, n = 73375, moderate certainty evidence (rated down for indirectness). The absolute risk of developing active TB within at least two years of follow-up was 1.7% in the placebo arms vs 0.6% in the INH arms overall. The number needed to prevent one case of active TB (NNT) was therefore 91 (95% CI 82 to 109). Assuming that the relative effect of the intervention remains constant, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively.
- There is probably little or no difference between 3HP vs INH, or 1HP vs INH on the outcome incidence of active TB (moderate to low certainty evidence).
- TB drug induced liver injury (DILI) is the most commonly reported adverse effect.
  - *INH vs placebo:* There may be 5 more cases of DILI per 1000 patients treated with INH (95% CI 2-11) compared to placebo (moderate certainty evidence). NNH 221 (95%CI 168 to 323) - one in every 221 treated with INH preventive therapy will develop DILI.
  - *3HP vs INH:* DILI was 84% lower the 3HP group compared to INH group RR 0.163 (95% CI 0.099 to 0.268]), 1 trial, n = 7799, moderate certainty evidence), that is 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP (ranging from 20 fewer to 25 fewer).
- INH resistance is important, however the data regarding this outcome is uncertain, for all comparison groups.
- Overall, INH probably reduces incidence of active TB and 3HP and 1HP may perform similarly for this outcome. DILI is increased when using INH compared to placebo but may be less when 3HP or 1HP is used. Impact on INH resistance needs further research evidence.
- The estimated total health care cost of expanding TPT to household contacts of all ages is very uncertain due to significant uncertainty in budget impact model parameters – especially primary healthcare utilization rates and clinic visit costs. The estimated *pharmaceutical acquisition costs* are less uncertain, with incremental costs (compared to current standard of care) calculated as R18.3 million for INH monotherapy for all ages, R72.9 million for the 3HP regimen (children <2y assumed to receive INH monotherapy), and R111.7 million for the 1HP regimen

(children <13y assumed to receive INH monotherapy). Estimations of total health care costs (per annum) are estimated as R19 million for current standard of care (INH monotherapy for children <5y), R167.6 million for INH monotherapy for all ages, R155.4 million for the 3HP regimen (with children <2y assumed to receive INH monotherapy), and R184.7 million for 1HP regimen (children <13y assumed to receive INH monotherapy). Refer to budget impact analysis report for detailed information.

- Feasibility is an important factor. As noted by in the WHO guideline, capacity of the health care provider to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and to detect latent TB infection (LTBI) by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations. Of concern, TPT coverage in under 5's to date is poor -56% and 51% in 2019 and 2020 respectively.
- Acceptability of introducing TPT for those who will be affected was considered and views may differ. There are several proponents in favour of introducing TPT, and although we did not conduct primary research on this, indirect evidence from patient perspectives from those who have HIV suggest that there may be several barriers to taking TPT in reality including economic hardship of attending clinic when well.
- The committee considered that on balance introducing TPT for all household contacts was not the preferred option. More may be achieved through improved TB treatment coverage, improved provision of TPT to children <5 years, ART coverage, infection prevention and control in healthcare settings, and multisectoral interventions towards socio-economic improvement of high-risk communities.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: Based on this review, the PHC/Adult Hospital Level Committee suggests not to use TB preventive therapy for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST).

Rationale: The absolute reduction in active TB cases with TB preventive therapy to household contacts is small. TB preventive therapy may cause serious adverse reactions such as drug-induced liver injury. There are substantial logistical challenges to implementation, and this may divert resources from other aspects of the TB control programme. In addition, it is unclear whether TPT implementation for all household contacts would be acceptable and there may be substantial barriers to acceptability for patients and healthcare providers. The cost of offering TPT to household contacts of all ages will be much higher than current costs incurred due to a larger eligible patient population (more than eight-fold increase). There are concerns regarding implementation and uncertainties on the overall impact of scaling up TPT to all household contacts on the health system.

Level of Evidence: Moderate certainty clinical evidence, low certainty costing information

Review indicators: New high-quality evidence of a clinical and community-wide relevant benefit. Reduction in cost of short course TPT regimens

NEMLC RECOMMENDATION (23 JUNE 2022):

The NEMLC accepted the recommendation proposed by the PHC/Adult Hospital Level Committee. NEMLC suggested that TB preventive therapy not be used for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST).

Some members indicated that while they did not question the quality of the review, they did not support the recommendation against the use of TPT for all household contacts, and preferred the following recommendation, "*We suggest using either the option or the alternative*".

Monitoring and evaluation considerations:

Research priorities: Local AST resistance evaluations for various TB preventive therapies; Impact of TB responses to measure the effect for each action

EXECUTIVE SUMMARY

Date: 21 June 2022
Medicine (INN): Isoniazid, rifapentine
Medicine (ATC): J04AC01, J04AB05
Indication (ICD10 code): Z29.2
Patient population: Paediatric, adults
Prevalence of condition: 1 044 000 household contacts of people diagnosed with drug-susceptible TB in one year (estimated incidence of TB: n = 360 000)
Level of Care: Primary Healthcare
Prescriber Level: Nurse prescriber
Current standard of care:

- Isoniazid TB prophylaxis to all HIV-infected children, and all uninfected children <5 years, exposed to a close contact with an infectious pulmonary TB case, or confirmed LTBI on TST (Paediatric Hospital STGS and EML, 2017).
- 12H for adult PLHIV starting antiretroviral therapy (Primary Healthcare STGs and EML, 2020).

Efficacy estimates: (preferably NNT) The number needed to prevent one case of active TB with isoniazid (6H/12H) was 91 (Smieja 1999). Most of the trials provided 12H. Based on one trial (Thompson 1982), there is probably little or no difference in the incidence of active TB between 6H and 12H, RR 1.41 (95% CI 0.84 to 2.37). Note that these studies were done pre-ART. There is probably little or no difference between 3HP vs INH, or 1HP vs INH on the outcome incidence of active TB (moderate to low certainty evidence).
Reviewer name(s): Jeremy Nel, Karen Cohen, Susan van Wyk, Ntombifuthi Blose, Tamara Kredo, Lindiwe Mvusi, Maryke Wilkinson, Trudy Leong
PTC affiliation: WC PTC - Karen Cohen

Name of author(s)/motivator(s)

Jeremy Nel, Karen Cohen, Susan van Wyk, Ntombifuthi Blose, Tamara Kredo, Lindiwe Mvusi, Maryke Wilkinson, Lesley Robertson, Trudy Leong.

Author affiliation and conflict of interest details

Jeremy Nel (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand), Karen Cohen (Division of Clinical Pharmacology, Department of Medicine, University of Cape Town); Susan van Wyk (Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University), Ntombi Blose (University of Cape Town; Cochrane South Africa, SAMRC);Tamara Kredo (Cochrane South Africa, South African Medical Research Council; Division Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University); Lindiwe Mvusi (National Department of Health, TB Directorate); Maryke Wilkinson (Better Health Programme South Africa); Lesley Robertson (Department of Psychiatry, Faculty of Health Sciences, University of the WItwatersrand); Trudy Leong (National Department of Health, Essential Drugs Programme, Affordable Medicines Directorate).
TK, NB and SvW are partly supported by the Research, Evidence and Development Initiative (READ-It). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies; and also part-funded through the Collaboration for Evidence Based Healthcare and Public Health in Africa (CEBHA+ COVID-19 funding). KC, JN, LM, MW, LR and TL have no conflicts of interest to declare pertaining to isoniazid and rifapentine.

INTRODUCTION/ BACKGROUND

Description of the condition

Tuberculosis (TB) is one of the top ten causes of death worldwide. It is estimated that globally 10 million people developed TB disease and approximately 1.5 million died of TB in 2019. (1) SA is one of eight countries accounting for two thirds of the global TB burden, with an estimated incidence of 615/100 000 population (n=360 000) in 2019. (1)

TB disease is caused by the bacillis *Mycobaterium tuberculosis* and mainly affects the lungs. *M. tuberculosis* is spread through the air by people with active TB, e.g. when they cough. People in close proximity to an active TB case have a high risk of contracting infection. Once infected with *M. tuberuculosis* a person can develop TB disease or remain infected with latent TB infection (LTBI) for life. (2) It is estimated that one third of the world's population have LTBI. LTBI can progress to disease at any stage, but the risk to disease progression is higher with recent infection and in immunocompromised individuals. (2)

Integrated person-centred TB care and prevention is one of three pillars of the WHO's 'End TB Strategy' and comprises early diagnosis of TB, treatment of all people with TB, collaborative TB/HIV care, and TB preventive treatment (TPT) of people at high risk. (1) For TB diagnosis, treatment, and prevention to be effective, the WHO emphasises the need for progress towards universal health coverage and multisectoral action on social determinants of TB including poverty, housing quality, social protection, undernutrition, and economic growth.

In 2020 in SA, the estimated incidence of TB was 554/ 100 000 population, with a treatment coverage of 58%. (3) The decline in incidence compared to 2019 is consistent with a declining trend since 2015, and treatment coverage was similar to that in 2019. In 2020 TPT was provided to 93% of HIV positive people newly enrolled on anti-retroviral therapy but to only 51% of children < 5 years who were household contacts. (3) The COVID-19 pandemic may have negatively affected preventive care of child household contacts as coverage, although still poor, was slightly higher in 2019 at 56%. (1)

Description of the interventions

Several TPT options are available. The most widely used antimicrobial for TB prevention is isoniazid. Isoniazid is a daily regimen for at least 6 months (6H). Adverse reactions include asymptomatic elevation of serum liver enzyme concentrations, peripheral neuropathy and hepatotoxicity. (4) In 2014 the Food and Drug Administration (FDA) approved a combination regimen of isoniazid and rifapentine for TB prevention. (5) This combination regimen was recently added as a recommended option for TPT by WHO in 2020. (6) The isoniazid and rifapentine combination is prescribed weekly for 3 months (3HP) or daily for 1 month (1HP). Adverse reactions to rifapentine include cutaneous reactions, hypersensitivity reactions, gastrointestinal intolerance and hepatotoxicity (4). The shorter duration of treatment and longer intervals between doses compared to isoniazid alone, makes the combination regimen potentially more acceptable and easier to implement.

How the intervention might work

TB preventive treatment has been shown to reduce the risk of disease progression in people with LTBI. (7) Household contacts of an infectious TB case are at high risk of TB infection and by excluding TB disease and providing TPT to these contacts, active disease can be prevented. However, uptake and adherence to isoniazid preventive treatment is generally reported to be poor. (8) The new combination regimens with shorter treatment duration has potential for improved uptake and adherence to TPT.

Why it is important to do this review

One of the global TB targets set by the UN high-level meeting on TB in 2018 is to provide at least 30 million people with TPT from 2018 to 2022. (1) This target is far from reached and scaled up provision of TPT is one of 10 priority recommendations of the UN Secretary-General's 2020 progress report on TB for actions needed to accelerate progress towards global TB targets.

South Africa (SA) is in the process of updating national TPT guidelines. The current SA Standard Treatment Guidelines and Essential Medicine List recommends 6 months of daily isoniazid for drug susceptible TB contacts under the age of 5 and 12 months of isoniazid for adult PLHIV starting antiretroviral therapy. To inform the updated recommended options for TPT in household contacts of infectious drug susceptible TB cases, this review assesses the efficacy and safety profile of 6H, 3HP and 1HP.

Local prevalence of drug-resistant TB
Of note is that a national cross-sectional survey (June 2012 to June 2014) of newly diagnosed and retreated TB adult patients (≥18 years old; n=101 422) showed that the prevalence of rifampicin-resistant TB was 4.6% (95% CI 3.5 to 5.7) and isoniazid-resistant TB was 9.3% (95% CI 7.9 to 10.7), higher than that of MDR tuberculosis (2.8%, 95% CI 2.0–3.6). (20)

Feasibility and acceptability considerations
The feasibility and acceptability of an expanded TPT program needs consideration before it is implemented. Although TPT initiation in HIV positive people commenced on ART was 93% in 2020 (3), commencing TPT relies on the HIV positive person returning to the clinic for ART, and ART coverage of people living with HIV was only 72% in 2020. (21) As TPT is envisaged for all household contacts, TPT coverage of children < 5years household contacts is probably a better indicator of feasibility. Of note, TPT coverage of children was only 56% in 2019 (1) and 51% in 2020. (3) While the reasons for poor coverage require exploration, possibilities include poor tracing of household contacts (particularly where healthcare providers are scarce), high transport costs for patients to get to clinics for treatment, and low acceptability among caregivers of these children. Poor TB treatment coverage (58% in 2019 and 2020) is also a concern, as it is not known if household contacts will be reached if the index case is not on treatment.

A further concern is whether TPT would be effective amidst high levels of poverty, household crowding, and undernutrition. The WHO is clear that, to be effective, TB diagnosis, treatment and prevention should occur within the context of socio-economic improvement. In Europe, approximately 50% of between country variation in TB incidence and prevalence is attributable to socio-economic disadvantage. (22) In Brazil, unemployment and household crowding have been identified as important variables associated with TB incidence which need attention. (23) Household crowding was also found to be associated with TB transmission and clustering of TB infections in Cape Town, SA. (24) The duration of effect and population level impact of TPT in a high prevalence, poor socio-economic setting with household crowding is questionable. (25)

High density patient queues in primary healthcare clinics in SA have also been identified as a risk factor for TB transmission. (26) In KwaZulu-Natal, simple infection prevention and control measures such as queue management systems, ventilation, and masks could possibly reduce incident TB cases in the community in 2021-2030 by 3.4%-8.0%.

It is possible that spending on TPT may give rise to a false sense of security, detracting from spending on social interventions and other measures of infection prevention and control. More may be achieved through improved TB treatment coverage, TPT of children <5 years, ART coverage, infection prevention and control in healthcare settings, and multisectoral interventions towards socio-economic improvement of high-risk communities.

PURPOSE/OBJECTIVE

In household contacts of people diagnosed with drug susceptible TB, what is the efficacy and safety of different TB preventive therapy options for reducing the incidence of TB?

Population:
Household contacts of patients with drug susceptible pulmonary TB with no restriction on age; regardless of TST/ IGRA testing and regardless of HIV status.
We excluded studies that assessed TPT in patients from specific risk groups only, e.g., transplant patients; therefore, in which contacts were not identified via a TB index case.

Intervention(s) and comparisons:
1. INH vs placebo/ no Rx
2. a) Rifapentine and INH for 3 months (3HP) vs INH

b) Rifapentine and INH for 3 months (3HP) vs placebo/ no Rx

3. a) Rifapentine and INH for 1 month (1HP) vs INH
   b) Rifapentine and INH for 1 month (1HP) vs placebo/ no Rx

Outcomes:

- Incidence of TB disease (Xpert or TB culture or specific case definition)
- Death
- Adverse events
- Isoniazid resistance (Xpert)
- Incidence of TB infection (TST or IGRA conversion to positive)

Study designs:

- Systematic review of randomised controlled trials
- WHO guidelines
- Randomized controlled trials

METHODS

Data sources

On 6 April 2021 we searched for WHO guidelines related to TB preventive therapy. Thereafter, we also searched for systematic reviews and randomized controlled trials in the following databases respectively:

- Epistemonikos (https://www.epistemonikos.org/en/)
- Cochrane library
- PubMed

Search strategy details are available in appendix 1.

Selecting studies for inclusion

Title and abstract and full-text screening were done in duplicate using COVIDENCE software (SvW and NB).

Data extraction

Data extraction was done by a single reviewer and checked by a second reviewer. For guidelines we extracted the relevant recommendations and evidence tables. For systematic reviews and trials, we extracted data on the methods; participants including population n, age, risk and setting; interventions including type of intervention, comparator and delivery; and primary and secondary outcomes.

Appraisal of study quality

Quality assessment was done in duplicate and conflicts were resolved with discussion (SvW and NB).

Guidelines:

We appraised the quality of guidelines using AGREE II https://www.agreetrust.org/agree-ii/

Systematic reviews:

We appraised the quality of systematic reviews using AMSTAR. Online checklist found here: https://amstar.ca/Amstar_Checklist.php

Trials:

We appraised randomised controlled trials using the standard Cochrane risk of bias assessment tool 2.0 which considers: random sequence generation, allocation concealment, blinding of participants, personnel and outcomes, incomplete outcome data, selective outcome reporting and other sources of bias (https://training.cochrane.org/handbook/current/chapter-08).

For trials included in systematic reviews we extracted and used the risk of bias assessment from the review.

Data synthesis

Data synthesis was descriptive. The relevant measures of effect with 95% CIs were reported for all outcomes under each comparison. For the comparison of INH with placebo, we used available data to conduct GRADE assessments of the overall certainty of the evidence (9).

Budget impact analysis

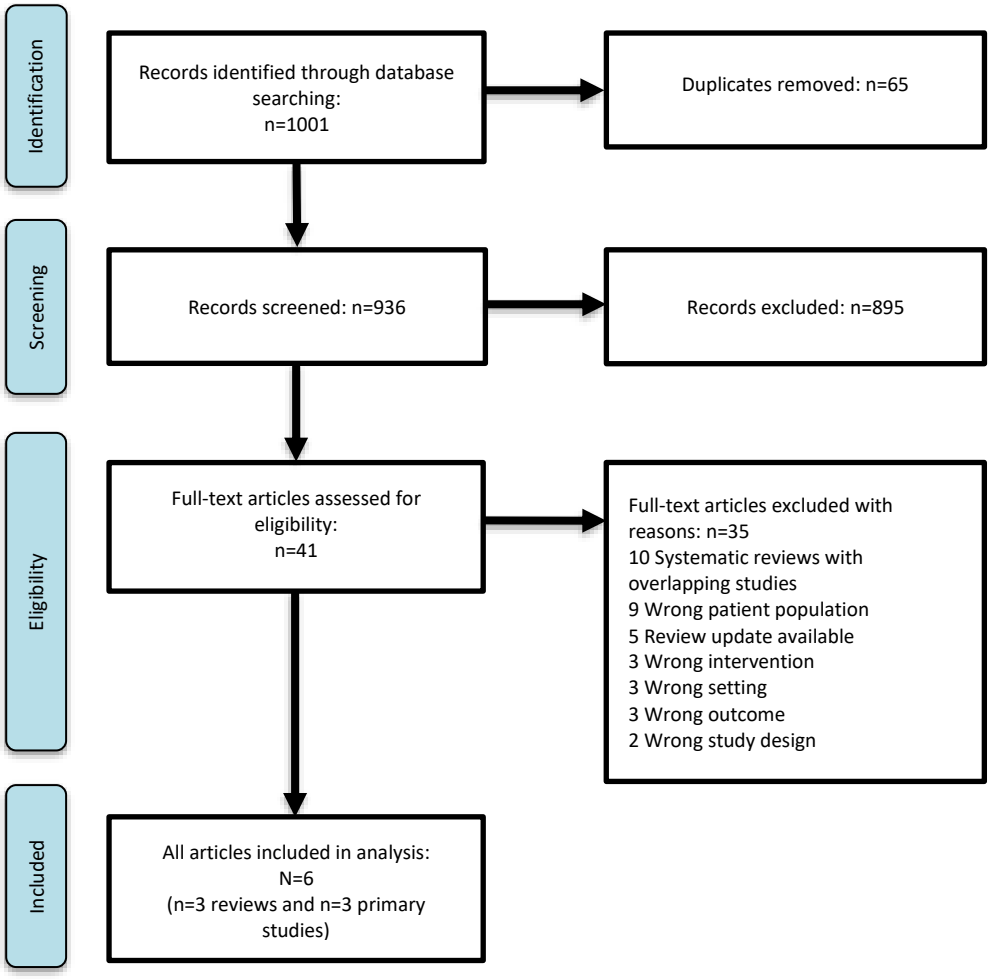
A budget impact analysis was conducted from a national public sector payer perspective. Pharmaceutical and other health care costs (and costs averted) was calculated for four TPT regimens: (1) Daily INH for 6 months for children aged <5years (standard of care), (2) Daily INH for 6 months for all ages, (3) 3HP for contacts aged >2years, daily INH for 6 months for children aged <2years , and (4) 1HP for contacts aged >13years, daily INH for 6 months for children aged <13years. The eligible population likely to receive TPT was estimated using incidence, average household size and mortality data, plus assumptions made regarding the likely uptake and discontinuation rates amongst the eligible population. Refer to budget impact analysis report for more detail and findings.

Findings

<u>Identification of studies</u>

We identified one guideline, three systematic reviews and three primary studies (see Figure 1).

Figure 1: PRISMA flow diagram



EVIDENCE SYNTHESIS

Description of guidelines and studies

Guidelines

The WHO guideline for tuberculosis preventive treatment was recently updated in 2020 and recommendations relevant to our review are provided in Table 1.

A prognostic review to inform the guideline, recommendation 6, reported that household contacts have higher risk of active TB compared to the general population regardless of age (see PICO 1: http://apps.who.int/iris/bitstream/handle/10665/260234/WHO-CDS-TB-2018.8-eng.pdf?sequence=1). However, the quality of this evidence was low. TB cases in the general population were detected passively, while TB cases in contacts were detected actively. The review also confirmed that older household contacts have lower risk of the development of active TB compared to children < 5 years. The following conditions to recommendation 6 were therefore noted:

"In this group (5 years and older) the confirmation of LTBI using either IGRA or TST would be desirable. Based on evidence of moderate to high quality, the 2015 LTBI guidelines strongly recommended the systematic LTBI testing and TB preventive treatment for contacts regardless of age in countries with a TB incidence lower than 100/100,000 population. In the current update, the guideline development group (GDG) considered that **this recommendation could be applied to any country regardless of TB burden if tests for LTBI and to rule out active TB were available and reliable.** Treatment may be justifiable without a LTBI test based on an assessment of the individual's risk of exposure and for the development of active TB in a given setting. **The GDG noted that the capacity of the health caregiver to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and the ascertainment of LTBI by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations in the implementation of these recommendations."**

Table 1: Characteristics of guideline(s)		
Citation (date published)	**Recommendation (pg)**	**AGREE II appraisal**
WHO consolidated guidelines on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.	5. Children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. ***(Strong recommendation, high certainty in the estimates of effect)*** 6. Children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. ***(Conditional recommendation, low certainty in the estimates of effect)*** 17. The following options are recommended for the treatment of LTBI regardless of HIV status: **6 or 9 months of daily isoniazid, or a 3-month regimen of weekly rifapentine plus isoniazid**, or a 3 month regimen of daily isoniazid plus rifampicin. ***(Strong recommendation, moderate to high certainty in the estimates of effect)***. **A 1-month regimen of daily rifapentine plus isoniazid** or 4 months of daily rifampicin alone may also be offered as alternatives. ***(Conditional recommendation, low to moderate certainty in the estimates of effect)***.	**6/7**

Studies

- ***Comparison 1: INH vs placebo/no treatment***

GRADE summary of evidence tables for this comparison in household contacts were not provided in the updated 2020 WHO guideline (Table 1). In previous WHO guidelines, the decision of six or nine months of daily INH for TB household contacts was based on the prevalence of LTBI in household contacts, risk of progression of LTBI to active disease and the effect of TPT for LTBI in preventing active TB in general. (10) GRADE summary of evidence tables for this comparison, in

household contacts specifically, were therefore not provided in previous guidelines either. We identified two systematic reviews relevant to this comparison: Smieja 1999 (11) and Balcells 2006 (12).

Smieja 1999 (11) included 11 RCTs that compared INH for 6 months or more with placebo in people with an increased risk of TB (Table 2). Participants were mainly household contacts of TB index cases, but also included whole populations from high burden villages, institutions and silicosis- and transplant patients. Most study participants were enrolled regardless of PPD status. Isoniazid compared to placebo was administered at varying doses for periods ranging from 6 to 24 months. Follow-up was at least 2 years. Trials reported on outcomes of active TB, extra-pulmonary TB, hepatotoxicity and deaths. The search for Smieja 1999 (11) was updated in 2003, but as the search did not identify any new studies since 1998, it was decided that the review findings were final and would not be updated in the future. The characteristics of the individual studies included in Smieja et al. are detailed in table 2.

Balcells 2006 (12) assessed the risk for INH resistance in people exposed to primary isoniazid preventive therapy. Thirteen studies that tested INH resistance were included, of which seven were in non-HIV infected people. These seven studies included participants who were TB case contacts, patients living at mental health hospitals, X-ray scanning attendees and silicosis patients with inactive TB (Table 3). Isoniazid compared to placebo, or no treatment was administered at varying doses for periods ranging from 12 weeks to 2 years, with or without observation. Different definitions for INH resistance were used. Only two of the seven studies (Ferebee 1962, Comstock 1967) were also included in Smieja 1999 (11), but the other five were not included, due to wrong comparator (Katz 1965, Horwitz 1966, Ferebee 1970, British MRC 1992) and incomplete follow-up (Pamra 1971). Details of the individual studies included in the Balcells review are laid out in table 3.

Table 2: Characteristics of studies included in Smieja 1999 (11)

Study	**Methods**	**Participants**	**Interventions** *(all placebo controlled)*	**Outcomes reported**
Comstock 1962	Randomization by family unit	7333 Alaskan villagers in 28 villages and 2 boarding schools Enrolled regardless of PPD status Infants 2 months and older were included	Isoniazid 300mg dly for 1 yr	Active TB
Del Castillo 1965	Randomization by family unit	400 HH contacts of index cases treated at Quezon Institute, Manila, Philippines	Isoniazid 5-10mg/kg for 1 yr	Active TB
Egsmose 1965	Randomization by household	626 Kenyan rural villagers, contacts of index cases	Isoniazid 300-500mg dly for 12-24 months	Pulmonary TB (sputum microscopy or culture) Deaths
Falk 1978	Individual randomization	7036 men in US VA hospitals; abnormal CXR 98% Men Mostly 30-50 years old 77% white. Majority of this group had previous TB treatment and were excluded from analysis. N=2389 participants included	Isoniazid 300mg dly 1-2 years	Active TB
Ferebee 1962	Randomization by family unit	25033 household contacts of newly diagnosed reported tuberculosis 2/3 under 20 years old	Isoniazid 300mg/kg or 5mg/kg for one year	Active TB Extrapulmonary TB Death
Ferebee 1963	Randomization by ward or building	24838 patients in 37 country institutions for chronic psychiatric or mentally retarded in Wisconsin, Georgia, and Massachusetts, USA PPD>5mm in 50% Age 2-100 >85% white Mean age 48 (men); 54 (women) 91% had normal CXR, 9% abnormal at baseline	Isoniazid 300mg dly for 12 months	Active TB Death
Girling 1992	Individual randomization	679 Chinese men with silicosis in Hong Kong Most 45-64 63% current smokers 94% > 10mm Criteria: silicosis diagnosis, no history TB, no evidence TB, negative sputum microscopy and culture	INH 300mg dly 6 months Rifampin 600mg dly 12 wks INH+Rif 12 weeks Placebo *Only the INH and placebo arms included in the reivew (N=199)	Active TB

John 1994	Individual randomization	184 transplant or dialysis patients in India	Isoniazid 300mg or placebo for one year. Low compliance	Active TB Hepatitis Death
Mount 1962	Randomization by family unit	2824 household contacts of known TB cases in USA 1/3 children 55% PPD<5mm 60% black	Isoniazid 300mg dly for one year	Active TB Extrapulmonary TB Deaths
Thompson 1982	Individual randomization	28000 adults in Eastern Europe: 115 clinics Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia Mean age 50 (20-65), attending chest clinic, abnormal chest x-ray, no previous treatment, no previous positive bacteriology 1/3 were age 55-65 PPD>6mm	Isoniazid for 3, 6 or 12 months or placebo Only placebo, 6 and 12 month arms included in analysis (N=20828)	Active TB Hepatitis
Veening 1968	Individual randomization	261 PPD positive contacts of active cases in Royal Netherlands Navy barracks	Isoniazid 600mg for 4 months then 400mg dly for total of 1 yr	Active TB
Note: **Risk of bias** not reported for each study. "Studies were assigned quality scores of 6 to 10, with a median score of 8. Agreement between observers was good (kappa=0.6). The studies which met the selection criteria were of high methodologic quality." (11)				

Table 3: Characteristics of studies included in Balcells 2006 (12)

Study	Methods	Participants	Intervention	Comparison	Randomization and treatment concealment**
Ferebee 1962	Double blinded*	Household contacts of TB patients	12 months INH, 4-7 mg/kg/day	Placebo	Unclear randomization
Katz 1965	Not blinded	Mental hospital patients with inactive lesions	2 years of INH, 300mg daily	No treatment	Assigned by odd or even hospital number
Horwitz 1966	Village/group randomization, Double blinded*	76 villagers, adults of Western Greenland	2x 13-week INH, 400 mg twice weekly	0.1 mg INH	Random number tables
Comstock 1967	Community/group randomization; Double blinded*	Residents of 28 villages and 2 boarding schools	12 months INH, 300 mg	Daily, placebo	Random number tables
Ferebee 1970	Not blinded	Household contacts with inactive lesions	INH		Unclear randomization
Pamra 1971	Group randomization Blinding not reported	424 X-ray screening attendees with inactive TB	12 months INH, 5 mg/kg/day observed for 6 years	Placebo	Unclear randomization
British MRC 1992 (Hong Kong Chest Service)	Double-blinded* placebo controlled clinical trial with matching placebos Individual randomization	679 Silicotic men subjects in Hong Kong	Group A: Rifampin for 12 weeks (R3) Group B: INH and Rifampin for 12 weeks (HR3) 24 weeks INH, 300mg/daily 2 and 5 years time points	Group C: INH alone for 24 weeks (H6) or placebo	Unclear randomization Treatment concealment – numbered packages containing isoniazid or matching placebo

Risk of bias:
A formal risk of bias assessment for each trial was not reported, but method of assigning treatment allocation, allocation concealment, blinding and publication bias were assessed
**Three studies reported a method of assigning treatment allocation (Katz 1965, Horwitz 1966, Comstock 1967); Only one study reported treatment concealment (British MRC 1992)
*Four studies were double-blinded (Ferebee 1962, Horwitz 1966, Comstock 1967, British MRC 1992)
"Funnel plots suggested little evidence of publication bias" (12)

- ***Comparison 2a: 3HP vs INH***

We identified 1 review (Hamada 2018 (13)) and 1 trial (Sun 2018 (14)) relevant to this comparison. The Hamada 2018 (13) review informed the identified WHO guideline. Hamada 2018 (13) compared 3HP with INH and included four trials. Two trials in HIV infected people were excluded as these were not household contact studies; one trial was in adults with LTBI (Sterling 2011 (15)) and one in children and adolescents with LTBI (Villarino 2015 (16)). We identified one trial which was published after the search for Hamada 2018 (13) was completed: Sun 2018 (14). Sun 2018 (14) compared 3HP with INH in a similar population of adults as Sterling 2011 (15). Characteristics of included trials are reported in Table 4a.

- ***Comparison 2b: 3HP vs no treatment***

We identified one trial relevant to this comparison: Gao 2018 (17). Gao 2018 (17) compared 3HP and 2HP to no treatment in an elderly population with LTBI. Due to a high frequency of adverse events, the treatment arms were adjusted to HP weekly for 8 weeks and HP twice weekly for 6 weeks. Characteristics are reported in Table 4b.

Table 4: Characteristics of trials comparing 3HP vs INH/no treatment

a) 3HP vs INH

Trials	RCT method	Participants	Interventions	Comparator	Outcomes reported	Risk of Bias
Sterling 2011 (15)	Open-label	US, Canada, Brazil, Spain Participants were at least 12 years of age at high risk for progression to active TB disease, which included: close contacts of a culture positive patient and positive TST; PLHIV with a positive TST or close contact with a TB patient; fibrotic changes on CXR with pos TST. Follow-up: 33 months post randomization	Observed 3 months weekly Rifapentine + INH	Self-administered 9 months of daily INH	Culture confirmed TB in children <18 years Clinical TB	β -High for performance and detection bias Unclear for 'other' bias Low for other domains
Villarino 2015 (16)	Open-label	US, Canada, Brazil, Hong Kong (China) and Spain Children (aged 2-17 years) at risk of active TB disease according to age, TST results and history of TB exposure. Proportion of participants with HIV was 2.3%. Follow-up: 3 years	12 once-weekly doses Rifapentine and INH for 3 months With supervision	270 daily doses of INH Without supervision for 9 months	Treatment discontinuation (due to AEs) Toxicity grades 1-4 Death of any cause	β -High for performance and detection bias Low for other domains
Sun 2018 (14)	Multicentre Randomized Controlled Trial	Asia, Taiwan LTBI contacts of index patients with a new diagnosis of pulmonary TB (Acid Fast Test) Aged >= 12 years with positive TST in four hospitals, within one month of unprotected exposure Follow-up: 2 years	3HP	9H Delivery: Direct observation and telephonic inquiries	Treatment completion (270-day treatment within 12 months in the 9H group and 12-dose treatment within 3 months in the 3HP group) Incidence of Adverse Drug Reactions (Hepatotoxicity)	High for performance and detection bias – RoB2 Low for other domains

b) 3HP vs no treatment

Gao 2018 (17)	Open label pragmatic Randomized Controlled Trial	China, Beijing. Rural residents aged 50-69 years with LTBI. Inclusion: 50–70-year-olds, local resident, IGRA positivity. Follow-up: 2 years	Arm A: Rifapentine plus INH (3 month once weekly) at a dose of up to 900mg, with incremental adjustments for subjects' weight <= 50 kg **(Adjusted to 8 weeks due to high frequency of AEs)** Arm B: Rifapentine (2 month twice weekly) at a dose of 600mg, with incremental adjustments for subjects' weight <= 50 kg **(Adjusted to 6 weeks due to high frequency of AEs)** Delivery: After meals with direct observation	Arm C: Untreated controls	Microbiologically confirmed active pulmonary TB or clinically determined pulmonary TB Completion of study therapy, permanent discontinuation of therapy and discontinuation due to AEs, death from any cause, grade 3 or 4 drug-related toxic effects	High for performance and detection bias – RoB2 Low for other domains
β – Cochrane Risk of Bias tool across 6 domains. "All studies were at risk of performance and detection bias for ascertaining adverse events due to lack of blinding. Three studies were at unclear risk of other bias, as the studies used a combination of individual and cluster randomization in which household members were assigned to the same group as the first enrolled member of their household. For other domains, we judged these to be at low risk of bias." (13)						

- ***Comparison 3a: 1HP vs INH***

Only one trial (Swindells 2019 (18)) reported this comparison and this trial was not in TB household contacts identified via a TB index case. Swindells 2019 (18) was an open-label trial in HIV-infected patients with LTBI, in which 1 month of daily rifapentine plus isoniazid was compared to 9 months of isoniazid alone. The outcomes reported were incident TB and death from TB or unknown cause. Details are available in table 5.

Table 5: Characteristics of trials comparing 1HP vs INH					
Trials	**Methods**	**Participants**	**Interventions**	**Comparator**	**Outcomes reported**
Swindells (18)	Open-label RCT, phase 3 noninferiority trial	HIV-infected patients living in areas with high TB prevalence Evidence of LTBI N=3000 Followed-up for median of 3.3 years 54% women Med age: 35 years Half of the patients were receiving ART	1-month regimen of daily rifapentine plus isoniazid	9 months of isoniazid alone	Diagnosis of TB Death from TB or unknown cause

- ***Comparison 3b: 1HP vs placebo/ no treatment***

We did not identify any reviews or trials relevant to this comparison.

Risk of bias of guidelines and included studies

Guidelines

The WHO consolidated guideline on TB was of high quality and scored 6/7 overall according to AGREE II appraisal (Table 1). The guideline was rated down because the search methods were not clearly reported.

Studies

- ***Comparison 1: INH vs placebo/no treatment***

For the two reviews relevant to this comparison, one was of low quality (Smieja 1999 (11)) and one of critically low quality (Balcells 2006 (12)).

- The Smieja 1999 (11) review was rated down based on unclear use of a comprehensive literature search strategy and failure to report on the funding sources of individual trials, using the AMSTAR checklist. However, due to the strict selection criteria, all the trials included in Smieja 1999 (11) were of high methodological quality and low risk of bias (Table 2).
- The Balcells 2006 (12) review was rated down for not stating publication restrictions and not presenting a list/flow diagram of excluded studies with reasons for exclusion. From the seven trials included in Balcells 2006 (12), three reported a method of assigning treatment allocation, only one reported treatment concealment and four studies were double-blinded (Table 3).

- ***Comparison 2a: 3HP vs INH***

The Hamada 2018 (13) review, relevant to this comparison was of low quality. It was rated down, because it was unclear if review methods were established before the conduct of the review and if data extraction was done in duplicate, no list of excluded studies was provided, sources of funding for included studies were not reported and the review authors did not account for risk of bias when they interpreted the results of the review.

The two studies included from the Hamada review (Sterling 2011 (15) and Villarino 2015 (16)) were at risk of performance and detection bias for ascertaining adverse events, due to lack of blinding. They also had unclear risk of 'other bias' as the studies used a combination of individual and cluster randomisation in which household members were assigned to the same group as the first enrolled member of their household. The other domains were judged at low risk of bias.

We assessed the newly identified trial, relevant to this comparison, with the Cochrane risk of bias tool. Sun 2018 (14) was an open label trial and also at risk of performance and detection bias for ascertaining adverse events as with Sterling 2011 (15) and Villarino 2015 (16).

- ***Comparison 2b: 3HP vs no treatment***

We assessed the one identified trial, relevant to this comparison, with the Cochrane risk of bias tool. In the Gao trial (17) outcome assessors were blinded to treatment allocation; however, it was an open label trial, controls did not receive any

treatment and patients could have reported symptoms (of clinically diagnosed TB) and treatment side effects differently between the arms.

- ***Comparison 3a: 1HP vs INH***

As we did not identify any reviews or new trials relevant to this comparison, we refer to the GRADE summary of evidence tables from the recent WHO guideline (see Comparison 3a under Effects of the intervention below).

Effects of the intervention

- ***Comparison 1: INH vs placebo/no treatment* (Table 6)**

1. **Incidence of TB disease:**
   The incidence of active TB is probably reduced by 60%, risk ratio (RR) 0.40 (95% CI 0.31 to 0.52), 11 trials, n = 73375, moderate certainty evidence. There are 10 fewer cases of active TB per 1,000 people who receive TPT compared to those who do not (ranging from 12 fewer to 8 fewer) within at least two years of follow-up. This translates to an overall number needed to treat (NNT) of 91 (95% CI 82 to 109).
   Given that the data included in the review spans both high and low prevalence settings, we are able to explore the likely NNT for different baseline risk of TB. Based on the relative effect of the intervention, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively (Table 7) We also report the RR and NNT for each trial separately (see Table 6, Appendix 2).
   Most of the trials provided 12 months of INH. Based on one trial (Thompson 1982), there is probably little or no difference in the incidence of active TB between 6 months and 12 months of INH, RR 1.41 (95% CI 0.84 to 2.37).
   Incidence of extra-pulmonary TB may be reduced, RR 0.34 (95% CI 0.16 to 0.71), 4 trials, n = 44636, low certainty evidence.

2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive TPT and those who do not, RR 1.10 (95% CI 0.94 to 1.28), n = 5, 33716, moderate certainty evidence.

3. **Adverse events:**
   No general report, here we report TPT related liver injury: there is probably an increase in TPT-related liver injury, RR 5.54 (95% CI 2.56 to 12.00), 5 more per 1,000 (from 2 more to 11 more), 1 trial (Thompson 1982), n = 20874, moderate certainty evidence. Based on this trial (Thompson 1982), there may be no difference in TPT related liver injury between 6 months and 12 months of INH, RR 0.75 (95% CI 0.48 to 1.17).

4. **Isoniazid resistance:**
   We are uncertain about the effect of TPT on development of INH resistance, RR 1.5 (95% CI 0.82 to 2.73). The studies are small and number of cases of resistance low. This remains a research gap.

