Government of Western Australia
North Metropolitan Health Service
Public Health and Clinical Excellence

Guidelines for Tuberculosis Control in Western Australia

Western Australian Tuberculosis Control Program

July 2025

nmhs.health.wa.gov.au

Contents

Version control

Document Version Control			
Date	Version	Author	Notes
Sept 2019	V1.0	Medical Director of WATBCP	Initial version.
July 2025	V2.0	Medical Director of WATBCP	Major review and revision of all content. Inclusion of a section on TB in Aboriginal people. Updated section on paediatric management of TB. Change in terminology from latent TB (LTBI) to TB infection (TBI). Inclusion of fixed dose combination medication information.

This document can be made available in alternative formats on request.

Acronyms and abbreviations

TB = tuberculosis

TBI = tuberculosis infection

In this guideline the term 'TB' is used to imply active disease. Occasionally 'TB disease' is used to specifically distinguish from pre-symptomatic, non-pathological infection or TBI where the text would otherwise be ambiguous. The word 'active' is only used to distinguish between x-ray changes associated with current disease as opposed to previous, healed infection.

AFB	acid-fast bacilli
ALT	alanine aminotransferase
ART	antiretroviral therapy
BAL	Bronchoalveolar lavage
BCG	Bacille Calmette-Guerin
BCG-IRIS	Bacille Calmette-Guerin vaccine associated immune reconstitution inflammatory syndrome
CDC	Centers for Disease Control and Prevention, United States of America
CDCD	Communicable Disease Control Directorate
CDNA	Communicable Diseases Network of Australia
CLSI	Clinical and Laboratory Standards Institute
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
DoHA	Department of Health and Aged Care
DOT	directly observed therapy
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
DS-TB	drug-susceptible tuberculosis
E	ethambutol
FDC	fixed-dose combination
FSH	Fiona Stanley Hospital
H	isoniazid
HCW	health care worker
HEHS	Humanitarian Entrant Health Service
HIV	human immunodeficiency virus
IFN	interferon
IGRA	interferon gamma release immunoassays
INH	isoniazid
INR	international normalised ratio
IRIS	immune reconstitution inflammatory syndrome

IU	international unit
IV	intravenous
Lfx	levofloxacin
LTBI	latent tuberculosis infection (now termed TBI)
MAC	mycobacterium avium complex
MDR-TB	multidrug-resistant tuberculosis
Mfx	moxifloxacin
MMR	measles mumps rubella vaccine
MRL	Mycobacterium Reference Laboratory
MTB	*Mycobacterium tuberculosis*
MTBC	*Mycobacterium tuberculosis* complex
NAAT	nucleic acid amplification test
NATA	National Association of Testing Authorities
NHMRC	Australian National Health and Medical Research Council
NNDSS	National Notifiable Diseases Surveillance System
NNRTI	non-nucleoside reverse transcriptase inhibitors
NTAC	National Tuberculosis Advisory Committee
NTM	non-tuberculous mycobacterium
PCR	polymerase chain reaction
PI	protease inhibitors
PPD	purified protein derivative (tuberculin)
PPT	primary preventative therapy
PRP	personal respiratory protection
pza	pyrazinamide
QEII	Queen Elizabeth II (Medical Centre)
QFT	QuantiFERON-TB Gold test
R	rifampicin
RCT	randomised controlled trial
RIF	rifampicin
RPH	Royal Perth Hospital
SAS	special access scheme
TB	tuberculosis (implies active disease, see note above)
TBI	Tuberculosis infection (previously termed LTBI)
TB-IRIS	tuberculosis associated immune reconstitution inflammatory syndrome
TBU	tuberculosis health undertaking
TDM	therapeutic drug monitoring
TNF	tumour necrosis factor
TST	tuberculin skin test
WA	Western Australia
WACHS	Western Australia Country Health Service
WANIDD	Western Australia Notifiable Infectious Diseases Database

WATBCP	Western Australia Tuberculosis Control Program
WGS	whole genome sequencing
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide
ZN	Ziehl-Neelsen

Chapter 1: Diagnosis of tuberculosis

1.1. Diagnosis of tuberculosis – laboratory

1.1.1. Introduction

The Mycobacteriology laboratory situated at PathWest Laboratory Medicine on the Queen Elizabeth II (QEII) hospital site in Nedlands is the state's Mycobacterium Reference Laboratory (MRL) and supports the Western Australia Tuberculosis Control Program (WATBCP). The laboratory is staffed by a Medical Scientist-in-Charge, who has tertiary and managerial oversight and a part-time Senior Medical Scientist with supervisory responsibility for the daily laboratory activities. Pathologist oversight and consultancy are available as required. PathWest laboratories at some other sites (e.g. tertiary hospitals) offer a limited range of tuberculosis (TB) services but otherwise refer all samples to the MRL.

The MRL undertakes the following functions:

- provision of basic TB diagnostic services (i.e., microscopy & culture) in cooperation with other public and private laboratories
- provision of specialised TB diagnostic services, such as mycobacterial identification, drug susceptibility testing, and rapid molecular detection of drug resistance
- provision of molecular typing (genotyping) by nationally approved methods
- provision of specialised laboratory services for investigating clinically- significant non-tuberculous mycobacteria (NTM) infections
- participation in national quality assurance programs.

Training of clinical, public health and laboratory personnel to maintain expertise in mycobacterial diagnostics in both the public and private sectors.

This guideline aims to outline the laboratory methods used in the diagnosis of TB disease in Western Australia (WA), particularly those performed at the WA MRL.

1.1.2. Overview of the Mycobacteria testing process

A variety of clinical specimens are processed and cultured utilising various growth media and incubated at temperatures appropriate to the requirements of the *Mycobacterium* species under investigation. Smears are made directly or from concentrated clinical material and examined for acid-fast bacilli (AFB), with a report generated within 24 hours of specimen receipt.

Sample-direct molecular testing is carried out according to internationally recommended algorithms using nucleic acid amplification tests (NAAT) for *Mycobacterium tuberculosis* and other *M. tuberculosis* complex (MTBC) members, such as *Mycobacterium bovis*. *Mycobacterium* spp. recovered from culture are fully identified by molecular methods.

Susceptibility testing of MTBC to first-line anti-tuberculous drugs is undertaken for new and suspected relapse cases. Susceptibility testing may take 7-14 days from the time of positive culture. Second-line susceptibility testing is performed on strains of multidrug-resistant TB

(MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin (RIF), or on the request of a TB specialist. Susceptibility testing of rapidly growing NTM and clarithromycin susceptibility testing of *Mycobacterium avium* complex (MAC) are performed on isolates from significant sites and/or following consultation, as per Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2018).

Genotyping is performed on all new isolates of MTBC using whole genome sequencing (WGS). WGS and associated bioinformatic tools can assign lineages, detect changes associated with antimicrobial resistance and determine the relatedness of sequenced isolates.

