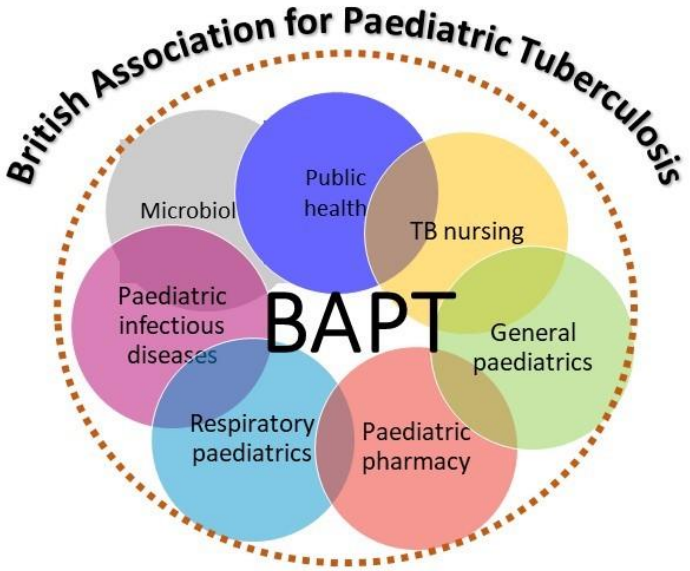

Clinical Guidance

Care of children and young people exposed to or infected with tuberculosis

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V1.4 / 14th October 2024

CONTENTS

LIST OF ABBREVIATIONS

AFB	acid fast bacilli
ART	antiretroviral therapy
ATS	American Thoracic Society
BAL	broncho-alveolar lavage
BAPT	British Association for Paediatric Tuberculosis
CAS	Clinical Advisory Service
CDC	Centres for Disease Control
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
DOT	directly observed therapy
EBUS	endobronchial ultrasound
EPTB	extrapulmonary tuberculosis
ERS	European Respiratory Society
ESR	erythrocyte sedimentation rate
EUS	oesophageal ultrasound
FNA	fine needle aspiration
GA	gastric aspirate
IGRA	interferon-gamma release assay
IRIS	immune reconstitution inflammatory syndrome
LFT	liver function test
LP	lumbar puncture
MDR	multidrug-resistant
MDT	multidisciplinary team
MRI	magnetic resonance imaging
NAAT	nucleic acid amplification test
NICE	National Institute for Health and Care Excellence
NPA	nasopharyngeal aspirate
NTM	non-tuberculous mycobacteria
PCR	polymerase chain reaction
PR	paradoxical reaction
TB	Tuberculosis
TBNA	transbronchial needle aspiration
TPT	tuberculosis preventive treatment

TST	tuberculin skin test
US	Ultrasound
VOT	video observed therapy
WHO	World Health Organization

INTRODUCTION

This document has been produced to support optimal clinical care. The guidance it contains relates both to provision of clinical services as well as individual patient management. It intends to complement other guidance, by setting standards for service provision and providing clinical guidance for scenarios not covered elsewhere. It covers a broad range of scenarios including children exposed to or infected with tuberculosis (TB). Only some exposed children become infected with Mycobacterium tuberculosis, the bacteria that causes TB. Only some infected children will develop radiological or clinical evidence of TB disease. Those infected without features of disease have historically been referred to as having 'latent TB infection'. This term is not used in this guidance as infection is not a latent process. In preference, once disease has been ruled out, the term 'TB infection' is preferred.

The guidance was written by a multidisciplinary Expert Writing Group (EWG), followed by extensive external stakeholder consultation prior to publication, to ensure that any advice given reflects best practice and up-to-date information. Whilst literature reviews were undertaken, a full systematic review of such a large area of practice was not feasible. Both primary references and citations of other guidelines are provided however where relevant. It provides a snapshot of knowledge and best practice at the current time, recognising this is a changing field. Membership of the EWG is listed in the Appendix.

SECTION 1: STANDARDS, NETWORKS & RESOURCES

Standards should be maintained by regular review of paediatric performance and outcomes at a regional level, which may be incorporated into a paediatric cohort review meeting. TB control boards or equivalent bodies may play an important role in receiving reports of performance and supporting improvement.

1.1 Age definitions for children and young people

1.1.1 All patients aged < 16 years are defined as children and are included within the scope of this guidance.

1.1.2 Care for young people aged 16-18 years should be determined according to local resources, mindful of standards set out in the *'You're Welcome'* (NHS England) quality criteria for young people friendly health services.

1.2 Access to BCG vaccination

1.2.1 Integrated Care Boards should ensure arrangements are in place for access to BCG vaccination of children of all ages as recommended by the guidance in the current version of *Green Book: Immunisation against infectious disease*(1). In some cases, this will require referral to a TB service to rule out TB infection prior to vaccination.
At the time of writing, children eligible for BCG vaccination include:

- all infants (aged under 12 months) with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater (For country information on incidence see: https://www.gov.uk/government/publications/tuberculosis-tbby-country-rates-per-100000-people)
- all infants (aged 0 to 12 months) living in areas of the UK where the annual incidence of TB is 40/100,000 or greater as per local policy
- previously unvaccinated children aged between one and five years with a parent or grandparent who was born in a country where the annual incidence of TB is 40/100,000 or greater. These children should be identified at suitable opportunities, and can normally be vaccinated without tuberculin skin testing (TST) or interferon-gamma release assay (IGRA) unless there has been a high risk of, or known, contact with infectious TB
- previously unvaccinated, TST/IGRA-negative children aged from six to under 16 years of age with a parent or grandparent who was born in a country where the

annual incidence of TB is 40/100,000 or greater. These children should be identified at suitable opportunities, TST/IGRA tested and vaccinated if negative

- previously unvaccinated TST/IGRA-negative individuals under 16 years of age who have had household or equivalent close exposure to cases of TB disease
- previously unvaccinated, TST/IGRA-negative individuals under 16 years of age who were born in or who have lived for a prolonged period (at least three months) in a country with an annual TB incidence of 40/100,000 or greater.

1.2.2 In addition, BCG is advised for babies living with or spending lots of time with somebody who has TB currently or in the past.

1.3 Staffing, facilities and estates

1.3.1 Children with suspected or confirmed TB disease should be investigated and managed by either a a specialist tertiary paediatrician (specialising in either paediatric infectious diseases or paediatric respiratory medicine), or by a general paediatrician with experience and training in paediatric TB with further advice as required from a specialist tertiary paediatrician or by Such individuals are referred to as the Named TB Consultant in the remainder of this document.

1.3.2 Paediatric TB services should not exist in isolation. Close links with adult TB services and microbiology are important and should be maintained. TB nurses working with children should have appropriate training for their role, and access and support from paediatric healthcare professionals as required, including support for child safeguarding. Training should include family-centred care, communication with children, young people and families, child safeguarding, paediatric resuscitation and emergency care, pain management including around procedures and supporting children and their parents/carers in taking medication.

1.3.3 All children with suspected TB infection or disease should have consistent and rapid access to appropriate specialist investigations and high quality multidisciplinary TB care. They should receive TB care as close to home as possible providing this does not compromise the quality of care they receive.

1.3.4 Care may need to be delivered within a regional clinical network if staff and facilities are not all available on site. There should be access as required within the network to expertise including paediatric radiology, paediatric pharmacy, play specialists, safeguarding, microbiology, histopathology, infection prevention and control and mental health support where required for patients and their parents/carers.

1.3.5 Services should participate in clinical case-based meetings such as virtual multi-disciplinary teams (MDTs) to support delivery of care closer to home whilst ensuring appropriately skilled staff manage care.

1.3.6 Arrangements should be in place to facilitate hospital admission where required, including access to a negative pressure cubicle in cases of suspected or confirmed multidrug-resistant (MDR) TB. MDR TB means disease caused by isolates resistant to at least both isoniazid and rifampicin. In all cases local infection control policy should be followed.

1.3.7 Arrangements should be in place to facilitate collection of induced sputum and other appropriate diagnostic samples on an inpatient and outpatient basis.

1.3.8 Standards should be maintained by regular review of paediatric performance and outcomes at a regional level, which may be incorporated into a paediatric cohort review meeting.

1.4 Regional Clinical Networks for Paediatric TB

1.4.1 Networks should put in place mechanisms to achieve the following objectives:

- To ensure clinical TB care for children is delivered in line with local, regional, national and international guidance, including those of BAPT (British Association for Paediatric Tuberculosis)
- To ensure adequate sampling and laboratory expertise for diagnosis of TB
- To achieve safe, effective and timely patient journeys
- To continually improve the experience for patients, carers, and their families
- To develop documentation and pathways to achieve these ends
- To review performance and outcomes of the network
- To proactively manage performance issues within the network
- To support and educate the workforce of the network
- To advocate for the needs of children and young people with regard to the development and provision of TB services
- To engage with patients and the public to advance services locally for children with TB
- To ensure safeguarding of vulnerable children
- To ensure and promote equitable access to healthcare for children and young people from underserved populations with increased exposure to TB

1.4.2 As TB disease is becoming less common in the UK, it is advised that all cases of TB disease are discussed with a specialist centre within the regional TB network. This

may include regular meetings including paediatric regional cohort review and other audits to provide service quality assurance, and identify issues requiring network-based solutions. Such meetings may provide opportunities for education and staff development.

1.4.3 In England, regional paediatric TB networks should align with areas covered by TB control areas where appropriate.

1.5 Safeguarding of children referred to and attending TB clinics

1.5.1 Consider the need to escalate safeguarding concerns if a child is repeatedly not brought to an appointment. Concern would be high in the case of a child with TB disease, and repeated non-attendance may require referral to children's social care. Concern would also be high for children and young people with TB exposure or infection who are highly susceptible to TB because of young age (especially below 2 years) or immune suppression or other medical conditions. This threshold may not be met for a well, older child without evidence of or high susceptibility to TB disease. .