5. **Incidence of TB infection:** not reported

Table 6. GRADE summary of evidence table for comparison 1: INH vs placebo

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	INH	Placebo	Relative (95% CI)	Absolute (95% CI)	
Incidence of active TB											
11	RCTs	not serious*	not serious	serious[a]	not serious	none	239/40262 (0.6%)	557/33113 (1.7%)	**RR 0.40** (0.31 to 0.52)	**10 fewer per 1,000** (from 12 fewer to 8 fewer)	⊕⊕⊕◯ Moderate
Incidence of extrapulmonary TB											
4	RCTs	not serious*	not serious	serious[b]	not serious	none	9/22379 (0.0%)	28/22257 (0.1%)	**RR 0.34** (0.16 to 0.71)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
TB related death											
2	RCTs	not serious*	not serious	not serious	serious[c]	none	3/16318 (0.0%)	10/9396 (0.1%)	**RR 0.29** (0.07 to 1.18)	**1 fewer per 1,000** (from 1 fewer to 0 fewer)	⊕⊕⊕◯ Moderate
TPT related hepatitis											
1	RCTs	not serious*	not serious	serious[d]	not serious	none	77/13884 (0.6%)	7/6990 (0.1%)	**RR 5.54** (2.56 to 12.00)	**5 more per 1,000** (from 2 more to 11 more)	⊕⊕⊕◯ Moderate
Hepatitis related deaths											
2	RCTs	not serious*	not serious	not serious	very serious[e]	none	5/16318 (0.0%)	0/9396 (0.0%)	**RR 4.13** (0.50 to 34.39)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ Low
Deaths all cause											
5	RCTs	not serious*	not serious	serious[f]	not serious	none	854/17243 (5.0%)	719/16473 (4.4%)	**RR 1.10** (0.94 to 1.28)	**4 more per 1,000** (from 3 fewer to 12 more)	⊕⊕⊕◯ Moderate
INH resistance [1]											
7	RCTs	serious[g]	not serious	serious[h]	serious[i]	none	19/110 (17.3%)	18/257 (7.0%)	**RR 1.50** (0.82 to 2.73)	**35 more per 1,000** (from 13 fewer to 121 more)	⊕◯◯◯ Very low

CI: confidence interval; **RR:** risk ratio

Explanations

*All individual trials were of high methodological quality.

a. Rated down by 1 level for indirectness. Studies ranged from 1962 to 1994. The participants were from many countries, duration of therapy was at least 1 year in the majority of studies. TB prevalence may differ from the current setting in SA.

b. Rated down by 1 level for indirectness. Most participants were contacts, but one study (Girling 1992) included silicosis patients. Duration of therapy was at least 1 year in the majority of studies. TB prevalence may differ from the current setting in SA.

c. Rated down by 1 level for imprecision due to low event numbers and wide 95% CI.

d. Rated down by 1 level for indirectness. No monitoring of serum liver enzymes or discontinuation of medication for biochemical or clinical signs of hepatotoxicity was done in this study.
e. Rated down by 2 levels for imprecision due to low event numbers and very wide 95% CIs.
f. Rated down by 1 level for indirectness. Treatment duration was 1 year or more in most of the studies. One study (John 1994) included dialysis patients, but the others were mostly contacts regardless of PPD status.
g. Rated down by 1 level. Only one study reported treatment concealment and three studies were not blinded.
h. Rated down by 1 level for indirectness. Eligible studies included participants who were TB case contacts, mental hospital patients, x-ray scanning attendees and silicosis patients with inactive TB. Isoniazid compared to placebo, or no treatment was administered at varying doses for periods ranging from 12 weeks to 2 years.
i. Rated down by 1 level for imprecision due to wide 95% CIs.

1.INH resistance from Balcells 2006; all other outcomes from Smieja 1999

Table 7. Anticipated absolute effects and NNT based on low (1%), moderate (2%) and high (5%) risk of TB in the comparison group, assuming constant relative effect of the intervention

Outcomes	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Placebo	**Risk with INH**	**NNT (95% CI)**			
Incidence of active TB	**Low (1% TB prevalence)**			**RR 0.40** (0.31 to 0.52)	73375 (11 RCTs)	⊕⊕⊕◯ Moderate[a]
	10 per 1,000	**4 per 1,000** (3 to 5)	**167** (143 to 200)			
	Moderate (2% TB prevalence)					
	20 per 1,000	**8 per 1,000** (6 to 10)	**83** (71 to 100)			
	High (5% TB prevalence)					
	50 per 1,000	**20 per 1,000** (16 to 26)	**33** (29 to 42)			

*__The risk in the intervention group__ (and its 95% confidence interval) 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; **NNT:** number needed to treat; **NNH:** number needed to harm

Explanations

a. Rated down by 1 level for indirectness. Studies ranged from 1962 to 1994. The participants were from many countries, duration of therapy was at least 1 year in the majority of studies.

- ***Comparison 2a: 3HP vs INH (Table 8)***

By age group:

Children and Adolescents (2 – 17 years)

1. **Incidence of TB disease:**
   There is probably little or no difference in incidence of active TB between those who receive 3HP and those who receive INH monotherapy, RR 0.132 (95% CI 0.007 to 2.542), 1 trial, n = 905, moderate certainty evidence. That is ranging from 7 fewer to 11 more cases of active TB per 1000 people who receive 3HP compared to those who receive INH monotherapy.
2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive 3HP and those who receive INH monotherapy, RR 0.183 (95% CI 0.009 to 3.802), 1 trial, n = 1032, moderate certainty evidence.
3. **Adverse events:**
   a) **Grade III or IV**
      There may be little or no difference in grade III or IV adverse events between those who receive 3HP and those who receive INH monotherapy, RR 0.875 (95% CI 0.320 to 2.396), 1 trial, n = 1032, low certainty evidence.
   b) **Hepatotoxicity**
      There is probably little or no difference in hepatotoxicity between those who receive 3HP and those who receive INH monotherapy, RR could not be estimated (no events), 1 trial, n = 1032, moderate certainty evidence.
4. **Isoniazid resistance:**
   Could not be estimated
5. **Incidence of TB infection:**
   Not reported

Table 8. GRADE summary of evidence table for comparison 2a (children and adolescent) – 3HP vs INH WHO TB Guidelines, 2020 (19)

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in children and adolescents

Population: Children and adolescents
Comparison: 6 or 9 months isoniazid
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	0/471 (0.0%)	3/434 (0.7%)	RR 0.132 (0.007;2.542)	6 fewer per 1000 (from 7 fewer to 11 more)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	0/539 (0.0%)	2/493 (0.4%)	RR 0.183 (0.009;3.802)	3 fewer per 1000 (from 4 fewer to 11 more)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(61)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious[3]	None	7/539 (1.3%)	8/493 (1.6%)	RR 0.875 (0.320;2.396)	2 fewer per 1000 (from 11 fewer to 23 more)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(61)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	0/539 (0.0%)	0/493 (0.0%)	Cannot be estimated	0 fewer per 1000 (from 4 fewer to 4 more)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TUBERCULOSIS												
0									Cannot be estimated		-	Important
COMPLETION RATE												
1 *(61)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	415/471 (88.1%)	351/434 (80.9%)	RR 1.089 (1.030;1.153)	72 more per 1000 (from 24 more to 124 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison against 6 months of isoniazid. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of the RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

Adults (25 – 50 years*) (Table 9)

*In Sterling 2011 (15) the median age was 36 years (IQR 25-47) in the 3HP arm and 35 years (IQR 25-46) in the INH arm.

1. **Incidence of TB disease:**
   There is probably little or no difference in incidence of active TB between those who receive 3HP and those who receive INH monotherapy, RR 0.438 (95% CI 0.179 to 1.074), 1 trial, n = 7731, moderate certainty evidence. That is ranging from 0 fewer to 3 fewer cases of active TB per 1000 people who receive 3HP compared to those who receive INH monotherapy.
2. **All-cause mortality:**
   There is probably little or no difference in all-cause mortality between those who receive 3HP and those who receive INH monotherapy, RR 0.740 (95% CI 0.462 to 1.183), 1 trial, n = 7745, moderate certainty evidence.
3. **Adverse events:**
   a) **Grade III or IV**
      There may be little or no difference in grade III or IV adverse events between those who receive 3HP and those who receive INH monotherapy, RR 0.873 (95% CI 0.733 to 1.040), 1 trial, n = 7799, low certainty evidence.
   b) **Hepatotoxicity**
      The incidence of hepatotoxicity is probably 84% lower in those who receive 3HP than in those who receive INH monotherapy, RR 0.163 (95% CI 0.099 to 0.268), 1 trial, n = 7799, moderate certainty evidence. That is 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP compared to those who receive INH monotherapy (ranging from 20 fewer to 25 fewer).
4. **Isoniazid resistance:**
   Isoniazid resistance not reported, here we report drug-resistant TB: there is probably little or no difference in drug-resistant TB between those who receive 3HP and those who receive INH monotherapy, RR 0.470 (95% CI 0.043 to 5.179), 1 trial, n = 7731, moderate certainty evidence.
5. **Incidence of TB infection:**
   Not reported

Note: Sun 2018 (14) reported on Grade III/IV adverse events (3/132 and 0/131 events in 3HP and 9H arms respectively) and hepatotoxicity (2/132 and 7/131 events in 3HP and 9H arms respectively), but the number of events was small and would not change the results from the Sterling 2011 (15) trial. We therefore did not include this trial in the GRADE summary of evidence table.

Table 9. GRADE summary of evidence table for comparison 2a (adults) – 3HP vs INH - WHO TB Guidelines, 2020 (19)

3-month weekly rifapentine plus isoniazid or daily isoniazid monotherapy for treatment of LTBI in adults without HIV

Population: Adults without HIV
Comparison: 6 or 9 months of isoniazid monotherapy
Overall quality: moderate

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3-month rifapentine + isoniazid	6 or 9 months isoniazid	Relative (95% CI)	Absolute (95% CI)		
ACTIVE TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[2]	None	7/3986 (0.2%)	15/3745 (0.4%)	RR 0.438 (0.179;1.074)	2 fewer per 1000 (from 0 fewer to 3 fewer)	⨁⨁⨁◯ Moderate	Critical
ALL-CAUSE MORTALITY												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	31/3986 (0.8%)	39/3759 (1.0%)	RR 0.740 (0.462;1.183)	3 fewer per 1000 (from 2 more to 6 fewer)	⨁⨁⨁◯ Moderate	Important
ANY ADVERSE EVENTS (GRADE III OR IV)												
1 *(60)*	RCT	Serious[4]	Not serious	Serious[1]	Not serious	None	229/4040 (5.7%)	244/3759 (6.5%)	RR 0.873 (0.733;1.040)	8 fewer per 1000 (from 3 more to 17 fewer)	⨁⨁◯◯ Low	Critical
HEPATOTOXICITY												
1 *(60)*	RCT	Not serious[5]	Not serious	Serious[1]	Not serious	None	18/4040 (0.4%)	103/3759 (2.7%)	RR 0.163 (0.099;0.268)	23 fewer per 1000 (from 20 fewer to 25 fewer)	⨁⨁⨁◯ Moderate	Critical
DRUG-RESISTANT TB												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious[3]	None	1/3986 (0.0%)	2/3745 (0.1%)	RR 0.470 (0.043;5.179)	0 fewer per 1000 (from 1 fewer to 2 more)	⨁⨁⨁◯ Moderate	Important
COMPLETION RATE												
1 *(60)*	RCT	Not serious	Not serious	Serious[1]	Not serious	None	3273/3985 (82.1%)	2585/3745 (69.0%)	RR 1.190 (1.159;1.221)	131 more per 1000 (from 110 more to 153 more)	⨁⨁⨁◯ Moderate	Critical

[1] No comparison with 6 months of isoniazid. The study included 2.7% HIV-positive participants. Although the trial was conducted in low TB incidence countries, this is unlikely to affect relative effect of rifapentine + isoniazid compared with isoniazid monotherapy. Downgraded by one level.
[2] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. The result also met pre-stated non-inferiority margin. Not downgraded.
[3] Although the 95% CI of RR is wide, the number of events was small and the CI of absolute effect is narrow. Not downgraded.
[4] An open-label design of the trial may have introduced ascertainment bias.
[5] Although the trial was open-label, this is unlikely to affect detection of hepatotoxicity, which is usually done by objective measurement (i.e. blood tests). Not downgraded.

- ***Comparison 2b: 3HP vs no treatment***

Elderly (50 – 69 years)

Gao 2018 (17) compared 3HP and 2HP to no treatment in an elderly population. Due to a high frequency of adverse events, the treatment arms were adjusted to HP weekly for 8 weeks and HP twice weekly for 6 weeks. Results are reported in Table 10.

Table 10: Results from Gao 2018 (17)

Outcome	Regimen A HP weekly for 8 weeks *	Regimen B HP twice weekly for 6 weeks *	No treatment	Statistical method	Effect size	GRADE
Active pulmonary TB	Cumulative incidence during 2 years of follow-up 10/1284 0.78% (95% CI 0.30–1.26%)	Cumulative incidence during 2 years of follow-up 6/1299 0.46% (95% CI 0.17–1.00%)	Cumulative incidence during 2 years of follow-up 14/1155 1.21% (95% CI 0.58-1.84%)	Adjusted HR	Regimen A: 0.63, 95%CI 0.27-1.43 Regimen B: 0.41, 95%CI 0.15-1.09 (Reg B)	⊕◯◯◯ Very low**
Death (adverse effects)	1/1279	0/1279		Chi square	p = 0.999	Not reported
Grade 3 drug-related toxic effects	30/1279	32/1279		Chi square	p = 0.797	Not reported
Grade 4/5 drug-related toxic effects	3/1279	1/1279		Chi square	p = 0.625	Not reported
Hepatotoxicity	13/1279	15/1279		Chi square	p = 0.704	Not reported

* Duration of treatment was reduced from 3 months to 8 weeks for regimen A and from 2 months to 6 weeks for regimen B due to high frequency of adverse events

**Downgraded for indirectness by one level: elderly population in China (50 – 69 years); Downgraded for risk of bias by one level: trial intervention amended due to high adverse event rate; Downgraded for imprecision: very low number of events and wide confidence interval

- ***Comparison 3a: 1HP vs INH***

1. **Incidence of TB disease:**
   There may be little or no difference in incidence of active TB between those who receive 1HP and those who receive INH monotherapy, Incidence Rate Difference per 100 person-years 0.058 (95% CI -0.240 to 0.350), 1 trial, n = 2986, low certainty evidence.
2. **All-cause mortality:**
   All-cause mortality was not reported. Here we report on incidence of active TB or death from any cause: there may be little or no difference in incidence of active TB or death from any cause between those who receive 1HP and those who receive INH monotherapy, Incidence Rate Difference per 100 person-years -0.13 (95% CI -0.52 to 0.27), 1 trial, n = 2986, low certainty evidence.
3. **Adverse events:**
   a) **Grade 3 or higher (nausea, vomiting, rash, drug-associated fever, elevated liver-enzymes and peripheral neuropathy)**
      There may be little or no difference in grade III or higher adverse events between those who receive 1HP and those who receive INH monotherapy, RR 0.86 (95% CI 0.58 to 1.27), 1 trial, n = 2986, low certainty evidence.
   b) **Serious adverse events**
      There may be little or no difference in serious adverse events between those who receive 1HP and those who receive INH monotherapy, RR 0.79 (95% CI 0.59 to 1.04), 1 trial, n = 2986, low certainty evidence.
4. **Isoniazid resistance:**
   We are uncertain about the effect of TPT on development of INH resistance, RR 1.63 (95% CI 0.17 to 15.99), 1 Trial, n = 26, very low certainty evidence.
5. **Incidence of TB infection:**
   Not reported

The GRADE summary of evidence table for this comparison is available in appendix 3.

BUDGET IMPACT ANALYSIS

Refer to the Budget Impact Analysis report, 21 June 2022.

Cost effectiveness analysis

No cost-effectiveness analysis was conducted specifically to inform this review. In response to the stakeholder consultation, one of the stakeholders submitted preliminary modeling estimates of the costs and cost-effectiveness of 3HP as delivered through IMPAACT4TB, an initiative to promote the scale-up of 3HP among people living with HIV and household contacts of people with detected TB disease. Their results indicate that 3HP is likely to be a cost-effective intervention for household contacts compared to current standard of care in South Africa (incremental cost-effectiveness ratio [ICER]: R10 412).

While this is a useful indicative analysis, the scope of their analysis does not completely align with the EML review question. In addition, there is considerable uncertainty regarding the ICER calculation and model parameters and structure. A full review of the analytical model (only a report was submitted) and more comprehensive examination of clinical and cost assumptions will be required to provide detailed feedback on the applicability and potential to adapt the IMPAACT4TB cost-effectiveness analysis to this medicine review decision. It should however be noted that It is not possible to use a single ICER output of a cost-effectiveness analysis to determine if an intervention is cost effective in the South African setting in absolute terms given the absence of an established cost effectiveness threshold to guide decision making.

EXTERNAL STAKEHOLDER ENGAGEMENT

On receipt of eternal comments, engagement was held with TB advocacy groups (TB proof and TB thinktank), including a collaborative meeting on 21 April 2022. Concerns raised and data presented in these discussions have been considered in updating this review.

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** **INH vs placebo** High ☐ Moderate ☒ Low ☐ Very low ☐ **3HP vs INH** High ☐ Moderate ☒ Low ☐ Very low ☐ **1HP vs INH** High ☐ Moderate ☐ Low ☒ Very low ☐ **3HP vs no treatment** High ☐ Moderate ☐ Low ☐ Very low ☒ *High quality: confident in the evidence* *Moderate quality: mostly confident, but further research may change the effect* *Low quality: some confidence, further research likely to change the effect* *Very low quality: findings indicate uncertain effect*	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Incidence of active TB: moderate certainty • All-cause mortality: moderate certainty 3HP vs INH (See GRADE summary of evidence table for comparison 2) • Incidence of active TB: moderate certainty • All-cause mortality: moderate certainty 1HP vs INH (See GRADE summary of evidence table for comparison 3) • Incidence of active TB: low certainty • Incidence of active TB or death: low certainty 3HP vs no treatment (See Table 7) • Incidence of active TB: very low certainty
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** *Outcome: Reduced incidence of TB disease* • ***Compared to placebo:*** **INH vs placebo** Large ☐ Moderate ☐ Small ☒ None ☐ **3HP vs no treatment** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ • ***Compared to INH:*** **3HP vs INH** Large ☐ Moderate ☐ Small ☐ None ☒ **1HP vs INH** Large ☐ Moderate ☐ Small ☐ None ☒	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Reduced incidence of active TB: RR 0.4 (95% CI 0.31 to 0.52); 0.6% (INH) vs 1.7% (placebo); NNT=91 (95% CI 82 to 109). Assuming that the relative risk reduction remains constant, the anticipated NNT for a low (1%), moderate (2%) and high (5%) proportion with active TB in the comparison group are 167 (95% CI 143 to 200), 83 (95% CI 71 to 100) and 33 (95% CI 29 to 42) respectively. • No difference in all-cause mortality: RR 1.10 (95% CI 0.94 to 1.28) 3HP vs INH (See GRADE summary of evidence table for comparison 2) • No difference in incidence of active TB: RR 0.132 (95% CI 0.007 to 2.542) in children and adolescents; RR 0.438 (95% CI 0.179 to 1.074) in adults • No difference in all-cause mortality: RR 0.183 (95% CI 0.009 to 3.802) in children and adolescents; RR 0.740 (95% CI 0.462 to 1.183) in adults 1HP vs INH (See GRADE summary of evidence table for comparison 3) • No difference in incidence of active TB: Incidence Rate Difference per 100 person-years 0.058 (95% CI -0.240 to 0.350) • Incidence of active TB or death: Incidence Rate Difference per 100 person-years -0.13 (95% CI -0.52 to 0.27) 3HP vs no treatment (See table 7) • Uncertain impact on incidence of active TB: Adjusted HR 0.63 (95% CI 0.27 to 1.43) for once weekly HP for 8 weeks – add other effect sizes Specific subgroups, such as HIV-positive household contacts, may benefit more, but the current evidence doesn't permit robust assessments of this.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** **INH vs placebo** High ☐ Moderate ☒ Low ☐ Very low ☐ **3HP vs INH** High Moderate Low x Very low **1HP vs INH**	INH vs placebo (See GRADE summary of evidence table for comparison 1) • TPT related hepatitis: moderate certainty • Grade III/IV adverse events: not reported 3HP vs INH (See GRADE summary of evidence table for comparison 2) • TPT related hepatitis: moderate certainty • Grade III/IV adverse events: low certainty of evidence 1HP vs INH (See GRADE summary of evidence table for comparison 3)

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
	High Moderate Low x Very low *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• TPT related hepatitis: not reported • Grade III/IV adverse events: low certainty of evidence • Serious adverse events: low certainty of evidence 3HP vs no treatment • Not reported
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** *Outcome: TPT related hepatitis* **INH vs placebo** Large Moderate x Small None **3HP vs INH** Large Moderate X Small None **1HP vs INH** Large Moderate Small X None	INH vs placebo (See GRADE summary of evidence table for comparison 1) • Increased TPT related hepatitis: RR 5.54 (95% CI 2.56 to 12.00); 5 more per 1,000 (from 2 more to 11 more) 3HP vs INH (See GRADE summary of evidence table for comparison 2) • TPT related hepatitis reduced in 3HP compared to INH RR 0.163 (95% CI 0.099 to 0.268) 23 fewer cases of hepatotoxicity per 1000 people who receive 3HP compared to those who receive INH monotherapy (ranging from 20 fewer to 25 fewer). No events in children and adolescents. • No difference in Grade III/IV adverse events: RR 0.875 (95% CI 0.320 to 2.396) in children and adolescents; RR 0.873 (95% CI 0.733 to 1.040) in adults 1HP vs INH (See GRADE summary of evidence table for comparison 3) • TPT related hepatitis: Not reported - Extrapolated from 1 RCT in PLHIV • No difference in Grade III/IV adverse events: RR 0.86 (95% CI 0.58 to 1.27) • No difference in serious adverse events: RR 0.79 (95% CI 0.59 to 1.04) 3HP vs no treatment • Not reported
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention Favours control Intervention = Control *or* Uncertain X	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: n/a	Should expanding TPT to all household contacts be recommended, consideration could be given to potential option of 3HP rather than INH as it performs similarly to INH but has different requirements that may improve feasibility/ acceptability.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes No Uncertain X	Capacity of current resources possibly insufficient and service delivery platform would need to be capacitated/ funded. Concerns of uptake of this parallel programme. To consider LTBI testing: To consider capacity to exclude TB disease before initiation of TPT, noting that in the 2018 National TB prevalence survey, 58% of culture confirmed TB cases were asymptomatic. From the WHO 2020 TPT guideline, ***"The GDG noted that the capacity of the health caregiver to assess the intensity of exposure, risk of infection and reinfection, the risk for development of active TB, and the ascertainment of LTBI by testing, as well as capacity to weigh harm versus benefit of treatment and ability to exclude active TB disease before initiation of treatment are important considerations in the implementation of these recommendations."*** The committee with insights from the programme considered that there are substantial barriers to introducing TPT. There were concerns about impact of implementation of this

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		intervention on treatment of active TB. TPT coverage of children < 5years in SA was low 56% in 2019 (1) and 51% in 2020. Possible reasons include poor tracing of household contacts (particularly where healthcare providers are scarce), high transport costs for patients to get to clinics for treatment, and low acceptability among caregivers of these children. These barriers may apply to expanding household contact TPT beyond under 5s
RESOURCE USE	**How large are the resource requirements?** More intensive: X Less intensive: Uncertain:	**Refer to the Budget Impact analysis report, 21 June 2022.** Net cost of providing TPT for all ages for one year (total costs – pharmaceutical, healthcare, adverse effects, costs averted): INH monotherapy for all ages: R148,577,833 3HP for >2y, INH monotherapy for <2y: R136,418,923 1HP for >13y, INH monotherapy for <13y: R165,638,824 *Estimation of total health care costs very uncertain due to significant uncertainty in budget impact model parameters.* Net pharmaceutical acquisition cost of providing TPT for all ages for one year : INH monotherapy for all ages: R18,265,490 3HP for >2y, INH monotherapy for <2y: R72,886,084 1HP for >13y, INH monotherapy for <13y: R111,735,429
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: Major: Uncertain: x **Is the option acceptable to key stakeholders?** Yes: No: Uncertain: x	There is no available local survey or qualitative data as this has not yet been introduced. Indirect evidence from a study conducted in South Africa, in KwaZulu-Nata in people living with HIV suggested several barriers to acceptability of TPT such as economic hardship, potential for stigma and cultural perceptions of TPT as introducing 'dirt' / toxins (Boffa 2019). Overall, we uncertain whether healthy individuals would find it acceptable to take a course of TPT, and what the implication may be in terms of access, social stigma and costs to visit clinics. We are uncertain of the impact and acceptability of additional workload for healthcare workers, and uncertain of community healthcare workers' involvement in the Programme. The committee considered that it is possible that focus on expanding TPT may give rise to a false sense of security, detracting from spending on social interventions and other measures of infection prevention and control.
EQUITY	**Would there be an impact on health inequity?** Yes: No: Uncertain: x	Other socio-economic factors need to be considered and TPT may possibly provide a false sense of security amongst contacts and providers. Access to TPT close to where people need it may be challenging in less urban settings.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	18 November 2021	JN, KC, SVW, TK, NB, MW, TL	TB preventive therapy for household contacts (beyond the current National policy that recommends TPT for uninfected children <5 years, exposed to a close contact of infectious pulmonary TB or LTBI confirmed on TST) not be recommended. Risk-benefit assessment, logistic and budget requirements does not favour expansion of the current TPT programme.

References

1. WHO. Global tuberculosis report 2020: executive summary. World Health Organization. 2020. Licence: CC BY-NC-SA 3.0 IGO.
2. Vynnycky E, Fine PEM. Lifetime risks, incubation period, and serial interval of tuberculosis. Am J Epidemiol. 2000;152(3):247–63.
3. WHO. Tuberculosis profile: South Africa. Estimates of TB burden. [Internet]. 2020 [cited 2022 Jun 13]. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22ZA%22
4. WHO. Consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Annex 3. GRADE evidence-to-decision tables. Geneva:

World Health Organization. 2020. Licence: CC BY-NC-SA 3.0 IGO.
5. SANOFI. Sanofi Receives FDA Approval of Priftin (rifapentine) Tablets for the Treatment of Latent Tuberculosis Infection [Internet]. December 2. 2014 [cited 2021 Apr 27]. Available from: http://www.news.sanofi.us/press-releases?item=136875#:~:text=Bridgewater%2C NJ – December 2%2C,LTBI) in patients two years
6. WHO. Consolidated guidelines on tuberculosis. Module 1: prevention - tuberuculosis preventive treatment. World Health Organization. 2020. Licence: CC BY-NC-SA 3.0 IGO.
7. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis Infection. N Engl J Med. 2015;372:2127–35.
8. Alsdurf H, Hill PC, Matteelli A, Getahun H, Menzies D. The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:1269–78.
9. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction - GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64:383–94.
10. WHO. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization. 2015. WHO/HTM/TB/2015.01.
11. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane Database Syst Rev. 1999;(Issue 1.Art):No.:CD001363.
12. Balcells ME, Thomas SL, Godfrey-Faussett P, Grant AD. Isoniazid preventive therapy and risk for resistant tuberculosis. Emerg Infect Dis. 2006;12(5):744–51.
13. Hamada Y, Ford N, Schenkel K, Getahun H. Three-month weekly rifapentine plus isoniazid for tuberculosis preventive treatment: A systematic review. Int J Tuberc Lung Dis. 2018;22(12):1422–8.
14. Sun HY, Huang YW, Huang WC, Chang LY, Chan PC, Chuang YC, et al. Twelve-dose weekly rifapentine plus isoniazid for latent tuberculosis infection: A multicentre randomised controlled trial in Taiwan. Tuberculosis. 2018;111:121–6.
15. Sterling TR, Villarino M, Borisov AS, Shang N, Gordin F, Bliven-sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. N Engl J Med. 2011;365(23):2155–66.
16. Villarino M, Scott N, Weis S, Weiner M, Conde M, Jones B, et al. Treatment for Preventing Tuberculosis in Children and Adolescents. JAMA Pediatr. 2015;176(3):247–55.
17. Gao L, Zhang H, Xin H, Liu J, Pan S, Li X, et al. Short-course regimens of rifapentine plus isoniazid to treat latent tuberculosis infection in older Chinese patients: A randomised controlled study. Eur Respir J. 2018;52:1801470.
18. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis. N Engl J Med. 2019;380(11):1001–11.
19. WHO. WHO Consolidated Guidelines on Tuberculosis. Annex 2. GRADE summary of evidence tables (for new rcommendations in 2018 & 2019 guidelines updates). Geneva: World Health Organization. 2020. Licence: CC BY-NC-SA 3.0 IGO.
20. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S et al. Prevalence of drug-resistant tuberculosisand imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87.
21. World Bank. Anti-retroviral coverage (% of people living with HIV) - South Africa. [Internet]. 2020 [cited 2022 Jun 13]. Available from: https://data.worldbank.org/indicator/SH.HIV.ARTC.ZS?locations=ZA
22. Ploubidis GB, Palmer MJ, Blackmore C, Lim TA, Manissero D, Sandgren A, et al. Social determinants of tuberculosis in Europe: a prospective ecological study. Eur Respir J. 2012;40(4):925-30.10.1183/09031936.00184011
23. Pelissari DM, Rocha MS, Bartholomay P, Sanchez MN, Duarte EC, Arakaki-Sanchez D, et al. Identifying socioeconomic, epidemiological and operational scenarios for tuberculosis control in Brazil: an ecological study. BMJ Open. 2018;8(6):e018545.10.1136/bmjopen-2017-018545
24. Tadokera R, Bekker LG, Kreiswirth BN, Mathema B, Middelkoop K. TB transmission is associated with prolonged stay in a low socio-economic, high burdened TB and HIV community in Cape Town, South Africa. BMC Infect Dis. 2020;20(1):120.10.1186/s12879-020-4828-z
25. Yates TA, Khan PY, Knight GM, Taylor JG, McHugh TD, Lipman M, et al. The transmission of Mycobacterium tuberculosis in high burden settings. Lancet Infect Dis. 2016;16(2):227-38.10.1016/S1473-3099(15)00499-5
26. McCreesh N, Karat AS, Govender I, Baisley K, Diaconu K, Yates TA, et al. Estimating the contribution of transmission in primary healthcare clinics to community-wide TB disease incidence, and the impact of infection prevention and control interventions, in KwaZulu-Natal, South Africa. BMJ Glob Health. 2022;7(4).10.1136/bmjgh-2021-007136

Appendix 1 – Search Strategy

Epistemonikos (19 May 2021)

Search strategy: (title:((tuberculosis OR TB) AND isoniazid) OR abstract:((tuberculosis OR TB) AND isoniazid))
Filtered by: Publication type: Systematic review; Systematic review question: Interventions
Records retrieved**:** 21 studies
Found no RCTs from 2018 onwards

Cochrane Central Register of Controlled Trials (CENTRAL), Issue 4 of 12, April 2021 (19 May 2021)

ID	Search	Hits
#1	[mh tuberculosis] or tuberculosis:ti,ab,kw or TB:ti,ab,kw	7903
#2	[mh isoniazid] or isoniazid:ti,ab,kw	1746
#3	#1 and #2 with Publication Year from 2018 to 2021, in Trials	230

Cochrane Library, Issue 5 of 12, May 2021 (19 May 2021)

ID	Search	Hits
#1	[mh tuberculosis] or tuberculosis:ti,ab,kw or TB:ti,ab,kw	7903
#2	[mh isoniazid] or isoniazid:ti,ab,kw	1746
#3	#1 and #2 in Cochrane Reviews	16

Pubmed (19 May 2021)

Search	Query	Results
#8	Search: (#3 AND #4 AND #5) NOT (animals[mh] NOT humans[mh]) Filters: from 2018/1/1 - 2021/5/19 Sort by: Most Recent	**837**
#7	Search: (#3 AND #4 AND #5) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	**8,472**
#6	Search: #3 AND #4 AND #5 Sort by: Most Recent	**9,081**
#5	Search: randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab] Sort by: Most Recent	**5,073,720**
#4	Search: isoniazid[mh] OR isoniazid[tiab] Sort by: Most Recent	**25,384**
#3	Search: #1 OR #2 Sort by: Most Recent	**249,576**
#2	Search: tuberculosis[tiab] OR TB[tiab] Sort by: Most Recent	**240,480**
#1	Search: "Tuberculosis/drug therapy"[mh] OR "Tuberculosis/prevention and control"[mh] Sort by: Most Recent	**52,684**

Search	Query	Results
#7	Search: (#3 AND #4) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review Sort by: Most Recent	127
#6	Search: (#3 AND #4) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	16,948
#5	Search: #3 AND #4 Sort by: Most Recent	18,220
#4	Search: isoniazid[mh] OR isoniazid[tiab] Sort by: Most Recent	25,384
#3	Search: #1 OR #2 Sort by: Most Recent	249,576
#2	Search: tuberculosis[tiab] OR TB[tiab] Sort by: Most Recent	240,480
#1	Search: "Tuberculosis/drug therapy"[mh] OR "Tuberculosis/prevention and control"[mh] Sort by: Most Recent	52,684

Appendix 2

Table 6: Breakdown of Smieja trials – INH vs placebo						
Study	**Participants**		**Total events (%) Treatment**	**Total events (%) Control**	**RR (95% CI)**	**NNT (95% CI)**
Egsmose 1965	Contacts	**Kenyan** Contacts of active TB cases **Excluded previous TB**	7/325 (2%)	18/301 (6%)	0.36 (0.15; 0.85)	26 (14; 130)
Ferebee 1962		**US:** Household contacts of newly diagnosed reported tuberculosis **52% skin test negative** 2/3 under 20 years old	8/8478 (0,1%)	36/8311 (0,4%)	0.22 (0.1; 0.47)	297 (204; 547)
Mount 1962		**US:** Household contacts of known TB cases – exposure had taken place months to years earlier, **previous TB excluded** **55% PPD<5mm** 1/3 children 60% black	6/1462 (0,4%)	12/1348 (0,9%)	0.46 (0.17; 1.22)	208 (906 harm; 93 benefit)
Del Castillo 1965		**Phillippines:** HH contacts of recently diagnosed index cases treated at Quezon Institute **83% skin test positive**	16/126 (13%) [8/16 (50%) initially skin test positive)	22/167 (13%) [18/22 (82%) initially skin test positive)	0.96 (0.53;1.76)	210 (14 harm; 12 benefit)
Ferebee 1963	Patients from institutions	**US:** Patients in 37 country institutions for chronic psychiatric or mentally retarded in Wisconsin, Georgia, and Massachusetts, USA **PPD>5mm in 50%** **91% had normal CXR**, 9% abnormal at baseline Age 2-100 Mean age 48 (men); 54 (women) >85% white	61/12339 (0,5%)	173/12499 (1,3%)	0.36 (0.27;0.48)	112 (89;154)
Comstock 1962	Villagers	**Alaskan** villagers in 28 villages and 2 boarding schools **45% Previous TB exposure, as judged by CXR and skin testing** Infants 2 months and older were included	50/2480 (2%)	128/2406 (5%)	0.38 (0.27;0.52)	30 (23;44)
Veening 1968	Recent skin test converters	Royal Netherlands Navy barracks **PPD positive contacts of active cases; recent, over 3 month period skin test converters** Aged 18-20 years	1/133 (0.8%)	12/128 (9%)	0.8 (0.01;0.61)	12 (7;29)
Falk 1978	Clinical risk groups	US: VA hospitals; **abnormal CXR, no previous TB treatment** 98% Men Mostly 30-50 years old 77% white	5/889 (0.6%)	15/772 (2%)	0.3 (0.11;0.81)	74 (42;329)
Girling 1992		**Chinese** men with **silicosis** in Hong Kong Most 45-64 **63% current smokers** **94% > 10mm** All had abnormal CXRs; no history TB, negative sputum microscopy and culture	20/100 (20%)	34/99 (34%)	0.58 (0.36;0.94)	7 (4;47)
John 1994		**India: Transplant or dialysis patients**	7/92 (8%)	10/92 (11%)	0.7 (0.28;1.76)	31 (20 harm;9 benefit)

Thompson 1982		**Eastern Europe:** 115 clinics Czechoslovakia, Finland, German Democratic Republic, Hungary, Poland, Romania, Yugoslavia **Attending chest clinic, abnormal CXR:** evidence of previous TB – fibrotic changes, no previous treatment, no previous positive bacteriology **PPD>6mm** Mean age 50 (20-65) 1/3 were age 55-65	58/13838 (0.4%)	97/6990 (1.4%)	0.3 (0.22;0.42)	103 (82;139)

Appendix 3 - GRADE summary of evidence table for comparison 3a – WHO TB Guidelines, 2020 (19)

PICO 7: In people of all ages at risk of active TB, does a 1-month daily rifapentine plus isoniazid regimen safely prevent TB disease compared to other recommended TB preventive treatment regimens?

Population: PLHIV at increased risk of active TB
Overall quality: low
Bibliography: (see reference 57)
Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, et.al. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis, N Engl J Med. 2019 Mar 14;380(11):1001-1011. doi: 10.1056/NEJMoa1806808.[a]

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	29/1488 (1.9%)	26/1498 (1.7%)	Incidence Rate Difference per 100 person-years 0.058 (-0.240 to 0.350)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	17/740 (2.3%)	15/746 (2.0%)	Incidence Rate Difference per 100 person-years 0.07 (-0.37 to 0.51)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB AMONG TST OR IGRA POSITIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[b,c]	not serious	serious[d]	not serious	none	9/337 (2.7%)	10/349 (2.9%)	Incidence Rate Difference per 100 person-years -0.069 (-0.830 to 0.690)	-	⨁⨁◯◯	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF BACTERIOLOGICALLY CONFIRMED TB (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION); DEATHS OF UNKNOWN CAUSE OR NOT RELATED TO TB CENSORED)												
1	randomised trials	serious[c,e]	not serious	serious[d]	not serious	none	18/1488 (1.2%)	14/1498 (0.9%)	Incidence Rate Difference per 100 person-years 0.08 (-0.15 to 0.31)	-	⨁⨁◯◯ LOW	CRITICAL
TIME TO TB DIAGNOSIS OR DEATH RELATED TO TB, WITH OTHER DEATHS TREATED AS COMPETING RISK (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious[f]	not serious	serious[d]	not serious	none	1488 participants	1498 participants	HR 1.10 (0.65 to 1.87) [Time to TB diagnosis or death related to TB, with other deaths treated as competing risk]	2 more per 1,000 (from 6 fewer to 15 more)	⨁⨁◯◯ LOW	CRITICAL
							-	1.7% g		2 more per 1,000 (from 6 fewer to 15 more)		
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))H												
1	randomised trials	serious[i]	not serious	serious[d]	not serious	none	32/1488 (2.2%)	33/1498 (2.2%)	Incidence Rate Difference per 100 person-years -0.023 (-0.350 to 0.300)	-	⨁⨁◯◯ LOW	CRITICAL
INCIDENCE OF ACTIVE TB OR DEATH DUE TO UNKNOWN CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (PER-PROTOCOL POPULATION))												
1	randomised trials	serious[i]	not serious	serious[d]	not serious	none	31/1456 (2.1%)	29/1381 (2.1%)	Incidence Rate Difference per 100 person-years 0.021 (-0.300 to 0.340)	-	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB OR DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE (MITT POPULATION))												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	45/1488 (3.0%)	51/1498 (3.4%)	Incidence Rate Difference per 100 person-years -0.13 (-0.52 to 0.27)	-	⨁⨁◯◯ LOW	CRITICAL
TIME TO DEATH FROM ANY CAUSE (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,l]	not serious	serious [d]	not serious	none	1488 participants	1498 participants	HR 0.75 (0.42 to 1.31) [Time to death from any cause]	5 fewer per 1,000 (from 11 fewer to 6 more)	⨁⨁◯◯ LOW	CRITICAL
							-	1.9% [g,l]		5 fewer per 1,000 (from 11 fewer to 6 more)		
TIME TO DEATH FROM TUBERCULOSIS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	serious [k]	none	3/1488 (0.2%)	3/1498 (0.2%)	HR 1.00 (0.20 to 4.93)	0 fewer per 1,000 (from 2 fewer to 8 more) l	⨁⨁◯◯ VERY LOW	CRITICAL
ADVERSE EVENTS (GRADE 3 OR HIGHER OF NAUSEA, VOMITING, RASH, DRUG-ASSOCIATED FEVER, ELEVATED LIVER-ENZYMES AND PERIPHERAL NEUROPATHY) (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	44/1488 (3.0%)	52/1498 (3.5%)	RR 0.86 (0.58 to 1.27)	5 fewer per 1,000 (from 15 fewer to 9 more)	⨁⨁◯◯ LOW	CRITICAL

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
SERIOUS ADVERSE EVENTS (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	serious [d]	not serious	none	83/1488 (5.6%)	108/1498 (7.2%)	RR 0.79 (0.59 to 1.04)	15 fewer per 1,000 (from 30 fewer to 3 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	1444/1488 (97.0%)	1341/1498 (89.5%)	RR 1.04 (0.99 to 1.10)	36 more per 1,000 (from 9 fewer to 90 more)	⨁⨁◯◯ LOW	CRITICAL
TREATMENT COMPLETION AMONG ART-NAIVE PARTICIPANTS AT ENTRY (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c,m]	not serious	serious [d]	not serious	none	720/740 (97.3%)	656/743 (88.3%)	RR 1.05 (0.97 to 1.14)	44 more per 1,000 (from 26 fewer to 124 more)	⨁⨁◯◯ LOW	CRITICAL
EMERGENCE OF DRUG RESISTANCE TO ISONIAZID AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	2/14 (14.3%)	1/12 (8.3%)	RR 1.63 (0.17 to 15.99)	52 more per 1,000 (from 69 fewer to 1,000 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO RIFAMPICIN AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	1/15 (6.7%)	1/12 (8.3%)	RR 0.81 (0.06 to 11.77)	16 fewer per 1,000 (from 78 fewer to 898 more)	⨁◯◯◯ VERY LOW	IMPORTANT
EMERGENCE OF DRUG RESISTANCE TO ETHAMBUTOL AMONG THOSE WITH CONFIRMED TB AND WITH DST												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/7 (0.0%)	1/7 (14.3%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	one month daily rifapentine plus isoniazid	nine months daily isoniazid	Relative (95% CI)	Absolute (95% CI)		
EMERGENCE OF DRUG RESISTANCE TO PYRAZINAMIDE AMONG THOSE WITH CONFIRMED TB AND WITH DST (FOLLOW UP: MEAN 3 YEARS; ASSESSED WITH: RCT EVIDENCE)												
1	randomised trials	serious [c]	not serious	very serious [d,n]	very serious [o]	none	0/6 (0.0%)	0/6 (0.0%)	not estimable		⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

[a] Randomized, open-label, phase 3 noninferiority trial comparing the efficacy and safety of a 1-month regimen of daily rifapentine plus isoniazid (1-month group) with 9 months of isoniazid alone (9-month group) in HIV-infected patients who were living in areas of high tuberculosis prevalence or who had evidence of latent tuberculosis infection. Primary end point was the first diagnosis of TB or death from TB or an unknown cause. Noninferiority would be shown if the upper limit of the 95% confidence interval for the between-group difference in the number of events per 100 person-years was less than 1.25. LTBI was not confirmed in about 80% of participants. Enrolment restricted to individuals ≥13 years old who were not pregnant or breastfeeding. Overall TB incidence observed in the trial was lower than expected. The number of patients with a CD4+ <250 cells per cu mm was small, and neither inferiority nor noninferiority of the 1-month regimen was shown in this stratum.

