Whittington Health NHS

TB Service – North Central London

Tuberculosis

Treatment and Chemoprophylaxis

Guideline for Adult and Paediatric patients with active or latent disease

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Version Control Sheet

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1.0	April 2014	Active	This guideline has been adapted from the UCLH Tuberculosis (TB) Treatment Guideline and the North Central London MDRTB Protocol. The guideline was developed in collaboration with stakeholders at Whittington Hospital, UCH, CNWL, RFH, GOSH and NCL TB South Hub Service.

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Contents

Abbreviations:

CCDC	Consultant in Communicable Disease Control – Health Protection Unit
CSF	Cerebrospinal fluid
DOT	Directly observed therapy
ECM	Enhanced case management
HIV	Human immunodeficiency virus
IGRA	Interferon gamma release assays
IPCT	Infection Prevention & Control Team
LTBR	London TB Register
MDRTB	Multidrug resistant tuberculosis
MDT	Multidisciplinary team
PCR	Polymerase chain reaction
PHE	Public Health England
TB	Tuberculosis
TST	Tuberculin skin test
XDRTB	Extensively drug resistant tuberculosis

List of Tables:

➢ Criteria for use

This guideline is intended to provide clinicians with guidance on the management (both treatment and prevention) of *Mycobacterium tuberculosis* (TB). This guideline provides evidence based and best practice on the management of patients with pulmonary and extra pulmonary TB. They include empirical antimicrobial therapy including doses, route and duration of therapy and where necessary microbiological investigations. All patients must be managed with input from a TB specialist and/or Microbiology/Infectious Diseases.

The guideline must be used in conjunction with the 'Whittington Health - Control of TB Policy' (http://whittnet.whittington.nhs.uk/document.ashx?id=7379) and the BNF.

Other environmental or atypical mycobacterial species (for example, *Mycobacterium avium* or *Mycobacterium malmoense*) and extensively drug resistant tuberculosis (XDRTB) are not covered by this guideline.

➢ General Information

a) Criteria for hospital admission

Most patients do NOT need to be admitted for public health reasons. Investigation and treatment of TB can generally be done as an outpatient. Hospital admission may be required if the patient:

- is severely unwell/unstable;
- has a side effects of treatment;
- has multi-drug resistant pulmonary TB (MDRTB); or
- is under a Public Health Section.

b) Infection Control Procedure

TB is only an infection risk if there is pulmonary involvement. Spread of tuberculosis from patients with non-pulmonary tuberculosis is uncommon. Patients with pulmonary tuberculosis who are expectorating sputum-containing mycobacteria are the most infectious.

- Possible or confirmed pulmonary TB patients MUST be isolated, preferably in a negative pressure room.
- Children are less infectious than adults, please discuss with Microbiology and the Lead Consultant Paediatrician for TB regarding isolation. Staff need to be aware that the parents of children suspected to have TB might also be infectious.

An FFP3 respirator is only required to be worn by health care workers in the patient area if MDRTB is suspected or with any patient when carrying out an aerosol generating procedure.

Refer to 'Control of TB Policy' on http://whittnet.whittington.nhs.uk/document.ashx?id=7379)

c) Referrals and multidisciplinary involvement

➢ Inpatients

Discuss all patients with a Microbiologist. *See list of contact details in page 22.*

TB Nurse Specialists must be involved prior to discharge to:

- check medication;
- initiate contact tracing;
- facilitate notification;
- risk assess for directly observed therapy (DOT); and
- arrange outpatient follow-up.

If the team is unable to visit prior to discharge and there are no obvious risk factors affecting adherence and follow up, discharge should not be delayed as the patient will be contacted within 24 working hrs of discharge and arrangements made for follow up either in clinic or at home by a member of the NCL TB service.

➢ Outpatients

Anyone with suspected or confirmed TB for outpatient management **must** be referred to the TB Clinic via the TB Nurse specialist or via email.

➢ Investigations

Specimens for TB Diagnosis

In all suspected cases (where possible), appropriate clinical samples must be sent for TB culture. These are important for both a definitive diagnosis and to obtain drug susceptibility.

Sputum from suspected pulmonary TB

- The optimal sample for the diagnosis of pulmonary TB.
- Three consecutive samples should be collected before treatment is initiated, if possible.
- Sputum induction or bronchoscopy should be performed (unless contra-indicated) in patients who are unable to produce a satisfactory sample. See Appendix 9: Sputum Induction.

Early morning urine specimens

- This is useful for the diagnosis of miliary or genitourinary TB and in immunocompromised patients.
- The entire, first voided urine of the day is collected. Use the recommended container with an appropriate preservative (this is available from the Microbiology Laboratory or TB Clinic).

IMPORTANT: Spot urine samples in universal containers are insensitive and will be discarded by the laboratory.

Surgical Specimens

- If histology is requested, please send a separate specimen to Microbiology for TB culture.
- The biopsy sample must NOT be in formalin (formaldehyde).
- Large volume aspirates (e.g. pus) may be sent neat.

Cerebrospinal fluid (CSF)

- A minimum of 6mls (based on the volume graduation on the specimen container label) of CSF should be taken for microbiological culture and PCR for suspected TB meningitis in adults.
- Paired samples of CSF and serum should also be sent for glucose and protein testing.

Interferon gamma release assays (IGRA) – e.g. Quantiferon Gold

- If you consider performing an Interferon gamma release assay (refer to Appendix 6, 7 and 8 for guidance), please contact the TB Clinic for outpatient TB service requests and Microbiology for all other requests (including all inpatient requests), as specialised tubes for collection are necessary.
- This investigation may be appropriate for the diagnosis of latent TB (e.g. screening contacts, healthcare workers) and patients who are planned to receive immunomodulatory treatment (as indicated in the NICE guidelines).
- They have a limited role in the diagnosis of active TB, and
- This investigation should be requested and interpreted with caution.

Tuberculin skin tests (TST)

- The recommended tuberculin skin test is the Mantoux test, which involves the administration of Tuberculin Purified Protein Derivative (Tuberculin PPD) 2TU in 0.1ml dose given via an intradermal injection.

Note: Live viral vaccines can suppress the tuberculin response. A Mantoux test should NOT be carried out within 4 weeks of receiving a live viral vaccine such as MMR.

- The results should be read 48 to 72 hours after the test is taken. The transverse diameter of the area of **induration** at the injection site is measured and interpreted (see Appendix 9).

HIV testing

- An HIV test should be offered to, and encouraged, for all patients with proven or suspected TB.

In suspected cases of MDRTB

Request for:

- Urgent sputum smear of AFB, and
- Urgent rapid molecular testing (please discuss with Microbiology).

A positive result of a molecular analysis for resistance to rifampicin should lead to the appropriate infection control measures being put in place, if not already undertaken. Patients under investigation for suspected MDRTB, as outpatients, should be admitted for negative pressure isolation. The hospital Infection Control team and Consultant in Communicable Disease Control (CCDC) at the North Central London Health Protection Unit should be informed.

Note: A positive result is helpful in confirming suspected MDRTB. However, cautious interpretation is required for negative results; while the sensitivity is greater than 90% for smear positive samples, it may be substantially less for those which are smear negative [16].

➢ Clinical Management

1. Standard Quadruple Therapy – for fully sensitive disease (unsupervised regimen)

1.1 Standard Quadruple Therapy

- Quadruple therapy should be initiated (see Table 1) unless drug resistance is suspected or known prior to starting treatment.
- Start quadruple therapy as soon as TB is suspected - do not wait for confirmatory laboratory investigations.
- Induction phase of the quadruple treatment is continued for 2 months until it is confirmed as fully sensitive.
- As soon as it is confirmed to be a fully sensitive mycobacterial TB, Ethambutol may be stopped.
- Pyrazinamide should be continued for 2 months of the induction phase but may be for longer if:
  (i) extensive cavitatory disease; and
  (ii) TB meningitis (as it has good blood brain barrier penetration).
- Rifampicin and Isoniazid should be continued to complete a total of 6 months. Longer courses are needed if:
  (i) patients have extensive cavitatory disease;
  (ii) there is any deviation (or interruption) from the above protocol;
  (iii) for TB meningitis/miliary, treat for 12 months; and
  (iv) spinal TB.
- All TB medicines may be taken at the same time, half an hour before food [WHO, 2010].
- For the intermittent supervised 6-month therapy (thrice weekly adult DOT regimens in NCL sector), refer to Appendix 3.

Table 1: Standard Quadruple Therapy (Unsupervised Treatment):

DRUG	DOSING REGIMEN	DURATION	FORMULATION	CAUTION	MONITORING
Rifampicin [a] (R or RIF)	**Adult dose:** <50kg: 450mg OD ≥50kg: 600mg OD **Paediatric dose (1 month - 18 years):** 15mg/kg OD (if <50kg: max 450mg OD; if ≥50kg: max 600mg OD)	6 months	**ORAL** ▪ 150mg capsule ▪ 300mg capsule ▪ 100mg/5ml syrup (contain sucrose) **IV INFUSION** ▪ 600mg vial	▪ Potent enzyme inducer ▪ Discoloration of fluids ▪ Hepatitis ▪ Failure of contraceptive pill – patient to use other methods of contraception.	LFTs
Isoniazid [a] (H or INH)	**Adult dose:** 300mg OD **Paediatric dose (1 month - 18 years):** 10mg/kg (max 300mg)OD	6 months	**ORAL** ▪ 50mg tablet ▪ 100mg tablet ▪ 50mg/5ml elixir (unlicensed) Tablet may crushed and mixed in water. **IV / IM INJECTION** ▪ 50mg/2ml ampoule	▪ Peripheral neuropathy ▪ Hepatitis	LFTs
[a] **Rifampicin** and **Isoniazid** should be given as a combined tablet **Rifinah**®. o If <50kg: Rifinah® 100/150 (rifampicin 150mg / isoniazid 100mg) – 3 tablets OD (pink tablets) o If ≥50kg: Rifinah® 150/300 (rifampicin 300mg / isoniazid 150mg) – 2 tablets OD (orange tablets) *(NB: Fixed dose combination preparation such as Rifinah are unlicensed for use in children. However, it may be used in older children where the respective dose of each drug is appropriate for the weight of the child.)*					
Pyrazinamide (Z or PZA)	**Adult dose:** <50kg: 1.5g OD ≥50kg: 2g OD **Paediatric dose (1 month - 18 years):** 35mg/kg OD (if <50kg: max 1.5g OD; if ≥50kg: max 2g OD)	≥2 months (see notes)	**ORAL** ▪ 500mg tablet ▪ 500mg/5ml suspension (unlicensed) Tablet may crushed and mixed in water.	▪ Rash. ▪ Gout.	LFTs
Ethambutol [b] (E or EMB)	**Adult dose:** 15mg/kg OD **Paediatric dose (1 month - 18 years):** 20mg/kg OD	≤2 months (see notes)	**ORAL** ▪ 100mg tablet ▪ 400mg tablet ▪ 400mg/5ml mixture (unlicensed) Tablet may crushed and mixed in water. **IV INFUSION** ▪ 1g/10ml ampoule (unlicensed)	▪ Retrobulbar neuritis.	Ophthalmic exam - Ishihara chart
Pyridoxine (Vitamin B_6) *Adjuvant therapy while on Isoniazid.*	**Adult dose:** 10mg OD **Paediatric dose [2]:** Neonate: 5mg OD 1mth-12yrs: 5–10mg OD 12-18yrs: 10mg OD	6 months (while on Isoniazid)	**ORAL** ▪ 10mg tablet ▪ 5mg/5ml mixture (unlicensed) Tablet may crushed and mixed in water.	▪ Prophylaxis against isoniazid-induced peripheral neuropathy.	

[b] *If obese, calculate ethambutol dose using Ideal Body Weight (IBW) : IBW= (male) 50kg or (female) 45.5kg + (0.91 x every cm over 152.4cm)*

NB: For paediatrics, doses should be rounded-up to suitable volumes of liquid or an appropriate strength of tablet to facilitate administration. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

See Appendix 3 - Paediatric TB Medication guide.

1.2 Alternative formulations for those unable to tolerate solid oral dose preparations

Choice of TB drugs in patients unable to swallow **MUST** be discussed on an individual patient basis with the TB clinic doctors or Microbiology SpR.

Table 2: Choice of formulations for patients who are unable to tolerate solid oral doses.