1.5.2 Decisions regarding escalation and referral to children's social care are often very situation-specific and may best be made by MDT discussion. Home visits by TB nurses may also identify other safeguarding needs and issues.

1.6 Suggested *Quality Measures* for audit

1.6.1 Initial assessment

- Any child who is **unwell** with symptoms highly suggestive of possible TB, or in whom a chest X-ray is highly suggestive of TB should be clinically assessed by a paediatrician and discussed with a named TB Consultant within one working day. This may require discussion with a tertiary specialist depending on local arrangements.
- TB nurses or referring clinicians should have **access every weekday** to a consultant from the TB team to discuss a patient about whom they have concerns.
- Asymptomatic children exposed to **an index case with sputum smear positive TB** should be screened and assessed by a TB nurse **within 1 week** of identification**.** Those patients with a positive TST (Mantoux ≥ 5mm) or IGRA should be seen by a consultant from the TB team within 2-4 weeks of the test result. Children aged under 2 should be seen by a consultant from the TB team **within 2 weeks** irrespective of results of TST/IGRA.

- All children who have been exposed to an **index case with smear negative pulmonary TB** should be screened for TB infection by a TB nurse/keyworker **within 2-4 weeks**.
- Asymptomatic children with positive screening tests following **new entrant screening** should be seen by a consultant from the TB team within 4 weeks.

1.6.2 Radiological Reporting

- Diagnostic imaging in children with suspected TB disease should be formally reported by a radiologist with appropriate experience and training within seven days.

1.6.3 Patients with TB disease

All children with TB disease should be notified to the National Enhanced TB Surveillance system by their lead team within three days of diagnosis under Health Protection Regulations (https://www.gov.uk/government/publications/tuberculosis-notifying-cases).

SECTION 2: TUBERCULOSIS-EXPOSED CHILDREN

2.1 How should the newborn infant of a mother with TB in pregnancy be managed?

Most TB infection in newborns and older infants occurs following postnatal exposure. Vertical transmission of TB leading to congenital TB is rare, but can be devastating and is difficult to diagnose. Usually this occurs following a delay or failure in diagnosing or treating TB in the mother.

2.1.1 Mothers with TB infection (and without disease) who decline tuberculosis preventive treatment (TPT) in pregnancy should be re-assessed for evidence of TB disease post-partum and offered treatment postnatally.

2.2.2 Infants born to mothers who have required TB treatment during pregnancy should be thoroughly assessed at birth for clinical signs of TB disease.

2.1.3 If the mother is no longer thought to be infectious, the baby is well and the household has been screened so that there are no ongoing risks of household TB exposure, the infant can be managed normally and offered BCG vaccine.

2.1.4 If the mother has infectious pulmonary TB, the infant should be assessed (clinically and with chest X-ray). If there are no features suggestive of TB disease, isoniazid should be started as tuberculosis preventive treatment (TPT) (with

pyridoxine) and continued for six months (see Table 1). Alternatively, rifampicin can be added to the isoniazid (with pyridoxine) at 1 month of age and combined treatment be given for a further three months. If TPT is initially declined, this should be considered a safeguarding issue and explored further.

2.1.5 We do not recommend interval testing or stopping TPT prior to completing the full course. The sensitivity of TB immune screening tests (TST/IGRA) are undefined in this age group and likely to be lower than for older children. The likelihood of progression to TB disease outweighs the benefits of a shorter treatment course.

2.1.6 In the absence of confirmed infection, at the end of treatment, a TST or IGRA should be performed and, if negative, BCG vaccination given. Do not give BCG if either TST or IGRA have been positive at any stage.

2.1.7 If TPT is declined, follow-up should continue for 2 years with a low threshold for chest X-ray if concern arises. We recommend monthly face to face assessment for the first 3 months, then 3 monthly.

2.2 How should a neonate who has been in contact with a person with infectious (pulmonary or laryngeal) TB postnatally be managed?

2.1.1 If a newborn is exposed to a person with infectious pulmonary TB (e.g. the index case has not yet received at least two weeks of treatment, or remains sputum smear positive after two weeks, or the treating clinician considers them infectious), a paediatrician should assess the newborn for TB (full clinical examination and a chest X-ray).

2.2.2 If there is no evidence of TB disease in the infant, TPT should be started as in Section 2.1.4 above. If TPT is initially declined, this should be considered a safeguarding issue and explored further. Pyridoxine should also be given concurrently with isoniazid. We do not recommend interval testing or stopping TPT prior to the end of treatment at 3 months (isoniazid/rifampicin combined treatment) or 6 months (isoniazid monotherapy). The sensitivity of TB immune screening tests (TST/IGRA) are undefined in this age group and likely to be lower than for older children. The likelihood of progression to TB disease outweighs the benefits of a shorter treatment course.

2.2.3 If TPT is declined, follow-up should continue for 2 years with a low threshold for chest X-ray if concern arises. We recommend monthly face to face assessment for the first 3 months, then 3 monthly.

2.3 How should a child <2 years of age who has been in contact with a person with infectious (pulmonary or laryngeal) TB be managed?

2.3.1 Children under 2 years, who have been exposed to TB, should have a clinical assessment and chest x-ray(2–4).

2.3.2 TPT should be offered to all children without clinical or radiological evidence of TB disease. We do not recommend interval testing or stopping TPT prior to completion of the full TPT course since the sensitivity of TB immune screening tests (TST/IGRA) are undefined in this age group and likely to be lower than for older children. See Section 4 for treatment options.

2.3.3 If they have not had BCG vaccine, a TST or IGRA should be performed at the end of treatment, and BCG vaccine given if negative.

2.3.4 If TPT is declined, follow-up should continue for 2 years with a low threshold for chest x-ray if concern arises.

2.4 How should a child 2 years or older be managed who has been exposed to a person with infectious pulmonary TB?

2.4.1 Children 2 years or older who have been exposed to TB should have a symptom screen and a TB immune screening test (TST/IGRA). If either of these tests are positive, clinical assessment and chest X-ray should be performed. If these are not suggestive of TB disease, treatment for TB infection should then be offered(5).

2.4.2 If these tests are negative, an IGRA and/or TST should be performed 8 weeks after last exposure. If this is negative, they can be discharged from further follow up and BCG vaccine recommended (if not previously received).

2.4.3 For children who are first screened more than 8 weeks after the last known exposure to the TB case, a second screening test is **not** required.

2.3.4 If TPT is declined, follow-up should continue for 12 months with a low threshold for chest x-ray if concern arises.

Box 1: Interpretation of tuberculin skin test (TST) (6):

TST <5mm: negative

TST 5-10mm with history of BCG: IGRA should be performed to confirm result

TST 5-10mm with no history of BCG: positive

TST ≥10mm regardless of previous BCG: positive

2.5 How should a child 2 years or older be managed who has been exposed to a person who has sputum smear negative pulmonary TB be investigated and managed?

2.5.1 These patients should be managed in the same way as those exposed to individuals with sputum smear positive pulmonary TB.

2.6 How should a child who has been exposed to a person who has Xpert MTB/RIF positive pulmonary TB be investigated and managed?

2.6.1 These patients should be managed in the same way as those exposed to an individual with sputum smear positive pulmonary TB.

2.7 How should a child be managed who has been exposed to a person who has extrapulmonary TB be investigated and managed?

2.7.1 As for pulmonary TB, all asymptomatic children who have been exposed to an individual with extrapulmonary TB should be offered a TB screening test, and clinical and radiological assessment if positive.

2.7.2 However, in this instance, repeat TST test or IGRA after six weeks is **not needed** if the initial screening test was negative. Children <2 years do **not** require primary TPT if exposed to an individual with non-infectious extrapulmonary TB and TST/IGRA negative.

2.8 Should inflammatory markers be tested in a patient who has been exposed to TB disease?

C-reactive protein (CRP) has been shown to be significantly elevated in pulmonary TB and extrapulmonary TB in children compared to healthy controls, and CRP and ESR levels have previously been shown to correlate with *M. tuberculosis* loads in sputum. However, elevated inflammatory markers cannot help distinguish between TB and other pathologies, and some studies identified that up to a third of children with TB had normal erythrocyte sedimentation rate (ESR)(7).

2.8.1 We do not recommend routine testing of inflammatory markers in well children with normal examination and chest X-ray.

2.9 Should a chest X-ray be performed in a child who has been exposed to a person with TB disease?

In children under 15 years of age who have been exposed to an individual with TB, the World Health Organization (WHO) guidelines recommend that chest X-rays should be performed alongside screening for symptoms (cough, fever, or poor weight gain). Sensitivity for TB disease of "any abnormality" as reported on chest X-rays in children under 15 years exposed to TB was reported as 84%, and specificity 91% compared to a composite reference standard(2,6,8).

2.9.1 Chest x-rays should be performed in all children with positive TB immune tests (TST/ IGRA), reported symptoms or in vulnerable groups (immunosuppressed children and children under 2 years of age irrespective of TST/IGRA).

2.10 How should an immunocompromised child exposed to infectious tuberculosis be investigated?

Immunocompromised children may have falsely negative tests for TB infection (i.e. TST and IGRA). If infected they are at higher risk of disease and of more severe disease.

2.10.1 Such children should be discussed with a tertiary paediatric TB specialist. If there is no evidence of TB disease, a low threshold is advised for treating for TB infection, even with negative tests for TB infection.

2.11 How should a patient who has received a full course of treatment for TB infection or disease, and is now presenting again with exposure to an individual with TB disease, be investigated?