[b] Unknown cause of death censored in this analysis, which may cause bias in incidence rate difference if some of these deaths were related to TB (dependent censoring)

[c] The GDG decided to downgrade by one level because of the open label design possibly leading to performance bias. The quality was not downgraded for Indirectness, but the GDG noted that the trial compared 1HP with 9H and therefore did not cover all other comparisons of the PICO, especially 6H, the most widespread standard of care in TB preventive treatment. The GDG noted that Inconsistency could not be judged given that there was only a single trial; results from more trials would be desirable.

[d] Trial conducted only in PLHIV and not in all people at risk of active TB.

[e] Probable TB diagnoses and deaths with non-bacteriologically confirmed TB censored at the time of event

[f] When cause of death was determined to be unknown or not related to TB by blinded external reviewers, these were treated as a competing risk rather than endpoint. Some of these may have actually been due to TB, which may bias estimate.

[g] The proportion of events among controls

[h] Per-protocol population consisted of all participants who completed treatment, or who had died or received a TB diagnosis while they were receiving treatment.

[i] Deaths were reviewed by blinded external reviewers. Unknown causes of death were included as an endpoint, but misclassification of cause of death may bias estimate

[j] There were 21 deaths in the one-month arm, 3 related to TB. There were 28 deaths in the nine-month arm, 3 related to TB.

[k] Small number of events

[l] Incidence Rate Difference per 100 person-years of 0.00 (-0.10 to 0.10)

[m] Assessed via participant self-report at clinic visits

[n] Resistance may be non-emergent and coming from infecting strain

[o] Small sample of bacteriologically confirmed TB who had drug susceptibility test results

South African National Essential Medicines List
South African National Essential Medicine List Primary Level Medication Review Process
Component: Respiratory conditions

Estimated budget impact of different TB preventive therapy options for reducing the incidence of TB in household contacts of people diagnosed with drug susceptible TB

21 June 2022

This analysis has been revised based on external stakeholder feedback received and further deliberation by the review team. Changes in the assumptions underlying the analysis led to changes in the results.

EXECUTIVE SUMMARY

Medicine: Isoniazid, rifapentine
Indication (ICD10 code): Z29.2
Research question: What is the potential budget impact of four TB preventive therapy (TPT) options for reducing the incidence of TB in household contacts of people diagnosed with drug susceptible TB?
Patient population: Household contacts of people diagnosed with drug-susceptible TB
Level of Care: Primary Health Care
Prescriber level: Nurse prescriber
Current Standard of Care/ Comparator(s): Household contacts of people diagnosed with drug-susceptible TB – only children aged <5 years (irrespective of HIV status)
Findings: The total estimated annual costs of providing TPT to the expanded populations are very uncertain due to significant uncertainty in model parameters – especially primary healthcare utilization and costs.

- The estimated ***pharmaceutical acquisition costs*** are less uncertain, with incremental costs (compared to current standard of care) calculated as:
  - *INH monotherapy for all ages – R18,265,490*
  - *3HP for >2y, INH monotherapy for <2y – R72,886,084*
  - *1HP for >13y, INH monotherapy for <13y – R111,735,429*
- The estimated *incremental costs (**total:** pharmaceutical, health resources, adverse events, costs averted)* of the expanded TPT options:
  - *INH monotherapy for all ages – R148,577,833*
  - *3HP for >2y, INH monotherapy for <2y – R136,418,923*
  - *1HP for >13y, INH monotherapy for <13y – R165,638,824*

Reviewer name(s): Maryke Wilkinson, Karen Cohen, Jeremy Nel, Tamara Kredo, Lindiwe Mvusi, Trudy Leong

Author(s)/motivator(s): Maryke Wilkinson, Karen Cohen, Jeremy Nel, Tamara Kredo, Lindiwe Mvusi, Trudy Leong.
Author affiliation and conflict of interest details: Maryke Wilkinson (Better Health Programme South Africa); Karen Cohen (Division of Clinical Pharmacology, Department of Medicine, University of Cape Town); Jeremy Nel (Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand), Tamara Kredo (Cochrane South Africa, South African Medical Research Council; Division Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University); Lindiwe Mvusi (National Department of Health, TB Directorate); Trudy Leong (National Department of Health, Essential Drugs Programme, Affordable Medicines Directorate). MW, KC, JN, LM, and TL have no conflicts of interest to declare pertaining to isoniazid and rifapentine. TK is partly supported by the Research, Evidence and Development Initiative (READ-It). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not

necessarily reflect the UK government's official policies; and also part-funded through the Collaboration for Evidence Based Healthcare and Public Health in Africa (CEBHA+ COVID-19 funding).

INTRODUCTION

Tuberculosis (TB) is a communicable disease and one of the top ten causes of death worldwide. Providing TB preventive therapy (TPT) to those at highest risk of developing active TB disease may decrease TB related morbidity and mortality.

The current South African Standard Treatment Guidelines and Essential Medicine List recommends that household contacts under the age of five (irrespective of HIV status) of people diagnosed with drug-susceptible (DS) TB receive isoniazid (INH) monotherapy for six months (1). Changes to national TPT guidelines in South Africa have been proposed. To inform consideration of changes in recommended options for TPT in household contacts of infectious DS TB cases, this budget impact analysis provides an estimate of the potential impact expansion of TPT to household contacts of all ages, and change in TPT regimen, will have on the healthcare budget.

METHODS

This analysis presents the potential budget impact of different TPT options for reducing the incidence of TB in household contacts of people diagnosed with DS TB. A review of clinical studies to assess the efficacy and safety of the TPT options for household contacts was conducted. The assumptions made in this budget impact analysis is based on the findings of that review, with additional references for South African-specific estimates to inform the budget impact analysis.

We included 4 TPT options (for household contacts):

- Standard of care: Daily INH for 6 months (children aged <5years),
- Daily INH for 6 months[1] (all ages),
- Weekly rifapentine plus INH for 3 months (3HP) (all ages covered[2]), and
- Daily rifapentine plus INH for 1 month (1HP) (all ages covered[2]).

All TPT populations include HIV positive and HIV negative household contacts.

The analysis was performed from the perspective of the National Department of Health of South Africa. The costs reflected in the analysis include the pharmaceutical acquisition costs, visits to primary healthcare (PHC) facilities, inpatient costs incurred as a result of severe adverse events (drug induced liver injury), and health system costs averted due to TB cases averted. It is assumed that people discontinuing TPT will incur 50% of medicine and clinic visit costs, but no adverse event costs and they will not contribute to the costs averted due to TB disease averted.

Costs are presented in nominal terms and undiscounted over time.

The costs represent complete (100%) adoption of the particular regimen for one course of TPT.

The assumptions and calculations that underpins the base-case analysis are presented in Appendix 1.

Univariate sensitivity analysis (varying one parameter at a time) was performed to assess the uncertainty of the model parameters. Parameters that were varied include inputs that changed population estimates (number of index cases, TB disease positivity rate amongst household contacts, discontinuation rates), the cost of INH monotherapy if 12 months of INH is given to HIV positive contacts weighing >25kg, cost and quantity of PHC clinic visits, length and risk of hospitalization due to adverse drug reactions, costs of DS TB treatment (representing healthcare cost averted), and the number needed to treat (NNT).

[1] Draft NDoH TPT guidelines recommends 12 months of INH monotherapy for HIV positive contacts who weigh more than 25kg, but this budget impact analysis assumed a TPT duration of 6 months for all patients irrespective of HIV status in line with WHO recommendation.

[2] Children not eligible to receive 3HP or 1HP will receive INH monotherapy for six months

RESULTS

The list of model parameters use in the base-case analysis is provided in Appendix 2.

The estimated size of the population likely to receive TPT will increase significantly (8 fold) compared to the population currently receiving TPT. The differences in the estimated size of the populations that will complete TPT options 1, 2 and 3 are due to variations in the number of people likely to discontinue TPT across the different regimens (see Table 1). The discontinuation rates used in the analysis are uncertain as real-world data is lacking. A sensitivity analysis was conducted to explore this uncertainty (see Table 3).

Table 1: Number of people likely to receive a course of TPT per year (by regimen)

	Estimated population size (n)		
TPT regimen	**Complete TPT course**	**Discontinue TPT course~**	**Total**
Standard of care: INH monotherapy (aged < 5 years)	17,301	8,953	26,254
TPT option 1: INH monotherapy (all ages included)	149,540	77,379	226,919
TPT option 2: 3HP for >2y, INH monotherapy for <2y (all ages included)	182,239	44,680	226,919
TPT option 3: 1HP for >13y, INH monotherapy for <13y (all ages included)	226,919	0	226,919

~Assumed that these people will incur half of medicine and clinic visit costs.

The estimated *incremental* (total) cost of expanding TPT to all household contacts of people diagnosed with PTB is R148.6 million for INH monotherapy, R136.4 million for 3HP regimen, and R165.6 million for the 1HP regimen (see Table 2).

The overall cost of TPT is largely driven by healthcare resource use costs (clinic visit costs) for INH monotherapy (see Figure 1). The parameters used to calculate the cost of clinic visits (the cost per visit and number of visits required) are highly uncertain. In addition, it is unclear if/to what extent additional clinic visits required for expansion of TPT can be absorbed by existing capacity within the health system and whether or not TPT can/will be provided using Chronic Medicines Dispensing (uncertainty is explored in sensitivity analysis - see Table 3). If clinic visit costs are not taken into account in the analysis, the estimated *incremental* cost of expanding TPT is R16 million for INH monotherapy, R68 million for the 3HP regimen, and R108 million for the 1HP regimen (see sensitivity analysis in Table 3).

The *per patient* pharmaceutical acquisition costs for the TPT regimens are more certain, with confidence in the estimated pharmaceutical acquisition costs for the *expanded TPT population* only reduced due to uncertainty regarding the population size used in the analysis. The estimated *incremental* pharmaceutical acquisition cost is R18.3 million for INH monotherapy, R72.9 million for 3HP regimen, and R111.7 million for the 1HP regimen (see Table 2).

The cost of adverse events contributed the least of all the cost components to the total cost of TPT for all options considered (see Table 2). This is due to the low risk of hepatotoxicity severe enough to result in hospitalisation. The cost of adverse events may however be underestimated in this analysis as the cost of medicines and tests conducted during the inpatient stay for hepatotoxicity has not been captured.

The estimated cost per TB case (reflecting the 'costs averted') is uncertain as there is no current empirical data that reflects the mean cost of DS TB treatment across South Africa taking into account its variation and/or its distribution. A cost per TB case calculated in a South African TB costing study (increased by 50% to account for potential underestimation of the cost) was used as base-case estimate in the analysis.

Based on the findings from the budget impact analysis, the per patient cost of initiating a person on TPT will be 15-18% of the cost of treating an active DS TB case.

Table 2. Estimates of annual budget impact

	Standard of care (INH for <5Y)	**INH monotherapy for all ages**	**3HP for >2Y, INH monotherapy for <2Y**	**1HP for >13Y, INH monotherapy for <13Y**
Size of population that will receive TPT (n)	17,301	149,540	182,239	226,919
GROSS COST				
Pharmaceutical cost	R2,528,859	R20,794,349	R75,414,944	R114,264,289
Healthcare resource use cost	R17,338,767	R149,863,013	R85,308,096	R75,034,561
Adverse events cost	R0	R4,227,420	R3,595,107	R6,414,901
Savings due to TB cases averted	-R842,487	-R7,281,810	-R8,874,084	-R11,049,788
Gross total cost	**R19,025,140**	**R167,602,973**	**R155,444,062**	**R184,663,963**
NET BUDGET IMPACT *(other TPT regimens - standard of care)*				
Net pharmaceutical cost	-	R18,265,490	R72,886,084	R111,735,429
Net healthcare resource use cost	-	R132,524,246	R67,969,329	R57,695,794
Net adverse events cost	-	R4,227,420	R3,595,107	R6,414,901
Net savings due to TB cases averted	-	-R6,439,323	-R8,031,598	-R10,207,301
Net total cost	**-**	**R148,577,833**	**R136,418,923**	**R165,638,824**

SENSITIVITY ANALYSIS

A univariate sensitivity analysis was conducted where single model parameters were varied to assess uncertainty in these variables. The list of parameters used in the sensitivity analysis is provided in Appendix 3. The results of the sensivity analysis are presented in Table 3.

For all new TPT options, changing the cost of a clinic visit resulted in the most significant change in overall costs, followed by a change in the number of clinic visits, and changing the number of index cases.

Figure 1: Cost drivers for TPT options

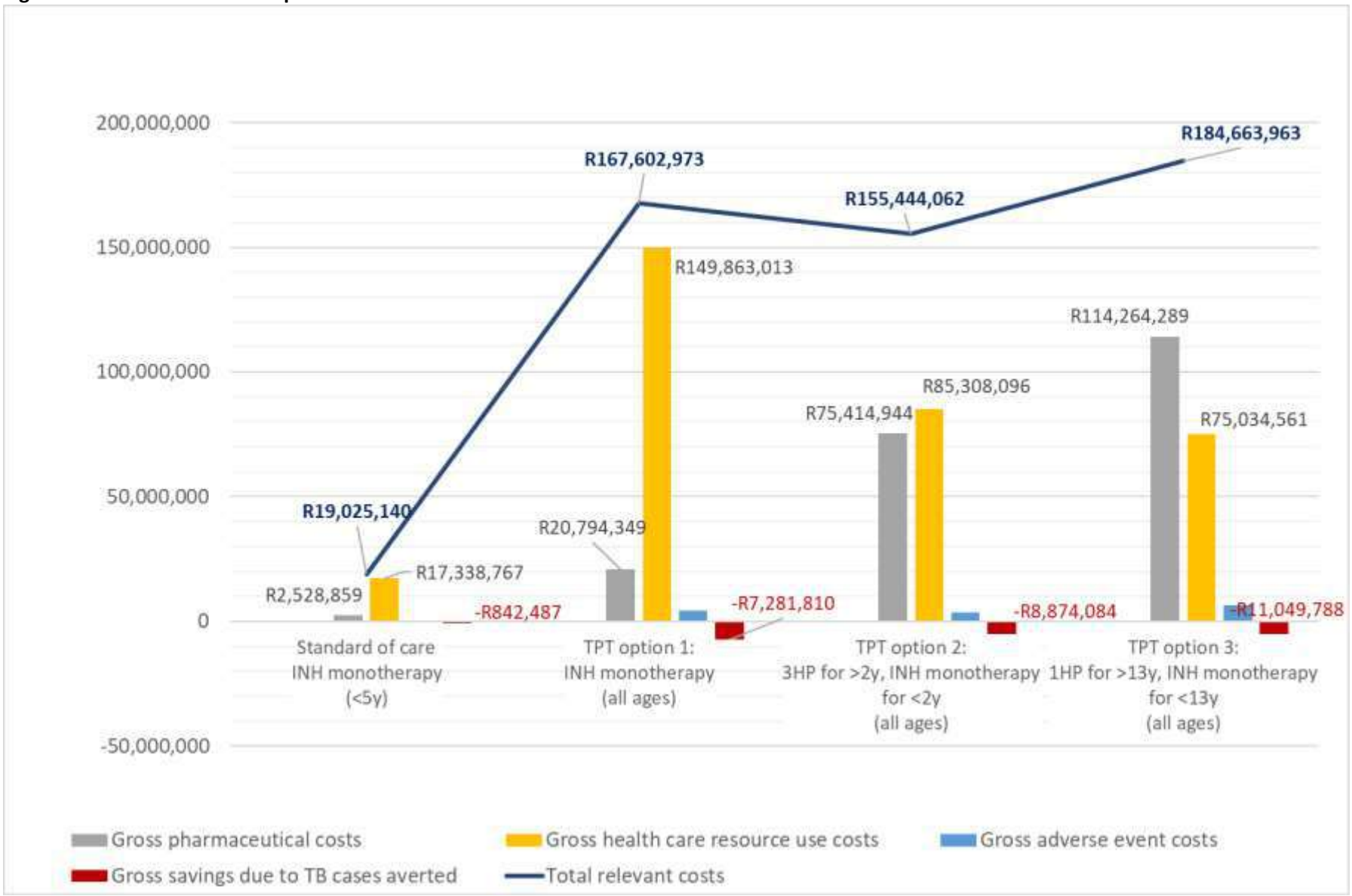


Table 3. Sensitivity analysis. Costs presented as NET COSTS (future - current treatment pathway costs)

			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Population increase from standard of care (SoC)	132,238	164,938	209,618
		Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net pharmaceutical costs	R18,265,490	R72,886,084	R111,735,429
SENSITIVITY ANALYSIS					
1. Changes to population parameters					
NUMBER OF INDEX CASES	175,530 Number of patients diagnosed and started on treatment in 2020 (2)	Population increase from SoC (n)	119,015	148,444	188,656
		Net total costs	R133,720,050	R122,777,031	R149,074,941
		Net pharmaceutical costs	R16,438,941	R65,597,476	R100,561,886
DIAGNOSED WITH TB DISEASE PRIOR TO TPT INITIATION	7.50% Proportion from Targeted Universal Testing for TB (TUTT) study (3)	Population increase from SoC (n)	126,234	157,448	200,100
		Net total costs	R141,831,265	R130,224,462	R158,117,556
		Net pharmaceutical costs	R17,436,097	R69,576,499	R106,661,788
DISCONTINUATION RATES	INH monotherapy: 31.0% 3HP: 17.9% Discontinuation rates reported by Stirling et 2011 (4)	Population increase from SoC (n)	138,459	168,186	208,804
		Net total costs	R151,291,433	R137,565,201	R165,307,209
		Net pharmaceutical costs	R18,606,798	R73,587,500	R111,688,175
	INH monotherapy: 37.51% 3HP: 21.66% 10% increase from base-case analysis	Population increase from SoC (n)	125,396	161,365	210,513
		Net total costs	R145,592,873	R135,158,017	R166,003,599
		Net pharmaceutical costs	R17,890,051	R72,114,526	R111,787,409

Table 3. Sensitivity analysis (continued)			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net pharmaceutical costs	R18,265,490	R72,886,084	R111,735,429
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
SENSITIVITY ANALYSIS					
2. Changes to cost of TPT					
AVG MEDICINE COST FOR TPT OPTION 1 and 3	TPT Option 1: R122.59 TPT Option 3: R506.44 HIV+ contacts: >25kg - 12 months INH TPT <25kg - 6 months INH TPT	Net total costs	R150,857,628	R136,418,923	R166,296,509
		Net pharmaceutical costs	R20,545,285	R72,886,084	R112,393,115
3. Changes to healthcare resource use and cost parameters					
NUMBER OF CLINIC VISITS	<u>Standard of care and TPT Option 1: all receive INH monotherapy</u> HIV- or not on ARVs - 6 visits, HIV+ and on ARTs - 0 visits <u>TPT Option 2: 3HP and INH</u> *3HP* >2y, HIV- or not on ARVs: 3 visits >2y, HIV+ and on ARVs: 0 visits *INH monotherapy:* <2y: 6 visits <u>TPT Option 3: 1HP and INH</u> *1HP* >13y, HIV- or not on ARVs: 1 visit >13y, HIV+ and on ARVs: 0 visits *INH monotherapy:* <13y: 6 visits	Net total costs	R136,211,826	R130,076,618	R160,255,155
		Net healthcare resource use costs	R120,158,239	R61,627,024	R52,312,125
	<u>Standard of care and TPT Option 1: all receive INH monotherapy</u> 1 screening visit + 6 visits <u>TPT Option 2: 3HP and INH</u> 3HP for >2y: 1 screening visit + 3 visits INH for <2y: 1 screening visit + 6 visits <u>TPT Option 3: 1HP and INH</u> 1HP for >13y: 1 screening visit + 1 visit INH for <13y: 1 screening visit + 6 visits	Net total costs	R170,665,207	R160,675,803	R192,860,143
		Net healthcare resource use costs	R154,611,621	R92,226,209	R84,917,113

Table 3. Sensitivity analysis (continued)			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
		Net adverse event costs	R4,227,420	R3,595,107	R6,414,901
		Net cost averted	-R6,439,323	-R8,031,598	-R10,207,301
SENSITIVITY ANALYSIS					
3. Changes to healthcare resource use and cost parameters (continued)					
MIX OF CLINIC VISITS AND MEDICINE COLLECTION VISITS	People receiving INH monotherapy 2 clinic visits + 4 medicine collection visits People on 3HP regimen 1 clinic visit + 2 medicine collection visits People on 1HP regimen 1 clinic visit	Net total costs	R107,976,731	R115,595,340	R154,435,163
		Net healthcare resource use costs	R91,923,144	R47,145,746	R46,492,133
COST OF CLINIC VISITS	R0	Net total costs	R16,053,587	R68,449,594	R107,943,030
		Net healthcare resource use costs	R0	R0	R0
	R279	Net total costs	R294,424,436	R211,221,052	R229,134,642
		Net healthcare resource use costs	R278,370,849	R142,771,458	R121,191,612
4. Changes to adverse events parameters					
INPATIENT - LENGTH OF STAY	7 days	Net total costs	R146,464,123	R134,621,369	R162,431,373
		Net adverse event costs	R2,113,710	R1,797,554	R3,207,451
SEVERE HEPATOTOXICITY	TPT option 1 (INH monotherapy): 0.11% TPT option 2 (3HP for >2y, INH for <2y): 0.07% TPT option 3 (1HP for >13y, INH for <13y): 0.11%	Net total costs	R145,834,044	R134,085,534	R161,475,259
		Net adverse event costs	R1,483,631	R1,261,718	R2,251,336
	TPT option 1 (INH monotherapy): 0.50% TPT option 2 (3HP for >2y, INH for <2y): 0.35% TPT option 3 (1HP for >13y, INH for <13y): 0.50%	Net total costs	R151,321,622	R138,752,312	R169,802,389
		Net adverse event costs	R6,971,209	R5,928,496	R10,578,467

Table 3. Sensitivity analysis (continued)

			TPT option 1: INH monotherapy	TPT option 2: 3HP for >2y, INH for <2y	TPT option 3: 1HP for >13y, INH for <13y
Base case analysis	*Base case assumptions*	Net total costs	R148,577,833	R136,418,923	R165,638,824
		Net healthcare resource use costs	R132,524,246	R67,969,329	R57,695,794
		Net adverse event costs	R4,227,420	R3,595,107	R6,414,901
		Net cost averted	-R6,439,323	-R8,031,598	-R10,207,301
5. Changes to healthcare costs averted					
COST DIAGNOSIS & TREATMENT OF DS-TB	R14,025	Net total costs	R134,636,447	R119,030,201	R143,539,619
		Net costs averted	-R20,380,709	-R25,420,320	-R32,306,505
NUMBER NEEDED TO TREAT (NNT)	NNT 33	Net total costs	R137,260,235	R122,302,782	R147,698,719
		Net costs averted	-R17,756,922	-R22,147,739	-R28,147,405
	NNT 83	Net total costs	R147,957,175	R135,644,793	R164,654,987
		Net costs averted	-R7,059,981	-R8,805,727	-R11,191,137
	NNT 167	Net total costs	R151,508,303	R140,074,021	R170,284,062
		Net costs averted	-R3,508,853	-R4,376,499	-R5,562,062

LIMITATIONS OF THE ANALYSIS

The budget impact analysis has been strengthened by feedback received from stakeholders and further deliberations by the review team[3]. Reducing the number of index cases (from estimated incidence to recorded incidence) and the unit cost of a PHC clinic visit were the main drivers for the reduction in total budget impact.

Population size calculation

The number of children aged <5 years who received TPT in 2020 was 22,689, which is lower than the estimated 'standard of care' population likely to start TPT calculated in budget impact analysis (26,254). In addition, real-world discontinuation rate data for the different TPT regimens are lacking, so the estimations of the number of people that will complete a course of TPT per year is less certain. Sensitivity analyses was conducted to explore this uncertainty (see Table 3).

Healthcare resource use costs

There is significant uncertainty in regards to the estimated healthcare resource use costs (clinic visit costs). The cost of clinic visits per TPT course is a major component of the total costs of INH monotherapy, and an area of potential efficiency savings for short-term TPT regimens (3HT and 1HT) which have higher drug acquisition costs but require less clinic visits. The inability to reliably predict the impact that implementation of the TPT options will have on healthcare resource use costs is a significant weakness of the analysis. Sensitivity analyses were conducted to explore this uncertainty.

The following costs have not been included in this analysis which adds to the uncertainty of the real healthcare resource use cost: 1) cost of following up people who default on TPT and restarting TPT when possible, 2) training required for implementation of the expanded TPT options, 3) monitoring and evaluation costs and 4) laboratory costs for tests to monitor for adverse drug events (e.g. liver function tests).

An ongoing TPT feasibility study may provide some insight into the healthcare resources required for implementation of the different TPT options as well as real-world discontinuation rates. These findings will hopefully inform future analyses in this area.

Healthcare costs averted

The costs averted due to DS PTB cases averted does not take population-level benefits of TPT into account. Costs averted relating to the transmission of TB to secondary cases (including costs for further contact tracing, diagnosis, and providing TPT or active treatment for secondary cases identified) are not included.

Lastly, some people eligible to receive TPT as a household contact might already be receiving TPT as part of comprehensive package of care, but this has not been adjusted for in the analysis.

[3] Across TPT regimens, the eligible population size reduced by more than 50%, pharmaceutical costs per patient changed slightly (less than 5%), healthcare resource use cost per patient reduced by around 50% (mainly due to change in cost of clinic visit used), adverse event costs per patient reduced by more than 50%, and healthcare costs averted due to TB cases averted has been added to the analysis.

APPENDIX 1: ASSUMPTIONS AND CALCULATIONS

1. ELIGIBLE POPULATION

The following assumptions were made in the calculation of the population eligible to receive TPT.

1.1. Population currently eligible for TPT (standard of care)

- INH TPT (duration: 6 months) is currently offered to all children <5 years (irrespective of HIV status) who have been exposed to a close/household contact diagnosed with PTB.
- People living with HIV (PLHIV) are offered TPT as part of a comprehensive package of care at the time of diagnosis, but PLHIV who have been exposed to a household contact diagnosed with PTB are not currently eligible to receive TPT (for 'household contact' indication) according to the Standard Treatment Guidelines.

1.2. Population that will be eligible for new TPT options proposed (INH monotherapy, 3HP, 1HP)

- TPT (one of 3 options) will be offered to people of all ages (irrespective of HIV status) who have been exposed to a household contact diagnosed with PTB.
- For TPT options 2 and 3, people not eligible to receive 3HP or 1HP due to age (aged <2y and <13y, respectively) will receive INH monotherapy.
- People will not receive more than one course of TPT per year and all people exposed to a patient newly diagnosed with PTB will be eligible to receive treatment.

1.3. Number of index cases

- The reported number of bacteriologically and clinically confirmed PTB cases[4] diagnosed and treated in 2020 (175,530 cases) (2) was adapted to reflect the number of diagnosed PTB cases for whom household contacts could be reached.
    - Initial loss to follow up of patients between diagnosis and treatment: 20% (Osman et al 2021 (6))
    - Adjusted down to 10% to account for lower likelihood that household contacts of PTB patients lost to follow up will be reached successfully
    - 195,033 index cases used as base-case estimate

  [A sensitivity analysis was conducted to estimate the budget impact if the number of patients diagnosed and started on treatment (175,530 cases) for PTB is used.]

1.4. Household contacts

- Used estimation of population at high risk for TB through household exposure in high-incidence countries reported by Ross et al 2021 (7) to inform:
    - Average household size: 3.5 people per household
      Assumed only one index case per household, so 2.5 people exposed per household
    - Proportion of population with household exposure to PTB aged <5 years: 11.74%

- Costs relating to contact tracing were not taken into account in the analysis, as it was assumed contact tracing activities will be conducted irrespective of whether TPT is available in order to rule out TB disease in close contacts.

1.5. Mortality rate in eligible population

Used 2019 mortality rates (8) due to significant impact COVID 19 had on death rates in 2020/21:

- Age under-five mortality rate (U5MR): 34.1 child deaths per1 000 live births
- Crude death rate (overall population): 8.7 deaths per 1000 population

[4] Excludes patients with extra pulmonary TB [EPTB]

1.6. Eligibility to be treated in public health sector

- The majority of the eligible population will be accessing public sector services: 95%

1.7. Ruling out active TB disease

- Assumed that 3.1% of contacts will be diagnosed with TB disease prior to initiation of TPT (9).

  [A sensitivity analysis was conducted to estimate the budget impact if the positivity rate recorded in the Targeted Universal Testing for TB (TUTT) study (3) *the is used. The TUTT study has not been published yet, so only limited details of study design and findings are available.]*

- Costs associated with ruling out TB disease (e.g. diagnostic tests, clinical evaluation) in household contacts were not taken into account in the analysis, as it was assumed that these investigations will be performed irrespective of whether TPT is available.

1.8. Eligible population likely to be started on TPT

- In 2020, 51% of children <5 years eligible for TPT accessed treatment (10).
- Assume % coverage will be the same for the extended population (same for all TPT options).
- People living with HIV receiving TPT as part of comprehensive package of care (not as an household contact) not adjusted for in the analysis.

1.9. Discontinuation rates

- Discontinuation rates reported by Stirling et al 2011 (4) were achieved under study conditions, with INH monotherapy TPT duration of 9 months, and the 3HP regimen administered as directly observed treatment.
- Increased Stirling et al 2011 discontinuation rates by 10% for base-case analysis to be more reflective of real-world scenario. Discontinuation rates used in base-case analysis:
  - INH monotherapy: 34.1%
  - 3HP: 19.7%

  [A sensitivity analysis was conducted to explore the impact of using the discontinuation rates reported by Stirling et al 2011 (4) *(as lower bound estimate) and using 10% higher discontinuation rates than those used in the base-case analysis (upper bound estimate)]*

- People who discontinue TPT will incur some health system costs. Therefore, the following is assumed in the analysis for people who discontinue TPT:
  - Will incur half of medicine and clinic visit costs (assumption aligned with Pooran et al 2013 (5) who assumed people who default on DS-TB treatment only incur half the costs)
  - Will incur no adverse event costs
  - No cost savings to the health system due to TB cases averted is expected
- For the one month regimen (1HP), the discontinuation rate is not relevant seeing that the medication would have been issued in its entirety at the start of treatment.

2. ACQUISITION COSTS OF TPT REGIMENS

The following assumptions were made in the calculation of the dosages and costs of TPT medicines.

2.1. Dose calculation

- Proportion of population exposed (as household contact of patients diagnosed with PTB) by age group obtained from Ross et al 2021 (7), in which estimates were provided in age groupings (0-4y, 5-14y, 15-49y and over 50y).
- To calculate the average doses (based on weight), disaggregated data on ages was required for children (aged < 16y) to estimate the relative cost contribution of an age group to the average cost of TPT for the relevant population. As this disaggregated data is not provided in Ross et al 2021, the proportion of the population in the grouped age

categories were evenly divided by the number of life years represented in that category, e.g. the 0-4y proportion of the population exposed was divided by 5 to estimate the proportion of children aged 0, 1, 2, 3, and 4 that will be exposed (relative to the total exposed population).

- Average weight for children aged up to 12 years were derived from a 2008 study validating weight measurement techniques in the Western Cape (11). The estimated weights are in line with the weight estimates for boys and girls in the World Health Organization (WHO) and Road to Health growth charts. The weight of children aged 12-16y were estimated.
- Assumed that people aged >16y all receive an adult dose.
- INH monotherapy dosing (168 doses required for 6 month's treatment) based on weight-based dosing recommended in the PHC STGs and EML, 2020 (1)
- 3HP dosing (12 doses required for 3 month's treatment) and 1HP dosing (28 doses required for 1 month's treatment) based on WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment (12).

2.2. Drug costs

- Cost per unit for TPT options based on average prices on contract circular (HP01-2021TB) on 4 March 2022.
- Average cost of a TPT regimen for the whole patient population indicated was calculated under assumption that people requiring TPT will be distributed across population in quantities relative to the size of that age group to the full exposed population

2.3. Frequency of treatment

- Assumed people will not receive more than one course of TPT per year

[Sensitivity analysis: Draft NDoH TPT guidelines include a recommendation for 12 months of INH TPT for household contacts who are HIV positive and weigh over 25kg (HIV positive children weighing <25kg will receive 6 months of INH TPT). A sensitivity analysis was conducted to explore the potential impact of this recommendation under the following assumptions:

- *HIV positive prevalence rate of 13.68%* (13)
- *Children <7y assumed to weigh <25kg* (11)*, which make up 16.37% of the eligible (extended) population (calculation based on Ross et al 2021* (7)*).*
- *Assumed no children aged <5y weighed >25kg, so no change in TPT duration for standard of care population*
- *TPT Option 1: INH medicine cost per patient for HIV negative population remains unchanged (R110), but INH cost for HIV positive population will increase - calculated as R199 per person. Average INH medicine costs for TPT option 1 (per person) calculated as R123.*
- *TPT Option 3: Medicine cost per patient for HIV negative population remains unchanged (R504), but cost for HIV positive population will increase - calculated as R525 per person. Average medicine costs for TPT option 3 (per person) calculated as R506.*
- *Number of clinic visits costed remains unchanged (6 clinic visits for INH monotherapy population)*
    - *For 12 month INH TPT regimen, HIV+ contacts would have required clinic visits for double the duration of a 6 month regimen. However, only 6 clinic visits were costed, under assumption that TPT will be provided as part of chronic dispensing services (TPT duration >6 months), and therefore clinic visits every second month will be required.*
    - *Assumed that TPT with duration of 6 months or less not eligible for chronic dispensing services.]*

3. HEALTHCARE RESOURCE USE COSTS

The following assumptions were made in the calculation of the primary health care (PHC) clinic visit costs associated with a course of TPT.

3.1. Number of clinic visits

- TPT initiated at first consultation, with monthly follow-up visits for monitoring and medicine collection.
- Number of visits = number of months on treatment

[A sensitivity analysis was conducted to explore the impact of varying the number of clinic visits:

- *Lower bound estimate – assumed that many HIV positive patients eligible to receive TPT due to household exposure will already be accessing health services on a monthly basis to collect ARVs/monitoring (68% of HIV+ population), so no additional clinic appointment will be required for these patients.*
- *Upper bound estimate - assumed patients will require an additional clinic visit for screening before TPT is initiated.]*

[A sensitivity analysis was conducted to explore the impact if TPT was provided through the Chronic Medicines Dispensing Programme. Assumed that patients receiving INH monotherapy will require 2 clinic visits at the start, followed by 4 medicine collection visits to complete treatment; patients on the 3HP regimen will require 1 clinic visit followed by 2 medicine collection visits, and patients on 1HP regimen will only require 1 clinic visit]

3.2. Cost per clinic visit

- Calculated average clinic visit cost based on clinic costs cited in TB publications (5,14–16): R.132.70
- Costs were converted to ZAR at rate noted in publication or average conversion rate for the year of analysis, and then adjusted for inflation using the South African Consumer Price Index.
- Applied same per-visit cost estimate to all age groups and regimens

[A sensitivity analysis was conducted to estimate the budget impact if the cost per clinic visit was changed:

- *Lower bound estimate - assumed that there is staff capacity within the health system to accommodate the additional clinic visits required, so all clinic costs excluded from analysis (clinic cost = R0.00)*
- *Upper bound estimate - clinic cost used in original analysis (R279) which has been used in previous EML analyses. Based on top-down costing using provincial and local government PHC expenditure]*

3.3. Costs not taken into account in analysis

- Diagnostic tests to screen for TB disease before initiation of TPT not included in analysis as assumed these costs would be incurred irrespective of TPT policy.
- Laboratory tests to screen for adverse drug events (e.g. liver function tests)
- Assumed that tuberculin skin test (TST) or Interferon Gamma Release Assay (IGRA) testing prior to initiation of TPT will not be a requirement.
- Following up patients who default on TPT
- Training requirements for implementation of one or more of the treatment options have not been included in the analysis.

4. ADVERSE EVENT COSTS

4.1. Probability of people experiencing severe hepatotoxicity (Grade3/4) over course of TPT

- Risk of hepatotoxicity in patients under the age of 18 years was considered negligible (17)
- Assumed people over the age of 18 years initiated on TPT had a defined risk of severe hepatoxicity resulting in hospitalization.
- Risk of severe hepatotoxicity resulting in hospitalization: Base-case
    - Used value midway between lower and upper bound estimates calculated (see below).
        - INH monotherapy: 0.30%
        - 3HP: 0.21%

- 1HP: 0.30%

- Risk of severe hepatotoxicity resulting in hospitalization: Lower bound
  - According to data reported by Stirling et al 2011, the risk of severe (Grade 3 or 4) hepatotoxicity was 0.11% for patients on INH monotherapy and 0.07% for patients on the 3HP regimen (18).
  - Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy (19).

  [Explored in sensitivity analysis]

- Risk of severe hepatotoxicity: Upper bound
  - Probability of drug-induced liver injury (DILI) due to INH reported as 0.5% (compared to placebo) (19)
  - Applied same reduction in risk of severe hepatotoxicity used in calculation of lower bound estimate for calculation of upper bound estimates of risk for 3HP (relative to INH risk of DILI).
  - Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy (19).

  [Explored in sensitivity analysis]

4.2. Number of inpatient days to treat severe hepatotoxicity

- Assumption that INH associated adverse drug reactions result in 2 weeks in hospital (20,21).

[A sensitivity analysis was conducted to estimate the budget impact if the duration of inpatient stay to manage severe hepatotoxicity is reduced to 7 days]

4.3. Cost of inpatient stay

- Assumed patients with severe hepatotoxicity are admitted for inpatient care at a Level 1 facility for an average of 2 weeks where they are under the care of a general medical practitioner.
- The UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021 was used to determine the unit costs for the inpatient care.

4.4. Costs not taken into account in analysis

- Tests to monitor hepatotoxicity not included.
- Additional costs not included in UPFS fee schedule incurred in and out of hospital to manage severe hepatotoxicity (e.g. medicines, follow-up visits).

5. SAVINGS TO THE HEALTH SYSTEM

- Calculation of number of cases of PTB averted based on needed to treat (NNT) calculated in Medicine Review and number of people who completed a TPT course.
- NNT to avert one PTB case assumed to be the same for all TPT options assessed (NNT=91).

[A sensitivity analysis was conducted to explore the impact if the NNT was adjusted for low (1%), moderate (2%) and high (5%) prevalence of TB in the comparison group. Anticipated NNT values: low TB prevalence: 167, moderate TB prevalence: 83, high TB prevalence: 33]

- Healthcare cost per TB case averted is derived from a reported estimate of 'Cost of diagnosis and management of DS-TB' by Pooran et al 2013 (5). The reported cost included PHC visits, TB drugs, diagnostic and monitoring tests, and adverse drug reactions, and the costs estimated for each of these cost categories were reported. To account for the uncertainty regarding the current cost of a TB case in South Africa and the potential that Pooran et al's estimate is an underestimation of the actual cost, a 50% increase on the Pooran et al estimate has been incorporated as the cost per TB case base-case estimate in the budget impact analysis (increased from R2,954 to R4,431).
- Expected cost savings due to PTB cases averted will (in practice) be achieved over two years (time horizon for study that informed NNT estimate), but all potential cost savings presented in analysis over one year.