1.1.3. Laboratory services

The MRL is the only WA laboratory to provide comprehensive mycobacterial services. Some general bacteriology laboratories may be able to provide direct acid-fast microscopy at short notice but do not attempt culture for mycobacteria and refer specimens to a higher-level laboratory. One large private laboratory in WA performs both acid-fast microscopy and mycobacterial culture and then refers isolates to the MRL for identification and susceptibility testing.

The National Tuberculosis Advisory Committee (NTAC) published guidelines for Mycobacteriology Laboratories in 2006. This extensive document, Guidelines for Australian Mycobacteriology Laboratories (National Tuberculosis Advisory Committee Australia, 2006), actively promotes high laboratory testing standards and addresses safety, quality and reporting issues for low- and high-volume laboratories. This includes reporting acid-fast examinations within 24 hours of specimen collection, identification of MTBC within an average of 10-14 days, and reporting drug susceptibility results within an average of 15-30 days. A physical containment level 3 (PC3) is a requirement when dealing with samples from patients with MDR-TB (Standards Australia, 2002). In 2017 this document underwent an extensive consultative review process involving the Australian MRL network and associated national bodies.

The PathWest MRL applies these NTAC and international Mycobacteriology Laboratory guidelines to analyse TB and MDR-TB samples.

After hours services

Currently, PathWest sites at QEII Medical Centre, Fiona Stanley Hospital (FSH) and Royal Perth Hospital (RPH) offer an urgent, after-hours AFB (Ziehl-Neelsen) microscopy service. This service is performed on sample-direct material to provide a provisional result and is usually only performed following consultation with the on-call Clinical Microbiologist at the respective site. The provisional report will always be followed by a formal microscopy report from the MRL performed on processed samples, i.e., samples subjected to mucolytic decontaminating agents and high-speed centrifugation or, if required, a review of the direct smear.

The larger 2 PathWest metropolitan sites (QEII & FSH) also offer an after-hours molecular TB detection service utilising the GeneXpert Ultra® system (Cepheid, USA). This system detects MTBC–specific DNA sequences and can detect some molecular markers for rifampicin resistance. Requests for this test are generally discussed with the Clinical Microbiologist and linked to requests for urgent microscopy.

1.1.4. Specimen collection

Laboratory guidelines exist that ensure optimal recovery of mycobacteria from samples. *Mycobacterium* When collecting specimens for mycobacterial microscopy and culture it is important to ensure the following:

- Obtain an adequate sample, particularly for body fluids where numbers of mycobacteria are often low
- Obtain optimal high-quality specimens, particularly relevant for sputum where specimens should contain minimal amounts or oral and nasopharyngeal material
- Prompt transport of specimens to the laboratory within 24 hours of collection

1.1.5. Microscopy

Microscopy is performed on all specimens submitted for AFB examination (with the exception of peripheral blood), and an attempt is made to quantify the number of AFB present. Microscopy is a simple and rapid procedure but is much less sensitive than culture. It has been estimated that 5,000-10,000 AFB per millilitre are required before they can be seen in Ziehl-Neelsen (ZN) stained smears. Culture techniques detect 10 to 100 viable *Mycobacterium* spp. per millilitre of sample.

Despite this lower sensitivity, microscopy remains helpful in several ways. Sputum examination can:

- provide a presumptive diagnosis of mycobacterial disease
- enable the rapid identification of the most infectious cases, pivotal for infection control regarding contagiousness
- be used to follow the progress of anti-tuberculous chemotherapy
- affect the patient's discharge back into the community.

Both fluorochrome (using ultraviolet fluorescence) and ZN methods are available. Fluorochrome smears are viewed at lower magnification (200–400x) than ZN (1000x). This lower magnification allows a much larger smear area to be scanned. Whilst the ZN method remains the reference standard for AFB microscopy, fluorochrome microscopy is the recommended screening method (GLI 2013).

1.1.6. Culture

Culture is performed using a validated commercial broth system, egg-based solid media, or a combination of these. Species such as *M. bovis, M. haemophilum, M. marinum* and *M. ulcerans* have special requirements in media and/or temperature of incubation. Communication between clinicians and the laboratory is required to ensure appropriate cultures techniques are performed. Direct culture remains the most sensitive and preferred isolation technique.

The mycobacteria growth indicator tube broth system (MGIT; Becton Dickinson) is routinely used in WA. It contains Middlebrook 7H9 medium with an oxygen-sensitive, fluorescent indicator located at the base of the culture tube. Cultures are read by exposing the tubes to long-wave ultraviolet light (typically 366 nm). Tubes with oxygen depletion emit a bright orange fluorescence.

In general, cultures from smear-positive specimens become positive at 37ºC within 1-2 weeks, while cultures from smear-negative (mycobacteria-containing) specimens become positive within 2-4 weeks. Respiratory cultures are incubated for 6 weeks before being discarded. Some cultures are retained for 12 weeks. Typically, those from non-pulmonary sites are also cultured at 30ºC.

1.1.7. Identification

The MRL identifies all isolates recovered *de novo* by the MRL or referred from another laboratory by using molecular techniques. *M. tuberculosis* and closely related species are differentiated from NTM by NAAT using a multiplex real-time polymerase chain reaction (PCR) system. Single-gene sequencing may identify further NTM isolates, with results generally available within 7 days. There are limitations associated with single-gene sequencing and a whole-genome analysis approach is currently under development. The additional resource demands limit its use to significant isolates. In this setting, a request for this requires a discussion with a Clinical Microbiologist.

All MTBC isolates and NTM isolates of clinical significance are stored at minus 80ºC indefinitely. All other isolates are stored for up to a year before discarding. Extracts of processed materials are stored according to National Association of Testing Authorities (NATA) Australia requirements.

Specimen-direct nucleic acid amplification testing

PathWest Laboratory Medicine utilises the Cepheid GeneXpert Ultra® as the primary NAAT test. This rapid platform employs 2 multi-copy targets to maximise the sensitivity of MTBC detection. It can also detect changes within a segment of the *rpoB* gene that may confer rifampicin resistance. However, as the *rpoB* gene is a single-copy target, MTBC may be detected without a result for the *rpoB* gene. PathWest Laboratory Medicine routinely operates an in-house real-time PCR test with results available within 24 hours. This test will be preferentially used where multiple PCRs are requested on a small volume sample (e.g., cerebrospinal fluid; CSF).

NAAT should not take preference over microscopy and culture for diagnosis of TB, especially if there is a limited amount of sample. NAAT is usually laboratory-initiated following consultation with a consultant Clinical Microbiologist who considers the test limitations and clinical and public health issues. All new smear-positive clinical samples, regardless of specimen origin and clinical presentation, are considered for NAAT.