2.11.1 If a child who previously received a full course of treatment for TB infection or disease has a new exposure to TB disease, we recommend performing a chest X-ray and clinical assessment to look for evidence of TB disease.

2.11.2 If there is no evidence of TB disease, consider the strength of evidence for the diagnosis of TB disease previously, the adequacy of previous tests for infection, the susceptibility of the child (age <2 years, immunosuppressed or comorbidity raising the risk), as well as the infectiousness of the person they were newly exposed to (pulmonary vs extrapulmonary and sputum smear / PCR/ culture positivity status, cavitation, intensity of exposure and whether others have been infected).

2.11.3 **Do NOT perform a TST** in a child with a previous diagnosis of TB infection or disease, as there is a risk of a severe skin reaction.

2.11.4 To guide decisions, an IGRA may be performed if the IGRA was previously negative or no previous IGRA result is available, but interpretation will require expert advice.

2.11.5 A decision on whether or not to offer a further course of treatment for TB infection should then be taken based on the risk assessment above, and in discussion with the family and taking expert advice if necessary. A positive IGRA does not confirm a new infection. There should be a low threshold for offering TPT for persons with previous TB with a new TB exposure, as individuals with previous TB are more likely/at higher risk of having recurrent TB.

2.12 What screening tests should be performed in a patient prior to starting anti-TNFa therapy?

2.12.1 Children who require treatment with biological agents or other significantly immunosuppressive treatments, should be screened for TB infection with an IGRA and treated as necessary prior to start of treatment. This may include patients who will undergo a solid organ transplant or stem cell transplant, chemotherapy for malignancy, or high dose corticosteroid therapy(9).

2.12.2 Patients should be screened for any symptoms of TB disease (persistent cough, fevers, faltering growth etc.).

2.12.3 All children should be offered an IGRA test. If the IGRA was performed whilst on any form of immune suppression, or if results, when repeated, remain indeterminate (which occurs more frequently in children with inflammatory conditions requiring treatment with biologic agents), then an individualised risk assessment, in conjunction with discussion with an expert and the family should determine the need for treatment for TB infection.

2.12.4 High risk groups include those previously treated for TB infection or disease, and anyone exposed to known or suspected TB. If the child or their parents were born in endemic areas, or they have travelled to an endemic area in the last year, they should be considered high-risk.

2.12.5 If the patient is identified as high risk, we would also recommend screening the immediate family, as treating their TB infection may prevent future exposure to the child.

2.13 How should patients exposed to MDR-TB be managed?

2.13.1 All children exposed to MDR-TB should be discussed with a specialist paediatric TB service. Baseline assessment should include as a minimum clinical review, chest x-ray, TB immune test (TST/IGRA) and microbiological sampling if clinically indicated. It is very important to confidently exclude TB disease in MDR-TB exposed children if they are given TPT using a single drug to ensure they do not develop disease with an organism resistant to that drug.

2.13.2 Specialists in paediatric TB may wish to discuss cases with the British Thoracic Society MDR-TB clinical advice service (CAS) for further advice on management, especially if there are additional clinical issues to consider (https://mdrtb.brit-thoracic.org.uk/WebPages/Login/frmLogin.aspx).

2.13.3 Exposed children should usually be offered six months TPT with levofloxacin (ref https://iris.who.int/bitstream/handle/10665/378536/9789240096196-eng.pdf?sequence=1).

2.13.4 Whether or not TPT is given, clinical review should take place every 3 months, and chest x-ray at 3, 12 and 24 months, or if clinically indicated at any time. All MDR-TB exposed children should be followed up for 24 months irrespective of treatment received.

2.13.5 If initial TST and IGRA are negative and the child is not on treatment, repeat this at 8 weeks post last exposure, and prior to end of clinical follow up. If they remain negative, and it has not been given previously, BCG should be offered. They should then be followed up as above.

SECTION 3: DIAGNOSIS OF TB DISEASE

3.1 Laboratory tests

3.1.1 Sputum, other respiratory samples (eg nasopharyngeal aspirate), gastric washing, cerebrospinal fluid (CSF), pleural fluids, ascites, joint fluid, urine, skin or tissue (including lymph node) biopsies or aspirates, bone, bone marrow, bronchoalveolar washings, blood, stool and post-mortem specimens may all be tested for the presence of mycobacteria(10–12).

3.1.2 Mycobacteria are usually detected by light microscopy with auramine-rhodamine fluorescent staining of a smear followed by Ziehl-Neelsen staining.

3.1.3 Laboratories may also offer nucleic acid amplification tests (NAAT) for the detection of *M. tuberculosis*. This should be performed routinely in the setting of suspected TB in children aged < 16 years. NAATs are also of value for the rapid detection of *M. tuberculosis* genetic mutations associated with drug resistance. These tests are generally faster than culture but less sensitive and should not replace culture. Some NAATs may also be available for other sample types but may not be validated/verified, meaning the result should be interpreted with specialist advice. Despite some NAATs being only approved by manufacturers for sputum testing, they are regularly used for gastric aspirates, CSF, and tissue (including lymph node) biopsy, as well as stool and nasopharyngeal aspirates in the diagnosis of TB. A Cochrane review concluded that Xpert MTB/RIF Ultra™ in sputum, gastric aspirate, stool, and nasopharyngeal aspirate is an accurate method for detecting pulmonary TB and rifampicin resistance in children(13). We advocate their use in testing any relevant sample from children following advice from a paediatric TB specialist or microbiologist.

3.1.4 The use of automated liquid culture systems, plus solid media, is recommended for greater recovery of mycobacteria. The combined application of both culture-based and molecular technologies gives the most efficient approach to the laboratory diagnosis of tuberculous disease.

3.2 Pulmonary TB

3.2.1 What samples should be sent for a child with suspected pulmonary TB?

3.2.1.1 The most appropriate diagnostic samples depend on several factors including patient age and developmental stage, the severity and site(s) of

suspected disease, local infection control and laboratory facilities, and local experience in obtaining a specific sample type.

3.2.1.2 In general, most untargeted samples (e.g. gastric aspirates, induced or spontaneous sputum, nasopharyngeal aspirates) for *M. tuberculosis* have a low sensitivity (<30%), especially in children who have paucibacillary disease. Therefore, it is recommended that multiple (minimum 3) high-quality samples are sent prior to initiating therapy. Sending a variety of samples increases the overall diagnostic yield and enables more samples to be sent in a shorter time period (e.g. compared with 3 early morning samples)(14–16). The following tests should be done on each sample:

- Microscopy for acid fast bacilli (AFB) (not performed on gastric aspirate or stool samples)
- *M. tuberculosis* complex NAAT
- Mycobacterial culture
- Histology (for biopsy samples including lymph node and those obtained at bronchoscopy)

3.2.1.3 Discussion with the microbiology laboratory prior to sending samples from children is strongly advised to ensure timely appropriate processing of samples.

3.2.1.4 Older children may be able to produce a spontaneous sputum sample

3.2.1.5 Early morning gastric aspirate (GA) sampling is easy to perform and well-established for the diagnosis of pulmonary TB in young children. The highest yield is seen in young infants, symptomatic children or those with more extensive disease, as well as from the first sample collected. To collect samples, a nasogastric tube should be inserted and left in-situ. A 5-10ml gastric aspirate sample should be collected soon after waking and prior to eating or drinking. This can then be repeated on subsequent mornings until sufficient samples have been obtained. Note that environmental mycobacteria may be detected on microscopy. Therefore this should not be performed on gastric aspirate samples. Other tests above including NAAT and TB culture should be performed.

3.2.1.6 Induced sputum samples have been shown to have similar or higher sensitivity for mycobacterium isolation compared with gastric aspirate samples. Following administration of a bronchodilator, sputum is induced by nebulised saline and respiratory physiotherapy, following which a sample is obtained from the patient, either by spontaneous expectoration, or suction. This aerosol generating procedure should take place in a negative pressure room or other

approved area wearing appropriate personal protective equipment. It can be performed in infants as well as older children who are unable to expectorate sputum and has the added advantage that it can be carried out at any time throughout the day

3.2.1.7 Broncho-alveolar lavage (BAL) may be performed with or without bronchoscopic targeting. As these are more invasive procedures, they should be considered when obtaining samples by the other methods is not feasible, or if the child has a general anaesthetic planned e.g. for imaging. Bronchoscopy may also allow the sampling of intrathoracic lymphadenopathy with endobronchial ultrasound guidance (EBUS, see below), and examination by histology as well as microbiology. BAL samples have a comparable yield to other respiratory samples for *M. tuberculosis*.

3.2.2 What are the infection prevention and control issues when performing induced sputum?

Most guidelines recommend conducting induced sputum sampling within a negative pressure room. In the absence of a negative pressure room within a paediatric area, discuss with Infection Prevention and Control for any other suitable local facility. If local facilities are not available, please discuss with your tertiary infectious diseases or respiratory centre.

3.2.3 Is testing a nasopharyngeal aspirate (NPA) sample advised?

Similar to the principle behind induced sputum, NPA samples can be collected from a child unable to expectorate sputum. Whilst some studies have shown similar positivity rate for *M. tuberculosis* PCR & culture compared with induced sputum, most nasopharyngeal samples are from the upper airway and do not contain sufficient lower respiratory tract material for diagnostic culture.