[A sensitivity analysis was conducted to explore an extreme cost scenario in which the WHO estimate of R14,025 was used as the cost per DS TB case. This cost was not used for the base-case analysis as the estimate does not include estimates of unit costs, so it isn't possible to judge the extent to which the resource use and costs reflected items of most relevance to this review]

APPENDIX 2: MODEL PARAMETERS FOR BASE-CASE ANALYSIS

Parameter	Value	Source/justification
ANNUAL TREATED NUMBERS		
Number of PTB cases diagnosed in 2020 - EPTB not included in this number	195,033	WHO DSTB data 2020 report (unpublished) (2) *- PTB cases (excluding EPTB) diagnosed and started on treatment in 2020 (all ages): 175,530* Osman et al 2021 (6) *- Initial loss to follow up of patients between diagnosis and treatment: 20%* *- Adjusted to 10% to account for lower likelihood that household contacts of PTB patients lost to follow up will be reached successfully*
Percentage of exposed population aged <5y	11.87%	Ross et al 2021 (7) *- Percentage of exposed population aged <5y: 11.87%*
Average number of household contacts of TB patients in South Africa	2.5	Ross et al 2021 (7) *- Average household size of people at high risk for TB through household exposure in SA: 3.5 people* *- Average number of household contacts: 2.5 people*
Under-five mortality rate (U5MR)	3.41%	StatsSA mid-year population estimates 2019 (8) *- Under-five mortality rate (U5MR): 34.1 child deaths per 1 000 live births* *- Used 2019 mortality rates due to significant impact COVID 19 had on death rates in 2020/21.*
Crude death rate	0.87%	StatsSA mid-year population estimates 2019 (8) *- Crude death rate: 8.7 deaths per 1000 population* *- Used 2019 mortality rates due to significant impact COVID 19 had on death rates in 2020/21.*
Percentage of eligible people treated in the public health sector	95.00%	Estimate *- Assumption that majority of the eligible population will be accessing public sector services*
Percentage of eligible patients likely to be diagnosed with active TB prior to initiation of TPT	3.10%	Fox et al 2013 (9) *- Prevalence of TB disease in household contacts* *- Studies from low- and middle-income settings included, including South Africa*
Proportion of eligible patients likely to be started on TPT (%)	51.00%	WHO TB profile for South Africa (10) *- Eligible household contacts aged <5y started on TPT in 2020* *- Assume similar uptake by expanded population*
Discontinuation rate INH monotherapy	34.10%	Estimate *- Increased discontinuation rate reported by Stirling et al 2011* (4) *by 10% as this was achieved under study conditions and participants were given 9 months of INH monotherapy TPT*
Discontinuation rate 3HP monotherapy	19.69%	Estimate *- Increased discontinuation rate reported by Stirling et al 2011* (4) *by 10% as this was achieved under study conditions and 3HP as administered as directly observed therapy*
Discontinuation rate 1HP	0.00%	N/A - receive full month's treatment at first appointment
HIV positive prevalence rate	13.68%	StatsSA mid-year population estimates 2021 (13)

Parameter		Value	Source/justification
MEDICINE ACQUISITION COSTS			
Average cost for a course of TPT (ZAR)	Standard of care: INH mono <5y	116.12	Calculation based on the following: - *Proportion of exposed population estimates from Ross et al 2021* (7) - *INH dosing weight-based dosing from PHC STGs and EML, 2020* (1) - *3HP and 1HP dosing based on WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment* (12) - *Drug prices: Average prices on contract circular (HP01-2021TB) on 4 Mar 2022*
	TPT option 1: INH monotherapy all ages	110.47	
	TPT option 2: 3HP >2y, INH <2y	368.63	
	TPT option 3: 1HP >13y, INH <13y	503.55	
Proportion of cost expected to be incurred by people who discontinue TPT		0.5	Estimate - *Pooran et al 2013* (5) *assumed that DS TB patients who default from treatment incur only half of the cost of a treatment regimen.* - *Same proportion applied to all TPT options*
HEALTHCARE RESOURCE USE AND COSTS			
Average number of visits per person on TPT course	Standard of care: INH monotherapy <5y	6	TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 1: INH monotherapy all ages	6	TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 2: 3HP >2y – 3 visits INH monotherapy <2y – 6 visits	3.1	Aged >2y: 3HP TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2 & 3). Aged <2y: INH TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
	TPT option 3: 1HP >13y – 1 visit INH monotherapy <13y – 6 visits	2.5	Aged >13y: 1HP TPT initiated at first consultation (visit 1). Aged <13y: INH TPT initiated at first consultation (visit 1), with monthly follow-up visits for monitoring and medicine collection (visits 2-6).
Cost of PHC clinic visit (ZAR)		132.70	Estimate - *Published clinic visit costs in reported for South Africa vary significantly.* - *Reviewed clinic cost estimates from 4 TB costing studies in South Africa* (5,14–16)*. Converted estimates from US$ to ZAR for year of analysis, and adjusted for inflation using the South African Inflation rate (StatsSA).* - *Costs ranged from R72 to R193. Calculated average between 4 studies.*
Proportion of cost expected to be incurred by people who discontinue TPT		0.5	Estimate - *Pooran et al 2013* (5) *assumed that DS TB patients who default from treatment incur only half of the cost of a treatment regimen.* - *Same proportion applied to all TPT options*

Parameter		Value	Source/justification
ADVERSE EVENTS			
Inpatient facility fee - level 1 facility (12 hours)		R439	UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021
Professional fee: general medical practitioner		R91	UPFS Fee Schedule for Full Paying Patients: 1 APRIL 2021
Number of inpatient days		14	Moosa et al 2020 (21) and Schultz et al 2012 (20) *- Assumption that adverse drug reactions due to DS-TB treatment will require 2 weeks of hospitalization*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) or DILI over course of TPT	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.30%	Estimate - midway between lower and upper bound estimates
	TPT option 2: 3HP >2y, INH <2y	0.21%	Estimate - midway between lower and upper bound estimates
	TPT option 3: 1HP >13y, INH <13y	0.30%	Estimate - midway between lower and upper bound estimates
COSTS AVERTED			
Cost of diagnosis and management of DS-TB		4431.23	Pooran et al 2013 (5) *- Converted estimates to ZAR and adjusted for inflation using the South African Consumer Price Index.* *- The cost include PHC visits, TB drugs, diagnostic and monitoring tests, adverse drug reactions.* *- Patient population: DS TB patients* *- 50% increase to account to potential underestimation of costs*
Number needed to treat to avert one PTB case		91	See Medicine Review *- Assumed same NNT to prevent one PTB case for all TPT options*

APPENDIX 3: MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS

Parameter (sensitivity analysis)	Value	Source/justification
ANNUAL TREATED NUMBERS		
Number of PTB cases bacteriologically and clinically confirmed in 2020 and started on treatment (all ages) - EPTB not included in this number	175,530	WHO DSTB data 2020 report (unpublished) (2) - PTB cases (excluding EPTB) confirmed and started on treatment in 2020 (all ages) - More restrictive population than the population under review (patients diagnosed)
Percentage of eligible patients likely to be diagnosed with active TB prior to initiation of TPT	7.50%	Lebina et al 2021 (3) *- Results from TUTT study: TB positivity rate of 7.5% of TB contacts tested (part of screening process)* *- Detailed description of study design and results not available (not yet published in peer reviewed journal).*
Discontinuation rate INH monotherapy (lower bound)	31.00%	Stirling 2011 (4) *- Under study conditions - self-administered, 9 months of INH TPT*
Discontinuation rate INH monotherapy (upper bound)	37.51%	Estimate *- 10% increase from base-case value*
Discontinuation rate 3HP monotherapy (lower bound)	17.90%	Stirling 2011 (4) *- Under study conditions - self-administered, directly observed therapy*
Discontinuation rate 3HP monotherapy (upper bound)	21.66%	Estimate *- 10% increase from base-case value*
MEDICINE ACQUISITION COSTS		
Average medicine cost for TPT Option 1 and 3	TPT Option 1: R122.59 TPT Option 3: R506	Draft NDoH TPT guidelines include a recommendation that HIV positive household contacts that weigh over 25kg should receive 12 months of INH TPT (HIV positive children weighing <25kg will receive 6 months of INH TPT). *- TPT Option 1: INH medicine cost per patient for HIV negative population remains unchanged (R110), but INH cost for HIV positive population will increase - calculated as R199 per person. Average INH medicine costs for TPT option 1 (per person) calculated as R123.* *- TPT Option 3: Medicine cost per patient for HIV negative population remains unchanged (R504), but cost for HIV positive population will increase - calculated as R525 per person. Average medicine costs for TPT option 3 (per person) calculated as R506.* *- Number of clinic visits costed remains unchanged (6 clinic visits for INH monotherapy population)* o *For 12 month INH TPT regimen, HIV positive contacts would have required clinic visits for double the duration of a 6 month regimen. However, only 6 clinic visits were costed under assumption that TPT will be provided as part of chronic dispensing services (TPT duration >6 months), and therefore clinic visits every second month will be required.* o *Assumed that TPT with duration of 6 months or less not eligible for chronic dispensing services.*

MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS (continued)			
Parameter (sensitivity analysis)		**Value**	**Source/justification**
HEALTHCARE RESOURCE USE AND COSTS			
Average number of visits per patient per TPT course (lower bound)	Standard of care: INH mono <5y	5.4	Estimate: *- Under assumption that many HIV positive patients eligible to receive TPT as a household contact will already be accessing health services on a monthly basis for ARVs/monitoring, so no additional clinic appointment will be required for these patients.* *- HIV positive prevalence rate of 13.68% used (StatsSA mid-year population estimates 2020* (13)*)* *- 68.21% ART coverage assumed (UNAIDS key population atlas 2019* (22)*)* *- Average number of clinic visits calculated for people of all ages eligible under described scenario*
	TPT option 1: INH monotherapy all ages	5.4	
	TPT option 2: 3HP >2y, INH <2y	2.8	
	TPT option 3: 1HP >13y, INH <13y	2.3	
Average number of visits per patient per TPT course (upper bound)	Standard of care: INH mono <5y	7.0	Estimate *- Under assumption that patients will require an additional clinic visit for screening before TPT is initiated.* *- Average number of clinic visits calculated for people of all ages eligible under described scenario*
	TPT option 1: INH monotherapy all ages	7.0	
	TPT option 2: 3HP >2y, INH <2y	4.1	
	TPT option 3: 1HP >13y, INH <13y	3.5	
Mix of clinic visits and medicine collection visits	Standard of care: INH mono <5y AND TPT option 1: INH monotherapy all ages	2 clinic visits + 4 medicine collection visits	Estimate *- Under assumption that patients will only attend one or two clinic visits at start of TPT (depending on regimen), followed by medicine collection visits only*
	TPT option 2: 3HP >2y (INH <2y same as above)	1 clinic visit + 2 medicine collection visits	
	TPT option 3: 1HP >13y (INH monotherapy <13y same as above)	1 clinic visit	
Cost of PHC clinic visit (ZAR) (lower bound)		0	Estimate *- Assumption that there is staff capacity within the health system to accommodate the additional clinic visits required, so all clinic costs excluded from analysis*
Cost of PHC clinic visit (ZAR) (upper bound)		278.73	Estimate from original analysis (Nov 2021) *- Top-down costing based on provincial and local government PHC expenditure* *- Value has been used in previous EML analyses*

MODEL PARAMETERS USED IN SENSITIVITY ANALYSIS (continued)			
Parameter (sensitivity analysis)		**Value**	**Source/justification**
ADVERSE EVENTS			
Number of inpatient days (lower bound)		7	Pooran et al 2013 (5) *- Assumption used in costing analysis*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) over course of TPT (lower bound)	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.11%	Supplement to Stirling 2011 (18) *- Severe hepatotoxicity (Grade 3/4) over course of TPT*
	TPT option 2: 3HP >2y, INH <2y	0.07%	Supplement to Stirling 2011 (18) *- Severe hepatotoxicity (Grade 3/4) over course of TPT*
	TPT option 3: 1HP >13y, INH <13y	0.11%	WHO Grade tables (Annex 3) 2020 (19) *- Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy*
Percentage of people experiencing severe hepatotoxicity (Grade 3/4) over course of TPT (upper bound)	Standard of care: INH mono <5y	0.00%	Villarino 2015 (17) *- For children aged <18y, assumed negligible severe drug-induced hepatotoxicity*
	TPT option 1: INH monotherapy all ages	0.50%	WHO Grade tables (Annex 3) 2020 (19) *- Relative risk: INH monotherapy vs placebo*
	TPT option 2: 3HP >2y, INH <2y	0.35%	Applied same reduction in risk of severe hepatotoxicity (compared to INH monotherapy) as for lower bound
	TPT option 3: 1HP >13y, INH <13y	0.50%	WHO Grade tables (Annex 3) 2020 (19) *- Assumed 1HP TPT pose no lesser nor greater risk for hepatotoxicity than INH monotherapy*
COSTS AVERTED			
Cost of diagnosis and management of DS-TB (upper bound)(ZAR)		14,025	WHO estimate for cost per TB case *- Extreme cost scenario based on global, generalised analysis by WHO*
Number needed to treat to avert one PTB case (high TB prevalence)		33	NNT estimate anticipated for high (5%) TB prevalence of TB in comparison group
Number needed to treat to avert one PTB case (moderate TB prevalence)		83	NNT estimate anticipated for moderate (2%) TB prevalence of TB in comparison group
Number needed to treat to avert one PTB case (low TB prevalence)		167	NNT estimate anticipated for low (1%) TB prevalence of TB in comparison group

NEMLC MEETING OF 23 JUNE 2022:
NEMLC accepted the updated report.

REFERENCES

1. The National Department of Health South Africa: Essential Drugs Programme. Primary Healthcare Standard Treatment Guideline and Essential Medicine List. 7th ed. [Internet]. Republic of South Africa; 2020. Available from: https://www.idealhealthfacility.org.za/docs/guidelines/Standard Treatment Guidelines and Essential Medicine List for Primary Health Care 7th ed - 2020.pdf
2. TB Programme (South Africa). WHO reporting: Drug-susceptible TB data. 2020.
3. Lebina L, Nonyane B, Berhanu R, Naidoo P. Targeted Universal Testing for TB in clinics in South Africa: A cluster randomized trial [Presentation to HIV Clinicians Society] [Internet]. 2021 [cited 2022 Mar 28]. Available from: https://sahivsoc.org/Files/TUTT_HIV%20Clinicians%20Soc.pdf
4. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection. New England Journal of Medicine [Internet]. 2011 Dec 8 [cited 2022 Mar 28];365(23):2155–66. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1104875
5. Pooran A, Pieterson E, Davids M, Theron G, Dheda K. What is the Cost of Diagnosis and Management of Drug Resistant Tuberculosis in South Africa? PLoS ONE [Internet]. 2013 Jan 18 [cited 2020 Feb 25];8(1):e54587. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23349933
6. Osman M, Meehan SA, von Delft A, du Preez K, Dunbar R, Marx FM, et al. Early mortality in tuberculosis patients initially lost to follow up following diagnosis in provincial hospitals and primary health care facilities in Western Cape, South Africa. PLOS ONE [Internet]. 2021 Jun 1 [cited 2022 Mar 28];16(6):e0252084. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0252084
7. Ross JM, Xie Y, Wang Y, Collins JK, Horst C, Doody JB, et al. Estimating the population at high risk for tuberculosis through household exposure in high-incidence countries: a model-based analysis. eClinicalMedicine [Internet]. 2021 Dec 1 [cited 2022 Mar 28];42. Available from: http://www.thelancet.com/article/S2589537021004879/fulltext
8. StatsSA. Mid-year population estimates 2019. 2020.
9. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. European Respiratory Journal [Internet]. 2013 Jan 1 [cited 2022 Mar 28];41(1):140–56. Available from: https://erj.ersjournals.com/content/41/1/140
10. World Health Organization. TB profile: South Africa [Internet]. 2020 [cited 2022 Mar 28]. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/
11. Geduld H. Validation of Weight Estimation by Age and Length based methods in the South African population. 2008.
12. World Health Organization. Consolidated guidelines on tuberculosis: tuberculosis preventive treatment. 2020.
13. StatsSA. Mid-year population estimates 2020. 2021.
14. Sinanovic E, Ramma L, Vassall A, Azevedo V, Wilkinson L, Ndjeka N, et al. Impact of reduced hospitalisation on the cost of treatment for drug-resistant tuberculosis in South Africa. International Journal of Tuberculosis and Lung Disease [Internet]. 2015 Feb 1 [cited 2020 Feb 25];19(2):172–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25574915
15. Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, Stevens W, et al. The impact and cost of scaling up GeneXpert MTB/RIF in South Africa. PLoS One [Internet]. 2012 May 31 [cited 2022 Apr 6];7(5). Available from: https://pubmed.ncbi.nlm.nih.gov/22693561/
16. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax [Internet]. 2013 Mar 1 [cited 2022 Apr 6];68(3):247–55. Available from: https://thorax.bmj.com/content/68/3/247
17. Villarino ME, Scott NA, Weis SE, Weiner M, Conde MB, Jones B, et al. Treatment for Preventing Tuberculosis in Children and Adolescents: A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid. JAMA Pediatrics [Internet]. 2015 Mar 1 [cited 2022 Mar 28];169(3):247–55. Available from: https://jamanetwork.com/journals/jamapediatrics/fullarticle/2089639
18. Sterling T, Villarino M, Borisov A. Supplement to: Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011;365:2155-66. [Internet]. [cited 2022 Mar 28]. Available from: https://www.nejm.org/doi/suppl/10.1056/NEJMoa1104875/suppl_file/nejmoa1104875_appendix.pdf
19. World Health Organisation. Consolidated guidelines on tuberculosis: tuberculosis preventive treatment. Annex 3. GRADE evidence-to-decision tables. 2020.
20. Schutz C, Ismail Z, Proxenos CJ, Marais S, Burton R, Kenyon C, et al. Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa. S Afr Med J [Internet]. 2012 [cited 2022 Mar 28];102(6):506. Available from: /pmc/articles/PMC3605782/
21. Moosa MS, Maartens G, Gunter H, Allie S, Chughlay MF, Setshedi M, et al. A Randomized Controlled Trial of Intravenous N-Acetylcysteine in the Management of Anti-tuberculosis Drug–Induced Liver Injury. Clinical Infectious Diseases [Internet]. 2021 Nov 2 [cited 2022 Mar 28];73(9):e3377–83. Available from: https://academic.oup.com/cid/article/73/9/e3377/5897464
22. UNAIDS. Key population atlas - South Africa [Internet]. [cited 2022 Mar 28]. Available from: https://kpatlas.unaids.org/dashboard

South African National Essential Medicine List
Primary Healthcare Medication Review process
Component: Respiratory conditions

EVIDENCE REVIEW

Title: To determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.

Date: 30 November 2021

Key findings

- We conducted a search for systematic reviews of randomised controlled trials, or individual randomized control trials, to determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.
- No systematic reviews or randomized controlled trials were identified. Therefore an AGREE assessment was performed on the World Health Organization's 2020 Tuberculosis Prevention Therapy (TPT) guidelines, which were based on observational data.
- WHO's TPT guidelines recommended fluoroquinolones could be considered for high risk individuals (e.g. children, immunocompromised people, including people living with HIV) on the basis of several small observational studies that were assessed as being of "very low" quality. However, the guideline suggested a careful individualised risk assessment that included the intensity of exposure, certainty of the source case, and reliable information on the drug resistance pattern of the index case and potential adverse events. If further noted that confirmation of latent TB status (e.g. by tuberculin skin test) would be required.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE 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: Based on this evidence review, the PHC/Adult Hospital Level Committee suggests not to use fluoroquinolones as prophylaxis for high risk contacts of cases of active MDR TB (conditional recommendation).
Rationale: Very low quality evidence based on small observational studies with substantial methodological problems. In addition the need to establish latent TB status by tuberculin skin testing was felt not to be feasible; and side-effect profile of longterm fluoroquinolone use and its possible impact on the development of drug resistance were concerns
Level of Evidence: Low certainty evidence
Review indicator: Randomised controlled trial evidence showing benefit.

NEMLC RECOMMENDATION (9 DECEMBER 2021): The NEMLC accepted the review and the proposed recommendation made by the PHC-AH ERC. The Committee added its concerns regarding the side-effect profile of longterm fluoroquinolone use and the possible inpact on the development of drug resistance.

Monitoring and evaluation considerations

Research priorities

1. Executive Summary

Date: 21 October 2021
Medicine (INN): fluoroquinolones
Medicine (ATC): J01MA
Indication (ICD10 code): Z29.2
Patient population: Adults and paediatrics
Prevalence: 6700 cases of MDR TB diagnosed in 2020 in South Africa [WHO Global TB Report 2021].
Level of Care: Primary healthcare
Prescriber Level: Nurse prescriber
Current standard of Care: n/a
Efficacy estimates: n/a
Motivator/reviewer name(s): Trudy Leong, Jeremy Nel
PTC affiliation: Jeremy Nel - Helen Joseph Hospital PTC

2. Authors, affiliation and conflict of interest details:

1) Trudy D Leong, Essential Drugs Programme, National Department of Health
2) Jeremy Nel, Helen Joseph Hospital, University of the Witwatersrand

TDL and JN have no interests related to DR-prophylaxis therapy.

Acknowledgements:

- Tamara Kredo (Cochrane-SA) assisted with the literature search and screening of the retrieved records.
- Millicent Reddy (BHPSA) assisted with the AGREE 2 assessment Module 1: Tuberculosis preventive treatment, 2020 of the World Health Organization Consolidated guidelines on tuberculosis.

3. Introduction/ Background

Latent tuberculosis infection (LTBI) is the "state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB".[1] The 2019 Global TB report[2] listed South Africa amongst the top high burden TB countries (520 per 100,000 population) for both drug sensitive (DS) TB and multi-drug resistant (MDR) TB. The most prominent risk factor was HIV-infection. Of note, was that the national HIV prevalence survey of TB in 2018[3] reported a higher rate of 737 per 100,000 population (highest amongst men, those aged 35-44 years and the elderly, ≥ 65 years of age).

To achieve the United Nations End TB Strategy targets,[4, 5] preventive actions have been recommended by the World Health Organization ranging from screening for active TB, infection control, prevention and care of HIV and other co-morbidities and health risks, access to universal health care, social protection and poverty alleviation, as well as TB preventive treatment (TPT).[1]

The National Department of Health's (NDoH's) TB Programme had tabled a draft national TPT Guideline for review and ratification by the National Essential Medicines List Committee (NEMLC), at a meeting that was convened on 30 January 2020.[6] The NEMC raised concerns and provided recommendations for a way forward. Related to drug-resistant (DR) TB, the NEMLC recommended that the evidence of efficacy and safety of fluoroquinolones for MDR-TB prophylaxis be provided.

Thus, an evidence review was conducted.

4. Purpose/Objective:

To determine whether fluoroquinolones are safe and effective as MDR TB prophylaxis for household contacts exposed to an index case.

PICO eligibility criteria:

Population	Household contacts of patient with MDR tuberculosis. No restriction on age.
Intervention	Fluoroquinolone administered alone or in combination with a second drug (e.g. isoniazid, ethambutol)
Comparator	placebo or active comparator e.g. isoniazid
Outcome	Active tuberculosis Drug resistance Adverse events and adverse reactions
Studies	Systematic reviews of randomised controlled trials, followed by randomised controlled trials if systematic reviews could not be sourced.

5. Methods:

Cochrane-SA (TK) assisted with a literature search for systematic reviews in 2 databases, conducted on 27 October 2020.

a. **Data sources** : Epistemonikos and PUBMED was searched.
b. **Search strategy :** See appendix I.
c. **Search yield:** 74 articles were screened, of which none were eligible and all were excluded. Excluded PUBMED records are listed below.
d. **Excluded studies:** See table 1, below.

Table 1: Excluded studies

Study		Reason for exclusion
1	Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017, Ahmad N, et al. Lancet. 2018 Sep 8;392(10150):821-834. doi: 10.1016/S0140-6736(18)31644-1.	PICO criteria not met (treatment of MDR-TB)
2	Marks SM, et al. Clin Infect Dis. 2017 Jun 15;64(12):1670-1677. doi: 10.1093/cid/cix208. Erratum in: Clin Infect Dis. 2017 Oct 15;65(8):1433-1434.	Trials were not RCTs, only 2 comparative trails conducted in endemic TB regions
3	Schaaf HS, et al.. Pediatrics. 2002 May;109(5):765-71. doi: 10.1542/peds.109.5.765. PMID: 11986434.	Observational study
4	Fregonese F, et al.. Lancet Respir Med. 2018 Apr;6(4):265-275. doi: 10.1016/S2213-2600(18)30078-X. Erratum in: Lancet Respir Med. 2018 Apr 18;:	IPD analysis of very low quality – "the quality of the evidence was very low. These results support the conduct of randomised trials to identify the optimum regimen for this important and common form of drug-resistant tuberculosis."
5	Goyal V, et al.. BMC Public Health. 2017 Oct 17;17(1):817. doi: 10.1186/s12889-017-4779-5.	PICO criteria not met (prevalence study)
6	Isaakidis P, et al.. Int J Tuberc Lung Dis. 2015 Aug;19(8):969-78. doi: 10.5588/ijtld.15.0123. PMID: 26162364.	PICO criteria not met (treatment of MDR-TB)
7	Lan Z, et al; Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017.. Lancet Respir Med. 2020 Apr;8(4):383-394. doi: 10.1016/S2213-2600(20)30047-3.	PICO criteria not met (treatment of MDR-TB)
8	Kwak M, et al. J Microbiol Methods. 2017 Oct;141:1-9. doi: 10.1016/j.mimet.2017.07.001.	PICO criteria not met (diagnostic study)
9	Mao X, et al. Ann Clin Lab Sci. 2015 Fall;45(5):533-44. Erratum in: Ann Clin Lab Sci. 2015 Fall;45(6):720.	PICO criteria not met (diagnostic study)
10	Falzon D, et al; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Eur Respir J. 2013 Jul;42(1):156-68. doi: 10.1183/09031936.00134712.	PICO criteria not met (treatment of MDR-TB)
11	Ziganshina LE, et al. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD004795. doi: 10.1002/14651858.CD004795.pub3. Update in: Cochrane Database Syst Rev. 2013;6:CD004795.	PICO criteria not met (treatment of MDR-TB)
12	Ahmad Khan F et al.. Eur Respir J. 2017 Jul 27;50(1):1700061. doi: 10.1183/13993003.00061-2017.	PICO criteria not met (treatment of MDR-TB)
13	Fox GJ, et al; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB.. PLoS One. 2016 Mar 29;11(3):e0151724. doi: 10.1371/journal.pone.0151724.	PICO criteria not met (treatment of MDR-TB)
14	Chang KC, et al.. J Antimicrob Chemother. 2010 Aug;65(8):1551-61. doi: 10.1093/jac/dkq202.	PICO criteria not met (diagnostic study)
15	Jacobson KR,et al.. Clin Infect Dis. 2010 Jul 1;51(1):6-14. doi: 10.1086/653115.	PICO criteria not met (treatment of XDR-TB)
16	Chang KC, et al.. Antimicrob Agents Chemother. 2013 Sep;57(9):4097-104. doi: 10.1128/AAC.00120-13.	PICO criteria not met (treatment of MDR-TB)
17	Mori T, et al. Kekkaku. 2012 Sep;87(9):565-75.	PICO criteria not met(Japanese epidemiology study)
18	Chen TC, et al.. Int J Infect Dis. 2011 Mar;15(3):e211-6. doi: 10.1016/j.ijid.2010.11.008. Epub 2010 Dec 30.	PICO criteria not met (treatment of MDR-TB)
19	Ziganshina LE, et al. Cochrane Database Syst Rev. 2013 Jun 6;2013(6):CD004795. doi: 10.1002/14651858.CD004795.pub4.	PICO criteria not met (treatment of MDR-TB) & update of #10
20	Theron G, et al. Cochrane Database Syst Rev. 2016 Sep 8;9(9):CD010705. doi: 10.1002/14651858.CD010705.pub3.	PICO criteria not met (diagnostic study) & update of # 29
21	Guan Y, et al.2020 Jun 19;99(25):e20648. doi: 10.1097/MD.0000000000020648.	PICO criteria not met (treatment of MDR-TB)
22	Bastos ML, et al; Collaborative Group for Meta-analysis of Individual Patient Data in MDR-TB. Clin Infect Dis. 2014 Nov 15;59(10):1364-74. doi: 10.1093/cid/ciu619.	PICO criteria not met (treatment of MDR-TB)
23	Chisompola NK, et al. BMC Infect Dis. 2020 May 13;20(1):344. doi: 10.1186/s12879-020-05031-5.	PICO criteria not met (genomic study)

24	Ahuja SD, et al., Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. PLoS Med. 2012;9(8):e1001300. doi: 10.1371/journal.pmed.1001300.	PICO criteria not met (treatment of MDR-TB)
25	Feng Y, et al. PLoS One. 2013;8(2):e55292. doi: 10.1371/journal.pone.0055292.	PICO criteria not met (diagnostic study)
26	Chang KC, et al. Int J Tuberc Lung Dis. 2015 Dec;19(12):1417-27. doi: 10.5588/ijtld.15.0216.	PICO criteria not met (treatment of MDR-TB)
27	Langendam MW, et al.. PLoS One. 2013;8(1):e53599. doi: 10.1371/journal.pone.0053599.	PICO criteria not met (comparative study of various fluoroquinolones)
28	Johnston JC et al.. PLoS One. 2009 Sep 9;4(9):e6914. doi: 10.1371/journal.pone.0006914.	PICO criteria not met (treatment of MDR-TB)
29	Theron G,et al.. Cochrane Database Syst Rev. 2014 Oct 29;(10):CD010705. doi: 10.1002/14651858.CD010705.pub2.	PICO criteria not met (diagnostic study)
30	Ziganshina LE, et al. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004795. doi: 10.1002/14651858.CD004795.pub2.	PICO criteria not met (treatment of MDR-TB) & review updated
31	Bisson GP, et al. Lancet. 2020 Aug 8;396(10248):402-411. doi: 10.1016/S0140-6736(20)31316-7. Erratum in: Lancet. 2020 Sep 26;396(10255):886.	PICO criteria not met (treatment of MDR-TB in HIV patients)

e. Evidence synthesis

As no systematic reviews of RCTs could be retrieved, the recent 2020 WHO guidelines[1] for TPT was appraised using the AGREE2 instrument.[7] Refer to the table below for the AGREE2 assessment conducted by TL and MR.

Guidance relevant to this review are provided in Table 2. The recommended targeted treatment options apply to children, adolescents and adults of all ages who are considered high-risk and are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines".

Table 2: WHO Guidelines 2020 recommendations for preventive treatment for contacts of patients with multidrug- or rifampicin-resistant TB

Citation (date published)	Recommendation (pg)	AGREE II appraisal
WHO consolidated guidelines on tuberculosis. Module 1: prevention - tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.	Pg 20. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. ***(Conditional recommendation, very low certainty in the estimates of effect)*** Examples of high risk-groups were defined as: • children, • people on immunosuppressive therapy • PLHIV Confirmation of infection by LTBI testing is usually required before treatment is initiated.	**6/7**

Remarks: The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events. The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV). The drugs should be selected according to the drug susceptibility profile of the source case. Confirmation of infection with LTBI tests is required. This recommendation must not affect on-going placebo-controlled clinical trials of MDR-TB contacts on ethical grounds. The results of such clinical trials are crucial for updating this recommendation. Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years are required, regardless of the provision of preventive treatment.

Rationale: Overall, the Guideline Development Group (GDG) judged that the potential benefits of targeted preventive treatment for MDR-TB contacts based on individual risk assessments outweigh the harm but acknowledged uncertainty about the efficacy of the intervention due to the lack of RCTs. It also noted that provision of preventive treatment for MDR-TB contacts would be acceptable, particularly to patients and health care workers. The GDG stressed that treatment should be given to selected individuals after a careful risk assessment, including intensity of exposure, certainty of the source case, reliable information on the drug resistance pattern of the index case and potential adverse events. It should be given only to household contacts at high risk (e.g. children, people on immunosuppressive therapy and people living with HIV). Confirmation of infection by LTBI testing is required before individualized treatment is initiated.

Table 2: GRADE evidence tables from the WHO Guidelines, 2020 for PICO 10: Should preventive treatment be recommended for contacts of patients with multidrug-resistant or rifampicin-resistant TB?

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB DISEASE (BOTH DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB)												
4 *(66-69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04;0.94)[4]	154 fewer per 1000 (273 fewer to 36 fewer)	⊕◯◯◯ Very low	Critical
							0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)		
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		
INCIDENCE OF MDR-TB												
3[2] *(66, 67, 69)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)	⊕◯◯◯ Very low	Critical
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		
MORTALITY												
0	No evidence								Cannot be estimated		-	Important

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
ADVERSE EVENTS												
0	No evidence								Cannot be estimated		-	Critical
DEVELOPMENT OF DRUG RESISTANCE												
0	No evidence											Important

[1] Risk of bias in selection of the control group, and none of the studies adjusted for confounders. Downgraded by two levels.
[2] The study by Shaaf et al. was excluded, as the incidence of MDR-TB was not reported.
[3] Small sample sizes and wide 95% CIs. Downgraded by two levels.
[4] Reference (68)
[5] Reference (66)
[6] Reference (67)
[7] Reference (69)

Overall quality: very low

Five studies that included fewer than 20 participants who completed preventive TB treatment were excluded. In addition, the study by Kritski [8] was excluded as only isoniazid monotherapy was given.

The updated review comprised 10 studies comparing participants who received preventive treatment for MDR-TB and those who did not. However, clinical heterogeneity among the studies prevented the conducting of a meta-analysis. One study was excluded because only isoniazid monotherapy was used, and five studies were excluded as less than 20 participants completed preventive TB treatment. Therefore, the quality of the evidence was based on only four studies. No active TB was reported in either the intervention or the control group in one study, while one person with active TB due to a drug-susceptible strain that was different from the presumed source was reported in another study. The remaining two studies addressed the efficacy of preventive treatment - In one cohort of 119 contacts, 104 with LTBI initiated fluoroquinolone-based preventive treatment, of whom 93 (89%) completed treatment, and none developed active TB; while 3 of 15 (20%) contacts who refused treatment developed MDR-TB (OR 0.02, 95% CI 0.00; 0.39). In the other study, confirmed or probable TB developed in 2 of 41 (4.9%) children receiving tailored preventive treatment and in 13 of 64 (20.3%) children who did not receive proper preventive treatment (OR 0.2, 95% CI 0.04; 0.94)

Conclusion

Targeted MDR-TB preventive treatment of high-risk groups exposed to an index case of MDR-TB or rifampicin-resistant TB is recommended in the 2020 WHO consolidated guidelines on TPT. However, this is based on very low-quality evidence, the guidelines recommends that "clients must be given detailed information about the benefits and harms of the preventive treatment and asked for explicit informed consent. In view of the uncertainty about the balance of benefit to harm, informed consent, preferably in writing, is required, based on the local context and practice in similar situations".

Appendix 1 – Search strategy

Database: **PubMed**
Date: **27 October 2020**

Search	Query	Results
#5	Search: (#1 AND #2) NOT (animals[mh] NOT humans[mh]) Filters: Systematic Review, Meta-Analysis	31
#3	Search: (#1 AND #2) NOT (animals[mh] NOT humans[mh])	1,201
#2	Search: Fluoroquinolones[mh] OR Fluoroquinolone[tiab] OR Fluoroquinolones[tiab] OR Fluroquinolone[tiab] OR Fluroquinolones[tiab] OR Ciprofloxacin[tiab] OR Fleroxacin[tiab] OR Enoxacin[tiab] OR Enrofloxacin[tiab] OR Gatifloxacin[tiab] OR Gemifloxacin[tiab] OR Moxifloxacin[tiab] OR Norfloxacin[tiab] OR Ofloxacin[tiab] OR Levofloxacin[tiab] OR Pefloxacin[tiab]	60,169
#1	Search: Tuberculosis, Multidrug-Resistant[mh] OR Multidrug-Resistant Tuberculosis[tiab] OR MDR Tuberculosis[tiab] OR Multi-Drug Resistant Tuberculosis[tiab] OR Drug-Resistant Tuberculosis[tiab]	10,814

Database: **Epistemonikos**
Date: **27 October 2020**

#	Query	Records
4	#3 filtered by systematic reviews	25
3	(title:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin) OR abstract:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin)) AND (title:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis") OR abstract:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis"))	77
2	(title:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin) OR abstract:(Fluoroquinolone OR Fluoroquinolones OR Fluroquinolone OR Fluroquinolones OR Ciprofloxacin OR Fleroxacin OR Enoxacin OR Enrofloxacin OR Gatifloxacin OR Gemifloxacin OR Moxifloxacin OR Norfloxacin OR Ofloxacin OR Levofloxacin OR Pefloxacin))	2011
1	(title:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis") OR abstract:("Multidrug-Resistant Tuberculosis" OR "MDR Tuberculosis" OR "Multi-Drug Resistant Tuberculosis" OR "Drug-Resistant Tuberculosis"))	519

Appendix 2: Adaptation of the WHO 2020 TPT Guidelines Evidence to decision framework

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No **x Yes** ○ Varies ○ Don't know	Rationale as per WHO guideline panel: "Drug-resistant TB continues to threaten global TB control, remains a major public health concern and poses a global health security risk. An estimated 580 000 people developed MDR or rifampicin-resistant TB in 2015, and 250 000 people died as a result (WHO Global report, 2016). Prevention of MDR-TB would reduce the global burden and also address demands from individuals to be protected against development of MDR-TB[9 10 11 12]". **South Africa.** Over 6700 patients developed MDR or rifampicin-resistant TB in South Africa in 2020.**Error! Reference source not found.**	
Balance of effects: Do the benefits outweigh the harms?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
X Yes ○ No ○ Equal ○ Uncertain	We conducted a systematic review of the effectiveness of preventive treatment for contacts of patients with MDR or rifampicin-resistant TB. The review covered 10 studies with control groups, of which five found no TB case in either group. The table above (table 2) summarizes the results after exclusion of studies with <20 participants who completed preventive TB treatment and those on isoniazid monotherapy. Common adverse events included gastrointestinal symptoms, muscle or joint pain, headache, dizziness and hepatitis. In four studies, ≥ 50% of participants experienced at least one adverse event. Bamrah et al. (74) reported no serious adverse events, defined as hospitalization or irreversible morbidity, attributable to fluoroquinolone-based preventive treatment. The median proportion of participants who discontinued treatment because of adverse events in all studies was 5.1% (IQR 1.9–30.2%). No study reported preventive treatment for contacts of rifampicin-resistant TB.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Yes ○ No ○ Equal **x Uncertain**	Very low quality evidence, based on small observational studies with significant methodological deficiencies [8-11]. There are rare but serious safety concerns associated with use of fluoroquinolones: • *Musculoskeletal:* tendonitis, tendon rupture, myalgia, muscle weakness, arthralgia, joint swelling; • *Nervous system:* peripheral neuropathy, psychosis, anxiety, insomnia, depression, hallucinations, suicidal thoughts, confusion, impairment of vision, hearing, smell and taste; • *Cardiac:* aortic aneurysm and dissection; endocrine: hypoglycaemic coma. (SAHPRA media statement, December 2018; FDA safety signal reports for fluoroquinolones; EMA safety signal report for fluoroquinolones)	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
X Very low o Low o Moderate o High o No included studies	As per WHO Guideline panel: "The overall quality of the evidence was very low because of very serious risks of bias and imprecision. In the study by Trieu et al.[9], active TB was ascertained during follow-up by checking cases identified in the TB registry. A meta-analysis was not conducted because of the heterogeneity of the drugs used".	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
o Important uncertainty or variability o No important uncertainty or variability **x Minimal uncertainty**	As per WHO Guideline panel: "We conducted an online survey to solicit the values and preferences of individuals affected by the recommendations (https://apps.who.int/iris/bitstream/handle/10665/260235/WHO-CDS-TB-2018.9-eng.pdf). Data were available from 142 respondents. More than 80% of the respondents reported that they would strongly or somewhat prefer to receive preventive treatment or give it to their children if they were exposed to someone with MDR-TB disease in the household. The reasons for not preferring preventive treatment included: limited evidence on preventive treatment for MDR-TB and concern about side-effects and development of drug resistance".	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
x Greater resource requirements with intervention o Less resource requirements with the intervention o Neither greater nor less o Varies o Don't know	Judgement as per WHO Guideline panel, no rationale provided	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		Providing preventive treatment could be cost–effective by preventing MDR-TB cases in settings with low transmission of MDR-TB. In settings with high risk of MDR-TB transmission, the potential benefit may wane and the cost–effectiveness becomes uncertain. The need for drug susceptibility testing, regimens used, risk of re-infection and adverse events could also affect cost–effectiveness.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Not applicable.	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased **X Increased** ○ Varies ○ Don't know		
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Not applicable.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ No ○ Probably no ○ Probably yes **X Yes** ○ Varies ○ Don't know	As per WHO Guideline panel: "Some national or clinical guidelines already recommend preventive treatment for contacts of MDR-TB"[13] [14] [15] South African National Department of Health's TB program recommends fluoroquinolones for DR-TB prophylaxis, in the draft TPT Guidelines.	Preventive treatment could be acceptable, particularly to patients and health care workers. The intervention may not be acceptable in some settings, particularly to programme managers for fear of development of XDR-TB and little experience in using TB preventive treatment for drug susceptible TB.
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINES, 2020**		
○ No ○ Probably no ○ Probably yes ○ **Yes** ○ Varies ○ Don't know		
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
X No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	The product is registered in South Africa with the South African Health Products Regulatory Authority, and is procured in the public sector. However, as per the WHO recommendation below, targeted treatment with individual risk assessment and the need to establish latent TB status by tuberculin skin testing was considered not to be feasible. WHO Guidelines, 2020 recommendation: *"In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.* ***(Conditional recommendation, very low certainty in the estimates of effect)****…. Confirmation of infection by LTBI testing is usually required before treatment is initiated".*	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	30 November 2021	TL, JN	Fluoroquinolones not to be used as prophylaxis for high risk contacts of cases of active MDR TB; very low quality evidence based on small observational studies. Targeted treatment needs individualized risk assessment and tuberculin skin testing.