MTBC smear-positive samples test NAAT positive. The performance of NAAT in smear-negative culture-positive MTBC is more variable, depending on the sample type (e.g., lymph node) and bacterial load.

PathWest follows the NTAC and Centers for Disease Control and Prevention (CDC) algorithm recommendations for NAAT testing and retesting (CDC, 2009; NTAC, 2017).

The use of NAAT for screening specimens from patients with suspected TB should be limited to:

- respiratory smear-positive specimens where the result is likely to influence clinical (treatment) and/or public health (isolation, contact investigation) decisions

- respiratory smear-negative specimens from a patient with a high probability of TB, when prompt management and public health decisions are required
- elected non-respiratory specimens (e.g. meningeal, some tissue biopsies) where a prompt management decision is necessary (recognising that such tests have not been validated or approved).

The use of NAAT is considered inappropriate in the following instances:

- when a patient is respiratory smear-negative and has a low probability of TB
- paucibacillary non-respiratory specimens (e.g. pleural fluid, ascitic fluid).

NAAT should not be used to monitor patients on anti-tuberculous treatment. Tests may remain positive for an extended period (e.g. more than 20 years is reported) regardless of whether DNA or RNA is the target for amplification.

1.1.8. Susceptibility testing

Any new MTBC isolate has susceptibilities performed to the first line antimycobacterial agents isoniazid, rifampicin, ethambutol, and pyrazinamide as a matter of urgency using the automated MGIT 960 system. Results are available within 7 to 14 days, dependent on the growth characteristics of the organism. The exception is Bacille Calmette Guerin (BCG) associated *M. bovis,* a standardised strain of known lineage. *M. tuberculosis* strains that show low-level resistance to isoniazid (at 0.1 µg/ml) are retested at a higher concentration (at 0.4 µg/ml) before classifying the strain as isoniazid resistant. *M. tuberculosis* strains showing resistance to isoniazid are routinely tested for fluoroquinolone susceptibility (at least) following NTAC guidelines. *M. bovis* is intrinsically resistant to pyrazinamide.

If an isolate demonstrates multiple resistance to first-line drugs, additional susceptibility testing is performed per the World Health Organization (WHO) guidelines for drug susceptibility testing of medicines used to treat drug-resistant TB (DR-TB) (World Health Organization [WHO], 2018). These tests are also performed using the automated MGIT 960 system.

Progress in understanding the genetic mechanisms of drug resistance in *M. tuberculosis* has resulted in the development of molecular methods for rapidly determining susceptibility profiles. Resistance to rifampicin is a valuable predictor of MDR-TB, and molecular methods have demonstrated a greater than 90% correlation with established phenotypic methods, with inter-regional variation in performance dependent on the dominant mutations. Molecular methods, including WGS, have a much poorer correlation with traditional methods for isoniazid, pyrazinamide, and ethambutol.

Some NTM (e.g., *M. marinum*) have uniform susceptibility patterns and do not require routine susceptibility testing. Clarithromycin susceptibility testing of MAC can be performed using the automated MGIT system by approved Clinical Microbiologist approved request. Rapidly growing species, such as the *M. fortuitum* and *M. chelonae / abscessus* groups, are tested by broth microdilution methods.

All susceptibility testing is performed in accordance with CLSI guidelines (2018).

1.1.9. Molecular epidemiology

WGS is the established method to genotype MTBC. WGS is routinely performed at PathWest Laboratory Medicine on all new isolates of MTBC. The sequences generated are examined

using bioinformatic tools to assign lineage, detect changes associated with antimicrobial resistance and determine relatedness of samples. WGS data can be shared between jurisdictions to permit in depth cross border contact tracing exercises. The previously preferred genotyping method, Mycobacterial Interspersed Repetitive Unit - Variable Number Tandem Repeat (MIRU-VNTR) cannot be determined using current sequencing technologies, preventing inter-compatibility of these 2 genotyping methods. WGS can be performed on historical isolates as part of cluster investigation, if required.

1.1.10. Quality control

All PathWest laboratories are NATA accredited and undergo regular audit. Molecular proficiency is assured through participation in national (Royal College of Pathologists Australasia and the Special Interest Group for Mycobacteria within the Australian Society for Microbiology) and international (QCMD - Quality Control for Molecular Diagnostics, Qnostics Ltd UK) quality assurance programs. These programs cover all aspects of tertiary mycobacteriology. PathWest laboratories offering AFB microscopy also undertake quality assurance to ensure competency. The MRL offers training and quality control materials as required.

1.1.11. Notification of results

All new AFB smear-positive and new culture-positive MTBC results are communicated by the Senior Medical Scientist to the duty Clinical Microbiologist or Registrar to contact the requesting doctor. Results associated with the WATBCP Clinic are phoned directly to the duty doctor at the Anita Clayton Centre. Infection control issues for all inpatients at public hospitals are managed by the Infection Control Officer, who will communicate the result to the requesting doctor and advise as appropriate. A consultancy service is available as required. Hard copy and electronic reports are managed via a laboratory information system.

The MRL will notify all new AFB smear-positive and new culture-positive MTBC to the Medical Director, WATBCP. This is done initially by fax and/or telephone call and then followed with a copy of the report.

1.1.12. Conclusion

The key roles of the MRL are rapid detection of *M. tuberculosis*, determination of antimicrobial susceptibility and reporting notifiable results. Microscopy and culture remain mandatory procedures in mycobacteriology. A viable culture is necessary for susceptibility testing, specific identification of MTBC to species level and for molecular epidemiological profiling. Nucleic acid amplification testing including GeneXpert® represents an important laboratory contribution to patient management and the public health control of TB but has limitations that preclude its use in direct screening of all clinical samples.

Rapid advances in laboratory technology, including those in unrelated areas of clinical and public health microbiology, make it vital for the laboratory to remain current with new platforms and technical developments. Regular strategic reviews are undertaken by the MRL to identify capability gaps that may then be integrated into strategic plans, thus ensuring correct alignment with its service delivery obligations to the WATBCP.

1.1.13. References

Centers for Disease Control and Prevention. (2009). Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *Morbidity and Mortality Weekly Review*, *58*(1), 7–10. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm

Clinical and Laboratory Standards Institute. (2018). *Laboratory detection and identification of Mycobacteria*. (2nd ed.). CLSI guideline M48. Clinical and Laboratory Standards Institute.

Clinical and Laboratory Standards Institute. (2018). *Performance Standards for susceptibility testing of Mycobacteria, Nocardia spp., and other aerobic Actinomycetes* (1st ed). CLSI supplement M62. Clinical and Laboratory Standards Institute.

Clinical and Laboratory Standards Institute. (2018). *Susceptibility testing of Mycobacteria, Norcardia spp and other aerobic Actinomycetes*. (3rd ed.). CSLI standard M24. Clinical and Laboratory Standards Institute; 2018

Global Laboratory Initiative. (2013). *Laboratory diagnosis of tuberculosis by sputum microscopy: The handbook.* (Global ed.). SA Pathology.