DRUG	DISSOLVE IN WATER	LIQUID	PARENTERAL
Rifampicin (R or RIF)	Not applicable. Do NOT open capsule – can cause contact sensitisation.	Syrup available. ▪ Some resistance to flushing via NG tube; mixed easily with water. ▪ Stop enteral feed at least 2 hours before the dose; do not re-start feed for 30 minutes after dose.	IV injection available. ▪ Same dose as oral. ▪ ***IV infusion:*** 600mg vial. Reconstitute vial with diluent provided. Further dilute with 500ml N/S or G5%. Infuse over 2 – 3 hours.
Isoniazid (H or INH)	Tablets crushed and dispersed in 10ml of water.	Elixir may be ordered for named patient. ▪ Unlicensed - from specials manufacturer. Check with pharmacy for availability.	IV / IM injection available. ▪ Same dose as oral. ▪ ***IV bolus:*** 50mg/2ml ampoule. Ready diluted. Over 3 - 5 minutes. ***IM:*** Ready diluted.
Ethambutol (E or EMB)	The tablets can be crushed and mixed with water, the film-coating takes a few minutes to dissolve.	Suspension may be ordered for named patient. ▪ Unlicensed - from specials manufacturer. Check with pharmacy for availability.	IV infusion / IM available ▪ Same dose as oral. ▪ Unlicensed - imported by IDIS. Check with pharmacy for availability. ▪ ***IV infusion:*** 1g in 10ml vials. Dilute required dose with 500ml N/S or G5%. Infuse over at least 2 hours.
Pyrazinamide (Z or PZA)	Tablets do not disperse readily in water; but can be crushed and mixed with water immediately prior to administration.	Suspension may be ordered for named patient. ▪ Unlicensed - from specials manufacturer. Check with pharmacy for availability.	No parenteral preparation available.
Pyridoxine	Tablets crushed and mixed with water immediately prior to administration.	Suspension may be ordered for named patient. ▪ Unlicensed - from specials manufacturer. Check with pharmacy for availability.	Discuss need. Alternatively consider Pabrinex IV / IM injection containing 50mg Pyridoxine.

If additional drugs are needed to provide sufficient anti-mycobacterial cover, the following options of parenteral TB medications may be considered (seek TB specialist and/or Microbiology advice):

- IV moxifloxacin
- IV amikacin
- IM streptomycin
- IV linezolid

1.3 Baseline monitoring

- ***Liver function test***. All patients need baseline liver function tests. LFTs should be monitored during the induction phase (and beyond if abnormal) in those with:
  - abnormal baseline levels;
  - background liver disease;
  - symptoms suggestive of hepatitis e.g. nausea and vomiting, right upper quadrant pain.

- ***Visual acuity test***. Before starting treatment, all patients on Ethambutol need a visual acuity test, and colour vision testing using an Ishihara chart. If an abnormal test occurs, refer the patient for a formal ophthalmology review.
  - If a young child, always refer to ophthalmology.
  - Advise patients to report any changes in vision promptly and record in the notes, that this advice has been given.
  - Patients who receive or are likely to receive prolonged (> 2 months) Ethambutol therapy, should be referred to the eye clinic for assessment. This will include patients being treated for atypical mycobacterial infections and those with known Isoniazid resistance.
- ***Severe renal impairment or unstable renal function***. Discuss with a TB specialist prior to prescribing. Refer to the checklist on Appendix 1 for further information.

1.4 Adverse effects

- Discuss and document in the notes that potential adverse effects have been explained, and what action advised should they occur (see Table 3).
- Advise patients that soft contact lenses and secretions may become stained by Rifampicin.

Table 3: Main adverse effects of TB medication.

Hepatitis	▪ Medication-related hepatitis is common and may be fatal. ▪ LFTs should be checked in all patients with nausea or vomiting. ▪ Modest elevations in LFTs are frequently seen in the first two months of therapy, but treatment should be continued, uninterrupted. The LFTs usually return to baseline after a couple of months. NB: Also test for the presence of Hepatitis B surface antigens (HBsAg) and Hepatitic C antibodies (anti-HCV). ▪ If the ALT is ≥5 times the upper limit of normal, or there is any elevation of bilirubin, or the development of symptomatic hepatitis with anorexia, nausea, vomiting or jaundice, stop all treatment temporarily. ▪ For seriously ill patients with extensive TB, treatment may be continued with a liver-sparing regimen (e.g. streptomycin and ethambutol – caution with monitoring and renal failure).
Arthritis	This is a common reaction to any of the drugs: ▪ Pyrazinamide can precipitate gout. ▪ Isoniazid can cause a lupus erythmatosus like syndrome. ▪ Rifampicin may cause 'bone pain' as part of an associated 'flu'-like syndrome. Specialist advice is needed to deal with these side-effects.
Visual changes	▪ Due to Ethambutol. ▪ Re-check the visual acuity and compare them with baseline measurements. If the visual acuity has worsened, stop the ethambutol immediately and refer the patient for an ophthalmic opinion.
Renal toxicity	▪ Due to aminoglycosides (e.g. Streptomycin or Amikacin). ▪ The renal function should be checked intensively when treatment is initiated, then weekly once stable levels have been achieved.
Ototoxicity	▪ Due to aminoglycosides (e.g. Streptomycin or Amikacin). ▪ Audiometric test to be performed at baseline, and then fortnightly.
Re-introduction of TB medication after development of side effects Treatment is re-introduced according to the BTS Guideline (http://thorax.bmj.com/content/53/7/536.full.pdf+html) or the BHIVA Guideline (http://www.bhiva.org/documents/guidelines/tb/hiv_954_online_final.pdf), with sequential introduction of drugs (Isoniazid, then Rifampicin, then Pyrazinamide, all in incremental doses). Patients need to be monitored closely and the reintroduction of drugs should be under the supervision of TB specialist.	

1.5 Drug interactions

- ***Rifampicin and Isoniazid.*** These are potent enzyme inducer and enzyme inhibitor respectively, hence prescribers must be aware of potential drug interactions (e.g. anticonvulsants, anticoagulants, oral contraceptives, methadone) and adjust the doses of other medications accordingly (usually require to be increased). Interactions are important to be considered when starting and stopping anti-tuberculosis treatment. Patients should be informed of potential interactions. For further information, refer to the current version of the BNF.
- ***Hormonal contraception.*** Patients using hormonal contraception, should be advised to use alternative birth control methods. For further information, refer to Faculty of Sexual & Reproductive Healthcare (FSRH) Clinical Guidance (http://www.fsrh.org/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf)
- ***Methadone***. For patients receiving methadone who are already on an established programme, liaise with the patient's Drug Dependency Unit (DDU) or refer them to a local DDU for advice. A dose increase in methadone may be necessary to prevent withdrawal symptoms when taking Rifinah.
- ***HIV and TB.*** Management of HIV/TB co-infection is complex and should always be discussed with an HIV specialist before initiating TB therapy. For further information, refer to HIV-druginteractions (www.hiv-druginteractions.org) or HIV InSite (http://hivinsite.ucsf.edu/InSite?page=ar-00-02).

1.6 Use of steroids in TB

- ***Indication***

  Steroids should be used in addition to standard TB therapy for:
  - TB meningitis;
  - TB pericarditis;
  - miliary TB (only for some patients - discuss with TB physician / Microbiology);
  - TB associated with Acute Respiratory Distress Syndrome (ARDS).

  Steroids may be considered if the patient has:
  - abdominal TB;
  - severe systemic features;
  - a mass effects threatening airways, blood vessels, brain or spinal cord.

- ***Dose.*** Standard starting doses (unless TB meningitis – see below):
  - Adult: Prednisolone 60mg orally once a day;
  - Children (<12 years): Prednisolone 1mg/kg/day (maximum: 40mg/day).

- ***Duration.*** Duration of steroid treatment will depend on clinical review and specialist opinion. Usually they are given for 4-6 weeks including steroid weaning, BUT may be longer in TB meningitis (see under TB meningitis).

- ***Interaction.*** In patients receiving Rifampicin, induction of cytochrome P450 by Rifampicin halves the effective steroid dose, so the dose will need to be doubled (seek Microbiology, specialist TB or pharmacy advice).

- ***Adjuvant therapy.*** Consider osteoporosis prophylaxis and GI prophylaxis for those patients who will require more than 3 months glucocorticoids.

- ***Pregnancy and breast feeding.*** Steroid use in pregnancy and breast feeding
  - Steroid use in pregnancy poses a small risk to the developing foetus. Contact pharmacy for further advice.
  - Steroids are excreted in small amounts in breast milk. The paediatrician should be made aware of this. Infants should be monitored for adrenal suppression if the

mothers are taking a higher dose (e.g. prednisolone exceeding 40mg/day)[35]. Recommend waiting at least 4 hours after a dose before nursing. Please be aware that infants may develop oral thrush.

- ***Further Information.*** All patients on steroids should:
  - carry a steroid treatment card (supplied with medication from Pharmacy) which must be kept up to date with dose changes;
  - be counselled not to stop treatment suddenly, to take doses in the morning after food and report any untoward effects experienced (blood glucose control will be altered);
  - avoid close contact with people who have chicken pox or shingles.

1.7 Chemoprophylaxis for TB contacts (*except for MDRTB contacts – see section 4*)

For contacts of TB cases who develop latent TB, chemoprophylaxis is recommended according to the criteria defined in Appendix 5 to 7.

Chemoprophylaxis should be offered (once active TB has been excluded) to [6.14. 22]:

(i) those who present with a positive tuberculin skin test (TST) and a positive interferon-gamma release assay (IGRA), or a single positive interferon-gamma release assay (IGRA) [14];

All close contacts aged 35 years or less should be offered Mantoux and interferon-gamma testing as appropriate. *Refer to Appendix 5 – Screening of Asymptomatic Household Contacts.*

(ii) neonates;

Newborn babies (up to 4 weeks old) should be given Isoniazid chemoprophylaxis (6H), and then Mantoux tested after three months[14]. Patients should be followed up as in *Appendix 6 – Neonates Contacts of Smear Positive Pulmonary TB.*

(iii) children older than 4 weeks but under 2 years AND who have NOT received BCG [14];

These children should be started on Isoniazid chemoprophylaxis (6H) and a Mantoux test performed[14]. Patients should be followed up as in *Appendix 7 – Screening of Smear Positive Pulmonary TB Contacts aged over 4 weeks to less than 2 years.*

(iv) all HIV-positive contacts ;

Patients with HIV who are in close contact with people with sputum smear-positive respiratory TB should have active disease excluded and then be given a course of Isoniazid chemoprophylaxis (6H) and then followed up long-term[14].

Patients eligible for TB chemoprophylaxis but who decline treatment, should be given 'Inform and advise' information about TB and have a chest X-ray at 3 and 12 months after the initial contact.

Chemoprophylaxis for the treatment of latent TB is given either as one drug for six months or, alternatively, two drugs for three months (see Table 4) [5, 14].

Table 4: Chemoprophylaxis regimen (exclude MDRTB contacts).

1st line regime **(Chemoprophylaxis of choice for neonates, children < 2yrs who have not had BCG and HIV-positive patients.)**		
6H (6 months of Isoniazid)	Adult and child >12 years:	Isoniazid 300mg PO once a day for 6 months*.
	Child 1month-12years:	Isoniazid 10mg/kg PO once a day (max. 300mg daily) for 6 months*.
	Neonate:	Isoniazid 10mg/kg PO once a day for 6 months*.
2nd line regime		
3RH (3 months of Isoniazid + Rifampicin)	Adult and child >12 years:	Isoniazid 300mg PO once a day for 3 months*. PLUS rifampicin 600mg (or 450mg if < 50kg) PO once a day for 3 months. OR (AS A COMBINATION PREPARATION): *If ≥ 50kg*: Rifinah 150/300 - 2 tablets PO once a day for 3 months*. *If < 50kg*: Rifinah 100/150 - 3 tablets PO once a day for 3 months*.
	Child 1month-12years:	Isoniazid 10mg/kg PO once a day (max. 300mg daily) for 3 months*. PLUS rifampicin 15mg/kg PO once a day for 3 months. (*If < 50kg: max 450mg daily, or if ≥ 50kg: max 600mg daily)*
For contacts of isoniazid-resistant TB cases		
6R (6 months of Rifampicin)	Adult and child >12 years:	Rifampicin 600mg (or 450mg if < 50kg) PO once a day for 6 months.
	Child 1month-12years:	Rifampicin 15mg/kg PO once a day for 6 months. *(If < 50kg: max 450mg daily, or if ≥ 50kg: max 600mg daily)*

** Give Pyridoxine (Vitamin B_6) while on isoniazid-containing therapy – see dose under section 1.1.*

2. TB Meningitis

2.1 Treatment regimen

- Prescribe standard quadruple therapy PLUS steroids (dexamethasone or prednisolone) in ALL patients.
- If known or suspected to be infected with an Isoniazid resistant organism, add Moxifloxacin for 4 months. If it is confirmed whilst on the standard induction regimen, continue Pyrazinamide for the duration of the course. This is because of the poor blood brain barrier penetration by some of the TB drugs.
- Ethambutol ophthalmic toxicity at standard doses occurs in fewer than 3% of patients, so although it is not possible to detect toxicity in unconscious patients, treatment will generally be advised, but should be discussed with a specialist.
- Consider using high dose intravenous rifampicin (13mg/kg) in patients with severe disease[34]. Discuss with microbiology or a TB specialist.