References:

[1] World Health Organization Consolidated guidelines on tuberculosis: Module 1: Tuberculosis preventive treatment, 2020. [Accessed 14 November 2021] https://www.who.int/publications/i/item/9789240001503

[2] World Health Organization Global TB report, 2019 [Accessed 14 November 2021]. https://www.who.int/teams/global-tuberculosis-programme/tb-reports

[3] NICD. The first National TB prevalence survey of South Africa, 2018. [Accessed 14 November 2021]. https://www.nicd.ac.za/wp-content/uploads/2021/02/TB-Prevalence-survey-report_A4_SA_TPS-Short_Feb-2021.pdf

[4] Moscow Declaration to End TB; First WHO global ministerial conference on ending TB in the sustainable development era: a multisectoral response. Geneva: World Health Organization and the Ministry of Health of the Russian Federation; 2017 [Accessed 14 November 2021] https://www.who.int/tb/features_archive/Moscow_Declaration_to_End_TB_final_ENGLISH.pdf?ua=1

[5] Resolution 73/3: Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. New York: United Nations General Assembly; 2018. [Accessed 14 November 2018] https://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/73/3

[6] Minutes of the NEMLC meeting of the 30 January 2020.

[7] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J, Zitzelsberger L; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010 Dec 14;182(18):E839-42. https://pubmed.ncbi.nlm.nih.gov/20603348/

[8] Kritski AL, Marques MJ, Rabahi MF, Vieira MA, Werneck-Barroso E, Carvalho CE, et al. Transmission of tuberculosis to close contacts of patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 1996;153(1):331–5. https://pubmed.ncbi.nlm.nih.gov/8542139/

[9] Bamrah S, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012. Int J Tuberc Lung Dis. 2014;18(8):912–8. https://pubmed.ncbi.nlm.nih.gov/25199004/ [cited as reference 66 in the WHO SOF table on page 5]

[10] Trieu L, Proops DC, Ahuja SD. Moxifloxacin Prophylaxis against MDR TB, New York, New York, USA. Emerg Infect Dis. 2015;21(3):500–3. https://pubmed.ncbi.nlm.nih.gov/25695482/ [cited as reference 69 in the WHO SOF table on page 5]

[11] Garcia-Prats AJ, Zimri K, Mramba Z, Schaaf HS, Hesseling AC. Children exposed to multidrug-resistant tuberculosis at a home-based day care centre: a contact investigation. Int J Tuberc Lung Dis. 2014;18(11):1292–8. https://pubmed.ncbi.nlm.nih.gov/25299860/ [cited as reference 67 in the WHO SOF table on page 5]

[12] Schaaf HS, Garcia-Prats AJ, Hesseling AC, Seddon JA. Managing multidrug-resistant tuberculosis in children: review of recent developments. Curr Opin Infect Dis. 2014;27(3):211–9. https://pubmed.ncbi.nlm.nih.gov/24751893/ [cited as reference 68 in the WHO SOF table on page 5]

[13] Fox GJ, Schaaf HS, Mandalakas A, Chiappini E, Zumla A, Marais BJ. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infectious cases. Clin Microbiol Infect. 2017;23(3):147–53. https://pubmed.ncbi.nlm.nih.gov/27592087/

[14] Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports. 2000;49(Rr-6):1–51. https://pubmed.ncbi.nlm.nih.gov/10881762/

[15] Cain KP, Nelson LJ, Cegielski JP. Global policies and practices for managing persons exposed to multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2010;14(3):269–74. https://pubmed.ncbi.nlm.nih.gov/20132616/

MEDICINE REVIEW

Guideline question: In adults diagnosed with RR-TB, should a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen?

Adolopment of the WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment 2022

Executive Summary

Date: 30 March 2023

Medicine (INN): bedaquiline, pretomanid, linezolid, moxifloxacin

Medicine (ATC): J04AK05; J01XX08, J04AK08, J01MA14

Indication (ICD10 code): A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0 + (U50.00-01)

Patient population: Adults with rifampicin resistant tuberculosis (RR-TB)

Prevalence of condition:

- In a cross-sectional study of identified tuberculosis cases in South Africa between 2012 and 2014, prevalence of multidrug resistant tuberculosis (MDR-TB) was 2.8% (95% CI 2.0, 3.6) and of extensively drug resistant tuberculosis (XDR-TB) was 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018)(1) https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30222-6/fulltext#supplementaryMaterial
- In 2021, there were approximately 21 000 incident cases of RR-TB in South Africa, as reported by WHO. (WHO Global Tuberculosis Report, 2022)(2) https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-3-drug-resistant-tb

Level of Care: Primary healthcare

Prescriber Level: Medical officer in consultation with a dedicated specialist center.

Motivator/reviewer name(s): Adolopment review team: Jessica Taylor (JT), Natasha Gloeck (NG), Sumayya Ebrahim (SE), Funeka Bango (FB), Norbert Ndjeka (NN), Gary Maartens (GM), Michael McCaul (MM) (methodologist), Jeremy Nel (JN), Tamara Kredo (TK) (methodologist), Karen Cohen (KC)

Declarations of interest: The review team have no interests to declare in the establishment of this evidence summary. KC, TK, MM, FB, NG, and SE are members of the South African GRADE Network.

Funding and acknowledgments:

NG, TK, MM, SE, FB are partly supported by the Research, Evidence and Development Initiative (READ-It) project. READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.

We would like to thank and acknowledge the following people:

- Trudy Leong, who supported FB with planning the economic analyses and presenting the results.
- Greg Fox, the reviewer of the WHO systematic review, for sharing the results.

- Fuad Mirzayev and Samuel Schumacher from WHO's TB Programme, for their engagement and willingness to share the WHO guideline information prior to publication.
- Beverly Stringer, Karen Lowton, Katherine Fielding, Martina Cusinato and the TB-PRACTECAL-PRO team for presenting the results of the qualitative component of the trial conducted in South Africa.

PTC affiliation: n/a

Key findings

- The South African TB programme is seeking to find the most efficacious, safe, acceptable, and cost-effective regimens to treat people with RR-TB. Therefore, we aimed to review whether a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone be used rather than 9-month or longer (18-month) regimen in adults with RR-TB?

- Current South African standard of care regimens for the treatment of RR-TB include the following:
  - A short-course treatment regimen for less extensive RR-TB disease, without fluoroquinolone resistance. This regimen consists of two months of linezolid (600mg daily), four to six months of high-dose isoniazid, six to nine months of bedaquiline and nine months of levofloxacin, pyrazinamide, ethambutol and clofazimine.
  - An 18-month long-course treatment regimen for RR-TB without additional fluoroquinolone resistance, but with extensive pulmonary or disseminated disease. This regimen consists of six months of bedaquiline and linezolid (600mg daily), and 18 months of clofazimine, terizidone and levofloxacin.
  - An 18-month long-course treatment regimen for RR-TB with additional fluoroquinolone resistance. This regimen consists of six months of bedaquiline and delamanid, and 18 months of clofazimine, terizidone and linezolid (600mg daily).

- In 2022, the WHO published an update of consolidated guidelines on drug-resistant tuberculosis treatment, in which they recommended the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional, very low certainty of evidence).*

- Additional remarks published alongside the above recommendation included:
  - "Results of drug susceptibility testing for fluoroquinolone resistance were recommended to guide the decision on whether moxifloxacin should be retained or dropped from the regimen."
  - "In cases of documented resistance to fluoroquinolones, it was recommended that BPaL without moxifloxacin should be initiated or continued."
  - "This recommendation applies only to the following populations: people with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR TB); people with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB; adults and adolescents aged 14 years and older; all people regardless of HIV status; patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out."
  - "This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid. "

- "The recommended dose of linezolid is 600mg once daily, both for the BPaLM and the BPaL regimen."

- To efficiently use available resources and to avoid duplication we conducted an adaptation of these guidelines using the GRADE 'adolopment' methodology.
  - The guideline was appraised in duplicate using the AGREE II instrument and found to be of sufficient quality for adolopment with an overall assessment score of 83%.
  - The systematic review that underpinned the WHO guideline was appraised in duplicate using the AMSTAR II critical appraisal tool and found to be of "critically low quality" as several aspects of reporting a systematic review were not available or were unclear. Despite the critically low quality we considered the WHO review and underlying evidence synthesis to be the most up to date (i.e., not missing important evidence), relevant (i.e., directly addressing our target PICOs) and GRADE evidence-to-decision aligned evidence available, and sufficient for guideline adaptation.

- We considered the evidence and judgements published in the WHO guideline evidence to decision framework with respect to effectiveness criteria (benefit, harms and balance of effects), economic criteria (resources and cost-effectiveness), and qualitative criteria (values, equity, feasibility and acceptability). Aligned with the purpose of adaptation to consider local context, we collected evidence of resources and economic consequences and data on acceptability from the perspective of patients from a trial specifically conducted in South Africa.

- The BPAL regimen (with linezolid dosed at 600mg daily for 26 weeks) compared to a WHO long course regimen may result in improved treatment success rates in pre-XDR TB RR 1.34, 95% CI 1.20 to 1.40, NNT 4, n = 872, very low certainty evidence) and MDR TB (RR 1.32, 95% CI 1.19 to 1.39, NNT 4, n = 893,very low certainty evidence), and lower levels of treatment failure, recurrence, death and loss to follow up (very low certainty evidence). Additionally, participants from the ZeNix trial receiving the BPaL (n = 43) regimen may have higher levels of treatment success (RR 1.52, 95% CI 1.38 to 1.55, NNT 3, very low certainty evidence) when compared to a cohort receiving the current South African short course regimen (n = 4 216), as well as reduced rates of death and loss to follow up. However, the risk grade 3 – 5 adverse events associated with BPaL in these comparisons was increased 3 to 4-fold and were judged to be moderate (very low certainty evidence).

- The BPaLM regimen (with linezolid dosed at 600mg daily for 16 weeks, then reduced to 300mg for 8 weeks) compared to local standard of care regimens in a study population with predominantly MDR-TB from the randomised control trial, TB-PRACTECAL, may result in improved treatment success rates (aRR 1.73, 95% CI 1.31 to 2.27, NNT 3, n = 128, very low certainty evidence), lower rates of treatment failure and recurrence (aRR 0.26, 95% CI 0.1 to 0.71, NNT 6, n = 128, very low certainty evidence), lower levels of grade 3 to 5 adverse events (aRR 0.41, 95% CI 0.04 to 0.61, NNT 3, n = 213, very low certainty evidence), and lower levels of loss to follow up (RR 0.16, 95% CI 0.12 to 0.52, NNT 6, n = 128, very low certainty evidence).

- As a result of the associated reduction in pill burden and treatment duration, both BPaL and BPaLM regimens were judged to probably be acceptable, feasible and to increase health equity.

- BPaL and BPaLM are both likely to have lower resource requirements and cost than the current South African long regimens, with similar costs when compared to the current South African short course regimen.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE 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: The PHC/Adult hospital ERC suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)

Although WHO recommend moxifloxacin for inclusion in their updated regimen (BPaLM), the PHC/Adult hospital level committee suggest that levofloxacin to be used as fluoroquinolone of choice.

Rationale: The recommended regimen is shorter in duration, less complex and may be cost-saving, particularly for those patients requiring treatment with current South African long regimens. Additionally, the recommended regimen was judged to probably be feasible and acceptable and to improve equity. However, the committee noted the very low quality of evidence on which WHO recommendations are based. In view of the paucity of evidence, the committee felt that the implementation of operational research and enhanced pharmacovigilance to detect safety signals is essential.

Level of Evidence: Very low quality evidence
Review indicator: New high quality evidence

NEMLC RECOMMENDATION (30 March 2023):
The committee supports the ERC's adapted recommendation as follows:
We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence) Levofloxacin to be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.

Monitoring and evaluation considerations
Operational research and enhanced pharmacovigilance essential.

Research priorities
Shortened regimens for paediatric and pregnant populations

Name of author(s)/motivators/Author affiliation and conflict of interest details

Dr. Jessica Taylor[1,7], Dr. Natasha Gloeck[2,3], Ms. Sumayya Ebrahim[2,3], Dr. Funeka Bango[2], Prof. Norbert Ndjeka[5], Prof. Gary Maartens[1,5], Dr. Michael McCaul[4,6], Dr. Jeremy Nel[6], Prof. Tamara Kredo[2,4], Prof Karen Cohen[1,6]

1. Division of Clinical Pharmacology, University of Cape Town
2. Health Systems Research Unit, South African Medical Research Council
3. Cochrane South Africa, South African Medical Research Council
4. Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University.
5. National Department of Health TB Programme
6. Adult-PHC Evidence Review Committee

Introduction/ Background

In 2021, approximately 450 000 people developed rifampicin resistant tuberculosis (RR-TB), and 191 000 deaths due to RR-TB were recorded globally.(2) A further 20% of these RR-TB cases were estimated to have additional fluoroquinolone resistance. In South Africa, at least 21 000 incident cases of RR-TB occurred during the year 2021. (2)

RR-TB is associated with poor treatment outcomes as a result of prolonged (9 - 18 months) treatment regimens that are difficult to adhere to, and consist of less effective and more toxic drugs.(3) Historically, aminoglycosides in particular, were associated with both treatment limiting nephrotoxicity and ototoxicity, leaving patients who had successfully completed RR-TB treatment with significant morbidity. The introduction of novel and repurposed drugs to achieve injectable-free regimens heralded a new era in RR-TB treatment, with some improvement in treatment outcomes. For example, a 2018 cohort of South African patients with RR-TB and additional fluoroquinolone resistance, recorded 73% of treatment outcomes as favorable when using bedaquiline containing regimens. ((3)

Since 2019, three all-oral treatment regimens have been made available in South Africa for the management of RR-TB in adults with pulmonary tuberculosis (TB)(4):

1. The shorter RR-TB regimen (SCR) is available for patients with RR-TB without additional fluoroquinolone resistance and less severe pulmonary disease. This 9-month treatment regimen consists of two months of linezolid, four to six months of high-dose isoniazid, six to nine months of bedaquiline and nine months of levofloxacin, pyrazinamide, ethambutol and clofazimine.
2. The longer RR-TB regimen (LCR-1) is available for patients with RR-TB without additional fluoroquinolone resistance but with extensive pulmonary disease. This 18-month treatment regimen consists of six months of bedaquiline and linezolid, and 18 months of clofazimine, terizidone and levofloxacin.
3. The fluroquinolone-resistant RR-TB regimen (LCR-2) is available for patients with RR-TB and additional fluoroquinolone resistance. This 18-month treatment regimen consists of six months of bedaquiline and delamanid, and 18 months of clofazimine, terizidone and linezolid.

Despite the national implementation of all-oral treatment regimens, free of the toxicities associated with aminoglycosides, these regimens are not without their own concerns. (5) These regimens remain long and are complicated for both patients to adhere to and healthcare workers to implement and are associated with a significant pill burden. Furthermore, the oral drugs included in these regimens are still associated with the potential for significant toxicity, some of which may be related to treatment duration. (6)

In 2022, the World Health Organization (WHO) recommended the use of a six month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM), rather than the nine month or longer regimens, for the treatment of pulmonary TB and all forms of extrapulmonary TB, except for TB involving the central nervous system, osteoarticular TB, and disseminated (miliary) TB.(7) Desirable characteristics of this regimen include the use of fewer drugs with a reduced pill burden and a shorter treatment duration.(8) To efficiently use available resources and to avoid duplication we conducted an adaptation of these guidelines using the GRADE 'adolopment' methodology. (7, 9)

Purpose/Objective and PICO prioritization

To determine if, in adults diagnosed with RR-TB, a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone is non-inferior to and/or safer than current standard-of-care regimens (9-month or 18-months).

Table 1. PICO eligibility criteria:

Population	Adults with RR-TB
Intervention	1. BPaL (bedaquiline, pretomanid, linezolid) 2. BPaLM (bedaquiline, pretomanid, linezolid, moxifloxacin)
Comparator	1. South African RR-TB short course regimen (SCR) 2. South African RR-TB long course regimen (LCR-1) 3. South African RR-TB with additional fluoroquinolone resistance long course regimen (LCR-2)
Outcome	1. Efficacy 1.1 Mortality 1.2 Treatment failure 1.3 Treatment success 1.4 Loss to follow-up 1.5 Time to sputum culture conversion

	2. Safety 2.1 Adverse events 2.2 Treatment interruption/substitution due to adverse events

Three specific PICO questions were prioritized by the review team:

a) Is BPaL (intervention 1) non-inferior to, and/or safer than the South African standard of care (comparator 3) in the treatment of adults with or without fluoroquinolone-resistant tuberculosis?
b) Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?
c) Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

Methods:

We conducted a guideline adaptation process using the GRADE adolopment methodology (9) which aims to use existing high-quality, timely and relevant clinical practice guidelines (CPGs) and evidence synthesis (i.e., systematic reviews) to answer prioritised guideline questions. We drew on supporting resources in evidence synthesis and rapid guideline development to further guide methods and processes.(10-12) The adolopment approach to guideline production combines guideline adoption, adaptation, and, as needed, *de novo* development of recommendations, by assessing the underlying relevance, timeliness and directness of synthesised evidence from a source guideline and translating this to the GRADE Evidence-to-Decision (EtD) table. In summary, steps include i) selection of the guideline topic, ii) PICO prioritisation and outcome ranking, iii) identification of appropriate source guidelines, iv) matching source guidelines and recommendations, v) assessment of the underlying evidence according to the EtD criteria and vi) populating the EtD framework and developing a recommendation.

The matched source guideline was appraised using the AGREE II Tool (13) with guideline appraisal by two authors independently for credibility. The underlying evidence synthesis was appraised using the AMSTAR II (14) tool for systematic reviews. We reviewed and extracted the underlying evidence per PICO for the effectiveness EtD criteria (benefit, harms and balance of effects), economic criteria (resources and cost-effectiveness) and qualitative criteria (values, equity, feasibility and acceptability) from the WHO guideline and assessed this for sufficiency. We aimed to supplement this with local contextual evidence (e.g. resources, acceptability, equity).

Identification of appropriate sources guideline

The WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment 2022 was identified as the most appropriate source guideline for adolopment.

Matching source guideline recommendations to each prioritized PICO and determining if a direct matching recommendation exists.

The specific PICO questions prioritized by the review team were matched to recommendations and sub-PICOs with corresponding evidence-to-decision frameworks (EtDs) from the WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment. All matched recommendations and sub-PICOs from the WHO consolidated guidelines were considered sufficiently direct. Table 2 outlines the matching process and directness of each matching recommendation and sub-PICO. Directness refers to the concept that the recommendations are appropriate to the context of the health care setting of interest by addressing population, intervention and prioritised outcomes of interest.

WHO sub-PICO questions 7.1, 7.2, 8.2, 8.3 and 8.5 were not linked to EtDs within the published guideline. These EtDs were requested from the guideline but unfortunately were not available, although additional data analysis was provided. Additional data analysis from original study authors was also requested.

Table 2.

Review target PICO questions	Matching WHO consolidated guideline recommendation	WHO Sub-PICO Number	WHO Target PICO or Sub-PICO	WHO Sub-PICO Recommendation	Directness
Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)	5.2	Should BPaL vs. WHO_long be used for pulmonary MDR/RR-TB? BPAL compared to WHO_Long in pulmonary MDR/RR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than longer (18-month) regimens is suggested in patients with MDR/ RR-TB and without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by review team. Although intervention is BPaL not BPaLM, comparator and population is appropriate.
		5.3	Should BPaL vs. SA_new be used for pulmonary MDR/RR-TB? BPAL compared to SA_new in MDR/RR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than the 9-month regimen (with linezolid) is suggested in patients with MDR/RR-TB without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by review team. Although intervention is BPaL and not BPaLM, comparator and population is appropriate.
		6.1	Should BPaLM vs local SoC (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB or pre-XDR-TB? BPaLM compared to TB-PRACTECAL comparator in pulmonary MDR/RRTB and pre-XDR TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than 9-month or longer (18-month) regimens is suggested in patients MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct. Appropriate intervention and comparator consists of regimens that are South African standard of care. However, population includes both MDR/RR-TB and pre-XDR-TB.
		6.6	"Should BPaL (linezolid 600mg/300mg) vs. local SoC regimens (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB and pre-XDR-TB? BPaL (linezolid 600mg/300mg) compared to TB PACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR-TB	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than 9-month or longer (18-month) regimens is suggested in patients MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct. Although intervention considered is BPaL not BPaLM, the comparator includes regimens that are South African standard of care. However, population includes both MDR/RR-TB and pre-XDR-TB.
		8.2	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPaLM vs WHO long-IPD 2021 in pulmonary MDR/RR TB	Not found	Considered sufficiently direct.
		8.3	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPALM vs SA_new in pulmonary MDR/RR-TB	Not found	Considered sufficiently direct.
Is BPaL (intervention 1) non-inferior to,	WHO suggests the use of the 6-month treatment regimen	4.1	Should a 6-month regimen using bedaquiline, pretomanid, linezolid vs. longer regimens be used for pulmonary pre-XDR-TB?	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid and linezolid (BPaL), rather than longer	Considered sufficiently direct.

and/or safer than the South African standard of care (comparator 3) in the treatment of adults with fluoroquinolone-resistant tuberculosis?	composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)		BPAL compared to WHO_Long in pulmonary pre-XDR TB	(18-month) regimen is suggested in patients with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB), who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	
		7.1	Should a 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB? TB PRACTECAL BPaLM vs WHO long-IPD 2021	Not found	Considered sufficiently direct by the review team. Although the intervention is BPaLM not BPaL, the comparators consists of regimens that are South African standard of care.
Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and moxifloxacin (BPaLM) rather than 9-monht or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence)	6.2	Should BPaLM vs BPaL (LD 600mg/300mg) be used for pulmonary MDR/RR-TB and pre-XDR-TB? BPaLM compared to BPAL (linezolid 600/300mg)	Conditional for the intervention. The use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM), rather than BPaL is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.	Considered sufficiently direct by the review team, despite population including those with MDR/RR-TB and pre-XDR-TB.
		7.2	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary pre-XDR-TB? TB PRACTECAL BPaLM vs BPaL (excluding 1200mg regimen) from PRACTECAL, ZENIX studies (4 cohorts) in pulmonary pre-XDR TB	Not found	Considered sufficiently direct by the review team despite the population consisting of those with pre-XDR-TB.
		8.5	Should 6-month regimen using bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance? TB PRACTECAL BPaLM vs BPaL (excluding 1200mg regimen) from PRACTECAL, ZENIX and NIX Studies (6 cohorts) in pulmonary MDR/RR-TB.	Not found	Considered sufficiently direct

a. Assess underlying evidence per recommendation.

i. Availability of an effectiveness systematic review underlying the recommendations

The evidence underpinning the recommendations in the WHO guideline was based on evidence synthesis of the datasets from the TB-PRACTECAL trial, the NIX trial, the ZENIX trial, the South African TB Program 2019 cohort, the South African TB Program 2017 cohort and 2021 WHO individual patient data (multiple cohorts following a public call for data from the WHO).(15-17) The evidence-to-decision (EtD) frameworks based on this data were available in the guideline. Those not available were sourced from the background review authors as highlighted previously.

ii. Evidence quality:

Guideline AGREE-II appraisal

The 2022 'WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment' was appraised by JT and NG using the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument.(13) We found the guideline to be of sufficient quality, with an overall assessment score of 83% (recommended with modifications). Individual overall domain scores can be reviewed in table 2. The individual scores and judgement comments of both appraisers can be found in appendix 1.

Table 2. AGREE-II Appraisal

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Overall Assessment
WHO consolidated guidelines on tuberculosis: Drug-resistant tuberculosis treatment, 2022	86%	78%	63%	89%	65%	67%	83%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigor of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Guideline AMSTAR II appraisal

The systematic review that underpinned the WHO guideline was appraised by SE and NG using the AMSTAR II critical appraisal tool.(14) Both reviewers rated this review as "Critically low quality" – there was no or minimal information around search strategy, study selection, data extraction, excluded studies with reasons, methods for assessing risk of bias in individual studies, sources of included study funding and meta-analysis methods. The individual AMSTAR II appraisal for both appraisers can be found in appendix 2.

Despite the critically low quality of the underpinning systematic review, the authors considered the WHO review and underlying evidence synthesis to be the most up to date (i.e. not missing important evidence), relevant (i.e. directly addressing our target PICOs) and GRADE EtD aligned evidence available, and sufficient for guideline adaptation.

iii. Qualitative evidence and sufficiency

A summary of the available qualitative evidence was presented at the ERC meeting (16 March 2023) by Beverly Stringer and team from TB-PRACTECAL-PRO, a qualitative sub study of TB-PRACTECAL that captured patient-reported experiences and quality of life outcomes. The results of this study were used to update the evidence presented by WHO and presented to the ERC.

iv. Economic evidence and sufficiency

Two studies were found to have assessed the cost effectiveness of the BPaL regimen as the intervention. Both these studies were assessed and included in the decision framework by the WHO. The studies were multinational analyses which included patients from South Africa in their study populations. The study population in the paper by Gomez et al. 2021 was patients with XDR-TB, MDR-TB failure and treatment-intolerant patients and compared BPaL to the 18-month XDR regimen.(18) Treatment outcomes for study were from the Nix and ZeNix trials. The second study which was also trial based (TB-PRACTECAL) by Sweeney et al. 2022 assessed the cost effectiveness of BPaL with or without moxifloxacin (BPaLM) or clofazimine (BPaLC).(19) Although this study focused on patients with RR-TB, the regimen used as a comparison was a mix of the long and short regimens. A summary of the economic evidence is included in table 3.We did not find a study that focused on patients with RR-TB which assessed the cost effectiveness of the BPaL regimen compared to the short oral regimen, which is one of the current standard of care regimens in South Africa.

A normative cost analysis of direct costs associated with BPaL and BPaLM regimens was conducted by the review team and included for consideration by the ERC.

Table 3. Summary of Economic Evidence

Study ID	Study Title	Participants	EE Methods	Study Perspective	Intervention	Comparison	Model	Input parameters	Outcome measure	Results	Unit costs for BPaL (M/C)	Cost for standard of care regimen (short oral regimen)
Gomez, et al. 2021.	Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines	Patients with XDR-TB, MDR-TB failure and treatment intolerant patients.	Cost-utility analysis	Provider's perspective	BPaL	Std of care (SA: 18 month regimen: 6 months of linezolid, bedaquiline, delamanid, clofazimine, terizidone, pyrazinamide, high-dose isoniazid (or ethionamide) and 12 months of linezolid, clofazimine, terizidone, pyrazinamide, high-dose isoniazid (or ethionamide)	Markov model	Demographics Treatment outcomes (Nix and ZeNix trials) Costs (drugs, visits, tests) Disability weights	1. DALYs averted 2. The potential maximum price at which the BPaL regimen could become cost neutral.	Study showed that BPaL for the treatment of XDR-TB compared to the 18 month regimen has the potential to be cost saving.	Presented per month in 2018 US$: $296,4 (drugs) $65,3 (delivery)	
Sweeney et al. 2022.	Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis	Patients with RR-TB, also potentially including resistance to isoniazid and/or fluoroquinolones	Cost-utility analysis	Provider's perspective	BPaL with and without moxifloxacin (BPaLM) or clofazimine (BPaLC)	Current mix of long and short standard of care (SOC) regimens to treat RR-TB	Markov model	Demographics Treatment outcomes (TB-PRACTECAL trial) Costs (drugs, visits, tests) Disability weights	DALYs averted	The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa	Costs presented in 2019 US$ Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470	Current SOC regimen mix (74% short, 26% long): $4,517

Evidence to Decision Framework

We populated one consolidated EtD framework per prioritised PICO as below. Overlapping evidence per EtD criteria from the WHO sub-PICOs were merged as necessary per target prioritised PICO.

We incorporated additional data analysis relevant to WHO sub-PICO 7.1 and 7.2, that was made available in the absence of individual EtDs in the guideline document. This data is listed as additional considerations in the EtDs labelled "b" and "c" respectively.

Subgroup analyses obtained from the authors of TB-PRACTECAL were included under additional considerations in the Etd labelled "b" due to the lack of a populated EtD for WHO sub-PICO 8.3, which was deemed to be of critical importance by the review team.

For each EtD criteria/domain the original WHO EtD evidence, judgement and if applicable additional considerations are presented alongside the PHC/Adult hospital level committee's judgements, local or updated evidence and additional considerations.

A summary of judgements per prioritised PICO is presented below:

a) Is BPaL (intervention 1) non-inferior to, and/or safer than the South African standard of care (comparator 3) in the treatment of adults with or without fluoroquinolone-resistant tuberculosis?

Should a 6-month regimen using bedaquiline , pretomanid, linezolid (600mg/300mg) vs. current South African standard-of-care regimes be used for pulmonary MDR/RR or pre-XDR TB? (Combined WHO sub-PICOs 4.1, 5.2, 5.3 and 6.6)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017.	Drug-resistant TB is a global challenge and access to treatment often problematic, with regimens typically being long, toxic, and expensive. More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse

	Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need). Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year. More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021)	events and preventing acquisition of additional drug resistance.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub- PICO 4.1)*** **Research evidence** The BPaL 600–26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with quinolone resistance was compared to a cohort of MDR/RR-TB patients with fluoroquinolone resistance from 2021 IPD, receiving longer regimens for treatment of MDR/RR-TB designed in line with 2020 WHO guidelines. Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (n=33) compared to participants receiving longer regimens for MDR/RR-TB (n=839) experienced higher levels of treatment success (100% vs 75%), i.e. a 34% relative increase (RR=1.34, 95%CI 1.20 to 1.40); lower levels of failure and recurrence (0.0% vs 6.6%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.08 to -0.04); lower levels of deaths (0.0% vs 9.9%), i.e. a 10% absolute reduction (RD=-0.10, 95%CI -0.12 to -0.01); lower levels of loss to follow-up (0.0% vs 9.1%), i.e. a 9% absolute reduction (RD=-0.09, 95%CI -0.11 to -0.01); higher levels of adverse events (15% vs 4.4%), i.e. a 3.4-fold increase (RR=3.44, 95%CI 1.44 to 8.17); and lower levels of amplification of drug-resistance (0.0% vs 7.4%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.09 to -0.03). BPaL 600–26 may improve treatment success, failure and recurrence, death, loss to follow-up and amplification of drug-resistance while leading to more adverse events but the evidence is very uncertain.	**Additional Considerations applicable to all sub-PICO's** Beyond the outcomes captured directly as research evidence in the presented statistical analyses, the WHO 'Target Regimen Profile for rifampicin-resistant tuberculosis' (WHO, 2016) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration, reduced pill burden and number of component drugs and manageable DDIs. Decrease in the treatment duration is therefore an important desirable effect. **Additional considerations applicable to sub-PICO 4.1 only**

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Treatment success	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 1.34** (1.20 to 1.40)	Study population	
				745 per 1 000	**253 more per 1 000** (149 more to 298 more)

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Failure and recurrence	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.07** (-0.08 to -0.04)	Study population	
				66 per 1 000	**70 fewer per 1 000** (71 fewer to 68 fewer)
Death	937 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.10** (-0.12 to -0.01)	Study population	
				99 per 1 000	**109 fewer per 1 000** (111 fewer to 100 fewer)
Lost to follow up	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.09** (-0.11 to -0.01)	Study population	
				91 per 1 000	**99 fewer per 1 000** (101 fewer to 91 fewer)
Amplification of drug resistance	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.07** (-0.09 to -0.03)	Study population	
				74 per 1 000	**79 fewer per 1 000** (81 fewer to 76 fewer)

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research evidence

The BPaL 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) from 2021 IPD, treated with longer regimens for MDR/RR-TB constructed in line with 2020 WHO guidelines.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL 600-26 regimen (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving WHO recommended longer regimens (n=850) experienced higher levels of treatment success (100% vs 74%), i.e. a 32% relative increase (RR=1.32, 95%CI 1.19 to 1.39); lower levels of failure and recurrence (2% vs 3%), i.e. a 29% relative reduction (RR=0.71, 95%CI 0.12 to 3.8); lower levels of death (0% vs 11%), i.e. 11% absolute reduction (RD= -0.11, 95%CI -0.12 to -0.030; lower levels of loss to follow-up (0% vs 12%), i.e. 12% absolute reduction (RD= -0.12, 95%CI -0.14 to -0.04); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 4 fold relative increase (aRR=3.99, 95%CI 1.67 to 9.57); and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute decrease (RD= - 0.02, 95%CI -0.04 to 0.06). The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

The panel noted moderate to large improvements for most of the critical outcomes. Additionally, the panel noted that with the intervention regimen, treatment duration is reduced by 12 – 18 months, i.e. $^1/_3$ to $^1/_2$ of duration of comparator regimen (6-9 months vs 18-24 months); and that pill burden of the intervention is significantly lower, by 5-6 times (on average from 3'400 to 530)

Considering this research evidence and the additional considerations, the GDG judged that BPaL with Linezolid 600–26 may have large desirable effects and noted the very low certainty of the evidence.

Additional considerations applicable to sub-PICO 5.2 only

Treatment duration reduced by 12-18 months, i.e. to 1/3 to ½ of duration of comparator regimen (6-9 months vs 18-24 months).
Pill burden: significant decrease 5-6 times (on average from 3'400 to 530).

Considering this research evidence and the additional considerations, the GDG panel judged that BPaL 600– 26 regimen may have large desirable effects and noted the very low certainty of the evidence.

Additional considerations applicable to sub-PICO 5.3 only

Treatment duration reduced by 0-6 months (6-9 months vs 9 – 12 months)

Considering this research evidence and the additional considerations, the GDG panel judged that the BPaL 600– 26 regimen may have large desirable effects and noted the very low certainty of the evidence.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Treatment success	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 1.32** (1.19 to 1.39)	Study population	
				739 per 1 000	**236 more per 1 000** (140 more to 288 more)
Failure and recurrence	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 0.71** (0.12 to 3.80)	Study population	
				33 per 1 000	**10 fewer per 1 000** (29 fewer to 92 more)

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Death	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.11** (-0.13 to -0.03)	Study population	
				111 per 1 000	**110 fewer per 1 000** (130 fewer to 30 fewer)
Lost to follow up	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.12** (-0.14 to -0.04)	Study population	
				118 per 1 000	**120 fewer per 1 000** (140 fewer to 40 fewer)
Amplification of drug resistance	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RD -0.02** (-0.04 to 0.06)	Study population	
				24 per 1 000	**20 fewer per 1 000** (40 fewer to 60 more)

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research evidence

The BPal 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) treated in South Africa with 9-month regimen with linezolid for two months.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL with linezolid 600-26 (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving 9-month regimen with linezolid (n=4 216) experienced higher levels of treatment success (100% vs 66%) i.e. 52% relative increase (RR= 1.52, 95%CI 1.38 to 1.55), lower levels of failure and recurrence (0% vs 1%), i.e.1% absolute reduction (RD= -0.01, 95%CI -0.02 to 0.07); lower levels of death (0% vs 18%), i.e. 18% absolute reduction (RD= -0.18, 95%CI -0.19 to-0.1); lower levels of loss to follow up (0% vs 15%), i.e. 15% absolute reduction (RD= -0.15, 95%Ci -0.16 to -0.07); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 3 fold increase (aRR=2.92, 95%CI 1.38 to 6.18); and lower levels of amplified resistance (0% vs 1%), i.e. 1% absolute reduction (RD= -0.01, 95%CI -0.01 to 0.08). The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Treatment success	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RR 1.52** (1.38 to 1.55)	Study population	
				659 per 1 000	**343 more per 1 000** (250 more to 363 more)

Additional considerations applicable to sub-PICO 6.6 only

The panel also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 24 weeks (5.5 months) so treatment duration is reduced compared to the control arm by between 3–18 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen, which includes shorter (9–12 months) and longer (18–24 months) regimens. The pill burden of the intervention regimen is lower than that for the comparator regimens. The exact magnitude of reduction in pill burden depends on the specific comparator regimen.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Failure and recurrence	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RD -0.01** (-0.02 to 0.07)	Study population 12 per 1 000	**10 fewer per 1 000** (20 fewer to 70 more)
Death	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RD -0.18** (-0.19 to -0.10)	Study population 180 per 1 000	**180 fewer per 1 000** (190 fewer to 100 fewer)
Lost to follow up	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RD -0.15** (-0.16 to -0.07)	Study population 149 per 1 000	**150 fewer per 1 000** (160 fewer to 70 fewer)
Amplification of drug resistance	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RD -0.01** (-0.01 to 0.08)	Study population 6 per 1 000	**10 fewer per 1 000** (10 fewer to 80 more)

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research evidence

The BPaL (B-Pa-Linezolid600->300) regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen).

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL (n=60) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (77% vs 52%), i.e. a 47% relative increase (RR=1.47, 95%CI 1.09 to 1.99); lower levels of failure and recurrence (13% vs 26%), i.e. a 48% relative reduction (RR=0.52, 95%CI 0.22 to 1.18); lower levels of deaths (0.0% vs 3.0%), i.e. a 3% absolute reduction (RD=-0.03, 95%CI -0.10 to 0.03); lower levels of loss to follow-up (10% vs 20%), i.e. a 40% relative reduction (RR=0.60, 95%CI 0.24 to 1.56); lower levels of adverse events (20% vs 51%), i.e. a 62% relative reduction (RR=0.38, 95%CI 0.24 to 0.60); and higher levels of amplification of drug-resistance (2.9% vs 1.9%), i.e. a 59% relative increase (RR=1.59, 95%CI 0.32 to 7.84).

BPaL may improve treatment success, failure and recurrence, death, loss to follow-up and adverse events while leading to more amplification of drug-resistance but the evidence is very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaL (Lzd 600mg/300mg)
Treatment success	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 1.47** (1.09 to 1.99)	Study population 515 per 1 000	**242 more per 1 000** (46 more to 510 more)
Failure and recurrence	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 0.52** (0.22 to 1.18)	Study population 258 per 1 000	**124 fewer per 1 000** (201 fewer to 46 more)
Lost to follow up	126 (1 RCT)	⨁◯◯◯ Very low[abcdefgh]	**RR 0.60** (0.24 to 1.56)	Study population 197 per 1 000	**79 fewer per 1 000** (150 fewer to 110 more)
Adverse events	210 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 0.38** (0.24 to 0.60)	Study population 509 per 1 000	**316 fewer per 1 000** (387 fewer to 204 fewer)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaL (Lzd 600mg/300mg)
Death	126 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RD -0.03** (-0.10 to 0.03)	Study population 30 per 1 000	**30 fewer per 1 000** (100 fewer to 30 more)

Considering this research evidence and the additional considerations, the GDG judged that BPaL may have large desirable effects and noted the very low certainty of the evidence.

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**

○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	The ERC considered all research relevant to efficacy presented by the WHO GDG in sub-PICO 4.1, 5.2, 5.3 and 6.6. No additional research was presented by the review team. Considering that all comparisons of BPaL to various comparator regimens demonstrated statistically significant increases in successful treatment outcomes and reduced mortality, and a trend towards reduced treatment failure or recurrence, combined with a shorter treatment duration and reduced pill burden that may favour adherence, the ERC judged the desirable effects of the intervention to be large.	Additional considerations and limitations highlighted by the ERC relevant to the comparisons in this EtD include: • That sub-PICO's 4.1, 5.2 and 5.3 are indirect comparisons of trial data to programmatic data. Clinical outcomes in clinical trials tend to be better.

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

- **WHO Guideline panel**

○Trivial
○ Small
x Moderate
○ Large
○ Varies
○ Don't know

BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)

Research Evidence

The BPaL 600–26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with quinolone resistance was compared to a cohort of MDR/RR-TB patients with fluoroquinolone resistance from 2021 IPD, receiving longer regimens for treatment of MDR/RR-TB designed in line with 202 WHO guidelines.

Participants with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance) receiving BPaL 600–26 (n=33) compared to participants receiving longer regimens for MDR/RR-TB (n=839) experienced higher levels of treatment success (100% vs 75%), i.e. a 34% relative increase (RR=1.34, 95%CI 1.20 to 1.40); lower levels of failure and recurrence (0.0% vs 6.6%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.08 to -0.04); lower levels of deaths (0.0% vs 9.9%), i.e. a 10% absolute reduction (RD=-0.10, 95%CI -0.12 to -0.01); lower levels of loss to follow-up (0.0% vs 9.1%), i.e. a 9% absolute reduction (RD=-0.09, 95%CI -0.11 to -0.01); higher levels of adverse events (15% vs 4.4%), i.e. a 3.4-fold increase (RR=3.44, 95%CI 1.44 to 8.17); and lower levels of amplification of drug-resistance (0.0% vs 7.4%), i.e. a 7% absolute reduction (RD=-0.07, 95%CI -0.09 to -0.03).