Global Laboratory Initiative. (2014). *Mycobacteriology laboratory manual*. (1st ed.).

National Tuberculosis Advisory Committee Australia. (2006). Guidelines for Australian mycobacteriology laboratories. *Communicable Diseases Intelligence, 30*(1), 116-128.

National Tuberculosis Advisory Committee Australia. (2017). *Revised guidelines for Australian laboratories performing mycobacteriology testing*. (Draft).

Standards Australia. (2010). *Safety in laboratories part 3: Microbiological safety and containment.* (AS:NZS 2243.3:2010).

Supply, P, Mazars, E, Lesjean, S, Vincent, V, Gicquel, B, & Locht, C. (2000). Variable human minisatellite-like regions in the *Mycobacterium tuberculosis* genome. *Molecular Microbiology*, *36*(3), 762-771. https://doi.org/10.1046/j.1365-2958.2000.01905.x

World Health Organization. (2018). *Technical manual for drug susceptibility testing of medicines used on the treatment of tuberculosis.* World Health Organization.

World Health Organization. (2018). *Technical report on critical concentrations for drug susceptibility testing of medicines in the treatment of drug-resistant tuberculosis*. (WHO/CDS/TB/2018.5). World Health Organization.

1.2. Diagnosis of tuberculosis – clinical

1.2.1. Introduction

The highest priority for TB control is the identification and cure of infectious cases of TB. Therefore, any person with symptoms suggestive of TB and epidemiological risk, including healthcare exposure - particularly cough for more than three weeks, should be investigated, initially with sputum for AFB smear.

The primary test should always be sputum microscopy and culture for AFB as mycobacterial culture remains the gold standard for the definitive diagnosis of TB. It is, however, important to stress that TB disease may be asymptomatic, and a significant percentage of pulmonary TB cases have negative-sputum smears but positive culture.

If you suspect TB

Pulmonary TB: Collect sputum for AFB culture urgently and note suspected TB on request form.

Extra-pulmonary TB: Collect sample from appropriate site, sent for AFB culture.

1.2.2. Classification of tuberculosis

TB is classified as pulmonary or extra-pulmonary.

Pulmonary TB is more common and refers to disease involving the lung parenchyma and the trachea or bronchi.

Extra-pulmonary TB is disease involving any other part of the body and includes lymph node, pleural space, skeletal, urogenital and disseminated TB.

TB of the pleura (with or without pleural effusion) or intra-thoracic lymph nodes (mediastinal and hilar), without radiological abnormalities in the lung parenchyma, are also classified as extra-pulmonary TB. This distinction is important from a public health perspective, as there is risk of community transmission with untreated pulmonary TB but not with these other forms of intrathoracic TB. The risk to community from extra-pulmonary TB outside of laryngeal disease is minimal (Hoffman & Churchyard, 2009).

A patient with both pulmonary and extra-pulmonary TB should be classified as a case of pulmonary TB.

1.2.3. Presentation of tuberculosis

TB usually has a subacute presentation. Disease can be detected in an asymptomatic patient, for example, through chest x-ray (CXR) screening or incidentally on radiology performed for other reasons.

TB is a serious disease, but it does not usually present with dramatic or acute symptoms. Most patients with TB are relatively well and still able to attend work or study.

TB can affect people of any age, but it is most common in young adults. These patients are usually well without other illness or immune compromise. While extremes of age, co-morbidity

and immunosuppression increase the risk of TB reactivation, most TB patients do not have these risk factors.

TB presentation in the elderly, like many other diseases, is characteristically non-specific and often subtle, so a high index of suspicion is required when considering the possibility of TB in this group.

The most important risk factor for TB in a person with relevant symptoms is the prior risk of exposure to TB.

In WA the main risk factor is birth or prior residence in a country with high TB incidence (>40/100 000 per year). For country-based TB incidences, refer to the WHO interactive site (https://worldhealthorg.shinyapps.io/tb_profiles/) (WHO, 2023). About half of TB cases in WA are diagnosed in people within 4 years of migration from a high TB incidence country.

Other important risk factors for TB infection include a history of contact with another person with TB, being a health care worker (HCW), being an Aboriginal Australian or being born prior to 1950.

1.2.4. Special situations

Human immunodeficiency virus infection

The clinical presentation of TB in human immunodeficiency virus (HIV)-infected persons are influenced by the degree of immunosuppression and whether TB is recently acquired or due to reactivation of latent infection.

In HIV-infected individuals with relatively preserved immunity, pulmonary TB presents in the typical adult pattern of upper lobe predominance and cavitation. In patients with severe immunosuppression, pulmonary TB can have atypical presentations such as non-cavitary lower or mid zone infiltrates (Nachega & Maartens, 2009). Disseminated TB is also more common in immunosuppressed patients.

TB progresses more rapidly in immunosuppressed patients and therefore should be diagnosed and treated with minimal delay. Investigations for pulmonary TB should begin if cough persists for more than 1 week rather than 3 weeks in HIV infected patients (Nachega & Maartens, 2009). For more detail on TB in HIV-infected persons please see section 4.5. HIV co-infection.

Anti-TNFα antagonist therapy

Patients who develop TB whilst on anti-TNFα antagonist therapy are more likely to develop extra-pulmonary and disseminated forms of TB compared to a non-immunosuppressed population (Keane et al., 2001). The non-specific presentation in this population may contribute to delays in investigation and the diagnosis of TB in patients undergoing TNFα antagonist therapy. For more detail, please see section 5.4. Testing prior to TNFα antagonist or other immunosuppressive therapy.

1.2.5. Investigations for tuberculosis

Direct microscopy by ZN or fluorochrome stain examination and AFB culture of clinical specimens (e.g. sputum, bronchoalveolar lavage fluid, fine needle aspiration, tissue biopsy,

CSF, pleural/pericardial and peritoneal cavity fluid or urine) are the first line investigations for TB.

Mycobacterial culture remains the gold standard for a definitive TB diagnosis. When microscopy or culture for AFB and NAAT are both positive, the diagnosis of TB is established.

The diagnosis is strongly supported by the histological appearance of granulomatous inflammation with caseation in tissue specimens within the appropriate clinical and epidemiological setting.

Treatment for TB is prolonged and complex and there is a potential for drug side effects. Therefore, diagnostic specimens should be collected before treatment is initiated and microbiological confirmation of the diagnosis should always be sought. Culture is also important because drug susceptibility testing of a *M. tuberculosis* isolate ensures the appropriateness of treatment.

Sputum collection for microbiological examination should be considered in all cases of TB, even when the primary presentation is extra-pulmonary TB, or the diagnosis is established by culture of an extra-pulmonary site. Sputum examination should always be done if a patient with extra-pulmonary TB has respiratory symptoms or an abnormal CXR. This is because of the potential for asymptomatic co-existent pulmonary TB and the public health implications of a positive result.