3.2.4 Is testing stool samples advised?

M. tuberculosis can be detected in stool by PCR, and the ease of sample collection makes it attractive as a diagnostic sample. Culture is not possible due the presence of extensive other bacteria. Sputum is coughed overnight by younger children and swallowed so stool can be considered a sample to detect pulmonary TB, as well as for gastrointestinal TB. However, there are several limitations to

the use of stool. As with all TB diagnostics in children, low sensitivity means it cannot be used to rule out TB disease. Further, without mycobacterial culture, drug sensitivities will be unavailable and Xpert MTB/RIF on stool may be unavailable at a laboratory level. Hence the use of stool for TB diagnosis should be considered only where other diagnostics have been unsuccessful and identifying TB will make a difference in management. The yield may be greater by using a combination of any of the above techniques. For example, sending 3 of a combination of induced sputum and gastric aspirates, plus stool samples. Samples with a lower yield, such as stool and NPA, should be in addition to other samples, rather than replacing them

3.3 Intrathoracic lymph node TB

3.3.1 What are the optimal samples to send for a patient with intrathoracic lymphadenopathy on chest x-ray or CT chest imaging?

3.3.1.1 EBUS transbronchial needle aspiration (EBUS-TBNA) can be used in older children (normally over 12 years or > 35kg, limited by the larger size of the US bronchoscope in paediatric patients) to sample appropriate nodal stations, such as large centrally located lesions adjacent to major airways e.g. right paratracheal, bronchial or hilar nodes. It can be performed under sedation without general anaesthetic although in practice in young adolescents, it is tolerated better with a general anaesthetic.

3.3.1.2 Oesophageal endoscopy can also be used for trans-oesophageal sampling of certain mediastinal lymph nodes (EUS) from an even younger age. Studies have shown a diagnostic yield between 50-80%, highest in older children and it is increasingly available(17–19).

3.1.1.3 These procedures should be discussed with a tertiary paediatric centre. They are particularly important in children who do not have a known source case.

3.3.2 Is further chest imaging (ultrasound (US) or computed tomography (CT)) helpful in assessing children with possible thoracic lymph node TB?

3.3.2.1 CT chest with contrast should be performed to evaluate pulmonary changes when chest X-ray changes are inconclusive or there is diagnostic

ambiguity e.g. intrathoracic lymphadenopathy and possible malignancy. It can also be used to assess the accessibility of lymph nodes for EBUS or EUS sampling, as well as investigation of chest wall involvement.

3.3.2.2 Lung US is attractive due to its advantages e.g. no radiation exposure, quick, low cost. However, due to the paucity and contradiction of available data in paediatric pulmonary TB, no conclusions can be drawn on diagnostic accuracy. It is therefore mainly useful in evaluating cases with pleural effusions /empyema(20).

3.4 Extra-pulmonary Tuberculosis (EPTB)

3.4.1 What are the diagnostic investigations in a child with suspected peripheral lymph node TB (TB lymphadenitis)?

3.4.1.1 It is important to distinguish between non-tuberculous mycobacterial and *M. tuberculosis* lymphadenitis as they have different treatment and public health implications. TST and IGRAs may be helpful in differentiating these two conditions. Diagnosis may not be straightforward and various factors need to be taken into consideration such as systemic symptoms, risk factors for *M. tuberculosis* (e.g. TB contact, travel to an endemic country).

3.4.1.2 The diagnosis of tuberculous lymphadenitis is established by histopathology examination (caseating granulomas) along with AFB smear, *M. tuberculosis* PCR and culture of lymph node material. In cases where the histology is inconclusive and microscopy is negative for AFB, use of TB PCR may help reach a confirmatory diagnosis sooner than TB culture, as well as providing rifampicin resistance information. The sensitivity and specificity for Xpert MTB/RIF™ for TB lymphadenitis varies between 83 to 94%(21,22). None of the commercial NAAT assays are approved for use in non-respiratory specimens. However, some laboratories may validate and perform (off-label) NAAT testing on non-respiratory samples. Ensure samples are collected appropriately for both microbiology and histopathology according to local protocols.

3.4.1.3 Given the broad differential of lymphadenopathy including non-tuberculous mycobacterial (NTM) infection and malignancy, consideration should be given to the type of sampling and, where malignancy is a concern, the patient should be discussed with the local haematology/oncology service prior to biopsy. Core and open biopsy (other than entire node excision) should be avoided; fine needle aspiration or excision biopsy are preferred. Both formalin

and plain samples should be collected. Close collaboration with relevant surgical specialists may facilitate this process. Investigations for malignancy and TB should proceed simultaneously as diagnostic delay may ensue from a sequential approach. PCR testing for non-tuberculous mycobacteria may also be performed on samples. It may be particularly helpful in patients with no known TB exposure and negative TB immune screening tests (TST/IGRA).

3.4.1.4 All patients being investigated for possible extrapulmonary TB should also have a chest X-ray.

3.4.2 Fine-needle aspiration (FNA)

FNA samples have a high sensitivity and specificity for TB. Samples should be sent for cytology as well as microbiology (AFB, PCR and mycobacterial culture)(23,24).

3.4.3 Excisional biopsy

Excisional biopsy should be considered in those cases where FNA has failed or is not diagnostic, as it has the highest diagnostic yield both in terms of histopathological examination and bacterial culture. Samples should be sent for AFB, PCR and mycobacterial culture. Incisional or core biopsy should be avoided where possible as it may lead to chronic sinus/fistula. This should be discussed with surgical colleagues.

3.5 Do IGRAs have a role in diagnosing TB disease

3.5.1 TB disease is diagnosed by evaluating a patient's medical history, conducting a physical examination, chest radiography, and identifying *M. tuberculosis* using microbiologic and molecular diagnostic methods. In some instances, the clinical diagnosis of TB disease is difficult and results may be inconclusive.

3.5.2 IGRAs cannot differentiate between TB infection and TB disease. There is currently uncertainty about the role and clinical utility of IGRAs in the diagnostic workup of suspected TB disease in routine clinical practice. However, there is some evidence in certain clinical situations (e.g. patients with extrapulmonary TB, patients with sputum smear negative disease and/or those negative for *M. tuberculosis* on culture, or those in which infection with NTM is in the differential diagnosis) IGRAs could contribute supplementary information as part of the diagnostic work-up. A negative IGRA does not rule out TB disease(6).

3.6 Do multiple immune tests help with the diagnosis of TB disease

TST is sensitive but non-specific in the diagnosis of TB disease. NICE recommends considering TST in combination with IGRA with expert input if it would alter management in cases of TB disease in under 15 year olds.

3.7 What additional investigations should be performed on a child with confirmed TB to look for other foci of disease?

There is no evidence to suggest that extensive imaging in the absence of signs and symptoms is beneficial.

3.2.1 If the child has an underlying immunosuppressive condition that puts them at risk of a higher burden of disease, or are unable to be assessed accurately clinically, then further investigations such as magnetic resonance imaging (MRI) brain, lumbar puncture (LP), US abdomen and CT chest should be considered. Similarly, children with disseminated or miliary disease, congenital TB or a child under the age of 2 years with symptomatic disease may benefit from further investigation.

Dilated fundoscopy should be performed in all children with miliary or congenial TB, suspected TB meningitis, or who are at high risk of disseminated TB

3.2.2 All of these children should be discussed with a tertiary paediatric infectious diseases centre.

3.8 What investigations are recommended for the parents/caregivers of a child with suspected TB

3.8.1 It is important to screen parents / caregivers with chest X-ray, sputum and IGRA / TST for several reasons. They may be the source of the child's infection and are more likely than children to produce culture positive samples with associated sensitivity/resistance results. In addition, if an individual in the household is diagnosed with TB infection or disease, it increases the probability of TB in the child, compared to a child with no known TB exposure. Until parents / caregivers are screened negative for infectious TB disease,, they should follow appropriate infection control precautions whilst in the hospital / ward to prevent possible transmission. They may have been exposed to the same index case as the child. In some cases, the child index case may be infectious.

3.8.2 It should be explained to local services that screening of the household of a child being investigated for possible TB is an essential part of the diagnostic workup of that

child themselves. It has potential infection control implications for management of the family in hospital including potential risk to others and therefore should not be delayed until there is a confirmed diagnosis of TB disease in the child. Ideally, screening should be initiated whilst the child is on the ward to ensure this information is gained as soon as possible.

3.9 What investigations are recommended for a newborn with possible perinatal TB

Perinatal TB (TB acquired either prior to, during or immediately after birth) is rare and presents with non-specific signs and symptoms. It has a high mortality due to a combination of lack of awareness, delayed diagnosis and treatment and rapid progression to severe disease. Maternal TB bacillaemia during pregnancy may result in infection of the placenta or the maternal genital tract. Transmission to the fetus can occur by hematogenous spread from the placenta to the umbilical vein or by aspiration or ingestion of amniotic fluid contaminated by placental or genital infection. Hematogenous spread leads to the formation of one or more primary complexes in the liver or lungs, whereas the aspiration or ingestion of infected amniotic fluid results in primary complex formation in the lungs or GI tract. Exposure during delivery or in the immediate post-natal period may also result in severe illness and may not be distinguished from infection in utero.

The most common manifestations of perinatal TB are poor appetite, fever, irritability, hypoplasia, weight loss, cough, respiratory distress, hepatosplenomegaly, splenomegaly, lymphadenopathy and abdominal distention. Severe manifestations include meningitis, septicaemia, miliary TB, unremitting or recurrent pneumonia, and disseminated intravascular coagulation(25,26).

See Section 2 for guidance on the management of babies born to mothers with treated/untreated TB infection and those exposed postnatally via maternal or household contact.

3.9.1 Recommended investigations in the baby include:

- Chest X-ray
- Gastric aspirate for PCR and mycobacterial culture
- BAL/tracheal aspirate (if intubated) for AFB, PCR and mycobacterial culture
- Abdominal imaging (US/CT abdomen) to identify hepatic lesions
- Brain imaging (US/MRI) and lumbar puncture
- Dilated fundoscopy

3.9.2 Evidence suggests that infection of the placenta or the maternal genital tract is necessary for in utero transmission. Appropriate clinical testing of the maternal genital

tract and placenta should be performed if possible. Many mothers are diagnosed only after perinatal tuberculosis has been identified in the infant.