BPaL 600–26 may improve treatment success, failure and recurrence, death, loss to follow-up and amplification of drug-resistance while leading to more adverse events but the evidence is very uncertain.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Adverse events	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 3.44** (1.44 to 8.17)	Study population	
				44 per 1 000	**108 more per 1 000** (19 more to 316 more)

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research Evidence

The BPaL 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) from 2021 IPD, treated with longer regimens for MDR/RR-TB constructed in line with 2020 WHO guidelines.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL 600-26 regimen (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving WHO recommended longer regimens (n=850) experienced higher levels of treatment success (100% vs 74%), i.e. a 32% relative increase (RR=1.32, 95%CI 1.19 to 1.39); lower levels of failure and recurrence (2% vs 3%), i.e. a 29% relative reduction (RR=0.71, 95%CI0.12 to 3.8); lower levels of death (0% vs 11%), i.e. 11% absolute reduction (RD= -0.11, 95%CI -0.12 to -0.030; lower levels of loss to follow-up (0% vs 12%), i.e. 12% absolute reduction (RD= -0.12, 95%CI -0.14 to -0.04); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 4 fold relative increase (aRR=3.99, 95%CI 1.67 to 9.57); and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute decrease (RD= - 0.02, 95%CI -0.04 to 0.06).
The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with WHO_long	Risk difference with BPaL
Adverse events	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]	**RR 3.99** (1.67 to 9.57)	Study population	
				47 per 1 000	**141 more per 1 000** (32 more to 403 more)

Additional considerations and judgments related to all comparisons:

Pretomanid safety

Rodent Toxicology Studies – evidence of direct testicular toxicity
Monkey Toxicology Studies – no evidence of direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition
Hormone Data from Clinical Studies – no changes in FSH, LH, Inhibin B consistent with testicular toxicity
Paternity Survey – 44 children fathered by 38 men (12%) who participated in pretomanid studies of 4 -6 months treatment duration
Semen Study – ongoing study measuring semen in men undergoing pretomanid treatment.

The panel was reassured by the presentation of preclinical and clinical data relevant to testicular toxicity of Pretomanid, judging that clinically relevant effects appeared to be unlikely.

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research Evidence

The BPal 600-26 arm of the ZeNix trial, where linezolid 600 mg daily was used for 26 weeks, and population included patients with MDR/RR-TB with or without quinolone resistance was compared to cohort of MDR/RR-TB patients (without quinolone resistance) treated in South Africa with 9-month regimen with linezolid for two months.

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL with Linezolid 600-26 (n=43) compared to participants with MDR/RR-TB (without quinolone resistance) receiving 9-month regimen with linezolid (n=4 216) experienced higher levels of treatment success (100% vs 66%) i.e. 52% relative increase (RR= 1.52, 95%CI 1.38 to 1.55), lower levels of failure and recurrence (0% vs 1%), i.e.1% absolute reduction (RD= -0.01, 95%CI -0.02 to 0.07); lower levels of death (0% vs 18%), i.e. 18% absolute reduction (RD= -0.18, 95%CI -0.19 to-0.1); lower levels of loss to follow up (0% vs 15%), i.e. 15% absolute reduction (RD= -0.15, 95%CI -0.16 to -0.07); higher levels of grade 3 to 5 adverse events (14% vs 5%), i.e. a 3 fold increase (aRR=2.92, 95%CI 1.38 to 6.18); and lower levels of amplified resistance (0% vs 1%), i.e. 1% absolute reduction (RD= -0.01, 95%CI -0.01 to 0.08).
The evidence is very uncertain about the effect of BPaL 600-26 regimen on all outcomes.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with SA_new	Risk difference with BPaL
Adverse events	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]	**RR 2.92** (1.38 to 6.18)	Study population	
				49 per 1 000	**95 more per 1 000** (19 more to 256 more)

.

The panel discussed the importance of adverse events in the treatment of RR/MDR-TB and noted the significantly higher number of adverse events observed with BPaL. It was acknowledged that recording of AEs as part of the ZeNix trial is much more detailed than for data sets arising from routine care (i.e. data for the longer regimens).

Considering the increased number of adverse events with BPaL, the GDG judged that BPaL may have moderate undesirable effects and noted the very low certainty of the evidence.

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research Evidence

The BPaL (B-Pa-Linezolid600->300) regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen).

Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaL (n=60) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (77% vs 52%), i.e. a 47% relative increase (RR=1.47, 95%CI 1.09 to 1.99); lower levels of failure and recurrence (13% vs 26%), i.e. a 48% relative reduction (RR=0.52, 95%CI 0.22 to 1.18); lower levels of deaths (0.0% vs 3.0%), i.e. a 3% absolute reduction (RD=-0.03, 95%CI -0.10 to 0.03); lower levels of loss to follow-up (10% vs 20%), i.e. a 40% relative reduction (RR=0.60, 95%CI 0.24 to 1.56); lower levels of adverse events (20% vs 51%), i.e. a 62% relative reduction (RR=0.38, 95%CI 0.24 to 0.60); and higher levels of amplification of drug-resistance (2.9% vs 1.9%), i.e. a 59% relative increase (RR=1.59, 95%CI 0.32 to 7.84).

(Judgement for WHO sub-PICO 6.6)

X Trivial
○ Small

BPaL may improve treatment success, failure and recurrence, death, loss to follow-up and adverse events while leading to more amplification of drug-resistance but the evidence is very uncertain.

○ Moderate ○ Large ○ Varies ○ Don't know	<table><tr><th rowspan="2">Outcomes</th><th rowspan="2">№ of participants (studies) Follow-up</th><th rowspan="2">Certainty of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects* (95% CI)</th></tr><tr><th>Risk with TB-PRACTECAL comparator</th><th>Risk difference with BPaL (Lzd 600mg/300mg)</th></tr><tr><td>Amplification of drug resistance</td><td>210 (1 RCT)</td><td>⨁◯◯◯ Very low[a,b,c,d,e,f]</td><td>RR 1.59 (0.32 to 7.84)</td><td colspan="2">Study population</td></tr><tr><td colspan="4"></td><td>19 per 1 000</td><td>11 more per 1 000 (13 fewer to 127 more)</td></tr></table> Considering this research evidence and the additional considerations, the GDG judged that BPaL may have trivial undesirable effects and noted the very low certainty of the evidence.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○Trivial ○ Small **x Moderate** ○ Large ○ Varies ○ Don't know	The ERC considered the research evidence presented by the WHO GDG, with no additional evidence presented. Based on the more doubled increase in relative risk of adverse events in 3 of 4 comparisons (sub-PICO 4.1, 5.2 and 5.3), but which may have arisen from differences in reporting between clinical trial and programmatic data, as well as the fact that there were trivial differences between TB PRACTECAL, the ERC recommended a summary judgment that the undesirable effects of the intervention (BPaL) are moderate. The ERC highlighted the few studies contributing to data for this domain, the high degree of uncertainty and the indirect comparisons.	Additional considerations and limitations highlighted by the ERC relevant to the comparisons in this EtD include: • That sub-PICO's 4.1, 5.2 and 5.3 are indirect comparisons of trial data to programmatic data. Programmatic data may underreport of adverse events. • That in sub-PICO 6.6, the BPaL arm of TB-PRACTECAL used reduced Linezolid dosing from 16 weeks, and thus adverse events reported for this arm may not reflect adverse events associated with a regimen of 26 weeks of Linezolid 600mg daily dosing.
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
X Very low ○ Low ○ Moderate ○ High ○ No included studies	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub-PICO 4.1)*** **Research Evidence** Certainty was rated *very low* for all outcomes. Risk of bias was very serious, due to likely unmeasured confounding, small event numbers in the BPaL 600–26 group that precluded adjustment for differences in baseline covariates (measured confounding) and likely measurement bias due to underestimates of death and relapse following treatment in the WHO IPD 2021. Inconsistency was serious due to differences in the outcomes between cohorts in the WHO	**Additional considerations applicable to WHO sub-PICO 4.1, 5.2 and 5.3** This is an indirect comparison of patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection

IPD 2021 (downgraded one level). We did not downgrade for indirectness. Imprecision was very serious, due to the small sample size in the intervention group (n=33) (downgraded two levels).

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Failure and recurrence	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Death	937 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Lost to follow up	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Adverse events	872 (15 observational studies)	⨁◯◯◯ Very low[a,c,d,e,f,g]
Amplification of drug resistance	872 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison is between one arm of ZENIX and an individual participant data meta-analysis of 14 datasets – i.e. a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX

b. Confounding bias. Baseline imbalances were observed in the age, gender, HIV status, prior TB and prior drug-resistant TB history, smear status and culture positivity at baseline between the two groups. In most comparisons we were unable to adjust for measured confounding as the small number of events in the intervention group did not allow this (<5 individuals with a positive or negative outcome). Confounding bias is therefore likely. This imbalance in measured covariates suggests unmeasured confounding is also likely.

c. Potential misclassification bias: As the WHO IPD data were collected under programmatic conditions, there is considerable potential to underestimate relapse, as details pertaining to the follow-up period is often missing. Misclassification of death during the follow-up period is also possible as there is no death registry to link to the cohort data for deaths that occurred after treatment completion.

d. Considerable variability was observed in the effect estimates between cohorts in the comparator group. The overall effect in the comparator is strongly influenced by a small number of larger cohorts, which have varying effect estimates.

e. The ZENIX study was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs (e.g. countries in Southeast Asia). The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. Hence, we have chosen not to downgrade the certainty due to indirectness

f. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels.

criteria, support during treatment and other interventions are likely to differ.

Treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions.

The GDG acknowledged that the indirect comparison and the propensity adjustment is leaving us with very low certainty.

Additional considerations applicable to WHO sub-PICO 6.6

As noted in the CoE assessment, it is important to highlight that:

- the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm)
- treatment outcomes for the comparator regimen differ for these populations and that 24% of patients were treated with regimens no longer recommended by WHO, e.g. containing injectable drugs and not containing Bdq

g. Confounding bias. Baseline imbalances were observed in the age, gender, HIV status, prior TB and prior drug-resistant TB history, smear status and culture positivity at baseline between the two groups. While we were able to adjust for these baseline covariates for the outcome of adverse events, this imbalance in measured covariates suggests unmeasured confounding is also likely.

BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)

Research Evidence

Adjustment for baseline covariates was not possible for any of the outcomes, except adverse events, owing to the small number of events occurring in one or more groups. Certainty was rated *very low* for all outcomes. Risk of bias was very serious, with confounding bias evident in the imbalance between baseline covariates between groups (adjustment not possible). Downgraded two levels for risk of bias. Indirectness was not serious. Inconsistency was serious, with variation in the outcomes between the WHO IPD 2021 cohorts. Imprecision was very serious, with small numbers in the intervention group (n=43), leading to a downgrading by two levels.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Failure and recurrence	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Death	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Lost to follow up	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Adverse events	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]
Amplification of drug resistance	893 (15 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison

	is between one arm of ZENIX and the WHO long (WHO IPD 2021) cohort – a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX. b. Confounding bias. Baseline imbalances were observed in the gender, HIV status, prior TB history, past DR-TB treatment status, smear status, culture status and fluoroquinolone-resistance status between the two groups (although by including FQ-R TB it is likely to result in worse outcomes for the intervention group due to unmeasured confounding factors linked to FQ-R). We were able to adjust for the aforementioned measured confounders for the outcomes of success, failure/recurrence, loss to follow-up and grade 3 and above adverse events. However, the small number of events precluded adjustment for these factors for death or amplified resistance. The substantial imbalance in measured covariates suggests unmeasured confounding is also likely. c. Potential misclassification bias: As the WHO IPD 2021 (WHO long) cohort data were collected under programmatic conditions, there is considerable potential to underestimate recurrence, as details pertaining to the follow-up period were often missing. Misclassification of death during the follow-up period was also possible, with no linked death registry data available in the comparator cohort. d. Considerable variability was observed in the effect estimates between cohorts in the comparator group. The overall effect in the comparator is strongly influenced by a small number of larger cohorts, which have varying effect estimates. e. The ZENIX study was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs (e.g. countries in Southeast Asia). The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. There was serious indirectness because the intervention was in a clinical trial, while the comparator was a programmatic dataset. Therefore, we have downgraded for indirectness. f. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels. ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** Adjustment for baseline covariates was not possible for any of the outcomes owing to the small number of events in one or more groups. Certainty was rated *very low*. Risk of bias was very serious, with confounding bias evident in the imbalance between baseline covariates between groups (adjustment not possible). Downgraded two levels for risk of bias. Indirectness was rated as not serious. Imprecision was very serious, with small numbers in the intervention group (n=43), leading to a downgrading by two levels	

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Failure and recurrence	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Death	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Lost to follow up	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Adverse events	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]
Amplification of drug resistance	4 259 (2 observational studies)	⨁◯◯◯ Very low[a,b,c,d,e]

a. Confounding bias. Baseline imbalances were observed in the gender, HIV status, prior TB treatment, smear status, culture positivity and fluoroquinolone resistance status between the two groups. In all comparisons we were unable to adjust for measured confounding as the small number of events in the intervention group did not allow this (<5 individuals with a positive or negative outcome). Confounding bias is due to measured confounding therefore serious. The substantial imbalance in measured covariates suggests unmeasured confounding is also likely.
b. Lack of allocation concealment in the intervention arm. In the ZENIX study, participants, trial investigators and staff (including laboratory staff) were blinded to the dose and scheduled duration of linezolid. Participants were unblinded to the use of bedaquiline and pretomanid. However, this comparison is between one arm of ZENIX and the WHO short (SA 2017) cohort – a non-randomised comparison. Therefore, we have not downgraded due to the partial blinding of ZENIX.
c. Potential misclassification bias: As the SA 2019 cohort data were collected under programmatic conditions, there is considerable potential to underestimate relapse, as details pertaining to the follow-up period is often missing. Misclassification of death during the follow-up period is also possible, although deaths reported in the South African death registry were linked to the participant follow-up data (using a national identification number).
d. The ZENIX study (intervention arm) was a clinical trial conducted in the Russian Federation, Republic of Moldova and South Africa. The procedures within the trial in these settings are not necessarily comparable with those used in other programmatic settings in which MDR-TB commonly occurs. The decision as to whether to downgrade for indirectness is a difficult one. Given that the study was conducted in three countries, the intervention and outcomes are more likely to reflect practice in a range of other settings. Given the important difference between a trial and programmatic setting, we have downgraded for indirectness.
e. The small number of individuals included in both the intervention group (n=43) results in a very serious risk of imprecision. Therefore, the certainty has been downgraded by two levels.

BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)

Research Evidence

Certainty was rated *very low*. Risk of bias was serious or very serious, for different outcomes. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These

concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in the population, definitions of outcomes and the comparator regimen. Imprecision was serious or very serious according to outcomes, with a small number of events for some outcomes.

The overall certainty is generally based on the lowest certainty for the agreed critical outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Failure and recurrence	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Death	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Lost to follow up	126 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,h]
Adverse events	210 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Amplification of drug resistance	210 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f]

a. An imbalance in measured covariates (prior TB, prior DR-TB) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.
b. Small numbers of events in some outcomes precludes adjustment in some comparisons.
c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen.
d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013).
e. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness.
f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level.
g. The number of participants in both intervention and comparator groups was small (n=60 and n=66). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.
h. A lack of blinding is important for loss to follow-up, and adverse event reporting where participant and clinician knowledge of the regimen may influence behaviours relating to treatment follow-up.

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

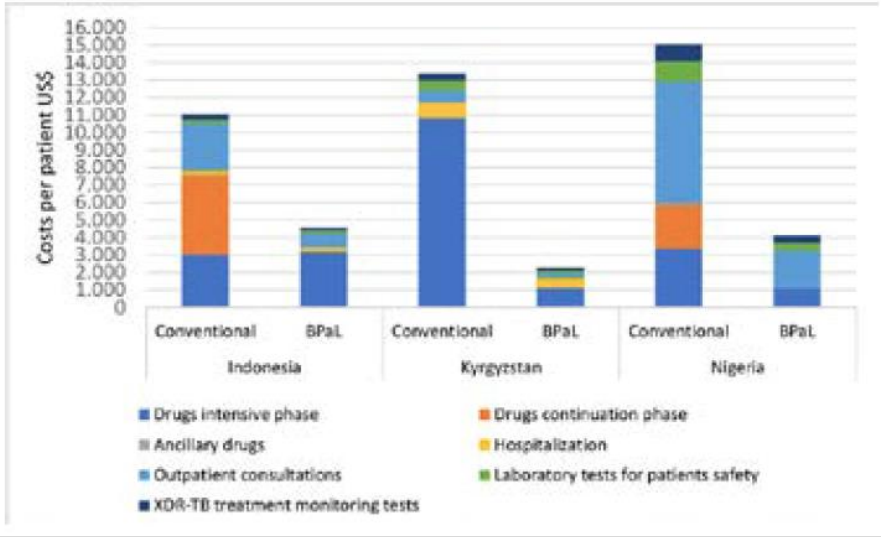
X Very low ○ Low ○ Moderate ○ High ○ No included studies	The ERC considered all information and research presented by the WHO GDG and agreed that the certainty of evidence is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research was presented by the review team. The ERC agreed with the WHO GDG that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** Nil additional ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** Nil additional ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** Nil additional The GDG judged the benefits of BPaL to be large and the undesirable effects to be trivial compared to WHO recommended standard of care regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL regimen.	**Additional considerations relevant to sub-PICO's 4.1 and 5.2 only** The panel highlighted (as noted in the CoE assessment) that we are comparing data from patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection criteria, support during treatment etc. are likely to differ. E.g. treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions. The GDG judged the benefits of BPaL with Linezolid 600-26 to be large and the undesirable effects to be moderate compared to WHO recommended longer regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favors BPaL with Linezolid 600-26. **Additional considerations relevant to sub-PICO 5.3 only** This is an indirect comparison of patients treated within a clinical trial to data from patients treated under routine programmatic conditions so selection criteria, support during treatment and other interventions are likely to differ. Treatment outcomes are typically better under trial conditions while AEs are typically underreported under programmatic conditions. The GDG acknowledged that the indirect comparison and the propensity adjustment is leaving us with very low certainty. The GDG judged the benefits of BPaL with linezolid 600-26 to be large and the undesirable effects to be moderate

		compared to receiving 9-month regimen with linezolid. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaL with linezolid 600-26. **Additional considerations relevant to sub-PICO 6.6 only** As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations and that 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq As a result, the balance of effects may be different in settings/populations with different FQ-resistance prevalence and if only currently recommended regimens are used.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The ERC considered all evidence presented by the WHO GDG and no additional research was presented. Considering the ERC judgements of large desirable effects, including reduction in treatment duration and pill burden, and moderate undesirable effects, with very low certainty evidence, the balance of effect s was judged to probably favour the intervention.	

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings **x Large savings** ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary pre-XDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** **Summary of findings from three publications on the cost of BPaL compared to WHO_long** (further detail on each study below) • From these three publications, the total cost (drugs+delivery) of **WHO_long appear to be between ~1.5x to 6x higher than for BPaL** when looking at comparative estimates within country • Note that studies are not 100% addressing the comparison of interest: Mulder and Gomez papers based on Linezolid dose of 1 200 (so cost of Linezolid in these publications is higher than intervention of interest here) and Sweeney is based on 600–300 for 24 weeks and a mixed RR/MDR/pre-XDR population **Mulder et al, 2022: Cost and budget impact analysis** [noting co-authors from TB Alliance and KNCV] **Methods** • Per-patient treatment cost of BPaL regimen was compared head-to-head with the conventional XDR-TB treatment regimen (i.e. WHO_long) in Indonesia, Kyrgyzstan and Nigeria based on cost estimates primarily assessed using microcosting method and expected frequency of each TB service • The 5-year budget impact of gradual introduction of BPaL against the status quo was assessed using a Markov model that represented patient's treatment management and outcome pathways **Findings** • The cost per patient completing treatment with BPaL was US$ 7142 in Indonesia, US$ 4782 in Kyrgyzstan and US$ 7152 in Nigeria – 57%, 78% and 68% lower than the conventional regimens in the respective countries. • A gradual adoption of the BPaL regimen over 5 years would result in a 5-year average national TB service budget reduction of 17% (US$ 12 880) in XDR-TB treatment related expenditure in Indonesia, 15% (US$ 700 247) in Kyrgyzstan and 32% (US$ 1 543 047) in Nigeria • BPaL regimen can be highly cost-saving compared with the conventional regimens to treat patients with XDR-TB in high drug-resistant TB burden settings.	**Additional considerations relevant to sub-PICO 4.1 and 5.2 only** Regimen cost at GDF prices: ~800 $ BPaL (600–26), ~1 300$ longer regimen. The panel judged that the costs for BPaL among patients with pulmonary pre-XDR-TB and among patients with pulmonary MDR/RR-TB are lower because costs of drugs are lower and cost of delivery are also lower due to the shorter duration of treatment and lower complexity **Additional considerations relevant to sub-PICO 5.3 only** Comparative costing analyses from Mulder and Gomez papers not applicable here since they are comparing to WHO_long (and, less importantly, are based on Linezolid dose of 1 200) **Additional considerations relevant to sub-PICO 6.6 only** The panel judged that the costs for BPaL are lower because costs of drugs are lower and cost of delivery are also lower due to the shorter duration of treatment and lower complexity. The GDG judged that the reduction in costs varies between moderate and large.

Figure: The drug and treatment management costs (in US$) per XDR-TB patient 100% adhering to the conventional regimens and BPaL by country. BPaL, bedaquiline, pretomanid and linezolid; XDR-TB, extensively drug-resistant tuberculosis



Gomez et al, 2021: Cost & cost-effectiveness [noting co-authors from TB Alliance]

Methods

- CEA using Markov model of BPaL (Nix regimen) in South Africa, Philippines and Georgia
- Primary and secondary outcome measures
  - (1) Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price;
  - (2) The potential maximum price at which the BPaL regimen could become cost neutral

Findings

- BPaL for XDR-TB is likely to be cost saving in all study settings
- when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits
- Cost savings from the introduction of the BPaL regimen are higher in settings with a more expensive current standard of care
- consequently, the threshold price at which BPaL becomes cost neutral is higher in less expensive settings: US$ 3 650 and US$ 3 800 for Georgia and the Philippines, respectively, and US$ 500 for South Africa for our base case of only patients with XDR-TB, after factoring in incremental cost of ART

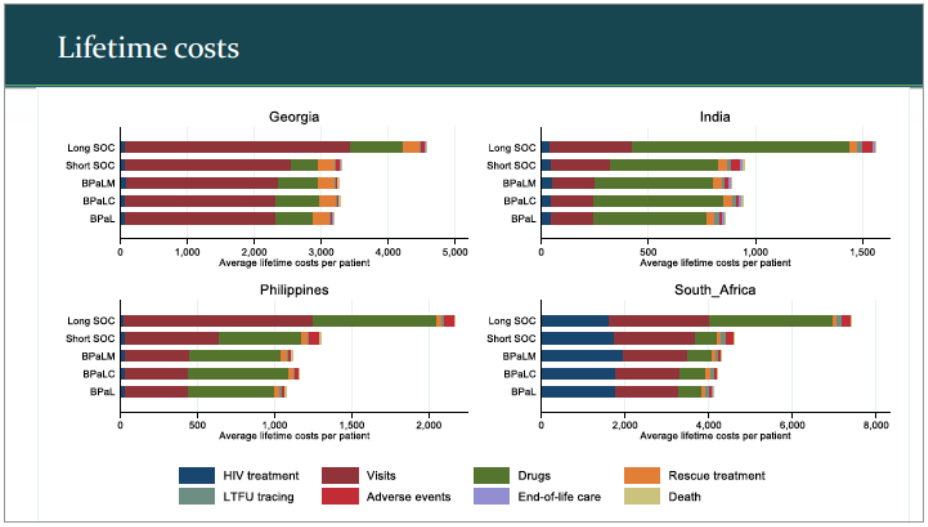
Table 2 Input cost estimates for cost-effectiveness analyses (US$2018 per month)				
	South Africa	**Georgia**	**The Philippines**	**Reference**
Standard of care (intensive phase)	558.9 (drugs) 64.9 (delivery)	424.6 (drugs) 25.0 (delivery)	424.6 (drugs) 30.1 (delivery)	35 51–55
Standard of care (continuation phase)	208.9 (drugs) 30.1 (delivery)	74.58 (drugs) 14.0 (delivery)	74.58 (drugs) 13.7 (delivery)	35 51–55
BPaL	296.4 (drugs) 65.3 (delivery)	214.0 (drugs) 31.0 (delivery)	214.0 (drugs) 38.3 (delivery)	35 51–55
Palliative care*	428.1	330.9	328.0	56
Antiretroviral treatment	249.2	–	–	57

*Average of 10% hospice inpatient unit; 40% community care and 50% no care.
BPaL, bedaquiline, pretomanid and linezolid.

(sub-PICO 5.3 judgement)
○ Large costs
○ Moderate costs
○ Negligible costs and savings
x Moderate savings
○ Large savings
○ Varies
○ Don't know

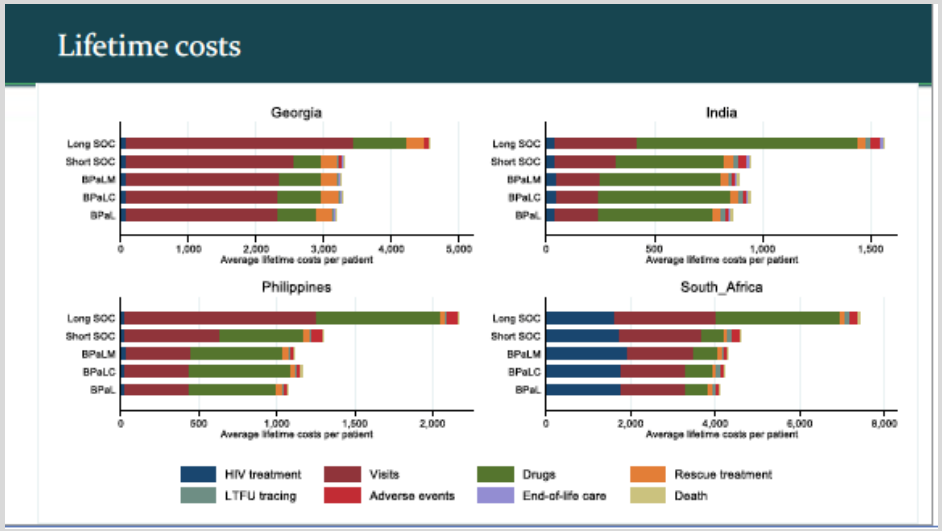
BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)
Research Evidence

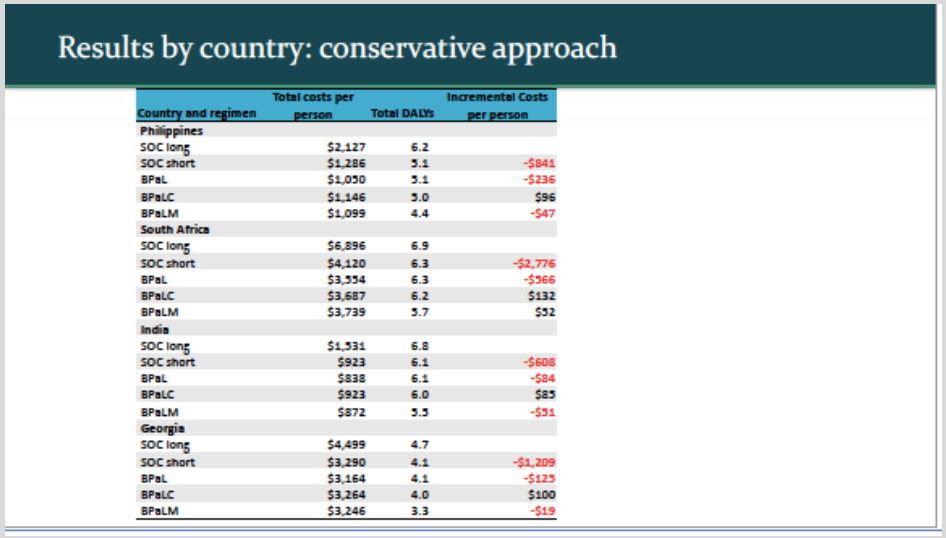
Sedona Sweeney's presentation on CEA of PRACTECAL regimens from pre-GDG webinar



Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented, the total cost (drugs + delivery) of BPaL appear to be between 4% - 18% lower than for WHO_short when looking at comparative estimates within country
- In most settings, BPaL is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests

(sub-PICO6.6 judgement) ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	• The study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator) and on BPaL 600-300 for 24 weeks, instead of BPaL 600-26 and using WHO_short rather than SA_new (i.e. Eto instead of Linezolid as the comparator. ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar • From the data presented, the total cost (drugs+delivery) of WHO_short appear to be between 4%-18% higher than for BPaL and between ~1.5x to 6x higher for WHO_long when looking at comparative estimates within country • In most settings, BPaL is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests • Note that the study presented by Sweeeney is not 100% addressing the PICO of interest (as it is based on 600-300 for 24 weeks, instead of 600-26)  	



Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person
Philippines			
SOC long	$2,127	6.2	
SOC short	$1,286	5.1	-$841
BPaL	$1,050	5.1	-$236
BPaLC	$1,146	5.0	$96
BPaLM	$1,099	4.4	-$47
South Africa			
SOC long	$6,896	6.9	
SOC short	$4,120	6.3	-$2,776
BPaL	$3,554	6.3	-$566
BPaLC	$3,687	6.2	$132
BPaLM	$3,739	5.7	$52
India			
SOC long	$1,531	6.8	
SOC short	$923	6.1	-$608
BPaL	$838	6.1	-$84
BPaLC	$923	6.0	$85
BPaLM	$872	5.5	-$51
Georgia			
SOC long	$4,499	4.7	
SOC short	$3,290	4.1	-$1,209
BPaL	$3,164	4.1	-$125
BPaLC	$3,264	4.0	$100
BPaLM	$3,246	3.3	-$19

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

BPaL vs. long course regimens for MDR and pre-XDR TB (sub-PICO 4.1, 5.2, 6.6) ○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings **x Large savings** ○ Varies ○ Don't know	Additional information presented by the review team included updated evidence from the Sweeney et al. publication (published since the WHO GDG meeting, and on which WHO GDG judgement is based) , and the normative cost analysis of direct costs conducted by the review team. **Updated version of Sedona Sweeney's presentation with official publication:**	

BPaL vs. SA_new_short (sub-PICO 5.3)

○ Large costs
○ Moderate costs
× Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

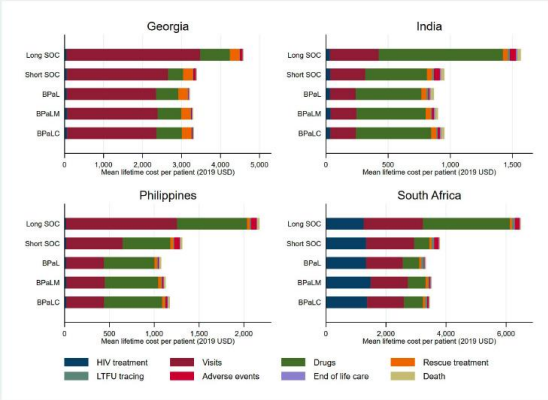


Fig 1. Average lifetime costs by country and regimen.

The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa. (Costs presented in 2019 US$; Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470.
Current SOC regimen mix (74% short, 26% long): $4,517)

Table 2. Base case results.

			Comparison with current SOC mix	
Country and regimen	**Total costs per person**	**Total DALYs per person**	**Incremental Costs Per Person**	**Incremental DALYs Averted Per Person**
Philippines				
Current SOC regimen mix (99% short, 1% long)	$1,329	5.4		
BPaL	$1,078	5.4	-$251	0.0
BPaLC	$1,174	5.3	-$155	0.1
BPaLM	$1,124	4.6	-$204	0.8
South Africa				
Current SOC regimen mix (74% short, 26% long)	$4,517	6.8		
BPaL	$3,344	6.6	-$1,173	0.2
BPaLC	$3,470	6.5	-$1,047	0.3
BPaLM	$3,520	6.0	-$997	0.8

Normative cost analysis conducted by review team. For more information consult Appendix 3.

Appendix 3.xlsx

Normative cost analysis based on specific direct costs						Sensitivity analysis excl.clinic vist costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	**15 649,49**	**12 968,70**
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	**17 862,78**	**15 181,99**
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	**17 207,81**	**14 575,25**
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	**17 805,05**	**15 172,49**
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	**17 284,25**	**14 651,69**
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	**34 467,47**	**30 059,87**
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	**60 328,21**	**53 746,81**

Note:
Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

The ERC noted that drug costs, and treatment monitoring costs are significantly affected by treatment duration. Based on the research presented by the WHO GDG and the normative costs analysis conducted for the locally relevant context, the ERC felt that BPaL regimen was associated with large savings when compared to the long course regimens for MDR and pre-XDR TB, and negligible costs when compared to the current South African short course regimen.

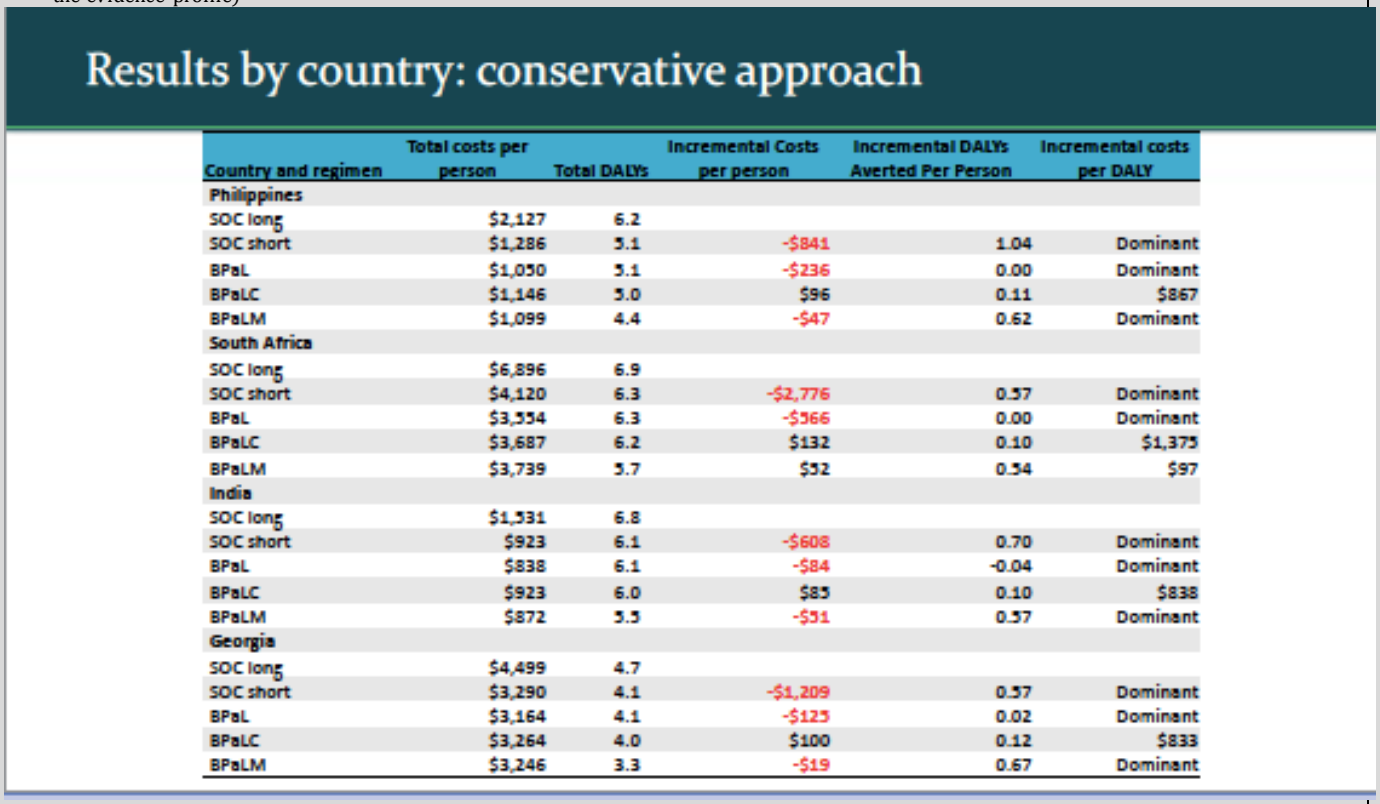
Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No research evidence searched for. ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence** The panel reviewed available data presented by the TB-PRACTECAL team from trial embedded study on cost effectiveness presented during one of the preparatory pre-GDG webinars by Sedona Sweeney and colleagues.	

	The panel judged the certainty of evidence of required resources to be very low since the study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator), on BPaL 600–300 for 24 weeks, instead of BPaL 600–26 and on the 9-month regimen using Ethionamide instead of Linezolid.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low **x Moderate** ○ High ○ No included studies	The ERC considered the evidence of resources required to be moderate as the normative cost analysis of direct costs was performed for the locally relevant context increasing the certainty.	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** **Research Evidence** **Gomez et al, 2021: Cost & cost-effectiveness** [noting co-authors from TB Alliance] • some indirectness as analyses were based on efficacy estimates from Nix study and a different comparator cohort but overall estimates of effect were similar **Methods** • CEA using Markov model of BPaL (Nix regimen) in South Africa, Philippines and Georgia • Primary and secondary outcome measures - (1) Incremental cost per disability-adjusted life years averted by using BPaL against standard of care at the Global Drug Facility list price; - (2) The potential maximum price at which the BPaL regimen could become cost neutral **Findings** • BPaL for XDR-TB is likely to be cost saving in all study settings • when BPaL is introduced to a wider population, including MDR-TB treatment failure and treatment intolerant, we observe increased savings and clinical benefits • Cost savings from the introduction of the BPaL regimen are higher in settings with a more expensive current standard of care • consequently, the threshold price at which BPaL becomes cost neutral is higher in less expensive settings: US$ 3 650 and US$ 3 800 for Georgia and the Philippines, respectively, and US$ 500 for South Africa for our base case of only patients with XDR-TB, after factoring in incremental cost of ART Given their prior judgements (balance of effects probably favours the intervention; intervention leads to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention. ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence**	.

Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented: "strong evidence that BPaL would be cost-effective" in the setting studied (costs reduced and DALYs averted)
- Note that estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO (CEA assumes smaller benefits of BPaL over comparator and thus estimates for DALYs averted would be conservative vis a vis data from the evidence profile)



Results by country: conservative approach

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person	Incremental DALYs Averted Per Person	Incremental costs per DALY
Philippines					
SOC long	$2,127	6.2			
SOC short	$1,286	5.1	-$841	1.04	Dominant
BPaL	$1,050	5.1	-$236	0.00	Dominant
BPaLC	$1,146	5.0	$96	0.11	$867
BPaLM	$1,099	4.4	-$47	0.62	Dominant
South Africa					
SOC long	$6,896	6.9			
SOC short	$4,120	6.3	-$2,776	0.57	Dominant
BPaL	$3,554	6.3	-$566	0.00	Dominant
BPaLC	$3,687	6.2	$132	0.10	$1,375
BPaLM	$3,739	5.7	$52	0.54	$97
India					
SOC long	$1,531	6.8			
SOC short	$923	6.1	-$608	0.70	Dominant
BPaL	$838	6.1	-$84	-0.04	Dominant
BPaLC	$923	6.0	$85	0.10	$838
BPaLM	$872	5.5	-$51	0.57	Dominant
Georgia					
SOC long	$4,499	4.7			
SOC short	$3,290	4.1	-$1,209	0.57	Dominant
BPaL	$3,164	4.1	-$125	0.02	Dominant
BPaLC	$3,264	4.0	$100	0.12	$833
BPaLM	$3,246	3.3	-$19	0.67	Dominant

Given their prior judgements (balance of effects probably favours the intervention; intervention leads to moderate to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention.

(sub-PICO 5.3 judgement)

○ Favours the comparison
○ Probably favours the comparison
○ Does not favour either the intervention or the

BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)

Research Evidence

Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar

- From the data presented: "strong evidence that BPaL would be cost-effective" in the setting studied (costs reduced and DALYs averted)

comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	• The study presented by Sweeney is not addressing the PICO of interest directly as it is based on a mixed RR/MDR/pre-XDR population (and thus mixed comparator) and on BPaL 600–300 for 24 weeks, instead of BPaL 600–26 and using WHO_short rather than SA_new (i.e. Eto instead of Linezolid) as the comparator • Estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO (CEA assumes smaller benefits of BPaL over comparator and thus estimates for DALYs averted would be conservative vis a vis data from the evidence profile) Comparative costing analyses from Gomez papers not applicable here since they are comparing to long WHO regimen (+ are based on Linezolid dose of 1 200 and efficacy estimates from Nix study). For sub-PICO 5.3 no studies of cost-effectiveness were included.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	The ERC considered all research evidence included in the WHO GDG judgement. No new cost-effectiveness studies were presented or considered. Based on the normative cost analysis of direct costs for South Africa performed by the review team, showing costs savings when the intervention is compared to current South African long course, the intervention would favour cost-effectiveness. However, evidence for cost-effectiveness for the intervention when compared to the current South African short course is based on the evidence from the study by Sweeney et al. that indirectly compared BPaL to South African standard of care regimens (a mix of 75% short course and 25% long course) and showed cost savings and reduced DALYs associated with the intervention. The ERC judged that overall, cost-effectiveness probably favours the intervention.	
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** No research evidence searched for. The panel judged that use of the BPaL regimen would probably increase equity.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaL regimen due to its reduced complexity and shorter duration.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	The ERC considered no additional research. The ERC agreed with the WHO GDG judgment that the intervention would probably increase health equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ No
○ Probably no
x Probably yes
○ Yes
○ Varies
○ Don't know
	BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)
	BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)
	
	Research Evidence
	
	van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective
	Methods
	• Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria
	  • 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110), other stakeholders interviewed were Laboratory stakeholders and Programmatic Stakeholders
	• semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL
	  • acceptability: anticipated benefits and challenges regarding DR TB management with the BPaL regimen by the stakeholders; recorded 3-point Likert scale (acceptable; neutral; unacceptable)
	
	Findings
	• Acceptability: overall high and rated as acceptable by >80% across domains
	• Stakeholders
	  • appreciated that BPaL would reduce workload and financial burden on the health care system
	  • expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements
	  • stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems
	
	Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective
	  • Positive impact of shorter treatment on employment status welcomed
	
	BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)
	Research Evidence
	
	No research evidence searched for.
	
	Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective: Positive impact of shorter treatment on employment status welcomed.
		Additional considerations relevant to sub-PICO 4.4 and 5.2 only
		
		For sub-PICO 5.2 findings from the study by van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective are listed under other considerations (instead of under research evidence) as acceptability was assessed for the pre-XDR population.
		
		For sub-PICO 5.3 analyses from van de Berg paper are not applicable here since in their study they asked about acceptability of using BPaL for pre-XDR patients and when compared to the long WHO regimen
		
		The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable.
		
		Additional considerations relevant to sub-PICO 5. 3 only

	BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6) **Research Evidence** **Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective** Positive impact of shorter treatment on employment status welcomed.	The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable. **Additional considerations relevant to sub-PICO 6.6 only** **van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective** • Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about acceptability of using BPaL for pre-XDR patients and when compared to the long WHO regimen • **Findings** Acceptability: overall high and rated as acceptable by >80% across domains The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaL regimen would probably be acceptable
• PHC/ADULT HOSPITAL LEVEL COMMITTEE		

○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know	**Additional Research Evidence presented by TB-PRACTECAL-PRO team:** All trial participants respiratory-specific QOL scores improved with treatment, irrespective of the regimen they received. However, faster improvement in the investigational arms as compared to SoC was noted by both the individual and their friends/family with a positive effect on treatment support. It was noted that a participant in the intervention arm experiences a 15% reduction (95% CI 12 to 18%) in the mean SGRQ symptom score per month versus an average of 5% (95% CI 0 – 9%) reduction experienced by a participant in the SoC arm. It was highlighted that South African participants were slightly underrepresented in the trial (32 South Africans of 137 participants) and that no analysis of QoL outcomes across countries was performed. For interviewees, in the qualitative study, supportive care experienced was as important as satisfaction and tolerability of the novel drug regimen. The ERC judged that the intervention is probably acceptable to key stakeholders.	

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline Panel**		
○ No ○ Probably no x Probably yes ○ Yes ○ Varies ○ Don't know	***BPaL compared to WHO_Long in pulmonary preXDR TB (WHO sub-PICO 4.1)*** ***BPaL compared to TB-PRACTECAL comparator in pulmonary MDR/RR-TB and pre-XDR TB (WHO sub-PICO 6.6)*** **Research Evidence** **van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective** **Methods** • Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria • 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110) • semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL • feasibility: stakeholders' expectations regarding the practical requirements for implementing the BPaL regimen within the context of their health system; recorded as overall likelihood of implementing BPaL (likely; neutral; unlikely) **Findings** • **Feasibility: 88% (146/166) of the stakeholders would likely implement BPaL** once available • Stakeholders - appreciated that BPaL would reduce workload and financial burden on the health care system - expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements - stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems	**Additional considerations applicable to sub-PICO 4.1 and 6.6 only** Noting that analyses from van de Berg paper are only partially applicable to sub-PICO 6.6 since in their study they asked about feasibility of using BPaL for pre-XDR patients and when compared to the long WHO regimen The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaL regimen for use in DST as a potential barriers to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible
(sub-PICO 5.2 and 5.3 judgement) ○ No ○ Probably no ○ Probably yes x Yes	***BPaL compared to WHO_Long in pulmonary MDR/RR TB (WHO sub-PICO 5.2)*** ***BPaL compared to SA_new in MDR/RR TB (WHO sub-PICO 5.3)*** **Research Evidence**	**Additional considerations applicable to sub-PICO 5.2 and 5.3 only** The panel considered the following aspects to affect feasibility (i.e. to be

○ Varies ○ Don't know	Nil	potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaL regimen for use in DST as a potential barrier to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is feasible. Listing findings from the study by **van de Berg et al, 2021** (based on 2019 KNCV report, funded by TB Alliance) on the **provider** perspective here under other considerations (instead of under research evidence) as feasibility was assessed for the pre-XDR population. **Methods** • Mixed-methods study among a cross-section of health care workers, programmatic and laboratory stakeholders between May 2018 and May 2019 in Indonesia, Kyrgyzstan, and Nigeria - 188 stakeholders participated in this study: 63 from Kyrgyzstan, 51 from Indonesia, and 74 from Nigeria; majority were health care workers (110) • semi-structured interviews and focus group discussions to assess perceptions on acceptability and feasibility of implementing BPaL - feasibility: stakeholders' expectations regarding the practical requirements for implementing the BPaL regimen within the context of their health

		system; recorded as overall likelihood of implementing BPaL (likely; neutral; unlikely) **Findings** • **Feasibility: 88% (146/166) of the stakeholders would likely implement BPaL** once available • Stakeholders - appreciated that BPaL would reduce workload and financial burden on the health care system - expressed concerns regarding BPaL safety (monitoring), long-term efficacy, and national regulatory requirements - stressed the importance of addressing current health systems constraints as well, especially in treatment and safety monitoring systems Analyses from van de Berg paper not applicable for sub-PICO 5.3 since in their study they asked about feasibility of introducing BPaL for pre-XDR patients and when compared to the long WHO regimen.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **× Probably yes** ○ Yes ○ Varies ○ Don't know	All research presented by the WHO GDG was considered by the ERC. The ERC also considered the impact of Pretomanid stock availability on feasibility of implementation of the regimen, and was reassured by the NDoH TB programme that stock and funding for drug costs is available, and that no supply issues are expected. The ERC also considered the need for enhanced pharmacovigilance to accompany implementation of the intervention. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care. The ERC judged that the intervention is probably feasible to implement.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaL in the treatment of drug resistant TB with or without fluoroquinolone resistance was suggested. The recommendation is conditional based on the very low quality of evidence underlying the WHO recommendation.

b) Is BPaLM (intervention 2) non-inferior to, and/or safer than the South African standard of care (comparator 1 and 2) in the treatment of adults with rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

Should BPaLM vs. local SoC regimens (TB-PRACTECAL comparator) be used for pulmonary MDR/RR-TB or pre-XDR-TB? (WHO Sub-PICO 6.1)

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need). Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year. More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021) More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse events and preventing acquisition of additional drug resistance.	Drug-resistant TB is a global challenge and access to treatment often problematic, with regimens typically being long, toxic, and expensive. More efficacious and shorter treatment regimens for DR-TB are necessary to optimize and improve treatment outcomes while minimizing adverse events and preventing acquisition of additional drug resistance.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		

○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	

Desirable effects: How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○Trivial ○ Small ○ Moderate **x Large** ○ Varies ○ Don't know	**Research evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen). Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (89% vs 52%), i.e. 73% relative increase (aRR=1.73, 95%CI 1.31 to 2.27); lower levels of failure and recurrence (8% vs 26%) i.e. 74% relative reduction (aRR=0.26, 95%CI 0.1 to 0.71); lower levels of death (0% vs 3%), i.e. 3% absolute reduction (RD= -0.03, 95%CI -0.1 to 0.03); lower levels of loss to follow-up (3% vs 20%), i.e. 84% of relative reduction (RR=0.16, 95%CI 0.12 to 0.52); lower levels of grade 3 to 5 adverse events (21% vs 51%), i.e. 59% relative reduction (aRR=0.41, 95%CI 0.04 to 0.61) and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute reduction (RD= -0.02, 95%CI -0.07 to 0.02). BPaLM may improve treatment success, failure and recurrence, death, loss to follow-up, amplification of drug-resistance and adverse events but the evidence is very uncertain. Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have large desirable effects and noted the very low certainty of the evidence.	The panel also considered the duration and pill burden with the intervention and comparator regimens. The duration of the intervention regimen is 24 weeks (5.5 months) so treatment duration is reduced compared to the control arm by between 3–18 months. The exact magnitude of reduction in time on treatment depends on the specific comparator regimen, which includes shorter (9–12 months) and longer (18–24 months) regimens. The pill burden of the intervention regimen is lower than that for the comparator regimens. The exact magnitude of reduction in pill burden depends on the specific comparator regimen. Beyond the outcomes captured directly as research evidence in the presented statistical analyses, the WHO 'Target Regimen Profile for rifampicin-resistant tuberculosis' (WHO, 2016) identified certain regimen characteristics as having desirable anticipated effects. These include a shorter treatment duration, reduced pill burden and number of component drugs and manageable DDIs. Decrease in the treatment duration was therefore identified as an additional important desirable effect.

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaLM
Treatment success	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 1.73** (1.31 to 2.27)	Study population 515 per 1 000	**376 more per 1 000** (160 more to 654 more)
Failure and recurrence	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.26** (0.10 to 0.71)	Study population 258 per 1 000	**191 fewer per 1 000** (232 fewer to 75 fewer)
Lost to follow up	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.16** (0.04 to 0.61)	Study population 197 per 1 000	**165 fewer per 1 000** (189 fewer to 77 fewer)
Adverse events	213 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.41** (0.26 to 0.63)	Study population 509 per 1 000	**300 fewer per 1 000** (377 fewer to 188 fewer)

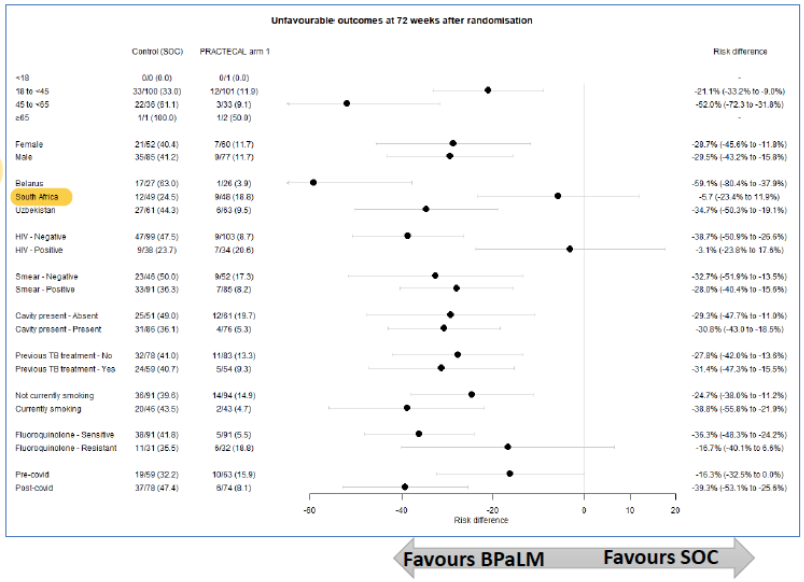
Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with TB-PRACTECAL comparator	Risk difference with BPaLM
Amplification of drug resistance	213 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.02** (-0.07 to 0.02)	Study population 19 per 1 000	**19 fewer per 1 000** (20 fewer to 18 fewer)
Death	128 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.03** (-0.10 to 0.03)	Study population 30 per 1 000	**31 fewer per 1 000** (33 fewer to 29 fewer)

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**

○Trivial
○ Small
○ Moderate
x Large

Additional evidence presented to the ERC by the review team included sub-group analysis of the South African sites from TB-PRACTECAL and the data relating to WHO sub-PICO 7.7 requested from Gregory Fox.

From TB-PRACTECAL presentation sent by Catherine Berry:

○ Varies ○ Don't know	In the subgroup analysis of efficacy by country, South African participants receiving BPaLM had more favourable outcomes as compared to participants receiving South African standard of care regimens (81.25% vs 75.5%; risk difference of 5.7 (95% CI -10.6% to 22%), although this result was not statistically significant.  **From WHO presentation of sub-PICO 7.1 (BPaLM (fluoroquinolone -resistant) vs WHO_long (fluoroquinolone-resistant) – IPD 2021) sent by Gregory Fox:** Based upon the point estimates with wide confidence intervals crossing no effect, BPaLM was associated with higher treatment success (adjusted RR 1.1; 95% CI 0.84, 1.45) (Certainty of evidence very low for all outcomes)	

PICO 7 Comparison 7.1	BPaLM (FQ-r) vs WHO long (FQ-r) (revised LTF, failure/recurren
Intervention	BPaLM (FQ-r) TB-PRACTECAL
Comparator	WHO long (FQ-r) - IPD 2021 (multiple cohorts, all-oral regimens c
Time of follow-up	18 months post treatment initiation

	Regimens		Outcome measures					Propensity score model
	BPaLM	WHO long	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in m
	n (%)	n (%)						
Total	11	839						
Outcomes								
Treatment success	9 (82%)	625 (74%)	1.1	(0.7, 1.28)	1.11	(0.84, 1.45)	0.4732	Age, sex, HIV status, ART treat AFB smear, previous DRTB
Failure & recurrence	2 (18%)	55 (7%)	2.77	(0.77, 7.63)			0.1647	
Death	0 (0%)	83 (10%)	-0.10	(-0.12, 0.16, RD)			0.613	
Loss to follow-up	0 (0%)	76 (9%)	-0.09	(-0.11, 0.17, RD)			0.612	
Grade 3 or more AE	5/18 (28%)	37 (4%)	6.3	(2.81, 14.14)	5.78	(2.39, 14.01)	0.0001	
Amplified resistance	0/18 (0%)	62 (7%)	-0.07	(-0.09, 0.1)RD			1	

The ERC, noting the improvement in treatment success and reduction in loss to follow up for all trial data in TB-PRACTECAL, as well as the shortened regimen with reduced pill burden, judged the desirable effects to be large. This judgement considers that the sub-group analysis and analysis of sub-PICO 7.1 consists of too few participants to show any definitive benefit in the FLQ resistant population only or when compared to South African standard or care regimens specifically.

Undesirable effects: How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

• **WHO Guideline panel**		
X Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Research Evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to comparator arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients treated with multiple local SoC regimens (including: 9–12-month injectable containing regimen; 18–24-month long WHO regimen (pre-2019); 9–12 month all oral regimen; 18–20 month all oral regimen). Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving WHO recommended standard of care regimens used in TB-PRACTECAL trial (n=66) experienced higher levels of treatment success (89% vs 52%), i.e. 73% relative increase (aRR=1.73, 95%CI 1.31 to 2.27); lower levels of failure and recurrence (8% vs 26%) i.e. 74% relative reduction (aRR=0.26, 95%CI 0.1 to 0.71); lower levels of death (0% vs 3%), i.e. 3% absolute reduction (RD= 0.03, 95%CI 0.1 to 0.03); lower levels of loss to follow-up (3% vs 20%), i.e. 84% of relative reduction (RR=0.16, 95%CI 0.12 to 0.52); lower levels of grade 3 to 5 adverse events (21% vs 51%), i.e. 59% relative reduction (aRR=0.41, 95%CI 0.04 to 0.61) and lower levels of amplified resistance (0% vs 2%), i.e. 2% absolute reduction (RD= 0.02, 95%CI 0.07 to 0.02). BPaLM may improve treatment success, failure and recurrence, death, loss to follow-up, amplification of drug-resistance and adverse events but the evidence is very uncertain. There were no undesirable effects among the specified outcomes Pretomanid safety Rodent Toxicology Studies – evidence of direct testicular toxicity Monkey Toxicology Studies – no evidence of direct testicular toxicity; abnormal sperm findings considered to be secondary to declining physical condition Hormone Data from Clinical Studies – no changes in FSH, LH, Inhibin B consistent with testicular toxicity Paternity Survey – 44 children fathered by 38 men (12%) who participated in pretomanid studies of 4 -6 months treatment duration Semen Study – ongoing study measuring semen in men undergoing pretomanid treatment.	**Additional considerations** Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have trivial undesirable effects and noted the very low certainty of the evidence.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
x Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	**From TB-PRACTECAL presentation sent by Catherine Berry:** Subgroup analysis of safety by country: Less SAE or Grade ≥ 3 were reported for in South African participants receiving BPaLM than those receiving South African standard of care regimes (16.1% vs 49.1%; RD -33.0%; 95% CI -50.9 to -15.1%)	The ERC noted that only one RCT with a very small sample size contributed to the data relating to efficacy and safety of BPaLM. However, this should be considered in light of the fact that current and previous standard of care regimens for the treatment of drug resistant TB were based on even less evidence . The ERC noted that the limitations of the available evidence and the resulting Imprecision do not prohibit a recommendation.

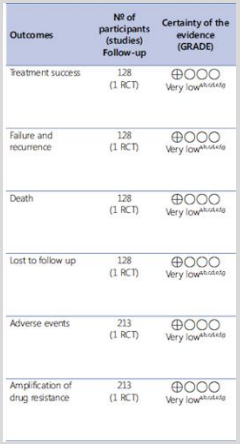
Country		SOC	BPaLM	BPaLC	BPaL
BY	n	29	28	21	21
	Grade ≥3 or SAE	9	4	6	5
	%	31.0%	14.3%	28.6%	23.8%
	Risk difference	0	-16.7%	-2.5%	-26.0%
	lower		-39.7%	-28.1%	-39.0%
	upper		6.2%	23.2%	-13.0%
UZ	n	69	67	57	55
	Grade ≥3 or SAE	37	21	19	13
	%	53.6%	31.3%	33.3%	23.6%
	Risk difference	0	-22.3%	-20.3%	-19.5%
	lower		-39.8%	-37.3%	-39.9%
	upper		-4.8%	-3.3%	0.9%
SA	n	53	56	48	46
	Grade ≥3 or SAE	26	9	13	11
	%	49.1%	16.1%	27.1%	23.9%
	Risk difference	0	-33.0%	-16.0%	-22.0%
	lower		-50.9%	-37.9%	-40.4%
	upper		-15.1%	5.8%	0.9%

From WHO presentation of sub-PICO 7.1 (BPaLM (fluoroquinolone -resistant) vs WHO_long (fluoroquinolone-resistant) – IPD 2021) sent by Gregory Fox:
Based upon the point estimates with wide confidence intervals crossing no effect, BPaLM was associated with higher rates of failure/recurrence (unadjusted RR 2.77, 95% CI 0.77, 7.63), lower mortality (RD – 0.10; 95% CI -0.12, 0.16), less loss to follow-up (RD -0.09; 95% CI -0.11, 0.17). BPaLM was associated with more Grade ≥ 3 adverse events (adjusted RR 5.78; 95% CI 2.39, 14.01). (Certainty of evidence very low for all outcomes)

PICO 7 Comparison 7.1	BPaLM (FQ-r) vs WHO_long (FQ-r) (revised LTF, failure/recurrence)							
Intervention	BPaLM (FQ-r) TB-PRACTECAL							
Comparator	WHO long (FQ-r) - IPD 2021 (multiple cohorts, all-oral regimens containing Bdq)							
Time of follow-up	18 months post treatment initiation							
	Regimens		Outcome measures					Propensity score model
	BPaLM	WHO long	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in model
	n (%)	n (%)						
Total	11	839						
Outcomes								
Treatment success	9 (82%)	625 (74%)	1.1	(0.7, 1.28)	1.11	(0.84, 1.45)	0.4732	Age, sex, HIV status, ART treatment (for those with HIV), AFB smear, previous DRTB treatment, site of disease
Failure & recurrence	2 (18%)	55 (7%)	2.77	(0.77, 7.63)			0.1647	Adjustment not possible
Death	0 (0%)	83 (10%)	-0.10	(-0.12, 0.16, RD)			0.613	Adjustment not possible
Loss to follow-up	0 (0%)	76 (9%)	-0.09	(-0.11, 0.17, RD)			0.612	Adjustment not possible
Grade 3 or more AE	5/18 (28%)	37 (4%)	6.3	(2.81, 14.14)	5.78	(2.39, 14.01)	0.0001	
Amplified resistance	0/18 (0%)	62 (7%)	-0.07	(-0.09, 0.1)RD			1	Adjustment not possible

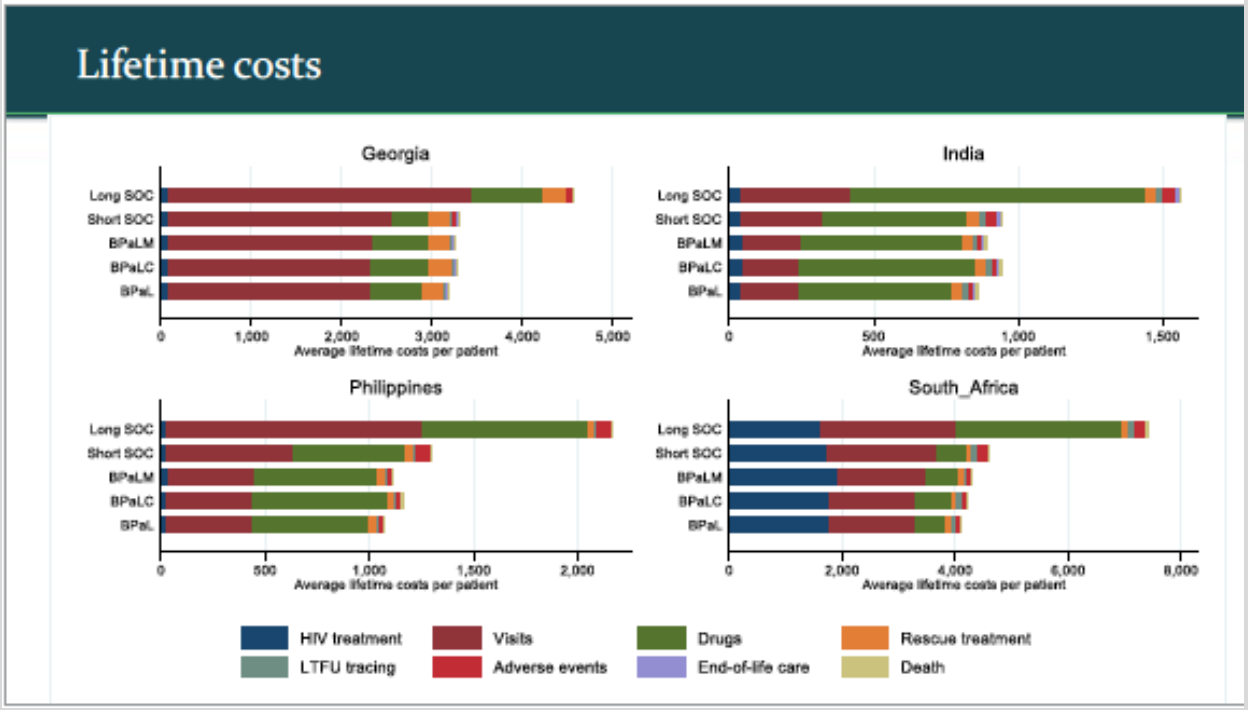
Overall, BPaLM was associated with less AEs than the SoC arms, and when stratified by country for South African SoC regimens specifically. Therefore, the ERC judgement found that the anticipated undesirable effects of the intervention are trivial.

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** The certainty of evidence was rated very low. The risk of bias was judged to be serious or very serious, depending on outcome. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in population and the comparator regimen by one level. Imprecision was serious or very serious according to outcomes, with a small number of events for some outcomes resulting downgrading by one to two levels according to outcomes.  Outcomes / № of participants (studies) Follow-up / Certainty of the evidence (GRADE) Treatment success — 128 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] Failure and recurrence — 128 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] Death — 128 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] Lost to follow up — 128 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] Adverse events — 213 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] Amplification of drug resistance — 213 (1 RCT) — ⊕○○○ Very low[a,b,c,d,e,f,g] a. An imbalance in measured covariates (gender, prior DR-TB, smear status) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely. b. Small numbers of events in some outcomes precludes adjustment in some comparisons. c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an outcome that may be influenced by patient or clinician knowledge of the regimen. d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013). e. Multiple comparator regimens were used, varying across site. This may explain some of the substantial inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is difficult. We did not downgrade for inconsistency as the issue of comparators was addressed under indirectness. f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level. g. The number of participants in both intervention and comparator groups was small (n=60 and n=66). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.	As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations, and that • 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

x Very low ○ Low ○ Moderate ○ High ○ No included studies	No additional research evidence was provided. The ERC agreed with the judgment that the certainty of evidence is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research was searched for by the review team. The ERC agreed with the WHO GDG judgement that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	**Research Evidence** Nil The GDG judged the benefits of BPaLM to be large and the undesirable effects to be trivial compared to WHO recommended standard of care regimens. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM regimen	As noted in the CoE assessment, it is important to highlight that: • the population included in the trial that gave rise to the data is a mix of MDR/RR and pre-XDR/XDR TB patients (82–92% RR/MDR, depending on study arm) • treatment outcomes for the comparator regimen differ for these populations, and that • 24% of patients were treated with regimens no longer recommended by WHO, e.g., containing injectable drugs and not containing Bdq As a result, the balance of effects may be different in settings/populations with different FQ-resistance prevalence and if only currently recommended regimens are used.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	The ERC considered that even if the benefits of BPaLM in comparison to South African SoC specifically are smaller than in the comparison of BPaLM to SoC arm in TB-PRACTECAL, the shortened duration of treatment and less complex treatment regimen that may favour adherence probably favours the intervention.	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		

○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	**Research Evidence** Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar From the data presented, the total cost (drugs and delivery) of WHO_short appear to be between 1%-15% higher than for BPaLM and between ~1.4x to 1.9x higher for WHO_long when looking at comparative estimates within country. In most settings, BPaLM is cost-saving; these cost savings are mostly due to reduced time in care and therefore reductions in numbers of outpatient visits, inpatient bed-days, and lab tests.  	The panel judged that the costs for BPaLM are lower because costs of drugs are lower, and cost of delivery are also lower due to the shorter duration of treatment and lower complexity. The GDG judged that the reduction in costs varies between moderate and large.

Results by country: conservative approach

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person
Philippines			
SOC long	$2,127	6.2	
SOC short	$1,286	5.1	-$841
BPaL	$1,050	5.1	-$236
BPaLC	$1,146	5.0	$96
BPaLM	$1,099	4.4	-$47
South Africa			
SOC long	$6,896	6.9	
SOC short	$4,120	6.3	-$2,776
BPaL	$3,554	6.3	-$566
BPaLC	$3,687	6.2	$132
BPaLM	$3,739	5.7	$52
India			
SOC long	$1,531	6.8	
SOC short	$923	6.1	-$608
BPaL	$838	6.1	-$84
BPaLC	$923	6.0	$85
BPaLM	$872	5.5	-$51
Georgia			
SOC long	$4,499	4.7	
SOC short	$3,290	4.1	-$1,209
BPaL	$3,164	4.1	-$125
BPaLC	$3,264	4.0	$100
BPaLM	$3,246	3.3	-$19

- **PHC/ADULT HOSPITAL LEVEL COMMITTEE**

BPaLM vs long regimens for MDR and Pre-XDR TB

Suggested ERC Judgment:

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
x Large savings
○ Varies
○ Don't know

BPaLM vs SA_New SCR

Resources required

Suggested ERC Judgment:

○ Large costs
○ Moderate costs
x Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

Additional information presented by the review team included updated evidence from the Sweeney et al. publication (published since the WHO GDG meeting, and on which WHO GDG judgement is based), and the normative cost analysis of direct costs conducted by the review team.

Updated version of Sedona Sweeney's presentation with official publication:

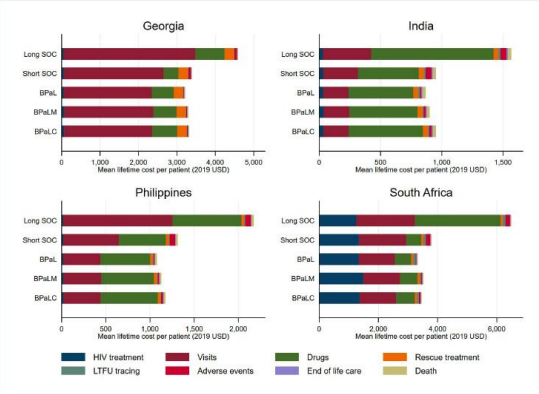


Fig 1. Average lifetime costs by country and regimen.

The cost savings associated with a move from the current SOC mix to BPaL for all MDR/RR-TB patients range was $1,173 per person in South Africa.
Costs presented in 2019 US$;
Total costs per person for South Africa: BPaL: $3,344, BPaLM: $3,520, and BPaLC: $3,470.
Current SOC regimen mix (74% short, 26% long): $4,517

Table 2. Base case results.

			Comparison with current SOC mix	
Country and regimen	**Total costs per person**	**Total DALYs per person**	**Incremental Costs Per Person**	**Incremental DALYs Averted Per Person**
Philippines				
Current SOC regimen mix (99% short, 1% long)	$1,329	5.4		
BPaL	$1,078	5.4	-$251	0.0
BPaLC	$1,174	5.3	-$155	0.1
BPaLM	$1,124	4.6	-$204	0.8
South Africa				
Current SOC regimen mix (74% short, 26% long)	$4,517	6.8		
BPaL	$3,344	6.6	-$1,173	0.2
BPaLC	$3,470	6.5	-$1,047	0.3
BPaLM	$3,520	6.0	-$997	0.8

Normative cost analysis conducted by review team. For more information consult Appendix 3.

Appendix 3.xlsx

Normative cost analysis based on specific direct costs						Sensitivity analysis excl.clinic vist costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	15 649,49	12 968,70
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	17 862,78	15 181,99
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	17 207,81	14 575,25
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	17 805,05	15 172,49
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	17 284,25	14 651,69
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	34 467,47	30 059,87
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	60 328,21	53 746,81

Note:
Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

Marginally increased drug costs associated with BPaLM regimen as compared to current South African short course regimen despite the reduced duration of treatment. Increased costs of treatment monitoring laboratory tests (such as monthly full blood and differential counts as recommend by WHO) driving the increased direct costs associated with BPaLM, which is not entirely offset by the reduced number of bacteriological treatment monitoring tests associated with the shorter duration of treatment.

Based on the normative cost analysis performed by the review team, the ERC judged that BPaLM when compared to the current South African short course regimen would be associated with negligible costs and/or savings. BPaLM when compared to the current South African long courses (for MDR and fluoroquinolone resistances) would be associated with large savings.

Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Nil	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low x Moderate ○ High ○ No included studies	The ERC considered the certainty of evidence of resource requirements to be moderate considering the normative cost analysis performed by the review team is locally relevant.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies	**Research Evidence** **Sedona Sweeney's presentation on cost & CEA of PRACTECAL regimens from pre-GDG webinar** From the data presented: «strong evidence that BPaLM would be cost-effective» in the setting studied (costs reduced and DALYs averted) Note that estimates of effectiveness (from which DALYs averted were derived) are different from those presented in the evidence profile for this PICO **Results by country: conservative approach** Given their prior judgements (balance of effects probably favours the intervention; intervention leads to moderate to large savings), the panel judged that the cost-effectiveness of the intervention probably favours the intervention	.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the	No additional research evidence was considered by the ERC. Based on the data and studies considered by WHO GDG, the ERC agreed that cost-effectiveness of the intervention probably favours the intervention.	

Country and regimen	Total costs per person	Total DALYs	Incremental Costs per person	Incremental DALYs Averted Per Person	Incremental costs per DALY
Philippines					
SOC long	$2,127	6.2			
SOC short	$1,286	5.1	-$841	1.04	Dominant
BPaL	$1,050	5.1	-$236	0.00	Dominant
BPaLC	$1,146	5.0	$96	0.11	$867
BPaLM	$1,099	4.4	-$47	0.62	Dominant
South Africa					
SOC long	$6,896	6.9			
SOC short	$4,120	6.3	-$2,776	0.57	Dominant
BPaL	$3,554	6.3	-$566	0.00	Dominant
BPaLC	$3,687	6.2	$132	0.10	$1,375
BPaLM	$3,739	5.7	$52	0.54	$97
India					
SOC long	$1,531	6.8			
SOC short	$923	6.1	-$608	0.70	Dominant
BPaL	$838	6.1	-$84	-0.04	Dominant
BPaLC	$923	6.0	$85	0.10	$838
BPaLM	$872	5.5	-$51	0.57	Dominant
Georgia					
SOC long	$4,499	4.7			
SOC short	$3,290	4.1	-$1,209	0.57	Dominant
BPaL	$3,164	4.1	-$125	0.02	Dominant
BPaLC	$3,264	4.0	$100	0.12	$833
BPaLM	$3,246	3.3	-$19	0.67	Dominant

comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ No included studies		
Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. Despite not being able to identify relevant research evidence, the panel used their collective experience to judge that there would likely be advantages associated with the use of the BPaLM regimen due to its reduced complexity and shorter duration. The panel judged that use of the BPaLM regimen would probably increase equity.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact **x Probably increased** ○ Increased ○ Varies ○ Don't know	No additional research evidence was considered by the ERC. The ERC was in agreement with the WHO GDG that due to the reduced complexity and shorter duration of the treatment regimen with resultant ability to decentralize care, the use of BPaLM would probably increase equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** **Beverly Stringer's presentation on PROs from pre-GDG webinar (qualitative study) on the patient perspective** Positive impact of shorter treatment on employment status welcomed.	**van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective:** • Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about acceptability of using

	The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaLM regimen would probably be acceptable.	BPaL for pre-XDR patients and when compared to the long WHO regimen. • **Findings:** Acceptability: overall high and rated as acceptable by >80% across domains
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Additional Research Evidence presented to the ERC by TB-PRACTECAL-PRO team:** All trial participants respiratory-specific QOL scores improved with treatment, irrespective of the regimen they received (intervention or SoC). However, faster improvement in the investigational arm as compared to SoC was noted. It was noted that a participant in the intervention arm experiences a 15% reduction (95% CI 12 to 18%) in the mean SGRQ symptom score per month versus an average of 5% (95% CI 0 – 9%) reduction experienced by a participant in the SoC arm. (Note: lower SGRQ symptom score associated with greater quality of life). The qualitative data showed that the improvement in QOL was noted by both the individual and their friends/family, with a resultant positive effect on treatment support. It was highlighted that South African participants were slightly underrepresented in the trial (32 South Africans of 137 participants) and that no subgroup analysis of QOL outcomes across countries or by site was performed. For participants interviewed in this qualitative study, the supportive care experienced was as important as the tolerability of the novel drug regimen. The ERC concluded that based on the research considered by the WHO GDG and additional information form the TB-PRACTECAL-PRO team the intervention is probably acceptable to stakeholders.	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINES, 2020**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** Nil additional The panel considered the following aspects to affect feasibility (i.e. to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. The panel noted limited availability of drugs in the BPaLM regimen for use in DST as a potential barrier to implementation and also noted that data on the critical concentration of Pretomanid for use in DST is limited. However, given the reduced duration, complexity and associated workload, the panel judged that implementation is probably feasible.	**van de Berg et al, 2021 (based on 2019 KNCV report, funded by TB Alliance) on the provider perspective:** Noting that analyses from van de Berg paper are only partially applicable here since in their study they asked about feasibility of using BPaL for pre-XDR patients and when compared to the long WHO regimen.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes	Additional barriers to implementation that may affect feasibility considered by the ERC included that need for an enhanced programmatic pharmacovigilance plan. The ERC considered feedback from the NDOH TB programme that planning for enhanced pharmacovigilance and data collection is underway. The ERC also considered concern around stock availability of pretomanid and consulted the NDOH TB programme. The ERC heard that currently, stock availability is not a potential barrier to implementation as pretomanid has been ordered and funding has been made available for further procurement.	

○ Varies ○ Don't know	With regard to the impact of drug resistance testing on the feasibility of implementation, the ERC heard that resistance testing for Bdq and Linezolid is already available, and provisions for resistance testing for pretomanid are being made. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care. After consideration of these potential barriers to implementation, the ERC judged that BPaLM is probably feasible to implement.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaLM in the treatment of drug resistant TB with or without fluoroquinolone resistance was suggested. The recommendation is conditional based on the very low quality of evidence underlying the WHO recommendation.

c) Is BPaL (intervention 1) non-inferior to, and/or safer than BPaLM (intervention 2) in the treatment of rifampicin-resistant tuberculosis without additional fluoroquinolone resistance?

Should BPaLM vs. BPaL (Linezolid 600mg/300mg) be used for pulmonary MDR/RR-TB and pre-XDR-TB? (sub-PICO 6.2)

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	**Research evidence** The COVID-19 pandemic has reversed years of progress in providing essential TB services and reducing TB disease burden. The most obvious impact is a large global drop in the number of people newly diagnosed with TB and reported. This fell from 7.1 million in 2019 to 5.8 million in 2020, an 18% decline back to the level of 2012 and far short of the approximately 10 million people who developed TB in 2020. Reduced access to TB diagnosis and treatment has resulted in an increase in TB deaths. Best estimates for 2020 are 1.3 million TB deaths among HIV-negative people (up from 1.2 million in 2019) and an additional 214 000 among HIV-positive people (up from 209 000 in 2019), with the combined total back to the level of 2017. Other impacts include reductions between 2019 and 2020 in the number of people provided with treatment for drug-resistant TB (-15%, from 177 100 to 150 359, about 1 in 3 of those in need). Globally in 2020, 71% (2.1/3.0 million) of people diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance, up from 61% (2.2/3.6 million) in 2019 and 50% (1.7/3.4 million) in 2018. Among these, 132 222 cases of MDR/RR-TB and 25 681 cases of pre-XDR-TB or XDR-TB were detected, for a combined total of 157 903. This was a large fall (of 22%) from the total of 201 997 people detected with drug-resistant TB in 2019, consistent with similarly large reductions in the total number of people newly diagnosed with TB (18%) and the total number of people diagnosed with bacteriologically confirmed pulmonary TB (17%) observed between 2019 and 2020. Worldwide, 150 359 people with MDR/RR-TB were enrolled on treatment in 2020, down 15% from the total of 177 100 in 2019. This level of enrolment was equivalent to about one in three of the people who develop MDR/RR-TB each year.	

	More positively, there have been improvements in treatment success rates. Globally in 2018 (the latest patient cohort for which data are available), the treatment success rate for MDR/RR-TB was 59%, reflecting steady improvements in recent years from 50% in 2012. (Global TB Report 2021)	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes **x Yes** ○ Varies ○ Don't know	In addition to the research evidence considered by the WHO GDG , the ERC considered the burden of disease in the locally relevant population. A cross-sectional study of identified tuberculosis cases, conducted in South Africa between 2012 and 2014, reported the prevalence of RR-TB as 4.6%, MDR-TB as 2.8% (95% CI 2.0, 3.6) and the prevalence of XDR-TB as 4.9% (95% CI 1.0, 8.8). (Ismail et al. 2018). More recently for the year 2021, the WHO reported an estimated 21 000 incident cases of RR-TB in South Africa. (WHO Global Tuberculosis Report, 2022) The ERC judged the problem to be a priority.	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial ○ Small **x Moderate** ○ Large ○ Varies ○ Don't know	**Research evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/ RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to BPaL arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients. Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving BPaL in TB-PRACTECAL trial (n=60) experienced higher levels of treatment success (89% vs 77%), i.e. 15% relative increase (aRR=1.15, 95%CI 0.95 to 1.38); lower levels of failure and recurrence (8.1% vs 13%), i.e. 47% relative reduction (aRR= 0.53, 95%CI 0.17 to 1.63); lower levels of loss to follow-up (3.2% vs 10%), i.e. 68% relative reduction (RR=0.32, 95%CI 0.08 to 1.34); no difference in death (0% vs 0%), i.e. 0% absolute difference (RD= 0.00, 95%CI −0.06 to 0.06); higher levels of grade 3 to 5 adverse events (21% vs 20%), i.e. 7% relative increase (aRR=1.07, 95%CI 0.62 to 1.88) and lower levels of amplified resistance (0% vs 3%), i.e. 3% absolute reduction (RD= −0.03, 95%CI −0.08 to 0.01). The evidence is very uncertain about the effect of the BPaLM regimen with linezolid on all outcomes.	