Empirical diagnosis of TB is infrequent but may occur, particularly in the setting of extra-pulmonary disease in patients with epidemiological risk and suggestive radiological or pathological features (e.g. CNS TB with suggestive CSF profile but negative culture). Decisions around treatment and investigation in this context should be guided by a specialist physician with expertise in TB management.

1.2.6. Sputum microscopy

Sputum smear microscopy is the most reliable and cost-effective method of diagnosing infectious cases of pulmonary TB. Whenever pulmonary TB is suspected in an outpatient, 3 spontaneous sputum samples should be collected and examined by microscopy for AFB. They are best collected in the early morning but patients who are very productive can have 3 specimens collected 8 hours apart within 24 hours. If induced sputum is collected (e.g. at the Anita Clayton Centre), 2 samples suffice.

While microscopy can be performed at PathWest Laboratory Medicine at all 3 major tertiary hospitals in metropolitan Perth, it is recommended, outside of emergency cases, that microscopy is performed at the MRL at PathWest Laboratory Medicine, QEII Campus. This is due to both the risk to laboratory staff but also the expertise of staff in preparation and interpretation of smears, especially in paucibacillary disease. Conversely, out-of-hours microscopy can be requested in unwell cases of suspected pulmonary TB to reduce delay to diagnosis, especially over a weekend.

1.2.7. Sputum culture

Culture of sputum for AFB is more sensitive and specific than direct smear microscopy and it is useful in detecting cases where the number of organisms is fewer and cannot be detected by direct smear microscopy.

In general, cultures from microscopy smear-positive sites become positive within 1-2 weeks, while cultures from microscopy smear-negative specimens become positive within 2-4 weeks.

Pulmonary TB can be classified based on the microscopy and culture findings as follows:

Smear-positive TB

- A patient with sputum or bronchoalveolar lavage smear positive for AFB by microscopy and GeneXpert MDR/RIF confirming *M. tuberculosis.*

OR

- A patient with at least one sputum smear positive for AFB by microscopy and sputum culture positive for *M. tuberculosis*.

Smear-negative TB

- A patient with at least three sputum smears negative for AFB by microscopy and CXR abnormalities consistent with pulmonary TB with a clinical diagnosis made a TB physician.

OR

- A patient whose initial sputum smear was negative for AFB, but whose sputum culture is positive for *M. tuberculosis.*

OR

- A patient whose sputum is smear negative for AFB, but positive on GeneXpert MDR/RIF for *M. tuberculosis.*

1.2.8. Nucleic acid amplification testing

Microscopy is rapid but an insensitive test requiring approximately 10,000 organisms/ml of sputum for it to be reliably positive. It is also not specific for *M. tuberculosis*.

Culture is the most sensitive method for diagnosis but can take 2-6 weeks to yield a positive result. Notwithstanding these limitations, microscopy and culture remain the first line tests for TB diagnosis.

NAAT is usually laboratory-initiated following consultation with a Clinical Microbiologist or on request by a TB physician. All new smear-positive respiratory tract samples, regardless of specimen origin and clinical presentation have a GeneXpert MDR/RIF performed to confirm or exclude *M. tuberculosis*. Where rifampicin resistance is identified, an XDR GeneXpert may be considered upon discussion with the MRL and TB Physician but is not routinely available outside this setting.

NAAT is very sensitive and can theoretically detect the presence of a single organism but in practice organism load and sample volume influence its sensitivity. The cut-off threshold for the sensitivity of the test is slightly lower than microscopy; ~100 - 1000 AFB/ml sputum (vs 10,000 AFB/ml for microscopy).

Automated PCR for TB DNA, and specifically GeneXpert MTB/RIF (Cepheid GeneXpert system), is routinely used in WA. It is sensitive even in single sputum samples that are smear negative (Boehme et al., 2010) and reliably detects mutations of the *rpoB* gene indicating

rifampicin resistance. GeneXpert MTB/RIF has a rapid turnaround with a result available 2 hours after sample reception. The test is available at RPH, FSH and QEII PathWest sites. It should be noted that the GeneXpert assay is currently only accredited for use on respiratory samples. Confirmatory methods (culture and susceptibility testing) are needed for both *M. tuberculosis* and rifampicin resistance detection at the time of reporting.

NAAT has not replaced smear and culture as first line tests because the smear result is important from a public health perspective and the culture result is required for a full phenotypic drug susceptibility profile.

NAAT is largely a confirmatory test i.e. confirming *M. tuberculosis* when an AFB is seen on microscopy or cultured. Occasionally NAAT is useful as a primary diagnostic test e.g. with paucibacillary small volume samples like CSF or post hoc examination of fixed histological samples. It should not take preference over microscopy and culture for TB, especially if there is a limited amount of sample. A negative NAAT test does not exclude TB, given the sensitivity is dependent on load of organisms present and may result in false-negative results in paucibacillary disease. Many platforms are also not validated for use on non-respiratory samples and their results should be interpreted cautiously.

NAAT should not be used to monitor patients on anti-TB treatment. Tests may remain positive for an extended period of time regardless of whether DNA or RNA is the target for amplification due to the presence of residual genetic material in non-viable organisms. Costs, relative lack of sensitivity, plus current concerns regarding technical issues that affect reliability and reproducibility preclude their use as a screening test. Microscopy and culture remain a mandatory component of mycobacterial investigations.

For more detail on laboratory methods of diagnosing TB please see section 1.1. Diagnosis of Tuberculosis - Laboratory.

1.2.9. Chest radiograph or x-ray

Diagnosis of active pulmonary TB by means of CXR alone is unreliable, because it lacks specificity. Abnormalities seen on a CXR, even when characteristic of pulmonary TB, may be caused by a variety of other conditions. In addition, CXR changes do not necessarily distinguish between active and inactive TB. Conversely, if there are characteristic CXR changes of TB in a patient considered at high risk for TB, then active TB should be assumed until an alternative diagnosis is proven and appropriate precautions taken.

CXR is a sensitive test for pulmonary TB. This means that false negatives are rare and a normal CXR nearly always rules out pulmonary TB. An important exception to this includes early miliary TB, which may only be reliably seen on chest CT scan. A CXR should be requested for all patients suspected of having TB whether the primary site is pulmonary or non-pulmonary as the two forms of the disease may coexist.

CXR appearances that are suggestive of pulmonary TB are:

- Patchy, mottling, miliary, nodular and/or linear shadows situated mainly in the apical/posterior segments of the upper, or the superior segment of the lower lobes.
- The above changes less commonly in the middle/or lingular lobes. Although changes are more common in the upper zones, approximately one third of pulmonary TB have lower zone changes and occasionally TB is only in the lower lobes.