3.9.3 A mother from a TB-endemic area should have a thorough clinical assessment for TB, particularly if she has a history of infertility or IVF treatment, as this may indicate previous genital TB.

Those identified as high risk prior to fertility treatment should also be investigated for TB.

3.9.4 If a pregnant woman has TB disease during pregnancy, her newborn should be checked for perinatal TB after birth, even if asymptomatic.

3.9.5 Recommended investigations in the mother include:

- Thorough clinical assessment and targeted investigations as appropriate
- Placental PCR (if available) and mycobacterial culture and histology
- Vaginal secretions PCR and mycobacterial culture

SECTION 4: TB Treatment in children and adolescents

Note that the treatment of TB infection is different to the treatment of TB disease. Treatment of TB infection is also referred to as TPT as the aim is to prevent progression to TB disease. Children with HIV infection should be discussed urgently with a specialist in the care of children with HIV infection prior to commencing anti-TB therapy.

4.1 Treatment of TB infection

4.1.1 What first line treatment should be used to treat TB infection in children?

The UK National Institute for Health and Care Excellence (NICE), in agreement with other international guidelines, recommends either 3 months of isoniazid and rifampicin combination therapy or 6 months of isoniazid monotherapy (for situations where rifampicin is contraindicated or not tolerated) (5,27,28). Guidance from WHO, United States Centers for Disease Control (CDC), and American Academy of Pediatrics also suggest 4 months of rifampicin as an alternative(29–31). Rifapentine may also be used in combination with isoniazid, using weekly doing where adherence to medication is challenging (32,33). When choosing the therapy regimen, drug availability, possible resistance in the index case, individual risks for toxicity and drug interaction, associated costs and adherence should be considered. Refer to Table 1 for dosing details.

4.1.2 What monitoring should be carried out during TB infection treatment?

During treatment, at least monthly assessment should be carried out to assess adherence, presence of adverse reactions, and weight (in order to adjust drug dosing, especially important in younger children). This could be done by an appropriately trained TB nurse or pharmacist with medical support as needed.

Baseline bloods (including liver function tests) should be considered before the start of TPT and repeated if risk factors or concerns about hepatotoxicity (such as comorbidities or concomitant medications) are present. There is no strong evidence for repeat chest X-ray and bloods if the child remains well on treatment. Re-assessment including a repeat chest X-ray may be recommended in children who struggled to adhere or complete TB infection treatment, or who develop mew symptoms.

4.1.3 What treatment and monitoring is recommended for children and adolescents with TB infection due to MDR-TB?

All children exposed to drug-resistant TB should be discussed with an expert in paediatric TB, and if considering TPT, should be discussed at the BTS MDR-TB Forum https://mdrtb.brit-thoracic.org.uk/WebPages/Login/frmLogin.aspx

All children should be assessed as for those exposed to drug-susceptible TB (clinical assessment, chest x-ray and immune screening test (TST/IGRA)). All children who are symptomatic or have an abnormal chest x-ray should have early clinical review and microbiological samples obtained (gastric washings, induced sputum etc.) for acid fast bacilli, TB PCR and culture. There should be a low threshold to perform CT chest and/or other symptom-directed investigations to determine if there is evidence of early disease including mediastinal lymph node enlargement.

Children and adolescents who are asymptomatic with a normal chest X-ray should be seen by a paediatrician and followed up for 2 years, regardless of the results of immune testing (positive or negative TST/IGRA). They should have a clinical review every 3 months, and chest X-ray at 3, 12 and 24 months, or if clinically indicated at another time.

TPT should be considered for children and adolescents who are household contacts of MDR-TB. The decision to treat should be on an individual basis, taking into account the sensitivities of the index case, vulnerability of the individual, intensity of the exposure, risk of drug adverse events, results of immune screening (TST/IGRA), age of child, drug availability and social and other factors which may affect adherence. TPT should only be considered when TB disease has been ruled out by clinical and radiological evaluation.

Studies to date have explored the benefit of levofloxacin with or without ethambutol or

ethionamide daily for 6 months(34). Direct or video observation of treatment should be considered and offered of feasible.

4.2 Treatment of drug-susceptible TB disease.

4.2.1 What is the treatment of non-severe TB in children and adolescents?

4.2.1.1 In children older than 3 months of age with non-severe TB (see 4.2.1.2 below) and without suspicion or evidence of drug resistance, a **4-month** treatment regimen should be used for treatment. This includes two months of quadruple therapy with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E); followed by another two months of dual therapy (HR)(35). Ethambutol should be part of the initial treatment regimen of non-severe cases, as UKHSA *Tuberculosis in England 2021* reports 8.1% of isolates having isoniazid resistances (36).

4.2.1.2 Non-severe TB disease is defined as:

- Peripheral lymph node TB.
- Intrathoracic lymph node TB without airway obstruction.
- Uncomplicated TB pleural effusion.
- Paucibacillary (sputum smear-negative) non-cavitating pulmonary TB confined to one lobe of the lungs.
- Lack of miliary pattern.

4.2.1.3 Refer to table 1 for dosing.

4.2.1.4 Pyridoxine (vitamin B6) is recommended concurrently with isoniazid to prevent the development of peripheral neuropathy. It is particularly relevant for people living with HIV, malnutrition, pregnancy, adolescents and exclusively breast-fed infants.

4.2.1.5 Children being treated with the 4-month regimen should be clinically and radiologically reassessed at 4 months prior to stopping treatment

4.2.2 What is the treatment of children and adolescents who do not meet the criteria of non-severe TB disease?

Children and adolescents who do not meet the criteria for non-severe TB should receive the previously standard **6-month treatment** regimen (2HRZE/4HR), unless they have disease specifically warranting a longer course (e.g. all central nervous system (CNS) disease, and some bone disease). Neonates and infants <

3 months of age should also receive at least the standard six-month regime (2HRZE/4HR), and not the shorter 4 month regimen. Refer to Table 1 for dosing.

4.2.3 What is the treatment of TB meningitis or TB with CNS involvement?

4.2.3.1 All children and adolescents with tuberculous meningitis (TBM) or CNS disease should be managed jointly by specialist paediatric infectious diseases, neurology and (if needed) neurosurgery services.

4.2.3.2 Children and adolescents with suspected or confirmed TBM should be treated for **12 months** (2HRZE /10HR). The latest WHO guidelines published in 2022 present as an alternative option a **shorter intensive regimen for HIV negative children with TBM**, which includes 6HRZ at elevated dosages and ethionamide (15-20 mg/kg/day) as the fourth agent instead of ethambutol (4,37). Ethionamide is not currently available in the UK; protionamide can be considered equivalent at the same doses. Refer to table 1 for dosing. There are insufficient data currently to support shorter regimens in patients with HIV coinfection, or with a tuberculoma. Therapeutic drug monitoring (TDM) should be used to optimise dosing in treatment of TB meningitis.

Ethambutol has poor cerebrospinal fluid (CSF) penetration. There are other second-line TB drugs which have good CSF penetration, such as ethionamide/protionamide and fluoroquinolones (levofloxacin and moxifloxacin). Currently, there are studies in paediatric patients exploring the use of fluoroquinolone as a fourth agent(38).

4.2.3.3 Systemic corticosteroids are recommended for treatment TBM (see below). Seriously unwell children, particularly those who also have gastro-intestinal involvement may initially require intravenous corticosteroids and anti-TB treatment. All TBM patients should be managed by tertiary services.

4.2.3.4 Adjuvant treatment of hydrocephalus depends on the level of CSF obstruction and needs to have a multi-disciplinary approach. Aspirin might play a role as an adjuvant therapy in the management of paediatric TBM, especially in the presence of infarction; but currently, evidence to generalise its use is lacking(39).

4.2.4 What is the treatment of miliary (disseminated TB)?

Disseminated TB is defined as simultaneous involvement of at least two non-contiguous organ sites of the body, or infection of the blood, bone marrow or liver, or with a characteristic Xray appearance of miliary TB. Children with

suspected miliary TB should have dilated fundoscopy, MRI brain and lumbar puncture to determine if there is CNS involvement. The start of the treatment should be standard (2HRZE) for children and adolescents diagnosed with miliary TB and may require higher CNS drug dosages. The total duration of treatment is not well defined and may vary from 6 to 12 months. Children with miliary TB should be managed in conjunction with a specialist in paediatric TB(40).

4.2.5 What is the treatment of bone and joint TB?

The initiation of treatment is standard (2HRZE), but duration of treatment varies up to a total of 6-12 months (4-10 HR). NICE guidelines advise a total duration of 6 months, whereas other international guidelines suggest longer courses. For spinal TB, there needs to be an assessment for possible meningeal involvement and the risk of paradoxical reaction after starting treatment resulting in new spinal cord or nerve root compression(41–43). Children with TB bone or joint involvement should be managed in conjunction with a specialists in paediatric TB and paediatric orthopaedic or spinal surgery.

4.2.6 What is the treatment of pericardial TB?

Standard six month anti-tuberculous treatment should be given for pericardial TB (2HRZE/4HR), with corticosteroids at the start of therapy (see below). Children should be managed jointly by tertiary paediatric TB specialists and paediatric cardiologists.

4.2.7 What is the treatment of ocular TB?

Standard anti-tuberculous regimens should be given for ocular TB (2HRZE/4HR), for at least 6 months. Longer courses (9–12 months total) might be required if there is slow improvement in eye disease or if the disease is severe initially(44). The use of either systemic or topic steroids needs to be guided by the extent of the disease, evidence of structural damage and response to treatment. Close liaison with specialists in paediatric TB and ophthalmology is advised, and concurrent pulmonary or disseminated TB should be ruled out.