2.2 Duration

- Treatment duration is 12 months.
- Pyrazinamide duration may be extended beyond the usual 2 month induction period, particularly if there are no culture results, as it cannot be assumed that the organism is sensitive to Rifampicin and Isoniazid.

2.3 Steroids in TB meningitis

Dose of steroids in TB meningitis:

- Adult (>14 years): Dexamethasone 0.4 mg/kg/day PO (maximum 24 mg). Reduce dose by 0.1mg/kg/day PO each week (then slowly reduce by 1mg each week) over a period of 8-10 weeks to stop.

  Note: Equivalent doses of prednisolone (5mg prednisolone = 0.75 mg dexamethasone) may be used.
- Children (≤14 years): Prednisolone 4mg/kg/day PO (max: 60mg/day) for 4 weeks then gradually reduce over 4 weeks to stop.

Please note available steroid tablet strengths and take into account the number of tablets the dose will require, especially when weaning:

- Prednisolone 25mg, 5mg and 1mg.
- Dexamethasone 0.5mg and 2mg.

3. Single Drug (Mono-) Resistant TB

The following regimens are appropriate for management of drug resistant TB [14].

Table 5: Suggested treatment regime for single drug (mono-) resistant TB.

Single drug resistance	Found before treatment started	Found whilst on quadruple therapy induction (including ethambutol)
Rifampicin CHECK NOT MDR	• Isoniazid 18 months • Ethambutol 18 months • Moxifloxacin 18 months • Pyrazinamide ≥2 months **NB:** Consider aminoglycoside (i.e. Streptomycin or Amikacin) for 2 months if sensitive.	• Isoniazid 18 months • Ethambutol 18 months • Moxifloxacin 18 months • Pyrazinamide complete ≥2 months **NB:** Consider aminoglycoside (i.e. Streptomycin or Amikacin). Stop Rifampicin.
Isoniazid	• Rifampicin 9 months • Ethambutol 9 months • Pyrazinamide 2 months • Moxifloxacin 4 months	• Rifampicin 12 months • Ethambutol 12 months • Pyrazinamide complete 2 months **NB:** Consider Moxifloxacin. Stop Isoniazid if highly resistant.
Pyrazinamide	• Rifampicin 9 months • Isoniazid 9 months • Ethambutol 2 months	• Rifampicin 9 months • Isoniazid 9 months • Ethambutol complete 2 months **NB:** Stop pyrazinamide

4. Multi-Drug Resistant TB (MDR-TB)

MDRTB is defined as disease due to *Mycobacterium tuberculosis* resistant to Rifampicin and Isoniazid, and possibly other anti-TB drugs.

MDR TB should be suspected if <u>one or more</u> of the following criteria are present:

(i) a history of previous treatment for TB;

(ii) birth, travel, or residence in a country with a recognised high prevalence of MDRTB;

A 3% prevalence of MDRTB in new cases is the customary threshold to define a "hot spot". Countries surveyed by WHO[21] and identified as hotspots on this basis are: Ecuador, Estonia, Israel, Kazakhstan, Latvia, Lithuania, Tomsk Oblast of the Russian Federation, Turkmenistan-Dashoguz, Uzbekistan-Karakalpakstan and the Henan and Liaoning provinces of China. Countries not surveyed may have higher prevalence rates.

(iii) contact with known or suspected MDRTB;

(iv) failure of clinical response to treatment or smear positivity after 2 months treatment or culture positivity after 3 months treatment [16];

(v) concomitant HIV infection;

(vi) rifampicin resistance on GenXpert - this will be confirmed by the reference laboratory and discrepant results discussed with microbiology.

4.1 Infection Control Procedures

If MDRTB is suspected and the patient potentially infectious i.e. pulmonary, inform the hospital infection prevention and control team (IPCT) immediately and arrange the following infection control measures.

- ***Negative pressure room.*** Patients must be isolated in negative pressure rooms until they are considered non-infectious by the TB Team and the IPCT. When a negative pressure room is not immediately available, the patient should be temporarily placed in a single room, which is not on an HIV, haematology, oncology, renal, or maternity ward. Aerosol generating procedures, including bronchoscopy or sputum induction, must only be carried out in a room with negative pressure ventilation and which has been tested by the IPCT.
- ***Transfer to another hospital.*** If a negative pressure room is not available at the time of recognition of risk for MDRTB, admission may be arranged to a hospital in the North Central London Sector where this facility is available. Transfer will require discussion between managerial staff at the sending and receiving hospitals. Transfer should only occur when it is clear that a bed in a negative pressure room is available. The patient will be treated at the receiving hospital until it is appropriate for them to be discharged into the community. Follow up should be provided by the most appropriate unit.
- ***Face masks (respirators).*** An unvalved FFP3 respirator must be worn by those entering the room (staff visitors and family) of a patient with known or suspected MDRTB. Valved FFP3 respirators are available for long term wear, e.g. critical care nurses. These must be worn until the patient is considered non-infectious by the IPCT in collaboration with the TB Team. Patients should wear normal paper surgical masks during transfer - they are not required to wear a mask in their room.
- ***Discharging MDRTB patients from isolation:***
  - Discharge from negative pressure isolation**.**

    – *Molecular analysis for MDRTB negative.*
    Following consultation with the IPCT, discharge to an ordinary single room may be considered, bearing in mind the limitations of molecular testing described above.

    – *Molecular analysis for MDRTB positive.*
    The patient must remain in a negative pressure room until three consecutive sputum samples taken over a period of 14 days are smear negative. Transfer may then be made in conjunction with the IPCT to an ordinary single room (if available), which is not on an HIV, haematology, oncology, renal, or maternity ward.

  - Discharge from an ordinary single room.

    In general, patients with confirmed MDRTB should remain in a single room until three consecutive sputum samples taken over a period of 14 days are culture negative.

    Discharge from a single room to the community should follow discussion between the referring physicians, the receiving physicians, and the relevant hospital IPCT and TB nurses.

  Arrangements must be in place at the time of leaving hospital, for satisfactory social circumstances including accommodation, and the receipt of benefits where appropriate. This will require liaison with the responsible social worker and discharge planning should start as soon as feasible after admission. Particular difficulty may arise when the patient is homeless and in these cases the local Homeless Persons Unit must be contacted.

IMPORTANT: All cases of MDRTB must be referred to the consultant responsible for TB.

4.2 Treatment regimens for MDRTB

Note: Most of the drugs (see Table 6) are unlicensed and are less effective at killing mycobacteria than the rifamycins and Isoniazid. These drugs have different toxicities than first line antimicrobials and may not be as well tolerated.

- Treatment of MDRTB should start with five or more drugs to which the organism is, or is likely to be, susceptible. When resistance is limited to Rifampicin and Isoniazid, ATS[1] and WHO[8] guidelines suggest that initial treatment should include Pyrazinamide, Ethambutol, an aminogycoside, a fluoroquinolone, and an additional drug such as Ethionamide or Cycloserine.
- Management must be discussed with the hospital TB specialist, Consultant Microbiologist and, where appropriate, the Public Health England (PHE) National Mycobacterium Reference Laboratory (NMRL) London.

Table 6: Commonly used second line drugs for TB.

Drug	Dosing regimen	Comments	Monitoring
Group 2: INJECTABLE ANTITUBERCULOSIS DRUGS			
Capreomycin (Cm) *Bactericidal*	Adult [1, 25] 15-20mg/kg/day (max 1g/day) Child 1 month to 18 years *Not licensed for paediatric use but suggested dose available* [31]. IM or IV [1, 25] Can reduce to 2-3 times per week during continuation phase [1, 25]. Dose adjustment [1, 27] If age>59: max 10mg/kg/day (max 750mg/day) [1] If renal impairment, refer to Renal Drug Handbook.	• Nephrotoxicity, proteinuria. • Ototoxicity. • Urticaria, rash • Electrolyte abnormalities [20] (low potassium, magnesium, calcium).	• U&E's – baseline, frequently after initiation in high risk patients and at least monthly in low risk. • Check vestibular/ audiometry at baseline and every fortnightly throughout the course of the treatment. • Monitor serum level (pre-dose trough level): Amikacin: twice a week if stable renal function. Aim for trough <5mg/L [5]. Streptomycin: after 3 doses then fortnightly. Aim for trough <5mg/L (or <1mg/l if renal impaired or over 50 years of age) [5, 26].
Streptomycin (S) *Bactericidal*	Adult and child ≥1mth [5, 25] 15mg/kg/day (max 1g/day) IM or IV [23, 24] Can reduce to 2-3 times a week during continuation phase [1, 25]. Dose adjustment [1, 25, 26, 27] If age>40 or weight <50kg: max. 500 – 750mg / day. If renal impairment, refer to Renal Drug Handbook.	• Maximum cumulative dose of 100g [5, 25]. • Nephrotoxicity. • Ototoxicity. Electrolyte abnormalities [20] (low potassium, magnesium, calcium). • Avoid in myasthenia gravis [5].	
Amikacin (Am) *Bactericidal*	Adult and child ≥ 1mth [5, 25] 15mg/kg/day (max 1.5g/day) *[If obese, use adjusted body weight =IBW + 0.4 (Actual weight – IBW)]* IM or IV [1, 20, 28] Can reduce to 2-3 times a week during continuation phase. Dose adjustment [27] If renal impairment, refer to Renal Drug Handbook.	• Nephrotoxicity. • Ototoxicity. Electrolyte abnormalities [20] (low potassium, magnesium, calcium). • Avoid in myasthenia gravis [5, 28].	

Group 3: FLUOROQUINOLONES			
Moxifloxacin (Mfx) *Bactericidal*	Adult [20, 25] 400mg once a day Child 1 month to 18 years *Not licensed for paediatric use but suggested dose available [31].* Oral or IV Dose adjustments In low-level fluoroquinolone resistance, consider 600mg OD (only if supported by AUC/MIC studies).	• Achilles tendonitis and rupture. • Can lower seizure threshold – caution in epilepsy. • Hyperglycaemia. • Prolongs QT interval. • Avoid in severe hepatic insufficiency. • Avoid antacids, iron, zinc – 2 hour before or after.	• Baseline ECG and monitor QT interval. • Monthly LFTs, renal function and glucose.
Group 4: ORAL BACTERIOSTATIC SECOND-LINE ANTITUBERCULOSIS DRUGS			
Para-amino salicylic acid (PAS) *Bacteriostatic*	Adult [20, 25] 150mg/kg/day or 8 -12g in 2-3 divided doses Child 1 month to 18 years [31, 25] 150mg/kg/day in 2 to 3 divided doses (max 12g/day) Oral Dose adjustments Increase dose gradually over few days to improve tolerance.	• Frequent GI intolerance – take with food (or mix in yogurt), or take with antacid. • Malabsorption of vitamin B_{12}, folate and lipids. • Hypothyroidism. • Hepatitis. • Caution in G6PD and aspirin allergy. NB: Delivery lead time.	• U&E's, LFTs, FBC, clotting. • TSH baseline, then 6 monthly.
Ethionamide* (Eto) Or **Prothionamide* (Pto)** *Bacteriostatic*	Adult and child ≥1mth [25, 31] 15-20mg/kg/day (max 1g/day) in 2 -3 divided doses with meals, or as a single daily dose after the evening meal or at bedtime. Oral Dose adjustments [30] Initiate dose at 250mg once a day then increase dose gradually over few days to highest tolerated dose.	• Frequent GI intolerance (take with antacid/antiemetics and lie supine for 20 minutes after dosing) • Hepatitis, hypothyroidism, poor diabetic control. • Optic neuritis, peripheral neuropathy (consider pyridoxine). • Mental disturbances. • Avoid excessive alcohol intake–↑ risk of psychosis. • Good CSF penetration [20]. NB: Delivery lead time.	• U&E's, LFTs, FBC, clotting, glucose. • TSH baseline, then 6 monthly. • Opthalmology assessment baseline and during treatment.
Cycloserine (Cs) *Bacteriostatic*	Adult and child >12 years [5] Initially 250mg 12hrly for 14 days, increase according to level and response to max. 500mg 12hrly. Child 2 to 12 years [5] Initially 5mg/kg (max 250mg) 12hrly, increase according to level and response up to 10mg/kg (max 500mg 12hrly). Oral Dose adjustments [27] If renal impairment, refer to Renal Drug Handbook.	• Neurological and psychiatric disturbances (potentiated by interaction with ethionamide / prothionamide) – give pyridoxine 50mg for each 250mg cycloserine [20] • Avoid excessive alcohol intake– ↑ risk of seizure. • Good CSF penetration [20].	• Monthly mental status assessment. • Monthly renal function and FBC. • Monitor serum level [32]: After 4th to 6th dose then every 10 to 30 days (depending on renal function). Aim for Pre: 10-20mg/l Post (3-4hr): 20-35mg/l