- Bilateral distribution in the upper zones, though this is nearly always asymmetrical (by contrast with sarcoidosis or silicosis).
- 'Soft' opacities that fluctuate over time suggest active disease.
- Cavities are usually thin-walled and if present are suggestive of active and infectious disease.

The decision to start on anti-tuberculous treatment should not be based solely on an abnormal CXR and all efforts should be made to obtain a microbiological diagnosis.

1.2.10. Computed tomography (CT) scan

Computed tomography (CT) scan of the thorax is not performed routinely in the assessment of TB, except when investigating the possibility of other differential diagnoses. It rarely adds any information beyond what is obtained on CXR. The main exceptions to this are early miliary TB and TB exclusively involving mediastinal lymph nodes. It may be of use in guiding investigations (i.e. bronchoscopy with bronchoalveolar lavage) or suggesting an alternate diagnosis.

1.2.11. Tuberculin skin test (TST)

The TST has been used in the management of TB since the 19th century. It is an indirect test that indicates sensitisation or the cellular immune response to mycobacterial antigens and cannot distinguish between individuals with TB infection (TBI, previously termed LTBI), TB disease or past TB infection.

A positive TST result suggests TB infection. It does not, however, indicate the presence or absence of TB disease. A positive TST may not indicate disease and a negative result will not rule out disease. The result of the TST must be interpreted with the patient's history, clinical presentation and reason for testing in mind. Generally, TST is not indicated as a diagnostic test for TB and should not be performed to diagnose or exclude active TB disease except in rare circumstances.

The TST can be used as supportive evidence of the diagnosis of TB in cases where obtaining samples for microbiological examination is difficult e.g. small children (see section 4.2. Paediatrics) or paucibacillary extra-pulmonary TB (e.g. tuberculous meningitis). If TB disease is suspected, then additional microbiological testing is needed to confirm a diagnosis.

1.2.12. Interferon gamma release immunoassays (IGRAs)

Interferon Gamma Release Immunoassays (IGRAs) are blood tests that detect host cell mediated immune responses to TB specific antigens secreted by *M. tuberculosis*. The QuantiFERON-TB Gold test (QFT) is used in WA. The antigens tested are present in all *M. tuberculosis* but absent from BCG vaccine strains and most NTM, with the exception of *M. kansasii*, *M. szulgai* and *M. marinum* (Mazurek et al., 2010).

Like the TST, a positive QFT may not necessarily indicate TB disease, and a negative result will not rule out TB disease. The results must be interpreted with the patient's history, clinical presentation and reason for testing in mind. The QFT test should not replace the standard diagnostic investigations of TB disease.

Generally, IGRAs are not indicated as a diagnostic test for TB disease. If TB disease is suspected, then additional testing is needed to confirm a diagnosis of TB. An IGRA should not be performed to diagnose or exclude active TB disease.

Further discussion on tuberculin skin testing and IGRAs is discussed in section 3.1. TB Infection - Diagnosis.

1.2.13. Samples for microbiological diagnosis

Every effort should be made to obtain appropriate pathological specimens for microbiological confirmation of TB disease and to obtain a *M. tuberculosis* isolate for drug susceptibility testing. Specimens need to be representative of the site of infection, they should be collected aseptically (if possible), be stored appropriately for the shortest possible time; and be transported to the laboratory as soon as able. Table 1 provides examples of common specimens for mycobacterial investigation according to disease site.

Table 1 Common clinical specimens for mycobacterial testing

Disease Site	Specimen
Pulmonary TB	• Sputum • Induced sputum • Bronchoalveolar lavage • Gastric aspirate • Transbronchial biopsy • Percutaneous lung biopsy • Open lung biopsy
Pleural TB	• Pleural fluid aspirate and/or biopsy
Lymph node TB	• Fine needle aspiration or core biopsy • Open lymph node biopsy
Tuberculous meningitis	• CSF
Miliary TB	• Liver or bone marrow biopsy
Gastrointestinal TB	• Peritoneal fluid aspirate or biopsy • Colonoscopy with biopsies • Stool specimen
Bone and joint TB	• Joint aspirate +/- synovial biopsy • Bone marrow aspirate
Uro-genital tract	• Early morning urine (sterile pyuria suggests the possibility of TB) • Renal biopsy • Bladder biopsy

Disease Site	Specimen
	• Prostate biopsy
Female Genital tract	• Hysteroscopy and endometrial biopsy • Laparoscopy with biopsies, washings

The common clinical specimens used to diagnose TB are:

Sputum

Three sputum samples should be collected on 3 consecutive days and early morning samples are preferable. Patients should be advised to collect sputum following deep inspiration and coughing as per this document. The specimens should not be saliva. Sputum samples expectorated in a health facility should be collected in a well-ventilated space, e.g. outdoors or in a negative pressure isolation room, but NOT in the bathroom or toilet area. This does not apply if the patient collects the sputum sample at home. Samples should be kept cool, for example in a refrigerator during the 3 days of collection, and then in an esky with an ice brick when transported to the laboratory on the third day.

Induced sputum or bronchoscopy

Induced sputum collection or bronchoscopy may be indicated when the patient is unable to obtain a spontaneous sputum sample. These 2 procedures have equal sensitivity (Conde et al, 2000 and McWilliams et al, 2002) and the choice between them is determined by the availability of the test, the risk of complications, and convenience for the patient.

Induced sputum collection is nearly always preferred because it is safer and more tolerable for the patient. It does not require a hospital admission, so it is less expensive and provides less risk of occupational exposure to bronchoscopy staff.

Induced sputum collection must be performed in a room with negative pressure air conditioning. It can be collected at any time of the day. Collection of induced sputum is performed on site at the WATBCP located at the Anita Clayton Centre. Induced sputum collection should only be performed by a suitably trained physiotherapist or registered nurse, and in accordance with approved standard operating procedures (refer to WATBCP if required).

An audit of the first 2 years of induced sputum collection at the WATBCP demonstrated a rapid turnaround time and high yield of adequate specimens, and diagnosis of TB with negligible serious adverse events. The audit also demonstrated that virtually all positive results were obtained from the first 2 sputum samples, therefore only 2 induced samples are collected (by contrast to 3 spontaneous samples). All patients referred for induced sputum should be asked to attempt collection of a spontaneous sample first, before undergoing sputum induction, even if they insist, they are unable to expectorate samples.

Bronchoscopy must be performed with appropriate personal protective equipment and isolation precautions to prevent transmission of TB, both within the hospital and the bronchoscopy suite.

Fine needle aspiration biopsy

Fine needle aspiration biopsy is a quick and safe diagnostic tool in suspected extra- pulmonary TB. It is especially useful in the investigation of suspected lymph node TB. Request forms should explicitly ask for both cytology and AFB culture.