4.2.8 When should steroids be added to the treatment of TB disease in children and adolescents?

4.2.8.1 Corticosteroids (prednisolone or equivalent) should be used in children with the following forms of complicated TB:

- TB meningitis.
- TB pericarditis.
- Severe airway obstruction caused by external lymph node compression.

4.2.8.2 Steroid therapy is usually initiated together with the anti-tuberculous medication. Oral prednisolone (or equivalent) is recommended at a dose of 2 mg/kg daily (maximum 60 mg daily) for four weeks followed by a tapering over two weeks (total six weeks). Gastric cover with a proton pump inhibitor should be associated and dosed based on age (as per British National Formulary for Children). Longer course of steroids may be required if there is evidence of symptoms / signs related to immune reconstitution/ paradoxical reaction(45,46) or tuberculomas.

4.2.9 What is the role of therapeutic drug monitoring (TDM) in the treatment of drug-susceptible TB disease?

TDM should be considered for children with severe disease, poor response to treatment or if there is concern about alterations in drug absorption or metabolism. Refer to table 2 for targets and timing of samples.

4.2.10 What follow up is required for children and adolescents treated drug-susceptible (fully sensitive) TB disease?

4.2.10.1 Education at the start of treatment is essential for the family. This should ensure that the child, adolescent, and caregiver(s) know what to expect from TB therapy, including potential toxicity and the importance of adhering to the prolonged regimen.

4.2.10.2 Before the start of treatment, a blood test should be performed, including full blood count, liver function tests (LFT, including at least alanine transaminase, alkaline phosphatase and bilirubin) and renal function (including at least creatinine), testing for blood borne viruses (HIV and hepatitis B and C). Further blood tests are only recommended if there are abnormalities at baseline, an increased risk of toxicity because of comorbidities or concomitant mediations, or if there are symptoms suggestive of toxicity (e.g. nausea,

vomiting, jaundice etc.). If concerned about drug-induced liver injury, advice should be sought from a tertiary paediatric TB specialist. Children receiving ethambutol should be monitored at the start of treatment and monthly during follow up for visual acuity and red-green colour discrimination if they are old enough to cooperate. This is especially important if ethambutol is continued for longer than the standard 2 months (e.g. in drug-resistant disease).

4.2.10.3 In those patients with a positive sputum smear result, repeat sputum collection for smear and culture to demonstrate bacteriological conversion should be performed prior to formally ending respiratory isolation. This usually occurs at two weeks into treatment but may be later in severely unwell children/adolescents. Children who are well enough to be at home do not need to be isolated in hospital unless they have MDR TB. Children who are smear negative at baseline can return to school after two weeks of treatment. Children smear positive at baseline can return to school once smear negative. Number of days to culture positivity also gives a useful indicator of decline in infectivity on treatment, especially in initially smear-positive, cavitaory or drug-resistant disease.

4.2.10.4 Repeated PCRs are not helpful in routine monitoring of children on treatment as they may detect DNA from dead bacteria.

4.2.10.5 All children should have regular clinical follow-up, including weight monitoring. Drug dosages should be adjusted with weight gain, if needed.

4.2.10.6 In certain circumstances, confirmation of therapy is required by direct observation (47). Situations include but are not limited to disease caused by suspected or confirmed drug resistant-TB, TBM or disseminated TB, and known or predicted poor medication adherence. Observation by parents/carers does not count as DOT. In addition to the TB nursing service, DOT may be supported by primary care, schools and nurseries, pharmacies and other services. Video-observed therapy (VOT) is an acceptable and effective option for supervision of the treatment, and may be less disruptive to family life and schooling. This may be particularly useful in areas where resources for DOT are limited, or in populations where in-person DOT might be difficult. Considerations should be made regarding access to the technology for VOT and whether they are capable of using it.

4.2.11 what toxicity should I consider when managing a child or adolescent on treatment for drug-susceptible TB disease?

Table 3 summarises the most common side effects associated with the treatment of drug-susceptible TB. Further information can be found at: http://www.tbdrugmonographs.co.uk/

4.2.12 When should the diagnosis of paradoxical reaction by considered?

4.2.12.1 A paradoxical reaction (PR) in the context of TB is defined as a clinical or radiological worsening of a pre-existing TB lesion in a patient who has initiated anti-tuberculous treatment despite good therapeutic compliance and in the absence of another diagnosis(45). It results from improved inflammatory responses following initiation of treatment, or due to nutritional rehabilitation, , or anti-retroviral therapy (ART) in children living with HIV (as part of the immune reconstitution inflammatory syndrome [IRIS]).

4.2.12.2 Whereas PR has been described extensively in people living with HIV, it has also been observed in immunocompetent children. The incidence in children with TB disease without HIV infection, varies between studies at 10-14%(42,46,48).

4.2.12.3 The onset of symptoms after the start of medication varies depending on the study. Whereas it tends to occur within the first three months, a range as broad as 10-181 days has been reported.

4.2.12.4 Beyond HIV infection, younger age, absence of BCG vaccination, lower weight for age or multiple sites of disease at initial presentation have been described as potential risk factors for PR presentation(41,45).

4.2.12.5 Children experiencing a PR should be managed by a tertiary specialist. For the management of PR, clinical observation or nonsteroidal anti-inflammatory agents may be sufficient in mild cases, while short-term use of systemic corticosteroids can be considered in more severe cases. TB or HIV treatments should not be interrupted without discussion by a paediatric TB-HIV MDT.

4.3 Treatment of drug-resistant TB disease.

4.3.1 MDT discussion of drug-resistant TB disease

Children and adolescents with presumed or confirmed drug-resistant TB should be discussed with experts in paediatric TB, and in the case of those with MDR-TB, should be discussed on the BTS MDR-TB Clinical Advice Service.

4.3.2 How should mono-resistance or drug intolerance be managed?

4.3.2.1 The duration of treatment may need to be re-evaluated when drug resistance is encountered. The treatment periods in Table 4 represent a minimum duration for patients where mono-resistance is identified or suspected without CNS involvement.

4.3.2.2 In the event of an adverse drug reaction, careful assessment is required and should be discussed in an MDT setting with experts in paediatric TB. Some adverse events may represent an absolute contra-indication to continued use of an agent, whereas others may be managed symptomatically without necessitating abandonment of the use of the drug.

4.3.2.3 It is expected that liver function tests will be altered by TB treatment. There is no need to interrupt therapy unless either the ALT/AST rises to five times the upper limit of normal, the bilirubin is elevated, or the child is symptomatic. In these cases, children should be discussed with a tertiary centre.

4.3.3 How should MDR-TB be managed?

4.3.3.1 *M. tuberculosis* that is resistant to both isoniazid and rifampicin is defined as MDR-TB. If this is confirmed, or is a possibility, then experts in paediatric TB should be involved, as individualised treatment is required.

4.3.3.2 The choice of agents is selected using WHO MDR-TB guidance, based on available drug susceptibility information. Due to the complexity of treatment regimens, and co-morbidity associated with TB disease, frequent monitoring is required, and all MDR-TB patients should be discussed in a regular MDT forum. In the UK, all children exposed to MDR-TB should be discussed on the BTS MDR-TB forum. https://mdrtb.brit-thoracic.org.uk/WebPages/Login/frmLogin.aspx

4.3.3.3 Full MDR-TB dosing and monitoring advice can be found on the TB Drug monographs website https://www.tbdrugmonographs.co.uk

4.3.3.4 Treatment should be initiated in a tertiary centre with experience of managing MDR-TB and admission while establishing the regimen may be

considered. For children and adolescents with smear, PCR or culture positive sputum, admission may be recommended until they are no longer infectious. These cases will be managed on an individualised basis with regular discussion with the MDT including experts in paediatric and MDR-TB.

4.3.3.5 Consider devices to improve adherence to medication such as physical compliance aids (e.g. dossette box) alongside support from paediatric pharmacists, play specialists and specialist nurses.

4.3.3.6 All children with MDR-TB should have either DOT or VOT.

4.4 Post-TB lung health

4.4.1 What care do children and young people need following pulmonary TB?

The long-term impact and need for investigation and follow up following successful treatment of pulmonary TB in children remains unclear. Further research is needed in this area. In the absence of specific evidence to guide practice, we recommend involvement of a paediatric respiratory specialist in the care of children with ongoing symptoms or significant radiological change at the end of anti-TB therapy.

Table 1a. Individual drug dosing of first line TB drugs*

Drug and oral formulations	Dosing (range)	Dosing for TBM
Isoniazid (H) 50mg/5ml liquid (unlicensed) 50mg tablet 100mg tablet	10 (7-15) mg/kg once a day Max 300 mg/day	20 mg/kg once a day Max 400 mg/day
Rifampicin (R) 100mg/5ml suspension 150mg capsule 300mg capsule	15 (10-20) mg/kg once a day Max 450 mg/ day (if <50kg) or 600 mg/day (if >50kg)	20 mg/kg once a day Max 600 mg/day
Pyrazinamide (Z) 500mg/5ml suspension (unlicensed) 500mg tablet	35 (30-40) mg/kg once a day Max 1500 mg/day (if <50kg) or 2000 mg/day (if >50kg)	40 mg/kg once a day Max 2000 mg/day
Ethambutol (E) 400mg/5ml liquid (unlicensed) 100mg tablet 400mg tablet	20 (15-25*) mg/kg once a day *Max 1600 mg/day [Use adjusted body weight in obesity (>98th centile BMI)]	Ethambutol has poor CNS penetration; consider protionamide 15–20 mg/kg once a day Max 1000 mg/day
Pyridoxine	5-10mg once a day. Can also be given as 25-50mg once weekly if preferred to reduce pill burden. Higher doses of pyridoxine may be required in MDR-TB and in patients greater than 50kg (up to 50-100mg daily)	

*Dosing may be adjusted based upon results of therapeutic drug monitoring when used.