Group 5: AGENTS WITH UNCLEAR ROLE IN DRUG RESISTANT-TB TREATMENT			
Linezolid *In vitro bactericidal activity*	Adult [20, 25] 600mg twice a day Most reduce the dose to 600mg once a day after 4-6 weeks to decrease adverse effects. Child <10years [31] 10mg/kg twice a day Child ≥ 10years to 12 years [31] 10mg/kg once a day Oral	• GI disturbances frequent. • Peripheral and optic neuropathy. • BM suppression. • ↓ platelets, anaemia. • Lactic acidosis. • Side effects more common after 28 days of therapy. • Interaction with antidepressants. • Good CSF penetration [25].	• FBC weekly. • Lactate if vomiting and malaise. • Visual function to be checked regularly if treatment >28 days.
Co-amoxiclav *Possible early bactericidal activity*	Adult [20, 25] 625mg three times a day Child < 12 years [20, 31] As for bacterial infection. See current version of BNF-C. Oral	• Do not give if penicillin allergy. • Risk of cholestatic jaundice for treatment >14 days.	• Monthly LFTs
Clofazimine *In vitro bactericidal activity*	Adult [20] 100–300mg once a day Some clinicians begin at 300 mg daily and decrease to 100 mg after 4 to 6 weeks. Child < 12 years [31] 3–5mg/kg/day (max.100mg/day) Oral	• GI disturbances frequent – take with food. • Stop treatment if severe abdominal pain/acute abdomen – risk of crystalline deposits [31]. • Skin, eye and body fluid discoloration (reddish-black or orange) – harmless but distressing. Skin discolouration is reversible but may take months to years. • Avoid the sun and use sunscreen. • Absorption increased with high-fat meal, and slightly decreased when given with orange juice or antacid [31]. • Avoid in severe hepatic insufficiency [20]. NB: Delivery lead time.	• Monitor side effects.
Clarithromycin *Bacteriostatic*	Adult [20] 500mg twice a day Child < 12 years [31] 7.5 – 15mg/kg twice a day (max. 500mg / dose). Oral	• Gastrointestinal disturbance. • Smell and taste disturbances. • Tongue and tooth discoloration. • Prolonged QT interval. • Use with caution in renal or hepatic failure [25].	• Enzyme inhibitor –drug interactions. May warrant other concurrent drugs to be dose adjusted e.g. statins, theophyllines, in particular carbamazepine as levels can triple within 24 hours.

4.2 Duration

- Treatment for MDRTB should be continued until sputum cultures become negative.
- Treatment must then be continued, with at least three appropriate drugs, for a minimum of nine further months.
- It may be necessary to extend treatment up to, or beyond 24 months depending on the in vitro drug resistance profile, available drugs, and the patient's HIV status [6].

4.3 Monitoring therapy

- While an inpatient, MDRTB therapy will be administered under direct observation by the ward nursing staff so that the patient is watched while all medication is swallowed.
- All patients with MDRTB should receive an enhanced case management (ECM)[37]. A named case manager will be responsible for coordinating a multi disciplinary approach to the management of the patient for the duration of treatment. They will assess the level of support required on discharge including the need and provision for directly observed therapy (DOT). A care plan will be agreed with the patient.
- Objective assessment of compliance will be made by regular urine or blood tests. All request for blood levels must be sent to the Microbiology Laboratory. Blood level assays are available for:
  - rifampicin;
  - aminoglycosides (including amikacin and streptomycin);
  - quinolones (including ciprofloxacin and moxifloxacin);
  - cycloserine; and
  - linezolid.

  The dosing regimen, as well as timing of both the last dose and blood sample must be given on the request form to assist the correct interpretation of the results.

4.4 Suboptimal compliance with therapy

- This is arbitrarily defined for the purpose of this protocol as unjustified failure to take a drug on three consecutive occasions, or on two occasions per week for two consecutive weeks.
- The case manager will be responsible for informing the responsible consultant in these circumstances.
- The team responsible for the case will consider changing therapy or social circumstances to enhance compliance. If these measures are not possible or unsuccessful, a multidisciplinary case meeting will be arranged as soon as possible. This will include the responsible hospital medical, nursing, and Infection Prevention and Control (IPC) staff, Consultant in Communicable Disease Control (CCDC), social workers and legal officers. The meeting will review details of the case and consider appropriate measures. These may include detention under Section 37/38 of the Public Health Act where the community is judged at risk of infection.

4.5 Follow-up

- The frequency of outpatient follow up will be determined by the responsible consultant on an individual basis.
- After treatment is completed, there should be 5 years outpatient follow up.
- Resectional surgery should be considered if sputum conversion does not occur or if there is a relapse [8]. Following surgery, the same regimen of medication should continue for at least 18 months [1].

4.6 Chemoprophylaxis for MDRTB contacts

Discuss individual cases with a TB specialist.

Chemoprophylaxis should not be started in close contacts of people with sputum-smear-positive MDRTB who are strongly Mantoux positive (15 mm or greater), as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease [14].

Long-term monitoring should be undertaken for active disease.

Management of contacts of MDRTB cases should be discussed as an MDT and decision regarding follow-up agreed and documented.

➢ Contacts

TB SPECIALIST	NAME	CONTACT DETAILS
Clinical Lead NCL Integrated TB Service		
Consultant TB Lead	Dr. Helen Booth	via UCLH switchboard
MDRTB lead South Hub:		
ID Consultant	Dr. Mike Brown	via UCLH switchboard
Nurse Specialist	Clare Stephenson	via UCLH switchboard
HIV-TB lead South Hub:		
HIV Consultant	Professor Rob Miller	via UCLH switchboard
Nurse Specialist	Lusha Kellgren	via UCLH switchboard
Lead Consultant Paediatrician for TB (Whittington):		
Consultant Paediatrician	Dr. John Moreiras	via Whittington switchboard
TB Nurse Specialist:		Ext. 3366 or email: tbservice@nhs.net
Pharmacy Outpatient Dispensary (Whittington)		Ext. 3387 or email: pharmacy.whitthealth@nhs.net
Pharmacist for TB Services (Whittington)		Ext. 5021

MICROBIOLOGY		CONTACT DETAILS
Consultant Microbiologist (Whittington)	Dr. Michael Kelsey Dr. Julie Andrews	Ext. 5082 Ext. 3894
Consultant Microbiologist (UCLH)	Dr Steve Morris-Jones	via UCLH switchboard
Microbiology Registrars (Whittington)	Mon-Fri; 9am – 5pm	Ext. 5085 / Bleep: 3069
	Out-of-office hours	via Whittington switchboard
Infection Prevention and Control Team (Whittington)		Ext. 3261 / Bleep: 2669
Lead Antimicrobial Pharmacist (Whittington)		Ext. 3732 / Bleep: 3183

Specialist reference laboratory services – Public Health England (PHE):	
National Mycobacterium Reference Laboratory (NMRL) London	0207 377 5895

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Appendix 1

Name and Hospital No.
(sticker if possible)

Checklist Whittington Health TB Service

Complete sections 1-3 for all patients starting/all new patients to TB clinic who are on TB treatment

	Yes	No	If Yes:	Done	Date	Sign
1. Significant Medical History						
Liver disease/excess alcohol			• Monitor LFTs • Max rifampacin 8mg/kg			
Severe renal impairment or unstable renal function			• Avoid ethambutol if possible • Reduce INH to 200mg/day if GFR<10ml/min • Dialysis – seek advice			
Contact of resistant TB			Review TB drug regimen			
2. Significant Drug Interactions						
Oral contraceptive pill			• Reduced efficacy of OCP • Advise alternative method			
Oral steroids			Double steroid dose			
Other immunosuppressants			Reduced effect – seek advice			
Highly active antiretroviral therapy (HAART)			Seek advice			
Methadone			• Increase methadone • Liaise with DDU			
Sulphonylureas			• Monitor BMs more closely • Consider ↑ diabetic tablets			
Warfarin			• INR reduced • Monitor INR closely • Inform anticoagulant clinic			
Phenytoin			• INH and Rifampicin effect levels differently • Monitor levels			
Carbamazepine			Reduce carbamazepine dose			
3. Side effects of Rx						
Has information leaflet			In English/appropriate language			
Side effects explained						
• Hepatitis/Vomiting			Stop Rx and let clinic know			
• Contact lenses			May damage lenses, advise glasses			
• Eye changes with ethambutol			• Advise any change in eyesight • Baseline Snellen chart • Refer to Opthalmology			
HIV status/testing. Complete this section when appropriate						
Serostatus already known before clinic attendance?			Tested prior to current illness (if –ve, proven within preceding 3 months)			
			Tested as inpt in current illness Negative/Positive			
HIV test offered in clinic (routinely at 2 month TB Rx)			Accepted/Refused			
HIV result given			Negative/Positive			
If +ve, can GP be informed						

Patients <u>stopping</u> TB Treatment. Complete sections 4-6

	Yes	No	If Yes:	Done	Date	Sign
4. Significant Drug Interactions						
Oral contraceptive pill			Restart but continue other contraceptive methods for 4 weeks after stopping rifampicin			
Oral steroids			Reduce (halve) steroid dose			
Other immunosuppressants			Reverse any dose change			
Methadone			• Decrease methadone • Liaise with DDU			
Sulphonylureas			Reverse any dose change/ ↓			
Warfarin			• Reverse dose change/ ↓ • Monitor INR closely • Inform anticoagulant clinic			
Phenytoin			• Reverse any dose change • Monitor levels			
Carbamazepine			• Reverse any dose change • Monitor levels			
5. Follow-up						
If pulmonary TB: • CXR normal/little abnormality • CXR very abnormal and/or risk of poor adherence			Discharge with advice			
			Follow-up appt 6 months with CXR			
If non-pulmonary TB			Probably discharge			
6. Treatment outcome (select one category)						
1. Treatment stopped – not TB						
2. Successful completion within twelve months of starting Rx						
3. Treatment course > 12 months:					Yes	No
3a. Treatment interrupted			Side effects/intolerance of treatment			
			Less than 80% prescribed Rx taken			
			Any other interruption			
3b. Treatment changed			Side effects/intolerance of treatment			
			Initial drug resistance			
			Development of new drug resistance			
			Failure to culture convert			
			Poor clinical response			
3c. On initial planned course Rx						

Appendix 2

Vitamin D in TB (Adults)

For Children please refer to http://whittnet/document.ashx?id=7325

Background

- Vitamin D modulates anti-mycobacterial immunity.
- Vitamin D deficiency is common in the general population including the TB population. Not clear whether cause or effect.
- Rifampicin increases vitamin D metabolism and reduces vitamin D blood levels.
- Oral Adcal D3 may be unpleasant to take and only provides a low dose of vitamin D (800units/day of cholecalciferol).
- Polypharmacy may affect compliance with anti TB medication.
- No evidence that supplementation improves outcome in our population group.

Recommendation

1. **Give general advice to all patients and contacts about vitamin D metabolism**
   - Recommend sun exposure for at least 10 minutes 3 times weekly (90% daily requirement is obtained from the sun's affect on skin vitamin D metabolites).
   - Adequate dietary intake: vitamin supplements particularly cod liver oil, oily fish, egg yolks, fortified dairy and cereal products, fresh meat.

2. **Perform vitamin D levels in patients with:**
   - malabsorption problems e.g. of small intestine;
   - symptoms suggestive of osteomalacia -chronic muscle aches and pains;
   - biochemical changes; low calcium, phosphate, alkaline phosphate (in adults);
   - poorly responding MDRTB, for whom (in the absence of convincing evidence of efficacy) such adjuvant therapies to potentially improve the immune response may be considered.

3. **Supplementation:**

Severe deficiency <25 nmol/l	**Treatment:** • Colecalciferol 300,000 units IM or oral as single dose, **OR** 40,000 units daily for 7 days, **OR** 60,000 units weekly for 6-8 weeks. • Monitor calcium at monthly intervals. • 25-OHD, ALP, PO4 and PTH should be repeated at 3 months. • Large bolus doses are as effective as daily doses and may be preferred when compliance with long term therapy is poor.
	Maintenance: • Following initial treatment, a maintenance dose (e.g. 2 tablets of Adcal D3 daily if calcium also required, **OR** 1,000 units daily) is usually required long-term as the patient remains at risk of deficiencies.
Insufficiency (maintenance dose) 25-50 nmol/l	• 10,000 units weekly **OR** 800-2,000 units daily (**OR** 2 tablets of Adcal D3 (containing calcium 600mg and colecalciferol 400 units / tablet) daily if calcium also required). This may need to continue for the duration of Rifampicin treatment. • Check levels every 3-6 months • Reinforce dietary / sunlight advice.
Adequate 50 – 75 nmol/l	Advise on diet and safe levels of sun exposure.