Excisional biopsies of lymph nodes may also be carried out to confirm TB diagnosis. Lymph node TB is typically paucibacillary and fine needle aspiration can therefore give a falsely negative result. An excised lymph node improves sensitivity through providing substantially more material for culture. It is important to ensure that at least half of the sample is sent for culture, and that the specimen is not only placed in formalin.

Fasting gastric aspirates

Gastric aspiration aims to collect swallowed sputum in gastric contents in order to culture for *M. tuberculosis*. Smear microscopy of gastric aspirates have a low yield (<15%) but the highest yield specimens are obtained first thing in the morning (Schaaf & Reuter, 2009). Gastric aspiration is usually reserved for young children who are unable or unwilling to expectorate sputum. A gastric aspirate should be obtained on each of 3 consecutive mornings and sent for smear AFB microscopy and culture.

1.2.14. Pleural and other serosal membrane tuberculosis

TB affecting serosal surfaces typically presents with an effusion, most commonly pleural, but can also be pericardial and peritoneal. Aspirated fluid can be sent for culture but is usually paucibacillary and therefore has a low yield and can be falsely negative. Substantially better yield is obtained from culture of a biopsy of the serosal membrane e.g. an Abram's needle biopsy or thoracoscopic biopsy of the pleura. This should always be considered when investigating an effusion for possible TB. A raised pleural fluid adenosine deaminase (ADA) and a high lymphocyte count (e.g. >90% of leucocytes) are also strong indicators of pleural TB, and these tests are routinely available if requested from the laboratory.

1.2.15. Central nervous system tuberculosis

TB involving the central nervous system (CNS) and especially tuberculous meningitis, can be rapidly progressive and a catastrophic illness. Therefore, if CNS TB is suspected and no alternative diagnosis explains the patient's presentation, then TB treatment should be started immediately after specimen collection and without waiting for results to confirm the diagnosis. Microbiological confirmation of TB from a CSF sample is often difficult because of the small CSF sample and the paucibacillary nature of this disease. The diagnosis can also be supported by the presence of a high CSF lymphocyte count, high CSF protein and positive NAAT for *M. tuberculosis* DNA.

1.2.16. References

Anderson, C., Inhaber, N., & Menzies, D. (1995). Comparison of sputum induction with fiber-optic bronchoscopy in the diagnosis of tuberculosis. *American journal of respiratory and critical care medicine, 152*(5 Pt 1), 1570–1574. https://doi.org/10.1164/ajrccm.152.5.7582296

Boehme, C. C., Nabeta, P., Hillemann, D., Nicol, M. P., Shenai, S., Krapp, F., Allen, J., Tahirli, R., Blakemore, R., Rustomjee, R., Milovic, A., Jones, M., O'Brien, S. M., Persing, D. H., Ruesch-Gerdes, S., Gotuzzo, E., Rodrigues, C., Alland, D., & Perkins, M. D. (2010). Rapid molecular detection of tuberculosis and rifampin resistance. *The New England journal of medicine, 363*(11), 1005–1015. https://doi.org/10.1056/NEJMoa0907847

Cotton, M., Graham, S., Jaspan, H., Hesseling, A., Marais, B., Mehtar, S., Rabie, H., Schaaf, H. S., & Zar, H. (2010). *Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach.* International Union against TB and lung disease.

Cruz, A., & Starke, J., (2014). Tuberculosis. In Cherry, J., Harrison, G. Kaplan, S., Hotez, P. & Steinbach, W., *Feigin and Cherry's Textbook of Pediatric Infectious Diseases* (7th ed., pp. 96, 957-988). Elsevier/Saunders.

Diallo, T., Adjobimey, M., Ruslami, R., Trajman, A., Sow, O., Obeng Baah, J., Marks, G. B., Long, R., Elwood, K., Zielinski, D., Gninafon, M., Wulandari, D. A., Apriani, L., Valiquette, C., Fregonese, F., Hornby, K., Li, P. Z., Hill, P. C., Schwartzman, K., Benedetti, A., … Menzies, D. (2018). Safety and side effects of Rifampin versus isoniazid in children. *The New England journal of medicine, 379*(5), 454–463. https://doi.org/10.1056/NEJMoa1714284

Ena, J., & Valls, V. (2005). Short-course therapy with rifampicin plus isoniazid, compared with standard therapy with isonazid, for latent tuberculosis infection: a meta-analysis. *Clinical Infectious Diseases, 40*(1), 670-676. https://doi.org/10.1086/427802

Fox, G. J., Dobler, C. C, Marais, B. J, & Denholm, J. T. (2017). Preventive therapy for latent tuberculosis infection – the promise and the challenges. *International Journal of Infectious Diseases, 56*, 68-76. https://doi.org/10.1016/j.ijid.2016.11.006

Graham S. M. (2011). Treatment of paediatric TB: revised WHO guidelines. *Paediatric respiratory reviews, 12*(1), 22–26. https://doi.org/10.1016/j.prrv.2010.09.005

Graham, S., Marais, B., & Gie, R. (2009). Clinical features and index of suspicion of tuberculosis in children. In A. Schaaf, & H. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 154-163). Elservier.

Graham, S., Marais, B., & Gie, R. (2009). Clinical features and index of suspicion of tuberculosis in children. In A. Schaaf, & H. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 154-163). Elservier.

Hesseling, A. C., Rabie, H., Marais, B. J., Manders, M., Lips, M., Schaaf, H. S., Gie, R. P., Cotton, M. F., van Helden, P. D., Warren, R. M., & Beyers, N. (2006). Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clinical Infectious Diseases, 42*(4), 548–558. https://doi.org/10.1086/499953

International Union Against Tuberculosis and Lung Disease (2010). *Desk guide for the diagnosis and management of TB in children*. https://www.tbonline.info/media/uploads/documents/desk-guide_for_diagnosis_and_management_of_tb_in_children_%282010%29.pdf

Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England journal of medicine, 345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110

Marais, B. J., Gie, R. P., Hesseling, A. C., Schaaf, H. S., Lombard, C., Enarson, D. A., & Beyers, N. (2006). A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics, 118*(5), e1350–e1359. https://doi.org/10.1542/peds.2006-0519

Marais, B. J., Gie, R. P., Schaaf, H. S., Hesseling, A. C., Obihara, C. C., Starke, J. J., Enarson, D. A., Donald, P. R., & Beyers, N. (2004). The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *The international journal of tuberculosis and lung disease, 8*(4), 392–402. https://pubmed.ncbi.nlm.nih.gov/15141729/

Marais, B. J., Wright, C. A., Schaaf, H. S., Gie, R. P., Hesseling, A. C., Enarson, D. A., & Beyers, N. (2006). Tuberculous lymphadenitis as a cause of persistent cervical lymphadenopathy in children from a tuberculosis-

endemic area. *The Pediatric Infectious Disease Journal, 25*(2), 142–146. https://doi.org/10.1097/01.inf.0000199259.04970.d1

Marais, B., & Donald, P. (2009). The natural history of tuberculosis infection and disease in children. In H. Schaaf, & A. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 133-145). Elsevier.