Table 1b. Dosing using fixed dose combination tablets for first line TB drugs

Fixed dose combination (FDC) tablets can be used to minimise pill burden in those able to swallow tablets. Dosing below optimises individual component dosing according to weight band.

Body weight (kg)	Rifinah 150/100	Voractiv	Isoniazid 50mg	Pyrazinamide 500mg	Ethambutol 400mg	Total tablets
15-20	1	1	1			3
20-25	2			1 ½	1	4 ½
25-30	1	2				3
30-35	1	2	1	½		4 ½
35-40	1	3				4
40-45	1	3				4
>45		4				4

Combination therapy by weight for TB disease treatment initiation (2 months). Rifinah 150/100: rifampicin 150mg, isoniazid 100mg. Voractiv: rifampicin 150mg, isonaizid 75mg, pyrazinamide 400mg & ethambutol 275mg

Body weight (kg)	Rifinah 150/100	Rifinah 300/150	Total tablets
10-15	1		1
15-20	1 ½		1 ½
20-25	2		2
25-30	2 ½		2 ½
30-35	3		3
35-40	1 ½	1	2 ½
>40		2	2

Combination therapy by weight for TB infection and continuation phase of disease. Rifinah 150/100: rifampicin 150mg, isoniazid 100mg. Rifinah 300/150: rifampicin 300mg, isoniazid 150mg

Table 2. Target levels and timing for sampling

Drug	Target level	Timing of samples
Isoniazid (H)	3 – 5mg/ L (Peak).	2 hours post dose. Repeat at 6 hours if suspect delayed absorption.
Rifampicin (R)	8 – 24mg/L (Peak).	2 hours post dose. Repeat at 6 hours if suspect delayed absorption.
Pyrazinamide (Z)	20 – 40mg/L (Peak).	2 hours post dose. Repeat at 6 hours if suspect delayed absorption.
Ethambutol (E)	2 – 6mg/L (Peak)	2 hours post dose. Repeat at 6 hours if suspect delayed absorption.

Further details available via Antimicrobial Reference Laboratory

https://www.nbt.nhs.uk/severn-pathology/pathology-services/antimicrobial-reference-laboratory/analytes

Table 3. Adverse events associated to the first line treatment drugs

Drug	Adverse effects
Isoniazid (H)	**Common:** Neurological: Peripheral Neuropathy. Hepatic: Transient increases in transaminases (ALT/AST). **Serious:** Dermatological: Skin reactions e.g. urticaria (uncommon). Haematological: Agranulocytosis, megaloblastic anaemia, thrombocytopaenia. Hepatic: Hepatotoxity (rare). Immunological: Drug-induced lupus (rare). Musculoskeletal: Arthralgia, rhabdomyolysis. Neurological: Peripheral neuropathy, seizure, psychosis (rare).
Rifampicin (R)	**Common:** Reddish discolouration of urine, sweat, sputum, tears, semen. Gastrointestinal: Anorexia, nausea, vomiting, heartburn. Hepatic: Transient increases in LFTs. Flu-like syndrome. **Serious:** Haematological: Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopaenia (rare, usually high-dose / intermittent therapy). Hepatic: Hepatotoxicity (rare). Renal: Nephrotoxicity (rare).
Pyrazinamide (Z)	**Common:** Hyperuricaemia. Arthralgia. Gastrointestinal: Anorexia, nausea, vomiting. Hepatic: Transient increases in LFTs. Dermatological: Rash. **Serious:** Haematological: Sideroblastic anaemia (rare), thrombocytopaenia (rare). Hepatotoxity.

Ethambutol (E)	**Common:** Endocrine: Hyperuricaemia. Gastrointestinal: Nausea, vomiting. **Serious:** Ophthalmic: Optic Neuritis (1-6%; greatest risk at doses >25mg/kg/day, or >2 months treatment), red/green colour blindness.

Table 4. Drug choices and treatment duration for patients with mono-resistant TB disease

Isolated resistance of intolerance	WHO guidance	NICE guidance (NG33 2016)	ATS/CDC/ERS guidance
Isoniazid (H)	6 months RZE plus levofloxacin (Lfx)	2 months RZE then 7 months RE (increase if severe disease)	6 months of RZELfx or Mox
Pyrazinamide (Z)	-	2 months RHE then 7 months RH	-
Ethambutol (E)	-	2 months RHZ then 4 months RH	-
Rifampicin (R) *	Treat as MDR-TB	Treat as MDR-TB - consult the BTS MDR TB CAS	2 months HEZMox then 10-16 months HE Mox

Abbreviations: Isoniazid (H), Pyrazinamide (Z), Ethambutol (E), Rifampicin (R.), Moxifloxacin (Mox), Levofloxacin (Lfx)

*Isolated rifampicin resistance should raise the suspicion of MDR-TB.

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Conflicts of Interest

The authors all confirm they have no potential conflicts of interest.

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REFERENCES

1. Public Health England. Tuberculosis: the green book, chapter 32 [Internet]. Immunisation against infectious disease. UK Health Security Agency; 2013 [cited 2022 Dec 16]. Available from: https://www.gov.uk/government/publications/tuberculosis-the-green-book-chapter-32

2. Huang CC, Tan Q, Becerra MC, Calderon R, Chiang SS, Contreras C, et al. The Contribution of Chest Radiography to the Clinical Management of Children Exposed to Tuberculosis. Am J Respir Crit Care Med. 2022 Oct 1;206(7):892–900.

3. Santos JM, Fachi MM, Beraldi-Magalhães F, Böger B, Junker AM, Domingos EL, et al. Systematic review with network meta-analysis on the treatments for latent tuberculosis infection in children and adolescents. J Infect Chemother. 2022 Dec 1;28(12):1645–53.

4. World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. p. 101.

5. Overview | Tuberculosis | Guidance | NICE [Internet]. [cited 2022 Dec 16]. Available from: https://www.nice.org.uk/guidance/ng33

6. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents [Internet]. [cited 2022 Dec 16]. Available from: https://www.who.int/publications/i/item/9789240046832

7. Kumar NP, Anuradha R, Andrade BB, Suresh N, Ganesh R, Shankar J, et al. Circulating Biomarkers of Pulmonary and Extrapulmonary Tuberculosis in Children. Clin Vaccine Immunol. 2013 May;20(5):704.

8. Vonasek B, Ness T, Takwoingi Y, Kay AW, van Wyk SS, Ouellette L, et al. Screening tests for active pulmonary tuberculosis in children. Cochrane database Syst Rev. 2021 Jun 28;6(6).

9. Parigi S, Licari A, Manti S, Marseglia GL, Tosca MA, Del Giudice MM, et al. Tuberculosis and TNF-α inhibitors in children: how to manage a fine balance. Acta Biomed. 2020;91(11-S):1–9.

10. UK SMI B 40: investigation of specimens for Mycobacterium species - GOV.UK [Internet]. [cited 2022 Dec 16]. Available from:

https://www.gov.uk/government/publications/smi-b-40-investigation-of-specimens-for-mycobacterium-species

11. Tuberculosis reference laboratories - GOV.UK [Internet]. [cited 2022 Dec 16]. Available from: https://www.gov.uk/guidance/tuberculosis-reference-laboratories#detection-of-mycobacteria

12. Wales. Position statement: Direct molecular testing for tuberculosis in England, Scotland and Wales July 2013 Direct molecular testing for tuberculosis in [Internet]. 2013 [cited 2022 Dec 16]. Available from: http://www.gov.uk/phe

13. Kay AW, Ness T, Verkuijl SE, Viney K, Brands A, Masini T, et al. Xpert MTB/RIF Ultra assay for tuberculosis disease and rifampicin resistance in children. Cochrane Database Syst Rev. 2022 Sep 6;2022(9).

14. Song R, Click ES, McCarthy KD, Heilig CM, McHembere W, Smith JP, et al. Sensitive and Feasible Specimen Collection and Testing Strategies for Diagnosing Tuberculosis in Young Children. JAMA Pediatr. 2021 May 1;175(5).

15. Click ES, Song R, Smith JP, McHembere W, Fajans M, Hariri P, et al. Performance of Xpert MTB/RIF and Mycobacterial Culture on Multiple Specimen Types for Diagnosis of Tuberculosis Disease in Young Children and Clinical Characterization According to Standardized Research Case Definitions. Pediatr Infect Dis J. 2022 Aug 1;41(8):671–7.

16. Zar HJ, Workman LJ, Prins M, Bateman LJ, Mbhele SP, Whitman CB, et al. Tuberculosis Diagnosis in Children Using Xpert Ultra on Different Respiratory Specimens. Am J Respir Crit Care Med. 2019 Dec 15;200(12):1531–8.

17. Dhooria S, Madan K, Pattabhiraman V, Sehgal IS, Mehta R, Vishwanath G, et al. A multicenter study on the utility and safety of EBUS-TBNA and EUS-B-FNA in children. Pediatr Pulmonol. 2016 Oct 1;51(10):1031–9.

18. Park M, Owles H, Williams A, Williams B, Whittaker E, Kon OM. Pediatric Endobronchial Ultrasound-Transbronchial Needle Aspiration Under Conscious Sedation for Suspected Tuberculosis in London. Pediatr Infect Dis J. 2020;39(10):E329–31.

19. Geweniger A, Janda A, Eder K, Fressle R, Kannan CV, Fahnenstich H, et al. High diagnostic yield of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in the diagnosis of adolescent pulmonary tuberculosis. BMC Infect Dis. 2021 Dec 1;21(1).