4. **Patient leaflet:**
   See Department of Health information:
   http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_111302.pdf

Appendix 3

Adult TB Medication (Standard therapy) – Daily Dosing Guide

DRUG	PREPARATION	DOSE according to PATIENT'S WEIGHT								DOSE FREQUENCY
		37 – 43.9kg	44 – 49.9kg	50 – 56.9kg	57 – 63.9kg	64 – 69.9kg	70 – 76.9kg	77 – 83.9kg	84 – 89.9kg	
2-months INITIAL PHASE										
Rifinah	**100/150** Rifampicin 150mg + Isoniazid 100mg	3 tablets	3 tablets							**All medications to be taken ONCE a DAY** (half an hour before food)
	150/300 Rifampicin 300mg + Isoniazid 150mg			2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	
Pyridoxine	10mg tablet	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	
Pyrazinamide	500mg tablet	1.5 g	1.5 g	2 g	2 g	2 g	2 g	2 g	2 g	
Ethambutol *	100mg, 400mg tablet	600 mg	700 mg	800 mg	900 mg	1000 mg	1100 mg	1200 mg	1300 mg	
Followed by 4-months CONTINUATION PHASE										
Rifinah	**100/150** Rifampicin 150mg + Isoniazid 100mg	3 tablets	3 tablets							**All medications to be taken ONCE a DAY** (half an hour before food)
	150/300 Rifampicin 300mg + Isoniazid 150mg			2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	
Pyridoxine	10mg tablet	10mg	10mg	10mg	10mg	10mg	10mg	10mg	10mg	

** If obese, calculate Ethambutol dose using Ideal Body Weight : IBW = (male) 50kg or (female) 45.5kg + (0.91 x every cm over 152.4cm)*

Appendix 4

Adult Thrice Weekly Direct Observed Therapy (DOT) regimen
- Intermittent Supervised 6-month Therapy for Adults in NCL Sector

Adapted from UCLH TB Guideline

Rifinah 150/300 = contains 150mg ISONIAZID (H) + 300mg RIFAMPICIN (R)

Drug	BNF dosage for intermittent supervised 6-month treatment	Duration	Weight				
			40kg	45kg	≥50kg	55kg	≥60kg
Isoniazid (H)	**15mg/kg (max 900mg) 3 times a week**	**6 months**	**600mg**	**700mg**	**750mg**	**850mg**	**850mg**
Rifampicin (R)	**600-900mg 3 times a week**	**6 months**	**600mg**	**600mg**	**900mg**	**900mg**	**900mg**
Rx: **Rifinah 150/300**	*- See dosage above -*	6 months	**2 tablets**	**2 tablets**	**3 tablets**	**3 tablets**	**3 tablets**
Rx: **Isoniazid (H) additional**	*- See dosage above -*	6 months	**300mg**	**400mg**	**300mg**	**400mg**	**400mg**
Rx: **Pyridoxine (Vitamin B_6)**	10mg once a day	6 months	**10mg**	**10mg**	**10mg**	**10mg**	**10mg**
Rx: **Pyrazinamide (Z)**	<50kg: 2g 3 times a week; ≥50kg: 2.5g 3 times a week	2 months	**2g**	**2g**	**2.5g**	**2.5g**	**2.5g**
Rx: **Ethambutol (E)**	30mg/kg* 3 times a week	2 months	**1200mg**	**1400mg**	**1500mg**	**1600mg**	**30mg/kg***

** If obese, calculate Ethambutol dose using Ideal Body Weight : IBW = (male) 50kg or (female) 45.5kg + (0.91 x every cm over 152.4cm)*

Appendix 5

Paediatric TB Medication (Standard therapy) for 1 month to 18 years of age – Daily Dosing Guide

Weight (kg)	RIFAMPICIN			ISONIAZID				RIFINAH			PYRAZINAMIDE			ETHAMBUTOL		
	PAEDIATRIC DOSING 15mg/kg/od (max 600mg)	SYRUP 100mg/5ml	CAPSULE 150mg, 300mg	PAEDIATRIC DOSING 10mg/kg/od (max 300mg)	SYRUP 50mg/5ml	TABLET 100mg		Rifampicin 150mg + Isoniazid 100mg	Rifampicin 300mg + Isoniazid 150mg		PAEDIATRIC DOSING 35mg/kg/od (max 2g)	SYRUP 500mg/5ml	TABLET 500mg	PAEDIATRIC DOSING 20mg/kg/od	SYRUP 400mg/5ml	TABLET 100mg, 400mg
		SYRUP	CAPSULE		SYRUP	TABLET		100/150	150/300			SYRUP	TABLET		SYRUP	TABLET
5	75mg	3.8ml		50mg	5ml		ISONIAZID plus RIFAMPICIN COMBINATION			ISONIAZID plus RIFAMPICIN COMBINATION	175mg	1.8ml		100mg	1.3ml	
6	90mg	4.5ml		60mg	6ml						210mg	2.1ml		120mg	1.5ml	
7	105mg	5.3ml		70mg	7ml						245mg	2.5ml		140mg	1.8ml	
8	120mg	6ml		80mg	8ml						280mg	2.8ml		160mg	2ml	
9	135mg	6.8ml		90mg	9ml						315mg	3.2ml		180mg	2.3ml	
10	150mg	7.5ml		100mg	10ml						350mg	3.5ml		200mg	2.5ml	
11	165mg	8.3ml		110mg	11ml						385mg	3.9ml		220mg	2.8ml	
12	180mg	9ml		120mg	12ml						420mg	4.2ml		240mg	3ml	
13	195mg	9.8ml		130mg	13ml						455mg	4.6ml		260mg	3.3ml	
14	210mg	10.5ml		140mg	14ml						490mg	4.9ml		280mg	3.5ml	
15	225mg	11.3ml		150mg	15ml						525mg	5.3ml		300mg	3.8ml	
16	240mg	12ml		160mg	16ml						560mg	5.6ml		320mg	4ml	
17	255mg	12.8ml		170mg	17ml						595mg	6ml		340mg	4.3ml	
18	270mg	13.5ml		180mg	18ml						630mg	6.3ml		360mg	4.5ml	
19	285mg	14.3ml		190mg	19ml						665mg	6.7ml		380mg	4.8ml	
20	300mg	15ml		200mg	20ml						700mg	7ml		400mg	5ml	
21	315mg	15.8ml		210mg	21ml						735mg	7.4ml		420mg	5.3ml	
22	330mg	16.5ml		220mg	22ml						770mg	7.7ml		440mg	5.5ml	
23	345mg	17.3ml		230mg	23ml						805mg	8.1ml		460mg	5.8ml	
24	360mg	18ml		240mg	24ml						840mg	8.4ml		480mg	6ml	
25	375mg	18.8ml		250mg	25ml						875mg	8.8ml		500mg	6.3ml	

NB: This table should only be used as a guide. Doses should be calculated according to the actual body weight (or if morbidly obese, according to the Ideal Body Weight) and rounded-up to suitable volumes of liquid or an appropriate strength of tablet to facilitate administration. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

Paediatric TB Medication (Standard therapy) for 1 month to 18 years of age – Daily Dosing Guide

Weight (kg)	RIFAMPICIN			ISONIAZID				RIFINAH			PYRAZINAMIDE			ETHAMBUTOL		
	PAEDIATRIC DOSING 15mg/kg/od (max 600mg)	SYRUP 100mg/5ml	CAPSULE 150mg, 300mg	PAEDIATRIC DOSING 10mg/kg/od (max 300mg)	SYRUP 50mg/5ml	TABLET 100mg		Rifampicin 150mg + Isoniazid 100mg	Rifampicin 300mg + Isoniazid 150mg		PAEDIATRIC DOSING 35mg/kg/od (max 2g)	SYRUP 500mg/5ml	TABLET 500mg	PAEDIATRIC DOSING 20mg/kg/od	SYRUP 400mg/5ml	TABLET 100mg, 400mg
		SYRUP	CAPSULE		SYRUP	TABLET		100/150	150/300			SYRUP	TABLET		SYRUP	TABLET
26	390mg	19.5ml		260mg	26ml		ISONIAZID plus RIFAMPICIN COMBINATION			ISONIAZID plus RIFAMPICIN COMBINATION	910mg	9.1ml		520mg	6.5ml	
27	405mg	20.3ml		270mg	27ml						945mg	9.5ml		540mg	6.8ml	
28	420mg	21ml		280mg	28ml						980mg	9.8ml		560mg	7ml	
29	435mg	21.8ml		290mg	29ml						1015mg	10.2ml		580mg	7.3ml	
30	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1050mg	10.5ml	1G	600mg	7.5ml	600mg
31	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1085mg	10.9ml	1G	620mg	7.8ml	600mg
32	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1120mg	11.2ml	1G	640mg	8ml	600mg
33	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1155mg	11.6ml	1.25G	660mg	8.3ml	600mg
34	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1190mg	11.9ml	1.25G	680mg	8.5ml	700mg
35	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1225mg	12.3ml	1.25G	700mg	8.8ml	700mg
36	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1260mg	12.6ml	1.25G	720mg	9ml	700mg
37	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1295mg	13ml	1.25G	740mg	9.3ml	700mg
38	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1330mg	13.3ml	1.25G	760mg	9.5ml	700mg
39	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1365mg	13.7ml	1.25G	780mg	9.8ml	800mg
40	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1400mg	14ml	1.5G	800mg	10ml	800mg
41	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1435mg	14.4ml	1.5G	820mg	10.3ml	800mg
42	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1470mg	14.7ml	1.5G	840mg	10.5ml	800mg
43	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	860mg	10.8ml	800mg
44	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	880mg	11ml	900mg
45	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	900mg	11.3ml	900mg
46	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	920mg	11.5ml	900mg
47	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	940mg	11.8ml	900mg
48	450mg	22.5ml	450mg	300mg	30ml	300mg		3 caps			1500mg	15ml	1.5G	960mg	12ml	900mg

NB: This table should only be used as a guide. Doses should be calculated according to the actual body weight (or if morbidly obese, according to the Ideal Body Weight) and rounded-up to suitable volumes of liquid or an appropriate strength of tablet to facilitate administration. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

Paediatric TB Medication (Standard therapy) for 1 month to 18 years of age – Daily Dosing Guide