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Treatment success	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 1.15** (0.95 to 1.38)	Study population	
				767 per 1 000	**115 more per 1 000** (38 fewer to 291 more)
Failure and recurrence	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.53** (0.17 to 1.63)	Study population	
				133 per 1 000	**63 fewer per 1 000** (111 fewer to 84 more)
Lost to follow up	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RR 0.32** (0.08 to 1.34)	Study population	
				100 per 1 000	**68 fewer per 1 000** (92 fewer to 34 more)

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Death	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,g]	**RD 0.00** (-0.06 to 0.06)	Study population	
				0 per 1 000	**0 fewer per 1 000** (60 fewer to 60 more)
Amplification of drug resistance	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]	**RD -0.03** (-0.08 to 0.01)	Study population	
				29 per 1 000	**30 fewer per 1 000** (80 fewer to 10 more)

	Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have moderate desirable effects and noted the very low certainty of the evidence.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○Trivial ○ Small ○ Moderate ○ Large ○ Varies **x Don't know**	Based on the wide confidence intervals, crossing no effect for the comparison of BPaLM vs BPaL from TB-PRACTECAL, the ERC judged that it is not known how substantial the desirable effects of the intervention are.	
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○Trivial **x Small** ○ Moderate ○ Large ○ Varies ○ Don't know	**Research Evidence** The BPaLM regimen arm of the TB-PRACTECAL trial with population including patients with MDR/ RR-TB with or without quinolone resistance (MDR/RR-TB or pre-XDR-TB) was compared to BPaL arm of the TB-PRACTECAL trial comprised of MDR/RR-TB or pre-XDR-TB patients. Participants with MDR/RR-TB (with or without quinolone resistance) receiving BPaLM regimen (n=62) compared to participants receiving BPaL in TB-PRACTECAL trial (n=60) experienced higher levels of grade 3 to 5 adverse events (21% vs 20%), i.e., 7% relative increase (aRR=1.07, 95%CI 0.62 to 1.88).	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with BPaL (Lzd 600mg/300mg)	Risk difference with BPaLM
Adverse events	207 (1 RCT)	⨁◯◯◯ Very low[abcdefg]	**RR 1.07** (0.61 to 1.88)	Study population 196 per 1 000	**14 more per 1 000** (76 fewer to 173 more)

	Considering this research evidence and the additional considerations, the GDG judged that BPaLM may have small undesirable effects and noted the very low certainty of the evidence.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies **x Don't know**	Additional evidence was presented to the ERC by the review team from data relating to WHO sub-PICO 7.2 provided by Gregory Fox. For sub-PICO 7.2, the comparison of BPaLM arm from TB-PRACTECAL only in participants with fluoroquinolone -resistant TB (n = 11) vs. BPaL from the ZeNix 600-26 arm in participants with fluoroquinolone-resistant TB (n = 33), BPaLM was associated with statistically significant less treatment success (unadjusted RR 0.82; 95% CI 0.52, 0.95) and higher rates of treatment failure/recurrence (RD 0.18, 95% CI 0.05, 0.48). There was no difference in mortality, loss-to-follow-up or amplification of resistance. Based on point estimate, with wide confidence interval crossing no difference, BPaLM in this population was also associated with more grade 3 ≥ adverse events (aRR 1.19; 95% CI 0.34, 4.21).	

The ERC considered that the possible increased risk of treatment failure and reduced treatment success reported in the additional research presented may have occurred as a result of chance (noting the small sample size), however, an alternate explanation is that the reduction in Linezolid dosing from 600mg to 300mg at 16 weeks in the BPaLM arm in TB PRACTECAL as compared to 600mg of Linezolid used for 26 weeks in the ZeNix trial may account for this difference in outcomes in the fluoroquinolone resistant population.

However, based on the wide confidence intervals that cross no effect for adverse events, in the comparison of the BPaLM and BPaL arms in TB-PRACTECAL, and the potential for more undesirable effects when used in those with fluoroquinolone resistance, the ERC judged that it is currently not known how substantial the undesirable effects of the intervention are.

PICO 7 Comparison 7.2	BPaLM (FQ-r) vs BPaL (FQ-r)							
Intervention	BPaLM (FQ-r) TB-PRACTECAL							
Comparator	BPaL (Zenix 600-26)							
Time of follow-up	18 months post treatment initiation							
	Regimens		Outcome measures					Propensity score model
	BPaLM	BPaL	Unadj. RR	(95% CI)	Adj. RR (or RD)	(95% CI)	p-value	Covariates included in mod
	n (%)	n (%)						
Total	11	33						
Outcomes								
Treatment success	9 (82%)	33 (100%)	0.82	(0.52, 0.95)			0.0581	Age, sex, HIV status, ART treatmen AFB smear, previous DRTB treatme
Failure & recurrence	2 (18%)	0 (0%)	0.18	(0.05, 0.48) RD			0.0581	As above
Death	0 (0%)	0 (0%)	0	(-0.11, 0.26)RD			1	As above
Loss to follow-up	0 (0%)	0 (0%)	0	(-0.11, 0.26)RD			1	As above
Grade 3 or more AE	5/18 (28%)	5 (15%)	1.83	(0.61, 5.5)	1.19	(0.34, 4.21)	0.7854	
Amplified resistance	0/18 (0%)	0 (0%)	0	(-0.11, 0.18)			1	Adjustment not possible

The University of Sydney

*Sensitivity estimates for aRR for treatment success

Certainty of evidence: What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Confidence limits were wide for most estimates. Certainty was rated *very low*. Risk of bias was serious or very serious, for different outcomes. There was a lack of blinding, early termination of the trial for benefit, measured confounding and likely unmeasured confounding and small event numbers precluding adjustment for some comparisons. These concerns resulted in downgrading by one or two levels depending upon outcome. We did not downgrade for inconsistency. We downgraded for indirectness due to differences in population and the comparator regimen by one level. Imprecision was serious or very serious according to outcome, with a small number of events for some outcomes resulting downgrading by one to two levels according to outcomes.	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)
Treatment success	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Failure and recurrence	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Death	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,g]
Lost to follow up	122 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Adverse events	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]
Amplification of drug resistance	207 (1 RCT)	⨁◯◯◯ Very low[a,b,c,d,e,f,g]

a. An imbalance in measured covariates (gender, past TB treatment, past DR-TB treatment, smear positivity, culture positivity and FQ-S proportion) likely arises from the small number of participants in each group. While the adjusted analyses will account for measured confounding, unmeasured confounding is also likely.
b. Small numbers of events in some outcomes precludes adjustment in some comparisons
c. A lack of blinding of patients, caregivers and those adjudicating outcomes may introduce bias in the conduct of the trial. Higher loss to follow-up was noted in the comparator group, which is an that may be influenced by patient or clinician knowledge of the regimen.
d. The trial was stopped early for benefit, with few events (<200). This can introduce bias. Formal stopping rules do not reduce bias (GRADE Handbook, 2013).
e. Multiple comparator regimens were used, varying across site. This may explain some of the inconsistency in the point estimates for treatment outcomes seen between countries (Belarus, South Africa and Uzbekistan). The decision whether to downgrade is a difficult decision. Confidence limits for these estimates do overlap, and so we have chosen not to downgrade for inconsistency.
f. A single trial. Serious indirectness (i) Populations: Differences in population of a trial and population to which guidelines will apply. (ii) Comparator: Some comparator regimens are sub-optimal, not according with the WHO standard of care (at the time or presently) and vary by country. Downgraded one level.
g. The number of participants in both intervention and comparator groups was small (n=62 and n=60). Very few events in the outcomes of interest, causing very serious imprecision. We downgraded two levels for imprecision for some outcomes, and one level for others.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	The ERC agrees with the WHO GDG panel judgement that the overall certainty of the evidence of the effects is very low.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	**Research Evidence** No evidence research searched for. Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients. The panel judged that there was probably no important uncertainty or variability in how much people value the main outcomes.	Higher treatment efficacy, shorter duration of treatment, lower pill burden and less adverse events are usually valued by patients.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		

○ Important uncertainty or variability ○ Possibly important uncertainty or variability **x Probably no important uncertainty or variability** ○ No important uncertainty or variability ○ No known undesirable outcomes	No additional research evidence was presented to the ERC by the review team. The ERC agrees with the WHO GDG judgment that there is probably no important uncertainty or variability in how much people value the main outcomes.	
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison **x Probably favours the intervention** ○ Favours the intervention ○ Varies ○ Don't know	**Research Evidence** Nil additional The GDG judged the benefits of BPaLM to be moderate and the undesirable effects to be small compared to BPaL. The certainty of evidence was judged to be very low. Based on this, the panel determined that the balance of health effects probably favours BPaLM.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison **x Does not**	Considering the previous ERC judgements, that the size of desirable and undesirable effects of the BPaLM intervention in comparison to the BPaL intervention is unknown, the ERC judged that based on the currently available data (or lack thereof) the balance of undesirable and desirable effects does not favour the intervention or the comparison. However, clinicians in the review team had concern that many patients may require termination of treatment with linezolid as a result of intolerance, in which case a treatment would only comprise two drugs. Therefore, the committee suggested that a fluoroquinolone be included in the regimen initially, and be continued for the duration of treatment if fluoroquinolone resistance is excluded. This recommendation is based on expert opinion rather than the data presented by WHO. In those	

favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ○ Don't know	whom fluoroquinolone resistance is detected, the fluoroquinolone may be omitted from the regimen. The ERC deliberated whether levofloxacin should be recommended rather than moxifloxacin as the fluoroquinolone of choice. The primary consideration by the Committee in support of levofloxacin over moxifloxacin as the fluoroquinolone of choice is the better safety profile of levofloxacin, specifically with regard to cardiotoxicity (specifically reduced QTc prolonging effects) which is well-documented in the literature. (20-22) In terms of the relative efficacy of levofloxacin and moxifloxacin, the consideration of interchangeability was based primarily on expert opinion, and supported by two publications.(23, 24)	

Resources required: How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings **x Varies** ○ Don't know	**Research Evidence** Nil additional	**Additional considerations** The cost savings from improved health outcomes were felt to be an important consideration as they could be substantial. However, the panel also felt that some of the cost will vary e.g., the savings from improved health outcomes will depend on underlying fluoroquinolone resistance prevalence. Cost may also be affected by access to fluoroquinolone DST and accordingly the ability to drop Moxi if resistance is found. Therefore, the GDG judged the resources required to vary.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		

○ Large costs ○ Moderate costs **x Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**The ERC considered the normative cost analysis conducted by review team. For more information consult Appendix 3.** Appendix 3.xlsx **Normative cost analysis based on specific direct costs** / **Sensitivity analysis excl.clinic vist costs** **Regimen** / **Drug costs (ZAR)** / **Bacteriological tests (Costs in ZAR)** / **Other lab tests (Costs in ZAR)** / **Clinic visit costs (ZAR)** / **Total costs per patient treated incl. clinic visit costs (ZAR)** / **Total costs per patient treated excl. clinic visit costs (ZAR)** Short oral course (Min) — 11 437,70 — 1 058,58 — 472,42 — 2 680,79 — **15 649,49** — **12 968,70** Short oral course (Max) — 13 650,99 — 1 058,58 — 472,42 — 2 680,79 — **17 862,78** — **15 181,99** BPaL (Lzd_Adjusted dose) — 11 710,64 — 705,72 — 2 158,89 — 2 632,56 — **17 207,81** — **14 575,25** BPaLM (Lzd_Adjusted dose) — 12 307,88 — 705,72 — 2 158,89 — 2 632,56 — **17 805,05** — **15 172,49** BPaLM (Lzd_Standard) — 11 787,08 — 705,72 — 2 158,89 — 2 632,56 — **17 284,25** — **14 651,69** Long course 1 (Basic) — 27 159,16 — 2 117,16 — 783,55 — 4 407,60 — **34 467,47** — **30 059,87** Long course 2 — 49 601,58 — 2 117,16 — 2 028,07 — 6 581,40 — **60 328,21** — **53 746,81** **Note:** **Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose** **1 US$ equivalent to R18.30** **Drug calculations all based on a 28 day cycle per month** **Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests** **Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.** The differences in cost between BPaLM and BPaL were considered negligible.	

Certainty of evidence of resource requirements: What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
x Very low ○ Low ○ Moderate ○ High ○ No included studies	**Research Evidence** Nil	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low **x Moderate** ○ High ○ No included studies	The ERC considered the certainty of evidence of resource requirements to be moderate considering the normative cost analysis performed by the review team is locally relevant.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	**Research Evidence** The cost-effectiveness study embedded in TB-PRACTECAL trial (Sweeney et al.) compared BPaL regimens to other longer regimens, therefore may not be useful for comparison between BPaL and BPaLM	Both regimens are of 6 months duration.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies **x No included studies**	Nil additional research comparing the cost-effectiveness of BPaLM to BPaL was available for presentation to the ER.	

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced **x Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. Implementation in some countries may be hampered by lack of availability of DST and that could have an impact on equitable roll out if DST for moxifloxacin is a requirement for implementation. However, the WHO GDG judged that the intervention would probably have no impact on health equity over the comparison.	The panel considered the treatment duration and the ability to decentralize treatment (to enable access for remote, underserviced settings and disadvantaged populations) to affect equity.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced **x Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Considering that both the intervention and the comparison are of similar durations, and not significantly complex, the ERC judged that they are likely to have the same impact on equity.	
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. The panel considered patients and health care providers as key stakeholders. The panel considered the following aspects as critical with regards to acceptability: regimen duration and drug safety monitoring needs (both relating to necessary travel, loss of income and general disruption of the life of patients; workload for the health care system), needs for drug susceptibility testing. The panel judged that the BPaLM regimen would probably be acceptable.	Both regimens are 6month regimens, only difference is Moxifloxacin in BPaLM.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	No additional evidence was presented to ERC committee. Considering previous judgements that BPaLM (EtD and PICO c) is probably acceptable to key stakeholder and that BPaL (EtD and PICO a) is probably acceptable to key stakeholders, the ERC judged that BPaLM (when compared to BPaL) would probably be acceptable to key stakeholders .	
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	**Research Evidence** No research evidence searched for. The panel noted that rapid DST to moxifloxacin is not available in all settings and that this is a potential barrier to implementation. The panel judged that implementation is probably feasible.	The panel considered the following aspects to affect feasibility (i.e., to be potential barriers to implementation): requirements for drug safety monitoring and requirements for drug susceptibility testing. Both BPaLM and BPaL are 6month regimens, only difference is Moxifloxacin in BPaLM.
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no **x Probably yes** ○ Yes ○ Varies ○ Don't know	The ERC considered the issues raised by the WHO GDG. Based on the indirect evidence of high feasibility of BPaL in preXDR-TB reported by van de Berg et al. and South Africa's ability to perform genotypic testing for fluoroquinolone resistance , the ERC judged the intervention (BPaLM) to be feasible. The ERC heard from the NDOH TB programme that feasibility could be impacted if the level of prescriber be restricted to medical officer only, as clinical nurse practitioners and clinical associates are important human resources for decentralized care.	

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	23 March 2023	JT, NG, SE, FB, NN, GM, MM, JN, TK, KC	Initial ERC discussion took place on 16th March 2023, with ongoing discussion and updated ERC decision at an extraordinary meeting of the ERC on 23 March 2023, where a conditional recommendation for the use of the BPaLM in the treatment of drug resistant TB without fluoroquinolone resistance was suggested. The recommendation is conditional and based only on the expert opinion and not on data presented by the WHO GDG. Furthermore, levofloxacin could be used instead of moxifloxacin as fluoroquinolone of choice for inclusion in the revised regimen.

Recommendations

Through the GRADE adolopment process, the following recommendation has been adapted from the WHO by the PHC/Adult hospital level Committee:

1. We suggest the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600mg) and a fluoroquinolone rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. (Conditional recommendation, very low certainty of evidence). Levofloxacin is to be used instead of moxifloxacin as fluoroquinolone of choice, for inclusion in the revised regimen.

The PHC/Adult hospital level committee has adopted the following remarks relevant to the recommendation above from the WHO:

2. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether the fluoroquinolone can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without the fluoroquinolone would be initiated or continued.
3. This recommendation applies to the following:
    a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
    b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
    c. Adults and adolescents aged 14 years and older.
    d. All people regardless of HIV status.
    e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
4. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
5. The recommended dose of linezolid is 600 mg once daily.

References

1. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779-87. 10.1016/S1473-3099(18)30222-6. https://www.ncbi.nlm.nih.gov/pubmed/29685458.
2. Global tuberculosis report 2022. Geneva: World Health Organization. 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-3-drug-resistant-tb.
3. Ndjeka N, Schnippel K, Master I, Meintjes G, Maartens G, Romero R, et al. High treatment success rate for multidrug-resistant and extensively drug-resistant tuberculosis using a bedaquiline-containing treatment regimen. Eur Respir J. 2018;52(6). DOI: 10.1183/13993003.01528-2018. https://www.ncbi.nlm.nih.gov/pubmed/30361246.
4. South African Department of Health. Management of rifampicin-resistant tuberculosis: A clinical reference guide. 2019. https://www.health.gov.za/wp-content/uploads/2020/11/management-of-rifampicin-resistant-tb-booklet-0220-v11.pdf.
5. Tack I, Dumicho A, Ohler L, Shigayeva A, Bulti AB, White K, et al. Safety and Effectiveness of an All-Oral, Bedaquiline-Based, Shorter Treatment Regimen for Rifampicin-Resistant Tuberculosis in High Human Immunodeficiency Virus (HIV) Burden Rural South Africa: A Retrospective Cohort Analysis. Clinical Infectious Diseases. 2020;73(9):e3563-e71. 10.1093/cid/ciaa1894. https://doi.org/10.1093/cid/ciaa1894.
6. Jaspard M, Butel N, El Helali N, Marigot-Outtandy D, Guillot H, Peytavin G, et al. Linezolid-Associated Neurologic Adverse Events in Patients with Multidrug-Resistant Tuberculosis, France. Emerg Infect Dis. 2020;26(8):1792-800. 10.3201/eid2608.191499.
7. 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.
8. World Health Organization. Target regimen profiles for TB treatment: candidates: rifampicin-susceptible, rifampicin resistant and pan-TB treatment regimens. 2016(WHO/HTM/TB/2016.16). https://apps.who.int/iris/handle/10665/250044.
9. Schünemann HJ, Wiercioch W, Brozek J, Etxeandia-Ikobaltzeta I, Mustafa RA, Manja V, et al. GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. J Clin Epidemiol. 2017;81:101-10. 10.1016/j.jclinepi.2016.09.009.
10. Florez ID, Amer YS, McCaul M, Lavis JN, Brouwers M. Guidelines developed under pressure. The case of the COVID-19 low-quality "rapid" guidelines and potential solutions. J Clin Epidemiol. 2022;142:194-9. 10.1016/j.jclinepi.2021.11.012. https://www.ncbi.nlm.nih.gov/pubmed/34780983.
11. McCaul M, Tovey D, Young T, Welch V, Dewidar O, Goetghebeur M, et al. Resources supporting trustworthy, rapid and equitable evidence synthesis and guideline development: results from the COVID-19 evidence network to support decision-making (COVID-END). J Clin Epidemiol. 2022;151:88-95. 10.1016/j.jclinepi.2022.07.008. https://www.ncbi.nlm.nih.gov/pubmed/35868494.
12. Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. Cmaj. 2014;186(3):E123-42. 10.1503/cmaj.131237.
13. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-42. 10.1503/cmaj.090449. https://www.ncbi.nlm.nih.gov/pubmed/20603348.
14. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, 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. 10.1136/bmj.j4008. https://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf.
15. Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook A, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. New England Journal of Medicine. 2020;382(10):893-902. 10.1056/NEJMoa1901814. https://www.nejm.org/doi/full/10.1056/NEJMoa1901814.
16. Conradie F, Bagdasaryan TR, Borisov S, Howell P, Mikiashvili L, Ngubane N, et al. Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(9):810-23. 10.1056/NEJMoa2119430. https://www.nejm.org/doi/full/10.1056/NEJMoa2119430.
17. Nyang'wa BT, Berry C, Kazounis E, Motta I, Parpieva N, Tigay Z, et al. A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis. New England Journal of Medicine. 2022;387(25):2331-43. 10.1056/NEJMoa2117166. https://www.nejm.org/doi/full/10.1056/NEJMoa2117166.

18. Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N, et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open. 2021;11(12):e051521. 10.1136/bmjopen-2021-051521.
19. Sweeney S, Berry C, Kazounis E, Motta I, Vassall A, Dodd M, et al. Cost-effectiveness of short, oral treatment regimens for rifampicin resistant tuberculosis. PLOS Global Public Health. 2022;2(12):e0001337. 10.1371/journal.pgph.0001337. https://doi.org/10.1371/journal.pgph.0001337.
20. Täubel Jörg, Prasad Krishna, Rosano Giuseppe, Ferber Georg, Wibberley Helen, Cole Samuel Thomas, et al. Effects of the Fluoroquinolones Moxifloxacin and Levofloxacin on the QT Subintervals: Sex Differences in Ventricular Repolarization. The Journal of Clinical Pharmacology. 2020;60(3):400-8. https://doi.org/10.1002/jcph.1534. https://accp1.onlinelibrary.wiley.com/doi/abs/10.1002/jcph.1534.
21. Tsikouris James P., Peeters Michael J., Cox Craig D., Meyerrose Gary E., Seifert Charles F. Effects of Three Fluoroquinolones on QT Analysis After Standard Treatment Courses. Annals of Noninvasive Electrocardiology. 2006;11(1):52-6. https://doi.org/10.1111/j.1542-474X.2006.00082.x. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1542-474X.2006.00082.x.
22. Noel G. J., Natarajan J., Chien S., Hunt T. L., Goodman D. B., Abels R. Effects of three fluoroquinolones on QT interval in healthy adults after single doses. Clin Pharmacol Ther. 2003;73(4):292-303. 10.1016/s0009-9236(03)00009-2.
23. Koh WJ, Lee SH, Kang YA, Lee CH, Choi JC, Lee JH, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2013;188(7):858-64. 10.1164/rccm.201303-0604OC. https://www.ncbi.nlm.nih.gov/pubmed/23927582.
24. Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR TB treatment, Ahmad N, Ahuja SD, Akkerman OW, Alffenaar JC, Anderson LF, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. Lancet. 2018;392(10150):821-34. 10.1016/S0140-6736(18)31644-1. https://www.ncbi.nlm.nih.gov/pubmed/30215381.

Appendix 1

A critical group appraisal of: WHO consolidated guidelines on TB using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Tasha Gloeck

Email: natasha.gloeck@mrc.ac.za

Date: 20 February 2023

URL of this appraisal: http://www.agreetrust.org/group-appraisal/18838

Guideline URL: https://www.who.int/publications/i/item/9789240063129

Comments

Domain 1. Scope and Purpose

Item 1

- Appraiser 2: \"This evidence review aims to evaluate the efficacy and safety of novel short-course oral regimens to treat MDR/RR-TB, in comparison to the 2020 WHO- recommended regimens. This will be undertaken by conducting analyses of data from clinical trials and individual patient data meta-analyses of cohorts treated for MDR/RR-TB in programmatic settings.\" p313 Annexes. \

  "This current module on DR-TB treatment provides specific recommendations on the treatment of DR-TB, including use of regimens for rifampicin-susceptible, isoniazid- resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens and undertaking surgery for patients on MDR-TB treatment.\" p3
- Appraiser 3: \"provide specific recommendations on the treatment of DR-TB, including use of regimens for rifampicin-susceptible, isoniazid resistant TB (Hr-TB), all-oral shorter regimens for MDR/RR-TB, longer regimens for MDR/RR-TB, monitoring patient response to MDR/RR-TB treatment, starting ART in patients on second-line anti-TB regimens and undertaking surgery for patients on MDR-TB treatment.\"

  Health intent: Treatment, monitoring, timing of ART initiation, use of surgery. Expected benefit: Not clearly stated; to inform national TB programmes and assist in policy development, reduced adverse effects associated with DR-TB treatment and shorten treatment duration. Targets: Patients with MDR/RR-TB and Hr-TB. Well written. Expected benefit or outcome not easy to find in the guideline.

Item 2

- Appraiser 2: Annex
  Population: Yes (p 313)
  Intervention: Yes (p 313)
  Comparator: Yes (p 314)
  Outcome: Yes (p 316)
  Context: inclusion criteria p 315, worldwide
- Appraiser 3: PICO questions including target population, intervention, comparator are clearly stated and easily found in each respective section. Health care setting/context is not explicitly stated.
  PICO subquestions for Section 1 are not found in guideline document but can be found in the annexes document.

Item 3

Appraiser 2: Pages 313 and 315 include population, as well as inclusion and exclusion criteria

- Appraiser 3: Target population and clinical condition: All eople with DR-TB, Hr-TB.
  No gender or age exclusions listed. No exclusions of specific severity or stages of disease. No exclusions of certain populations or comorbidites.

  The lack of exclusionary criteria is not specifically highlighted in the guideline, but assumed based on the recommendations.

Domain 2. Stakeholder Involvement

Item 4

- Appraiser 2: Web Annex 1. Methods and expert panels - page 7 Name: YES Discipline/content expertise (e.g., neurosurgeon, methodologist): YES Institution (e.g., St. Peter's hospital): YES Geographical location (e.g., Seattle, WA): YES Description of the member's role in the guideline development group: YES Appraiser 3: For
- each member of guideline development group name, discipline/content expertise, institution and geographical location where stated. The description the members specific role in guideline development was not found.

  Item easily found at start of the guideline. Members are appropriate match for the topic and scope. Methodological experts included in the development group.

Item 5

- Appraiser 2: Web Annex 1. Table A1.3 - perspectives from patients with recommendation.

  ONE former MDR-TB Patient was included in the guideline development group. Not

  really sufficient information.
- Appraiser 3: \"The methods used to develop and formulate the recommendations complied with WHO standards for guideline development and were based on up-to- date evidence reviews, complemented with additional information on values and preferences, feasibility and acceptability, and cost.\"

  End-user\'s and former DR-TB patient are noted to have been included in the guideline development group and as external reviewers. However, there is no clear statement on additional strategies used to capture patients/public views and preferences.

  This item was not easy to find in the guideline but is noted in the methods section of the annexe document.

Item 6

Appraiser 2: Yes - p5 of module 4

- Appraiser 3: Page 5: policy makers in ministries of health, or managers of NTPs who formulate country-specific TB treatment guidelines or are involved in the planning of TB treatment programmes. For use by health professional, including doctors, nurse, educators.

  Clear, concise and well written. Appropriate for scope of guideline.

Domain 3. Rigour of Development

Item 7

- Appraiser 2: \"Evidence gathering and analysis
  Evidence provided for the GDG review on using 6-month novel regimens was from the TB-PRACTECAL trial (evidence on using BPaLM, BPaLC, BPaL regimens), ZeNix trial (evidence on using the BPaL regimen with difference dosing schemes of linezolid use) and Nix-TB study (evidence on using the BPaL regimen). Evidence on using a new 9- month shorter regimen was from the programmatic data provided by the National TB Programme in South Africa. In addition, evidence was available on the use of other treatment regimens that were used as external comparators required for comparisons with the intervention regimens. The evidence included data on the use of WHO recommended shorter all- oral bedaquiline-containing regimen, which were from the programmatic implementation provided by South Africa; and WHO recommended longer regimens, which were provided by several country programmes from Belarus, Republic of Moldova, Georgia, Russian Federation, India, South Africa, and Somalia; or cohort studies (EndTB studies) provided by Médecins Sans Frontières and Partners in Health.
  In preparation to the guidelines update, WHO/GTB also received the data from the Newer and Emerging Treatment for MDR/RR-TB (NExT) trial that was a phase II/III open-label randomized controlled trial evaluating the effectiveness of an all-oral 6–9- month regimen for treatment of MDR-TB in South Africa (21), against a local standard of care regimen at the time. Sharing of the data by the principal Investigator and colleagues in the University of Cape Town and the South African Medical Research Council, is gratefully acknowledged\"

  No search methods, no search strategy BUT data collated from various large trials and in collaboration with large TB programmes
- Appraiser 3: For the updated section of the guideline (section 1 and 2) no strategy for the search of evidence is provided. Evidence was obtained through collaboration and engagement with NTPs, researchers and TB alliance as well as the WHO call for data.

  Evidence for section 3, 4,5 obtained from meta-analysis of IPD. No search strategy provided.

Item 8

- Appraiser 2: Annex p 315
  A5.2 Eligibility for inclusion in this evidence review

  Annex p 314
  Regimens excluded from analyses

  Also included in the GL page 3
- Appraiser 3: No description on criteria for evidence selection in guideline document. Web Annexes describe eligibility criteria for dataset inclusion and participant exclusion. Datasets from a public call for data were included.

Item 9

- Appraiser 2: GRADE evidence summary tables available with five GRADE domains and reasons
- Appraiser 3: The WHO Guideline Development process uses specific criteria to assess the characteristics of a body of evidence, such as within-study bias (methodological quality), consistency, precision, directness or applicability of the evidence, and others.

  The strengths and limitations of body of evidence are assessed, well written and clear and concisely described in the Web annex document in the Methods section and GRADE evidence summary tables but not in the main guideline.

Item 10

- Appraiser 2: GRADE EtD tables available for each PICO with recommendations Appraiser 3:
- A formal process and evidence-to-decision framework was used to arrive at recommendations. Decisions reached through discussion and consensus, where consensus through discussion not reached, the GDG voted on decisions. Here, decisions were made based on the vote of the majority.
  (information from annex. - not easily found.)

Item 11

- Appraiser 2: Yes, included in EtD
- Appraiser 3: Supporting data and report of benefits included in the Etd frameworks in the web annexes per PICO and also in the guideline. Recommendations do reflect considerations of both benefits, harms and risks. This discussion is integral to the document.

Item 12

- Appraiser 2: EtD available with link to evidence
- Appraiser 3: Each recommendation is linked to a discussion of the key evidence in the evidence-to-decision frameworks in the annexes document. Evidence summaries are provided for each sub-PICO in the guideline. Where evidence is lacking it is clearly stated in the guideline that recommendations are based on consensus of the guideline development group.

Item 13

- Appraiser 2: An External review group is listed (Web Annex 1 page 7), there is a specific acknowledgment statement (GL page vi), otherwise scanty information as to what the external review group did
- Appraiser 3: An external review group was assembled to review the updated recommendations based on the inputs of the guideline development group. External review group members are listed with qualifications and affiliation and are appropriate.
  Not easily found in the guideline, but available in web annex document. No indication of how information provided by review group was used by guideline development group. No indication of the purpose or intent of the review, methods undertaken or a summary of key findings.

Item 14

- Appraiser 2: This guideline is an update. No timescale found around when the next update will be
- Appraiser 3: No clear statement of when guideline will be update, the explicit time interval or criteria to guide decisions or methodology of updating procedure.

Domain 4. Clarity of Presentation

Item 15

- Appraiser 2: EtD tables - recommendations provided with remarks around applicability

  Recommendations available in GL, also clear what updates/changes have been made from previous GLs
- Appraiser 3: The recommendations are concrete and precise, specifically in the remarks underlying each recommendation.

Item 16

- Appraiser 2: Extensive information available in EtDs - not necessarily alternatives thus rated down slightly. Recommendations in GL also quite specific
- Appraiser 3: Different options for management are presented: either BPAL, BPALM or BPLAC rather than SOC.
  Different options for LZD dosing and BDQ dosing is presented.
  Specific recommendations are made for children, pregnant women, HIV positive patients and patients with extrapulmonary TB. This information can be found under appropriate headings in the guideline.

Item 17

- Appraiser 2: Yes, once the correct PICO is found.
- Appraiser 3: Recommendations are summarised in a box at the start of the guideline and are clear and concise.

Domain 5. Applicability

Item 18

- Appraiser 2: Within the EtDs and GL, the guideline panel discussed acceptability, feasibility, equity, cost-effectiveness. required resources, balance of effects, etc.

  There are also implementation and subgroup considerations.
- Appraiser 3: In Web Annexes document facilitators and barriers discussed in EtD frameworks that assessed acceptability, feasibility required resources, cost effectiveness etc.

Item 19

- Appraiser 2: There are implementation and subgroup considerations listed with each PICO in the EtD but these do not necessarily provide sufficient information to actually implement.
- Appraiser 3: An implementation section is found in the guideline. No summary documents, algorithms or check lists are found, although a summary of the recommendations is listed at the start of the guideline.

  Some references to guideline facilitators for example for sections \"Care and Support\" - reference supplied to WHO Consolidated guidelines on tuberculosis: Module 4: Treatment - tuberculosis care and support\"

  Appendices do not contain useful implementation resources.

Item 20

- Appraiser 2: Yes - in the EtD, cost effectiveness and feasiblility have been considered. Appraiser
- 3: Regimen costs were estimated in US$ for regimens based on GDF prices. Studies of cost-effectiveness of regimens were included in the guideline.
  Resource implications are considered in the EtD framework.

It does not appear that any health economist were part of guideline development group.

Item 21

- Appraiser 2: Yes, monitoring and evaluation section available in the EtDs
- Appraiser 3: No clear schedule of monitoring of relevant clinical and laboratory tests is provided, besides the following:
  1. Recommend monitoring patients with monthly sputum cultures
  2. Patients should be followed up for 12 months after the completion of treatment for possible relapse with sputum culture and smear.
  3. Test samples of patients with no bacteriological conversion after month 4 on BPaLM/BpAL regimen with DST.
  4. ECG should be done at baseline prior to start of treatment.

Domain 6. Editorial Independence

Item 22

- Appraiser 2: The WHO is the funding agency through grants from USAID. WHO is also the publisher. No statement on influence.
- Appraiser 3: Statement that update was funded by grants provided to WHO by USAID. No statement that funding body did not influence content of guideline.

Item 23

- Appraiser 2: Web Annex 2: declarations of interest. Also listed in EtD where a GDG member was excluded in specific PICOs due to competing interests
- Appraiser 3: A description of competing interests is found in the Web Annexes document. The methods by which competing interests were sough was not clear.

  WHO policy is noted to have been applied in the EtD frameworks to recuse panel members with potential-conflicts of interest.

Overall Assessment

- Appraiser 2: Recommended for use for adolopment
- Appraiser 3: 1. No information provided regarding systematic search for evidence.
  2. Lack of implementation resources
  3. Complicated, information for AGREE II assessment not always easily found in the document.
  4. Clearer descriptions on role, contributions and findings of end users, external reviewers should be provided.
  5. More specific monitoring criteria should be described.

Created online at www.agreetrust.org 20 February 2023

A critical group appraisal of: WHO consolidated guidelines on TB using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator: Tasha Gloeck

Email: natasha.gloeck@mrc.ac.za

Date: 20 February 2023

URL of this appraisal: http://www.agreetrust.org/group-appraisal/18838

Guideline URL: https://www.who.int/publications/i/item/9789240063129

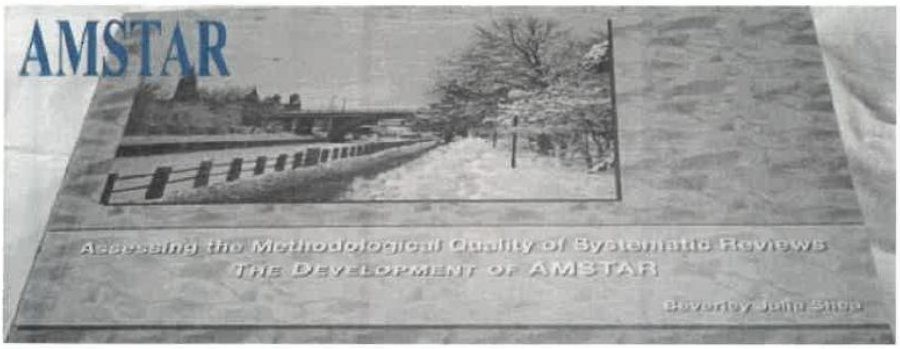
Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
86%	78%	63%	89%	65%	67%	83%	Yes - 1, Yes with modifications - 1, No - 0

Domain 1. Scope and Purpose		
	Appraiser 2	Appraiser 3
Item 1	6	5
Item 2	7	6
Item 3	7	6
Domain 2. Stakeholder Involvement		
	Appraiser 2	Appraiser 3
Item 4	7	6
Item 5	5	4
Item 6	6	6
Domain 3. Rigour of Development		
	Appraiser 2	Appraiser 3
Item 7	4	1
Item 8	5	6
Item 9	6	6
Item 10	7	5
Item 11	6	6
Item 12	7	6
Item 13	5	3
Item 14	2	1
Domain 4. Clarity of Presentation		
	Appraiser 2	Appraiser 3
Item 15	7	6
Item 16	6	7
Item 17	6	6
Domain 5. Applicability		
	Appraiser 2	Appraiser 3

Item 18	6	6
Item 19	4	2
Item 20	6	5
Item 21	6	4
Domain 6. Editorial Independence		
	Appraiser 2	Appraiser 3
Item 22	4	3
Item 23	7	6
Overall Assessment		
	Appraiser 2	Appraiser 3
OA1	6	6

Created online at www.agreetrust.org 20 February 2023

Sumayyah Logout My Account



Home About Us Publications Checklist FAQs Contact Us

AMSTAR Checklist

Printer Friendly Version

Article Name:
WHO consolidated guidelines on tuberculosis

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:
- ☑ Population
- ☑ Intervention
- ☑ Comparator group
- ☑ Outcome

Optional (recommended)
- ☑ Timeframe for follow up

- ☑ Yes
- ☐ No

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?

For Partial Yes:
The authors state that they had a written protocol or guide that included ALL the following:
- ☑ review question(s)
- ☐ a search strategy
- ☑ inclusion/exclusion criteria
- ☑ a risk of bias assessment

For Yes:
As for partial yes, plus the protocol should be registered and should also have specified:
- ☐ a meta-analysis/synthesis plan, if appropriate, and
- ☐ a plan for investigating causes of heterogeneity
- ☐ a plan for investigating causes of heterogeneity

- ☐ Yes
- ☑ Partial Yes
- ☐ No

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:

For Partial Yes (ALL the following):	For Yes, should also have ALL the following:	
☐ described populations	☑ described population in detail	☐ Yes ☐ Partial Yes ☑ No
☐ described interventions	☑ described intervention in detail (including doses where relevant)	
☐ described comparators	☑ described comparator in detail (including doses where relevant)	
☐ described outcomes	☑ described study's setting	
☐ described research designs	☑ timeframe for follow-up	

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?

RCTs

For Partial Yes, must have assessed RoB from	For Yes, must also have assessed RoB from:	
☐ unconcealed allocation, and	☐ allocation sequence that was not truly random, and	☐ Yes ☐ Partial Yes ☑ No ☐ Includes only NRSI
☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

NRSI

For Partial Yes, must have assessed RoB:	For Yes, must also have assessed RoB:	
☐ from confounding, and	☐ methods used to ascertain exposures and outcomes, and	☐ Yes ☐ Partial Yes ☑ No ☐ Includes only RCTs
☐ from selection bias	☐ selection of the reported result from among multiple measurements or analyses of a specified outcome	

10. Did the review authors report on the sources of funding for the studies included in the review?

For Yes

☐ Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	☐ Yes ☑ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

For Yes:

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?

For Yes:

☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias	☐ Yes ☐ No ☑ No meta-analysis conducted

---

16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

For Yes:

☐ The authors reported no competing interests OR ☑ The authors described their funding sources and how they managed potential conflicts of interest	☑ Yes ☐ No

---

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.

Assess Article

AMSTAR 2 Results

Printer Friendly Version

Article Name: WHO consolidated guidelines on tuberculosis - module 4

WHO consolidated guidelines on tuberculosis - module 4 is a Critially 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?	YesYes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes Yes
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	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? **RCT**	Yes
NRSI	
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? **RCT**	Yes
NRSI	
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?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes

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?	No
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	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.

<< Back

Appendix 3

Normative cost analysis based on specific direct costs						Sensitivity analysis excl.clinic vist costs
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	**15 649,49**	**12 968,70**
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	**17 862,78**	**15 181,99**
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	**17 207,81**	**14 575,25**
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	**17 805,05**	**15 172,49**
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	**17 284,25**	**14 651,69**
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	**34 467,47**	**30 059,87**
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	**60 328,21**	**53 746,81**

Note:

Where weight calibrated dosing is recommended, drug costs have been applied at the maximum weight band/adult dose
1 US$ equivalent to R18.30
Drug calculations all based on a 28 day cycle per month
Diagnostic Xpert, microscopy, culture and DST not included in costs for bacteriological tests
Clinic visits classified according to nature of clinical visits and based on secondary data representing a fully decentralised model.

Resource requirement for Sub-PICO 4.1: BPaL vs. WHO_Long in pulmonary preXDR TB and Sub-PICO 5.2: BPaL vs WHO_Long in pulmonary MDR/RR-TB						
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	**17 207,81**	**14 575,25**
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	**17 805,05**	**15 172,49**
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	**17 284,25**	**14 651,69**
Long course 1 (Basic)	27 159,16	2 117,16	783,55	4 407,60	**34 467,47**	**30 059,87**
Long course 2	49 601,58	2 117,16	2 028,07	6 581,40	**60 328,21**	**53 746,81**

Resource requirement for Sub-PICO 5.3: BPaL vs. SA_new in MDR/RR-TB						
Regimen	Drug costs (ZAR)	Bacteriological tests (Costs in ZAR)	Other lab tests (Costs in ZAR)	Clinic visit costs (ZAR)	Total costs per patient treated incl. clinic visit costs (ZAR)	Total costs per patient treated excl. clinic visit costs (ZAR)
BPaL (Lzd_Adjusted dose)	11 710,64	705,72	2 158,89	2 632,56	**17 207,81**	**14 575,25**
BPaLM (Lzd_Adjusted dose)	12 307,88	705,72	2 158,89	2 632,56	**17 805,05**	**15 172,49**
BPaLM (Lzd_Standard)	11 787,08	705,72	2 158,89	2 632,56	**17 284,25**	**14 651,69**
Short oral course (Min)	11 437,70	1 058,58	472,42	2 680,79	**15 649,49**	**12 968,70**
Short oral course (Max)	13 650,99	1 058,58	472,42	2 680,79	**17 862,78**	**15 181,99**