20. Fentress M, Henwood PC, Maharaj P, Mitha M, Khan D, Jackpersad R, et al. Thoracic ultrasound for TB diagnosis in adults and children. Public Heal action. 2022 Mar 10;12(1):3–6.

21. Minnies S, Reeve BWP, Rockman L, Nyawo G, Naidoo CC, Kitchin N, et al. Xpert MTB/RIF Ultra Is Highly Sensitive for the Diagnosis of Tuberculosis Lymphadenitis in a High-HIV Setting. J Clin Microbiol. 2021 Nov 18;59(12):e0131621.

22. Denkinger CM, Schumacher SG, Boehme CC, Dendukuri N, Pai M, Steingart KR. Xpert MTB/RIF assay for the diagnosis of extrapulmonary tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2014 Aug 1;44(2):435–46.

23. Ellison E, Lapuerta P, Martin SE. Fine needle aspiration diagnosis of mycobacterial lymphadenitis. Sensitivity and predictive value in the United States. Acta Cytol. 1999;43(2):153–7.

24. Lau S, Wei W, Hsu C, Engzell U. Efficacy of fine needle aspiration cytology in the diagnosis of tuberculous cervical lymphadenopathy. J Laryngol Otol. 1990;104(1):24–7.

25. Cantwell MF, Shehab ZM, Costello AM, Sands L, Green WF, Ewing EPJ, et al. Congenital Tuberculosis. https://doi.org/101056/NEJM199404143301505. 1994 Apr 14;330(15):1051–4.

26. Li C, Liu L, Tao Y. Diagnosis and treatment of congenital tuberculosis: A systematic review of 92 cases. Orphanet J Rare Dis. 2019 Jun 10;14(1):1–7.

27. Cruz AT, Ahmed A, Mandalakas AM, Starke JR. Treatment of Latent Tuberculosis Infection in Children. J Pediatric Infect Dis Soc. 2013;2(3):248–58.

28. Villarino ME, Scott NA, Weis SE. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015;169(3):247–55.

29. Lewinsohn DM, Leonard MK, Lobue PA, Cohn DL, Daley CL, Desmond E, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. Clin Infect Dis. 2017 Jan 15;64(2):111–5.

30. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 1, Prevention : tuberculosis preventive treatment. p. 41.

31. LTBI: A Guide for Primary Health Care Providers| Guides & Toolkits | Publications & Products | TB | CDC [Internet]. [cited 2022 Dec 17]. Available from: https://www.cdc.gov/tb/publications/ltbi/default.htm

32. Borisov AS, Bamrah Morris S, Njie GJ, Winston CA, Burton D, Goldberg S, et al. Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to Treat Latent Mycobacterium tuberculosis Infection. MMWR Morb Mortal Wkly Rep. 2018 Jun 29;67(25):723–6.

33. Moore DP, Baragwanath CH, Schaaf S, Marais BJ, Nuttall J, Moore DP, et al. Guideline: Childhood tuberculosis guidelines Childhood tuberculosis guidelines of the Southern African Society for Paediatric Infectious Diseases. J Epidemiol Infect. 2009;24(3).

34. Potter JL, Capstick T, Ricketts WM, Whitehead N, Kon OM. A UK-based resource to support the monitoring and safe use of anti-TB drugs and second-line treatment of multidrug-resistant TB. Thorax. 2015 Mar 1;70(3):297–8.

35. Chabala C, Turkova A, Thomason MJ, Wobudeya E, Hissar S, Mave V. Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial. Trials. 2018;19(1):237.

36. Tuberculosis in England [Internet]. 2021 [cited 2022 Dec 16]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1064395/TB_annual-report-2021.pdf

37. Solomons RS, Van Toorn R, Cresswell F V., Seddon JA. Update on the Treatment of Pediatric Tuberculous Meningitis. Pediatr Infect Dis J. 2022 Sep 1;41(9):E393–5.

38. Seddon JA, Tugume L, Solomons R, Prasad K, Bahr NC, Aarnoutse RE, et al. The current global situation for tuberculous meningitis: epidemiology, diagnostics, treatment and outcomes. Wellcome Open Res. 2019;4.

39. Rohilla R, Shafiq N, Malhotra S. Efficacy and safety of aspirin as an adjunctive therapy in tubercular meningitis: A systematic review and meta-analysis. EClinicalMedicine. 2021 Apr 1;34:100819.

40. Sharma SK, Mohan A. Miliary Tuberculosis. Schlossberg D, editor. Microbiol Spectr. 2017 Mar 10;5(2).

41. Brown CS, Smith CJ, Breen RAMC, Ormerod LP, Mittal R, Fisk M, et al. Determinants of

treatment-related paradoxical reactions during anti-tuberculosis therapy: a case control study. BMC Infect Dis. 2016 Sep 6;16(1).

42. Carazo Gallego B, Moreno-Pérez D, Nuñez Cuadros E, Mesa Fernandez A, Martin Cantero M, Obando Pacheco P, et al. Paradoxical reaction in immunocompetent children with tuberculosis. Int J Infect Dis. 2016 Oct 1;51:15–8.

43. Breen RAM, Smith CJ, Bettinson H, Dart S, Bannister B, Johnson MA, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax. 2004;59(8):704–7.

44. Kon OM, Beare N, Connell D, Damato E, Gorsuch T, Hagan G, et al. BTS clinical statement for the diagnosis and management of ocular tuberculosis. BMJ Open Respir Res. 2022 Mar 1;9(1):e001225.

45. Thampi N, Stephens D, Rea E, Kitai I. Unexplained deterioration during antituberculous therapy in children and adolescents: clinical presentation and risk factors. Pediatr Infect Dis J. 2012 Feb;31(2):129–33.

46. Meintjes G, Lawn SD, Scano F, Maartens G, French MA, Worodria W, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. Lancet Infect Dis. 2008;8(8):516–23.

47. Brett K, Severn M. Direct Observational Therapy for the Treatment of Tuberculosis: A Review of Clinical Evidence and Guidelines. Direct Obs Ther Treat Tuberc A Rev Clin Evid Guidel. 2020 Nov 24;

48. Olive C, Mouchet F, Toppet V, Haelterman E, Levy J. Paradoxical reaction during tuberculosis treatment in immunocompetent children: clinical spectrum and risk factors. Pediatr Infect Dis J. 2013 May;32(5):446–9.

49. Sterling TR, Villarino ME, Borisov AS, Shang N, Gordin F, Bliven-Sizemore E, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med. 2011 Dec 8;365(23):2155–66.

50. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, Van Der Werf MJ. Treatment of Latent Tuberculosis Infection: An Updated Network Meta-analysis. Ann Intern Med. 2017 Aug 15;167(4):248–55.

51. von Both U, Gerlach P, Ritz N, Bogyi M, Brinkmann F, Thee S. Management of childhood

and adolescent latent tuberculous infection (LTBI) in Germany, Austria and Switzerland. PLoS One. 2021 May 1;16(5).

52. Assefa Y, Assefa Y, Woldeyohannes S, Hamada Y, Getahun H. 3-month daily rifampicin and isoniazid compared to 6- or 9-month isoniazid for treating latent tuberculosis infection in children and adolescents less than 15 years of age: an updated systematic review. Eur Respir J. 2018;52(1).

53. Gaensbauer J, Aiona K, Haas M, Reves R, Young J, Belknap R. Better Completion of Pediatric Latent Tuberculosis Treatment Using 4 Months of Rifampin in a US-based Tuberculosis Clinic. Pediatr Infect Dis J. 2018 Mar 1;37(3):224–8.

54. Smieja M, Marchetti C, Cook D, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV infected persons. Cochrane database Syst Rev. 2000 Jan 25;1999(2).

55. Feiterna-Sperling C, Brinkmann F, Adamczick C, Ahrens F, Barker M, Berger C, et al. [Consensus-Based Guidelines for Diagnosis, Prevention and Treatment of Tuberculosis in Children and Adolescents - A Guideline on Behalf of the German Society for Pediatric Infectious Diseases (DGPI)]. Pneumologie. 2017 Oct 1;71(10):629–80.

56. Park JS. Issues Related to the Updated 2014 Korean Guidelines for Tuberculosis. Tuberc Respir Dis (Seoul). 2016 Jan 1;79(1):1–4.

57. Spyridis NP, Spyridis PG, Gelesme A, Sypsa V, Valianatou M, Metsou F, et al. The effectiveness of a 9-month regimen of isoniazid alone versus 3- and 4-month regimens of isoniazid plus rifampin for treatment of latent tuberculosis infection in children: results of an 11-year randomized study. Clin Infect Dis. 2007 Sep 15;45(6):715–22.

58. Bright-Thomas R, Nandwani S, Smith J, Morris JA, Ormerod LP. Effectiveness of 3 months of rifampicin and isoniazid chemoprophylaxis for the treatment of latent tuberculosis infection in children. Arch Dis Child. 2010;95(8):600–2.

59. Hsu KH. Thirty years after isoniazid. Its impact on tuberculosis in children and adolescents. JAMA. 1984 Mar 9;251(10):1283–5.

60. Diseases C. Management of Latent Tuberculosis in children up to 16 years [Internet]. 2016 [cited 2022 Dec 17]. Available from: www.health.qld.gov.au

61. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human

immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. N Engl J Med. 1997 Sep 18;337(12):801–8.

62. Moulding T, Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? [1]. Int J Tuberc Lung Dis. 2000;4(5):485–7.

63. Chapter 6: Canadian Tuberculosis Standards 7th Edition: 2014 – Dick Menzies, MD, MSc, Gonzalo G. Alvarez, MD MPH, FRCPC, Kamran Khan, MD MPH, FRCPC - Canada.ca [Internet]. [cited 2022 Dec 17]. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-18.html

64. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med. 2008 Nov 18;149(10):689–97.