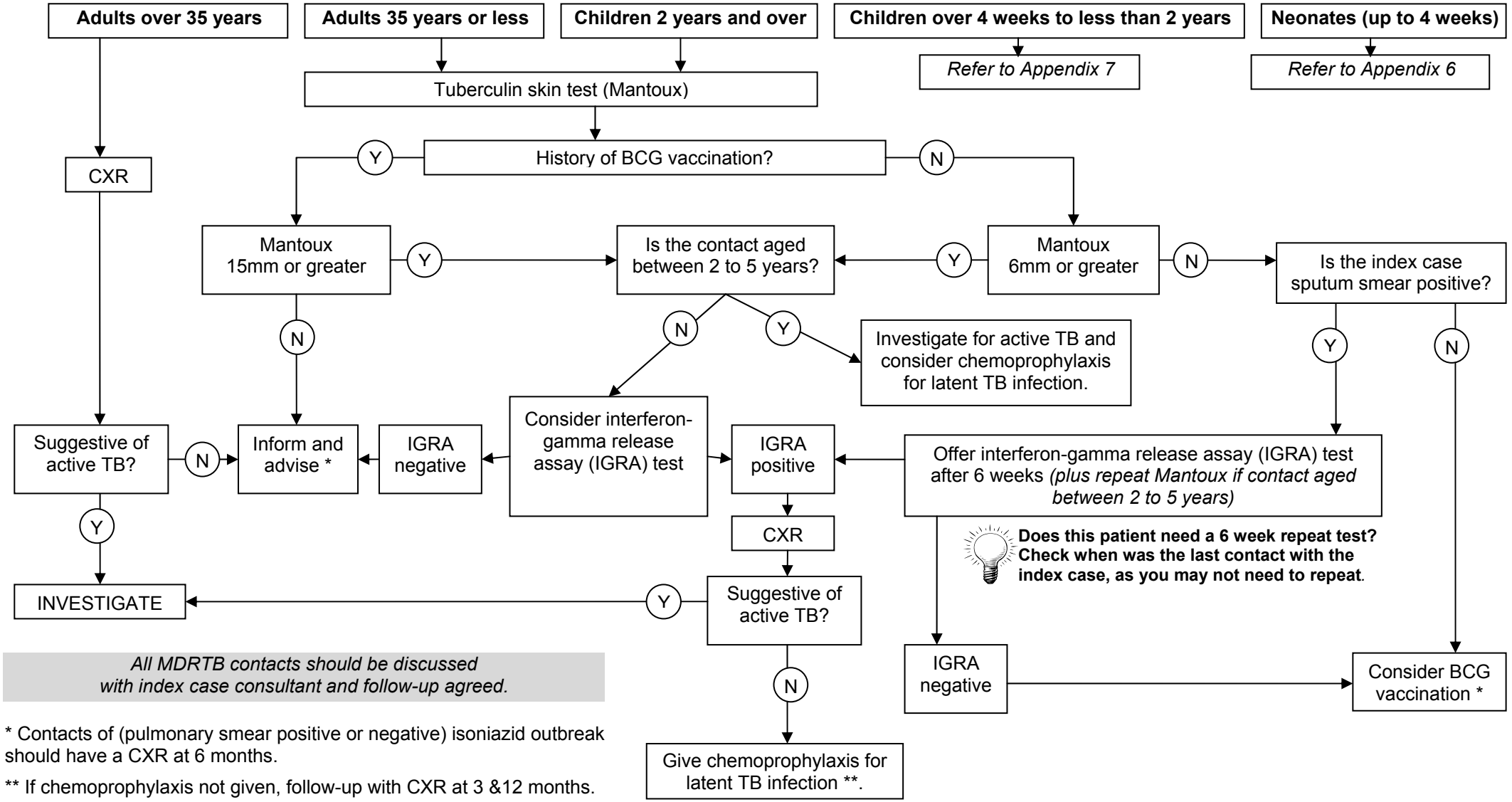
Weight (kg)	RIFAMPICIN			ISONIAZID				RIFINAH			PYRAZINAMIDE			ETHAMBUTOL		
	PAEDIATRIC DOSING 15mg/kg/od (max 600mg)	SYRUP 100mg/5ml	CAPSULE 150mg, 300mg	PAEDIATRIC DOSING 10mg/kg/od (max 300mg)	SYRUP 50mg/5ml	TABLET 100mg		Rifampicin 150mg + Isoniazid 100mg	Rifampicin 300mg + Isoniazid 150mg		PAEDIATRIC DOSING 35mg/kg/od (max 2g)	SYRUP 500mg/5ml	TABLET 500mg	PAEDIATRIC DOSING 20mg/kg/od	SYRUP 400mg/5ml	TABLET 100mg, 400mg
		SYRUP	CAPSULE		SYRUP	TABLET		100/150	150/300			SYRUP	TABLET		SYRUP	TABLET
49	450mg	22.5ml	450mg	300mg	30ml	300mg	ISONIAZID plus RIFAMPICIN COMBINATION	3 caps		ISONIAZID plus RIFAMPICIN COMBINATION	1500mg	15ml	1.5G	980mg	12.3ml	1000mg
50	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1750mg	17.5ml	1.75G	1000mg	12.5ml	1000mg
51	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1785mg	17.9ml	1.75G	1020mg	12.8ml	1000mg
52	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1820mg	17.5ml	1.75G	1040mg	13ml	1000mg
53	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1855mg	18.6ml	1.75G	1060mg	13.3ml	1000mg
54	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1890mg	18.9ml	1.75G	1080mg	13.5ml	1100mg
55	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1925mg	19.3ml	2G	1100mg	13.8ml	1100mg
56	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1960mg	19.6ml	2G	1120mg	14ml	1100mg
57	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		1995mg	20ml	2G	1140mg	14.3ml	1100mg
58	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		2000mg	20ml	2G	1160mg	14.5ml	1100mg
59	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		2000mg	20ml	2G	1180mg	14.8ml	1200mg
60	600mg	30ml	600mg	300mg	30ml	300mg			2 caps		2000mg	20ml	2G	1200mg	15ml	1200mg

NB: This table should only be used as a guide. Doses should be calculated according to the actual body weight (or if morbidly obese, according to the Ideal Body Weight) and rounded-up to suitable volumes of liquid or an appropriate strength of tablet to facilitate administration. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

Appendix 6

Screening Asymptomatic Household Contacts of ALL Cases of Active TB

- adapted from North Central London TB Contact Tracing Guidelines and based on NICE Guideline 2011



All MDRTB contacts should be discussed with index case consultant and follow-up agreed.

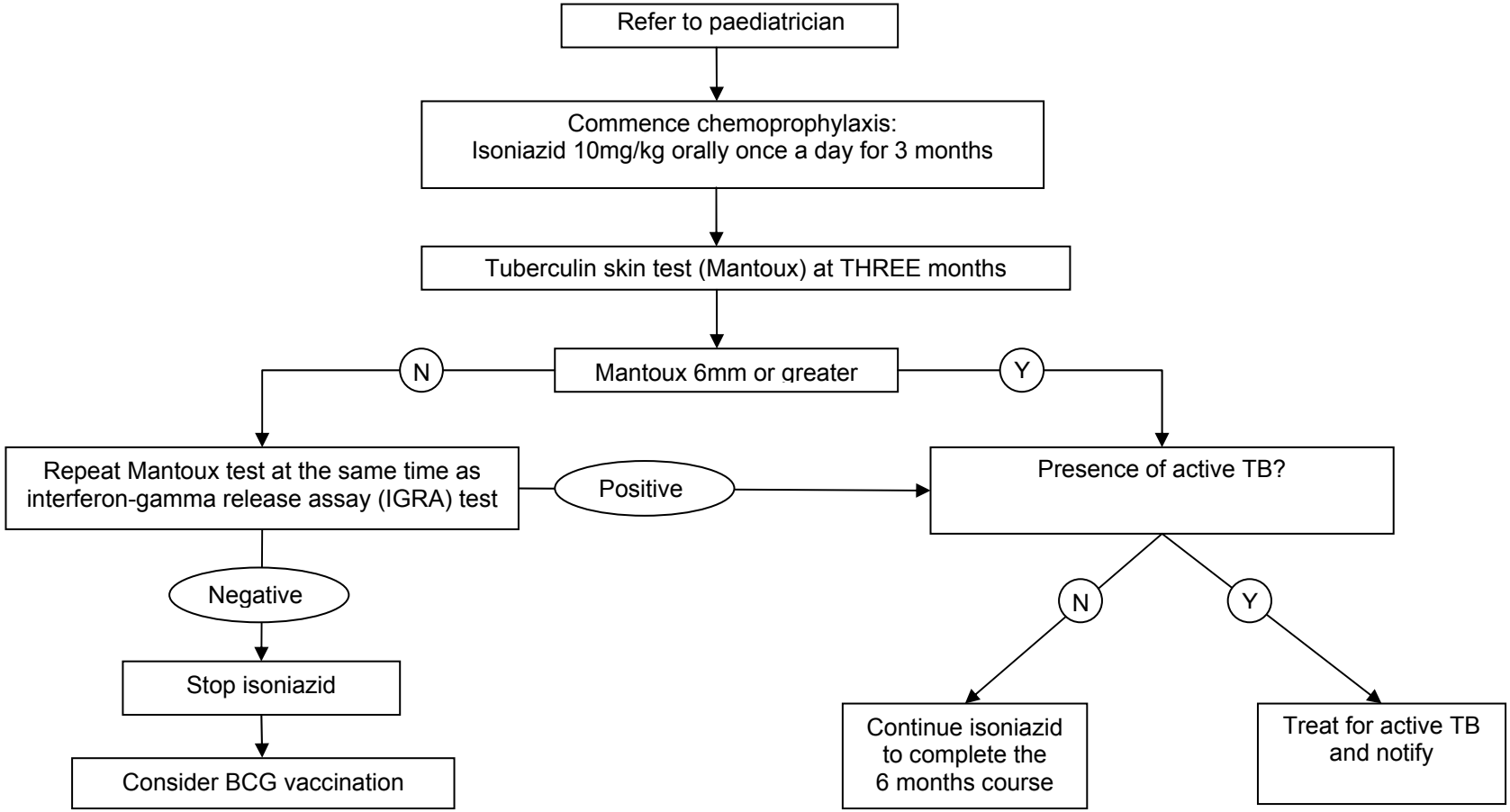
* Contacts of (pulmonary smear positive or negative) isoniazid outbreak should have a CXR at 6 months.

** If chemoprophylaxis not given, follow-up with CXR at 3 &12 months.

Appendix 7

Neonates (up to 4 weeks) Contacts of Smear Positive Pulmonary TB

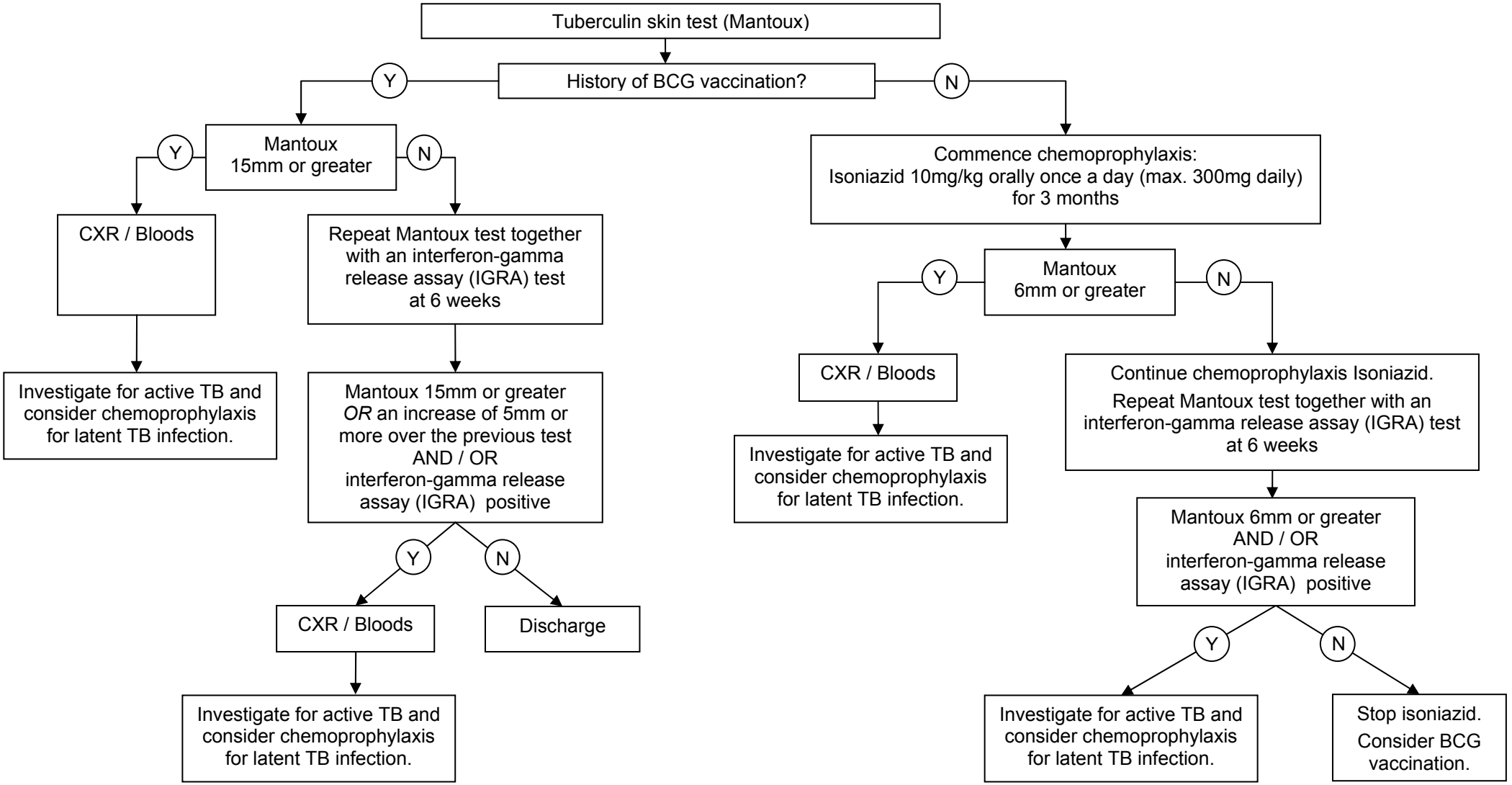
- adapted from North Central London TB Contact Tracing Guidelines and based on NICE Guideline 2011



Appendix 8

Screening of Smear Positive TB Contacts aged over 4 weeks to less than 2 years

- adapted from North Central London TB Contact Tracing Guidelines and based on NICE Guideline 2011



Appendix 9

Sputum Induction (for Adults) - Guidance

- adapted from Royal Free Hospital Standard Operating Procedure for Sputum Induction

1. Introduction

Sputum induction is a generally well-tolerated and non-invasive technique used to aid the diagnosis of *Mycobacterium tuberculosis*.

The procedure is used to collect adequate sample of secretions from the lower airways for microbiology testing, in patients with radiological evidence of tuberculosis (TB) who are unable to produce sputum spontaneously.

Patients are required to inhale nebulised hypertonic saline, which liquefies airway secretions, promotes coughing and allows expectoration of respiratory secretions.

2. Inclusion criteria (must fulfil all the following criteria)

- Aged 16 years and over.
- FEV1 >65% predicted.
- Clinically stable.
- Appropriate history or risk of TB.
- Unable to self expectorate (a good quality self-expectorated sample has the same yield as induced sputum).

3. Exclusion criteria / contraindication:

- Severe asthma or severe chronic obstructive pulmonary disease (COPD).
- Baseline spirometry of FEV1 < 65% predicted.
- Oral steroid treatment for an acute exacerbation of either of asthma or COPD in the previous month.
- Resting oxygen saturations <90% on appropriate supplemental oxygen.
- Requiring > 8L min of oxygen.
- Severe bronchospasm.
- Respiratory rate > 25 breaths per minute.
- Unwilling to consent to the procedure after explanation.
- Unable to comply with the procedure, or severely anxious or confused.
- Pleural effusions (high risk of worsening effusion and pneumothorax). Diagnostic tap indicated instead of induced sputum.

4. Limitations

Induced sputum procedures have a significant false negative rate for TB. Samples cannot always be obtained despite induced sputum. The yield is similar between both expectorated and induced samples as long as an adequate sample is obtained.

Possible side effects include:

- Breathlessness
- Hypoxia
- Nausea
- Bronchoconstriction
- Rapid progression of small pleural effusion to large pleural effusion

5. Process

a) Referral

- All requests for induced sputum for TB should be directed through the TB nurse.
- The ‘Request for Induced Sputum’ form (see below) must be completed for all inpatient requests and submitted to the TB clinic prior to the procedure.

- The patient will be assessed by the TB nurse to ensure they are suitable for the procedure to be carried out.
- The patient, their medical team and the ward staff (if applicable) will be informed of a date and time that the procedure will be carried out.

b) Infection control

- The procedure should only be performed by practitioners (e.g. registered nurses or physiotherapists) who have been trained in the procedure.
- Practitioners must be familiar with the local infection control policies, familiar with the equipments used, able to recognise respiratory distress and able to administer oxygen and salbutamol appropriately.
- Sputum inductions must be carried out in a negative pressure room. The door must remain closed during and immediately after the procedure to ensure that a negative pressure environment is maintained. An FFP3 respirator must be worn at all times, when entering or inside the negative pressure room. Any member of staff supervising this procedure must have been trained in the correct use of an FFP3 respirator, this should include "fit testing".
- Single use equipments e.g. nebuliser mask, tubing, filter, cup and lid must be dispose into the orange clinical waste bag for incineration according to hospital infection control policy.
- After each patient use, the ultrasonic nebuliser must be decontaminated according to the local decontamination policy for re-usable medical devices.
- After each session, the negative pressure room must be cleaned and disinfected with Actichlor Plus according to hospital infection control policy.

c) Equipments

- Ultrasonic nebuliser (Devilbiss UltraNeb 2000 & 3000)
- 2 parts elephant tubing
- 1 part elephant tubing
- 1 Intersurgical disposable cup and
- 1 Intersurgical disposable lid
- 1 Intersurgical disposable nebuliser mouth piece
- 1 Intersurgical disposable filter
- 1 clear plastic autoclave bag
- 1 large specimen pot ('honey' pot) per procedure
- Peak flow meter for single patient use or hand held spirometer plus filter
- Pulse oximeter for oxygen saturation monitoring
- Oxygen that can be delivered via nasal prongs
- Resuscitation equipment (bag and mask; Guedel airway; intravenous cannulae)

Instruction for setting up the equipment:

i. Fill the nebuliser chamber with sterile water to between the minimum and maximum fill line, with the level lying on the crosshatch (do not overfill as this will damage the equipment).
ii. Place the disposable nebuliser cup into the nebulising chamber (important that the water does not go over the maximum mark when displaced by the cup).
iii. Pour 40ml hypertonic 3% sodium chloride into the disposable nebuliser cup.
iv. Attach the lid to the cup – tape to secure if necessary.
v. Attach the filter to the nebuliser.
vi. Attach 1 part elephant tubing to filter and other end to lid.
vii. Attach 2 parts elephant tubing to 2nd outlet from lid and attach nebuliser mouth-piece to the other end.
viii. Check that the output setting is set to maximum.
ix. Turn the green switch on and ensure that saline mist is coming from the nebuliser.

d) Drugs

These drugs must be prescribed by a doctor prior to the procedure:

Drug	Dosing and administration instructions
Standard protocol:	
• Hypertonic 3% sodium chloride nebules	Give 40 ml via an the ultrasonic nebuliser over 20 minutes stat for sputum induction. *NOTE: Nebulised 3% hypertonic sodium chloride can cause bronchoconstriction. Hence, pre-treatment with a short acting β_2 agonist bronchodilator is recommended as part of the standard protocol. Consider 0.9% sodium chloride instead for 3% hypertonic sodium chloride for patients who are at a greater risk of bronchospasm.*
• Salbutamol 100microgram inhaler	Inhale 2 puffs stat BEFORE the procedure.
PRN (when required) drugs:	
• Salbutamol 2.5mg nebules	*For acute bronchospasm:* Inhale the contents of one 2.5mg nebule via the nebuliser as required during or after the procedure.
• Oxygen	*For acute bronchospasm:* Refer to the Oxygen Guideline on the intranet. Administer via nasal specs.
• Cyclizine 50mg injection	*For nausea or vomiting:* Give 50mg intravenously as a slow bolus over 3-5 minutes or intramuscularly as required (maximum 8 hourly).

Emergency drugs (must be readily available in case of an anaphylaxis reaction:

- Adrenaline 1:1,000 (1mg in 1ml) injection – 0.5mg IM. Repeat after 5 minutes if necessary
- Hydrocortisone 100mg injection – 200mg IV as a slow bolus over 3-5 minutes or IM stat
- Chlorphenamine 10mg injection – 10mg IV as a slow bolus over 1minute or IM stat

e) Procedure

i. The patient should be given patient information leaflet (see below) prior to the procedure and a verbal consent should be obtained. Explain the procedure (aim to collect sputum samples from deep within the lung and not saliva) and possible side effects to the patient (e.g. coughing, dry mouth, nausea and excess salivation).

ii. The negative pressure room must be checked to ensure that a negative pressure is being maintained, the gauge above the door will indicate that the extract fans are working.

iii. Microbiology must be informed that the procedure will be taking place - as samples must be processed within 2 hours.

iv. Set up the nebuliser. Check that oxygen and nebulised salbutamol are available to administer in the event of bronchospasm.

v. If the patient is nauseous or vomiting, pre-treat with anti-emetic.

vi. Instruct the patient to remove any dentures (if applicable), rinse their mouth with water, and to blow their nose into tissues as required (to avoid the collection of post-nasal drip).

vii. Put the 'DO NOT ENTER' sign on the outside of the door.

viii. Attach the pulse oximetry to the patient.

ix. The patient should be administered two puffs of salbutamol 100mcg inhaler (pre-procedure bronchodilator).

x. The baseline peak expiratory flow rate (PEFR)/spirometery and oxygen saturations should be measured 5 minutes after the inhaler.

xi. Re-measure PEFR after 5 minutes. Note: If PEFR (or FEV_1) declines by >15% from the baseline PEFR (or FEV_1), discontinue the procedure.

xii. The patient should be administered 40mls of 3% hypertonic sodium chloride via the ultrasonic nebuliser over 20 minutes.
xiii. The patient should be encouraged to take deep breaths regularly.
xiv. The patient should gargle with sterile water and spit out the saliva prior to expectorating to reduce oral contamination.
xv. The patients should be asked to cough and expectorate into the large specimen pot ('honey' pot) after 5 minutes, and then repeat every 3-5minutes throughout the procedure.
xvi. Continuously monitor the pulse oximetry readings:
    - If the oxygen saturation drops – administer supplemental oxygen via nasal specs.
    - If the oxygen saturation cannot be maintained > 90% with supplemental oxygen – stop the procedure.
xvii. If there is haemoptysis, vomiting or any other signs of distress stop the procedure.
xviii. Once the procedure is finished, continue oxygen saturation monitoring for 10–15 minutes.
xix. Sputum samples should be delivered immediately to Microbiology.
xx. Record the procedure, outcome and any adverse effects in the medical notes.

Induced Sputum Patient Information Leaflet

What is an induced sputum sample?

Induced sputum sampling is a way of getting sputum (phlegm) from your lungs. It is a simple procedure, carried out if your chest is dry and you cannot cough up a sputum sample yourself or if we need a sample from the deep tissues of your lungs.

Why do you need to give an induced sputum sample?

For certain diseases analysing a sample of your sputum is the most useful way of diagnosing your problem.

Before you give the sputum sample the physiotherapist / doctor / nurse will assess your chest and explain what is going to happen. You will be given a nebuliser before the procedure. A nebuliser is a machine that produces very small water droplets (vapour) that you breathe in through a facemask. Drugs can be added to the water so that they go straight to your lungs and open the airways. This will make it easier to produce the sample of sputum.

What happens beforehand?

Induced sputum samples are always taken in a negative pressure room. Your healthcare carer will stay with you while you produce the sample. Being in a single room gives you some privacy and makes sure that if you do have an infection it is not spread to other people when you cough. To protect themselves against possible infection your carer will be wearing a mask.

What is involved?

First you will be asked to brush your teeth, gums and tongue and rinse your mouth with water. This clears out any bits of food and makes sure they do not contaminate your sample.

Next you will be asked to sit down and be given a facemask to wear. The mask is linked to a nebuliser. You will be asked to deeply breath in a vapour of salt water, this loosens the phlegm in your chest and will help you to cough up the sample needed.

Giving the sample can make you feel wheezy or sick. If you feel like this it is important that you let your carer know and the procedure will be stopped.

You will have to stay in the room where you give the sample until you have finished coughing. This is to make sure any infection does not spread.

How many samples?

This depends on what your doctor is testing you for. Normally between one and three samples are required.

How long does it take?

Giving one induced sputum will take between 20 minutes and an hour. You are free to go home once you have finished coughing.

Other options?

If the induced sputum is unsuccessful, your doctor may want to discuss alternative methods of obtaining a sample.

Results:

The particular tests requested by the doctor will determine when the results are available. The majority will be available within a week, but some may take up to 6 weeks. Please feel free to discuss this with your doctor or nurse at the time.

Any more questions:

If you have any more questions please contact the TB Service on 020 7288 3366.

Request for Induced Sputum (Inpatients)

Date of Referral:

Referred by:

Patients Name:

Hospital Number:

D.O.B:

Ward:

Diagnosis:

Reason for Request:

Relevant Medical History:

Essential Info:

Does the patient have severe asthma or severe COPD?	Y	N
Has the patient received oral steroid treatment for an acute exacerbation for either of the above in the previous month?	Y	N
Are the patient's resting oxygen saturations <90% on appropriate supplemental oxygen?	Y	N

Please Complete:
Baseline Observations:

SpO_2 %:	RR/min:	HR/min:
FEV_1 L:	FVC L:	FEV_1 % predicted:

Clinician to complete:

Has the procedure been fully explained to the patient?	Y	N
Is the patient willing to undergo the procedure?	Y	N
Is the patient able to comply with the procedure?	Y	N
Date given and documented in medical notes?	Y	N

Appendix 10

MANTOUX TEST - PROTOCOL

This protocol should be used in conjunction with the recommendations in the current British National Formulary, The Green Book and the description of the individual product.

Mantoux test is used as a screening test for tuberculosis infection or disease. It involves injecting Tuberculin PPD SSI intradermally and assessing the individual's sensitivity to the tuberculin protein. The greater the reaction, the more likely it is that an individual is infected or has active TB disease.	
Drug:	Tuberculin Purified Protein Derivative (Tuberculin PPD) RT 23 SSI
Active ingredient:	Tuberculin PPD is a purified protein fraction obtained from a culture of seven selected strains of *M. tuberculosis*. [22] **NOTE**: It does not contain live bacteria.[22]
Preparation:	Solution for injection presented in a 1.5ml multidose glass vial.
POM/P/GSL/▲	Prescription Only Medicine (POM). **NOTE**: Tuberculin PPD SSI do not have a UK Marketing Authorisation (previously a product licence). It is available as an unlicensed parallel import. The country of origin is Denmark. This product must only be administered according to a prescription or a written instruction (e.g. Patient Specific Direction - PSD) by a doctor.
Dose:	2TU in 0.1ml
Route:	Intradermal injection
Instructions:	1. The skin <u>only</u> needs to be cleaned if it is visibly dirty (washed with soap and water and allowed to dry thoroughly). 2. Use a specific tuberculin syringe or alternatively a 1ml graduated syringe fitted with a <u>21G</u> needle to draw up 0.1ml of Tuberculin PPD SSI from the multidose vial. 3. The 21G needle should then be removed and replace with a short bevel <u>26G</u> needle (0.45mm x 10mm) for administration.[22] The needle should be primed and any air expelled, while still sheathed. *IMPORTANT: A separate syringe and needle should be used for each individual and the needle should not be left in the vial for multiple redraws.* 4. Tuberculin PPD SSI is given as an intradermal injection on the flexor surface of the left forearm at the junction of the upper third with the lower two thirds. The skin should be stretched between the thumb and the forefinger of one hand and with the other slowly inserts the needle, with the bevel upwards, about 3mm into the superficial layers of the dermis almost parallel with the surface. The needle can usually be seen through the epidermis.[22] 5. Slowly inject the 0.1ml dose. 6. A <u>tense, blanched raised bleb</u> (typically 7mm in diameter) should appear and <u>considerable resistance</u> is felt when the fluid is being injected. 7. The bleb should disappear after approximately 10 minutes. **NOTE:** If little resistance is felt when injecting and a diffuse swelling occurs as opposed to a tense, blanched bleb, the needle is too deep. In these circumstances, the test should be repeated on the other arm using a full dose with a new syringe and needle. All sites used should be recorded. If the same arm is used, the injection site should be separated at least 4cm from the first injection site.

Additional information	• Tuberculin PPD SSI vials must be stored in its original packaging at temperatures between +2 degrees Celsius and +8 degrees Celsius and protected from light. Avoid freezing as it may cause loss of activity. • Once opened the vial must be used within 24 hours and stored in a fridge when not in use.[36] • Tuberculin PPD SSI should not be drawn up in advance of an immunisation session.	
Interpreting the result:	The results should be read 48 to 72 hours after the test, although a valid reading can usually be obtained up to 96 hours later [22]: (i) A skin test reaction is seen as a flat, uneven, slightly raised induration surrounded by an area of redness. (ii) The transverse diameter of the area of induration at the injection site is measured with a transparent flexible plastic ruler and the result recorded in millimetres. The area of erythema is irrelevant. (iii) The response to the Mantoux test is interpreted according to Table 7. **NOTE:** There is some variability in the time at which the test develops its maximum response. Few patients may have their maximum response just before or after the standard time.	
Contraindications:	Mantoux test is contraindicated in patients with [36]: (i) known anaphylactic reaction to any of the excipients – refer to Summary of Product Characteristics; or (ii) a history of severe skin (local or general) reaction to Tuberculin products – a doctor should be consulted. **NOTE**: Although anaphylaxis is rare, facilities for its management should always be available during Mantoux tuberculin skin test.	
Special precautions:	• The stoppers do not contain latex.[22, 36] • Mantoux test is considered safe during pregnancy and lactation.[36] • If an individual is acutely unwell, administration should be postponed until they are fully recovered. • Reaction to tuberculin protein may be suppressed by the following [22, 36]: (i) **Viral infections;** Viral infections in general - including those of the upper respiratory tract and in particular measles, mononucleosis (causes glandular fever), varicella and influenza, can lower the tuberculin reactivity for a few months. (ii) **Live viral vaccines;** Mantoux testing should NOT be carried out within four weeks of having received a live viral vaccine e.g. MMR, BCG, yellow fever, polio (oral) or typhoid (oral) vaccines – as live viral vaccines can suppress the tuberculin response. Where these live viral vaccines are not required urgently it should be delayed until the Mantoux has been read. (iii) **Immunosuppression.** Immunosuppression due to treatment (e.g. corticosteroid therapy) or disease (e.g. cancer, HIV infection and sarcoidosis) can cause false negative tuberculin reactions. • Mantoux tests can be undertaken at the same time as inactivated vaccines administration.[22]	
Identification and management of adverse reactions	• Local reaction/pain at injection site (common) • Fever, headache (uncommon)	→ Advise to take paracetamol according to manufacturer instructions. Usually resolve after a few days.
	• Enlargement of regional lymph nodes (uncommon) • Vesiculation, skin necrosis or urticaria (rare)	→ Usually resolve after a few days. Seek further advice if severe reaction.

	• Immediate reactions e.g. bronchospasm, urticaria, anaphylaxis, and angio-oedema (very rare) → Treat immediately with 0.5ml Adrenaline 1 in 1,000 intramuscular injection. **NOTE**: Although anaphylaxis is rare, facilities for its management should always be available during Mantoux tuberculin skin test. Patients should be monitored for at least 5 – 10 minutes for signs of anaphylactic reactions.
Record:	A record of the administration must be documented in the patient's medical notes and a copy sent to the GP. Details to be recorded include: • consent (detail of the consent to the administration – including persons that have consented on the patient's behalf and that person's relationship to the patient; must also be recorded); • dose and route of administration; • site of injection; • brand / manufacturer; • batch number; • expiry date; • date and time of administration; • name and signature of practitioner who administered the Mantoux test (signature not needed for computer based records with password protection); • any contraindication to the Mantoux test or any exclusion criteria that requires deferral of the administration; • referral arrangements including proposed date of next follow up if applicable; • advice given to patient (including side effects and caring for the site); • details of any adverse drug reaction and actions taken e.g. documentation in the patient's record and reporting to the doctor and/or MHRA if appropriate; • administration errors – follow trust's incident reporting procedure.

Table 7: Interpretation of the Mantoux test [22]

Diameter of induration	Postivity	Interpretation
Less than 6mm	Negative. No significant hypersensitivity to tuberculin protein.	Previously unvaccinated individuals may be given BCG provided there are no contraindications.
6mm or greater, but less than 15mm	Positive. Hypersensitive to tuberculin protein.	May be due to previous TB infection / BCG / exposure to non-tuberculous mycobacteria. *Note: If in the context of contact-tracing, where the patient has not previously been vaccinated with BCG, consider referring to the TB clinic for further investigation.*
15mm and above	Strongly positive. Strongly hypersensitive to tuberculin protein.	Suggests tuberculosis infection or disease. Should be referred for further investigation and supervision (which may include preventive chemotherapy).

(Mantoux) Skin Test for Tuberculosis

What is the purpose of the skin test?

This test is called the Mantoux skin test. It is used, with other tests, to check if a person has been infected with the bacteria that cause tuberculosis (TB).

Before having the skin test

If any of the following apply, you should inform the nurse before having the skin test:

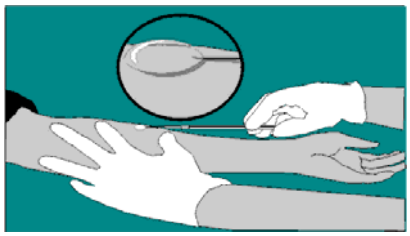
- previously had a BCG vaccination
- had a fever or was generally unwell in the last 2 to 3 days
- had a cold, flu, sore throat, measles or chickenpox infection within the last few months
- had MMR, BCG, yellow fever, polio (oral) or typhoid (oral) vaccination in the last 4 weeks
- receiving steroid therapy (such as prednisolone, dexamethasone or hydrocortisone)
- receiving chemotherapy or radiotherapy for the treatment of cancer
- HIV positive

The nurse will let you know whether it is appropriate for you to have the skin test.

What is involved?

The skin test involve the nurse or doctor injecting a substance called PPD tuberculin under the skin, usually on the inside of the left forearm (see Figure 1). You will need to come back to the TB clinic in 2 to 4 days to have the result assessed.

Figure 1 - Injection given under the skin and usually resulting in a small raised bubble on the surface.



Please record the date and time you will need to come back to the TB clinic:

Date: _____

Time: _____

The skin test should not make you feel ill. You can carry on with your normal activities.

How to care for the skin test site?

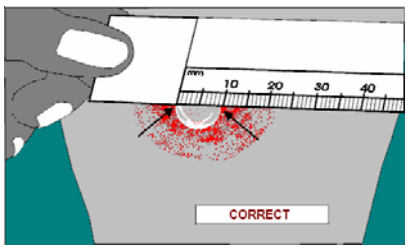
Make sure you do not put a bandage or any cream on the test spot. It is important not to scratch the spot. If the area itches, put an ice cube or cold cloth on it. You can wash and bathe as normal with soap and water. Pat the area dry with a towel.

You may notice a lump developing over a course of two to three days.

Results

When you return to the clinic in 2 to 4 days, the nurse or doctor will look at the test spot and measure any bump (skin reaction to the PPD tuberculin) that appears. The nurse will let you know if your test is negative or positive. You will be informed if any further action or tests need to be taken.

Figure 2 - The result of the skin test is measured after 2 to 4 days.



Any more questions

If you have any more questions please contact the TB Service on 020 7288 3366.

To be completed and attached to any procedural document when submitted to the appropriate committee for consideration and approval

		Yes/No	Comments
1.	**Does the procedural document affect one group less or more favourably than another on the basis of:**		
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
	• Disability - learning disabilities, physical disability, sensory impairment and mental health problems	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the procedural document likely to be negative?**	No	
5.	**If so can the impact be avoided?**	N/A	
6.	**What alternatives are there to achieving the procedural document without the impact?**	N/A	
7.	**Can we reduce the impact by taking different action?**	N/A	

If you have identified a potential discriminatory impact of this procedural document, please refer it to the Director of Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact the Director of Human Resources.

Checklist for the Review and Approval of Procedural Document

To be completed and attached to any procedural document when submitted to the relevant committee for consideration and approval.

	Title of document being reviewed:	Yes/No	Comments
1.	**Title**		
	Is the title clear and unambiguous?	Yes	
	Is it clear whether the document is a guideline, policy, protocol or standard?	Yes	
2.	**Rationale**		
	Are reasons for development of the document stated?	Yes	
3.	**Development Process**		
	Is it clear that the relevant people/groups have been involved in the development of the document?	Yes	
	Are people involved in the development?	Yes	
	Is there evidence of consultation with stakeholders and users?	Yes	
4.	**Content**		
	Is the objective of the document clear?	Yes	
	Is the target population clear and unambiguous?	Yes	
	Are the intended outcomes described?	Yes	
5.	**Evidence Base**		
	Are key references cited in full?	N/A	
	Are supporting documents referenced?	N/A	
6.	**Approval**		
	Does the document identify which committee/ group will approve it?	Yes	
7.	**Dissemination and Implementation**		
	Is there an outline/plan to identify how this will be done?	Yes	
8.	**Document Control**		
	Does the document identify where it will be held?	Yes	
9.	**Process to Monitor Compliance and Effectiveness**		
	Are there measurable standards or KPIs to support the monitoring of compliance with and effectiveness of the document?	Yes	
	Is there a plan to review or audit compliance with the document?	Yes	

10.	**Review Date**		
	Is the review date identified?	Yes	
	Is the frequency of review identified? If so is it acceptable?	Yes	
11.	**Overall Responsibility for the Document**		
	Is it clear who will be responsible for co-ordinating the dissemination, implementation and review of the document?	Yes	

Executive Sponsor Approval			
If you approve the document, please sign and date it and forward to the author. Procedural documents will not be forwarded for ratification without Executive Sponsor Approval			
Name		Date	
Signature			
Relevant Committee Approval			
The Director of Nursing and Patient Experience's signature below confirms that this procedural document was ratified by the appropriate Governance Committee.			
Name		Date	
Signature			
Responsible Committee Approval – only applies to reviewed procedural documents with minor changes			
The Committee Chair's signature below confirms that this procedural document was ratified by the responsible Committee			
Name		Date	
Name of Committee		Name & role of Committee Chair	
Signature			

Tool to Develop Monitoring Arrangements for Policies and guidelines

What key element(s) need(s) monitoring as per local approved policy or guidance?	Who will lead on this aspect of monitoring? Name the lead and what is the role of the multidisciplinary team or others if any.	What tool will be used to monitor/check/observe/Assess/ inspect/ authenticate that everything is working according to this key element from the approved policy?	How often is the need to monitor each element? How often is the need complete a report ? How often is the need to share the report?	What committee will the completed report go to?
Element to be monitored	**Lead**	**Tool**	**Frequency**	**Reporting arrangements**
Appropriate use of antibiotics according to guideline	Lead Antimicrobial Pharmacist with support from Microbiology and Pharmacy	JAC electronic prescribing report.	Refer to antibacterial audit programme.	Infection Prevention and Control Committee (IPCC)
Appropriate use of hospital isolation facilities	Infection Prevention and Control Team (IPCT)	Isolation audit tool	Quarterly and as required	Infection Prevention and Control Committee (IPCC)