Mazurek, G. H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., Castro, K., IGRA Expert Committee, & Centers for Disease Control and Prevention (2010). Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports, 59*(RR-5), 1–25.

McWilliams, T., Wells, A. U., Harrison, A. C., Lindstrom, S., Cameron, R. J., & Foskin, E. (2002). Induced sputum and bronchoscopy in the diagnosis of pulmonary tuberculosis. *Thorax, 57*(12), 1010–1014. https://doi.org/10.1136/thorax.57.12.1010

Nachega, J., & Maartens, G. (2009). Clinical aspects of tuberculosis in HIV-infected adults. In H. Schaaf, & A. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 524-531). Elsevier.

Nahid, P., Dorman, S. E., Alipanah, N., Barry, P. M., Brozek, J. L., Cattamanchi, A., Chaisson, L. H., Chaisson, R. E., Daley, C. L., Grzemska, M., Higashi, J. M., Ho, C. S., Hopewell, P. C., Keshavjee, S. A., Lienhardt, C., Menzies, R., Merrifield, C., Narita, M., O'Brien, R., Peloquin, C. A., … Vernon, A. (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases*, *63*(7), e147–e195. https://doi.org/10.1093/cid/ciw376

National Institute for Health and Clinical Excellence. (2011). *Tuberculosis: Clinical diagnosis and management of tuberculosis and measures for its prevention and control.* (NICE Clinical Guidelines, No. 117). https://pubmed.ncbi.nlm.nih.gov/22720337/

Schaaf, H., & Reuter, H. (2009). Practical approaches to ordering diagnostic tests. In H. Schaaf, & A. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 216-226). Elsevier.

Starke, J. R. (2004). Tuberculosis in Children. *Seminars in Respiratory Critical Care Medicine*, *25*(3), 353-364. https://doi.org/10.1055/s-2004-829507

World Health Organization. (2014). *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. World Health Organization. https://www.who.int/publications/i/item/9789241548748

World Health Organization. (2016). *WHO treatment guidelines for drug-resistant tuberculosis: 2016 update*. World Health Organization. http://apps.who.int/iris/bitstream/10665/250125/1/9789241549639-eng.pdf

World Health Organization. (2017). *Guidelines for the treatment of drug-susceptible tuberculosis and patient care, 2017 update*. World Health Organization. https://www.who.int/publications/i/item/9789241550000

Chapter 2: Tuberculosis treatment

2.1. Medical treatment of drug-susceptible tuberculosis

2.1.1. Introduction

This chapter describes the drug treatment for adults with TB that is susceptible to first-line anti-TB drugs. Treatment of DR-TB is described in section 2.2. Medical treatment of drug-resistant tuberculosis. Treatment of TBI is described separately in section 3.2. Tuberculosis infection - treatment. The management of TB in children, including drug treatment, is described in section 4.2. Paediatrics. There are also separate sections on the management of TB in specific circumstances such as in prisoners and detainees (section 4.3.), and in pregnancy (section 4.4.).

Case management refers to the nurse-led, individual patient-based care that ensures treatment is adhered to and completed satisfactorily. It is essential for the successful drug treatment of TB as it is never adequate to prescribe drug therapy alone. This prescription must always be accompanied by case management. Case management is described in detail in section 2.3. Case management.

2.1.2. Principles of drug treatment of tuberculosis

Principles that underpin the drug treatment of TB are described below.

Standardised regimens

Drug regimens for TB are strongly evidenced based and have been well established for decades. Adherence to internationally accepted standardised regimens is associated with superior treatment success and lower rates of drug resistance. This is a recommendation of the WHO international agreed strategy for TB control (WHO, 2022).

Multidrug regimens

Single drug treatment inevitably induces drug resistance in TB. Therefore, apart from short-term challenge regimens used to re-introduce drugs after severe drug side effects (see Adverse drug reactions below), TB should never be treated with a single drug. For this reason, it is essential when treating TBI (with a single drug) to first ensure that TB disease is excluded.

Free of charge

Patients should not incur financial cost when supplied with TB drugs. See section 8.1. Fees and charges related to the diagnosis and management of tuberculosis and leprosy.

2.1.3. Pre-treatment considerations

Assessment prior to TB treatment initiation must include the following considerations (see Appendix 2.1: Checklist when starting tuberculosis treatment).

Disease type

The anatomical site(s) and the extent of the disease influence the length of treatment and the addition of supplementary treatment such as prednisolone. In deciding the appropriate treatment it is necessary to ascertain whether there is more than one site involved, whether there is sub-clinical pulmonary TB in a patient presenting with extra-pulmonary TB, and whether "privileged" sites are involved (i.e. sites that have poor drug penetration such as the CNS and bones).

Bacteriological confirmation and drug susceptibility

Confirmation of TB via mycobacterial culture should be pursued in all cases. Even when empiric treatment is warranted, consideration should be given to collection of samples for mycobacterial culture prior to the commencement of drug treatment.

Past treatment

Past treatment predicts drug resistance in TB. It is essential to obtain a thorough history and, if possible, documentation of any previous treatment with TB drugs. This includes treatment with drugs against TB that were used for treatment of other infections e.g. rifampicin or fluoroquinolones.

Co-morbidity

A directed clinical assessment for conditions that influence the efficacy of TB treatment or increase the risk of side effects should be obtained. In particular, note should be made of renal and hepatic impairment, HIV risk factors, malnutrition and risk factors for peripheral neuropathy (e.g. diabetes). Alteration to treatment in these circumstances is detailed below.

Weight

Patient weight should be measured with shoes and clothes on. In cases of fluid overload, the patient's 'dry' weight should be used (e.g. in patients receiving renal dialysis, the weight after dialysis).

Other drug treatment

Particular consideration should be given to potential drug interactions with TB drugs, especially with rifampicin (see Appendix 2.2: Drug interactions with tuberculosis treatment).

2.1.4. Tuberculosis treatment – fully drug-susceptible tuberculosis

Table 2 below shows agents used for the treatment of TB in WA. The majority (>95%) of TB cases are adequately and most appropriately treated with standard regimens. If empirical treatment of presumed TB is being considered in discussion with a TB physician, the treatment should only include standard therapy as for drug-susceptible (DS) TB.

Table 2: Tuberculosis medications

Drug Name	Abbreviation
Isoniazid (INH)	H
Rifampicin (RIF)	R
Pyrazinamide (PZA)	Z
Ethambutol (EMB)	E

The full name of a medication should be always used when prescribed in a medication chart. Otherwise, medication abbreviations can be used according to the standard format illustrated in Figure 1.

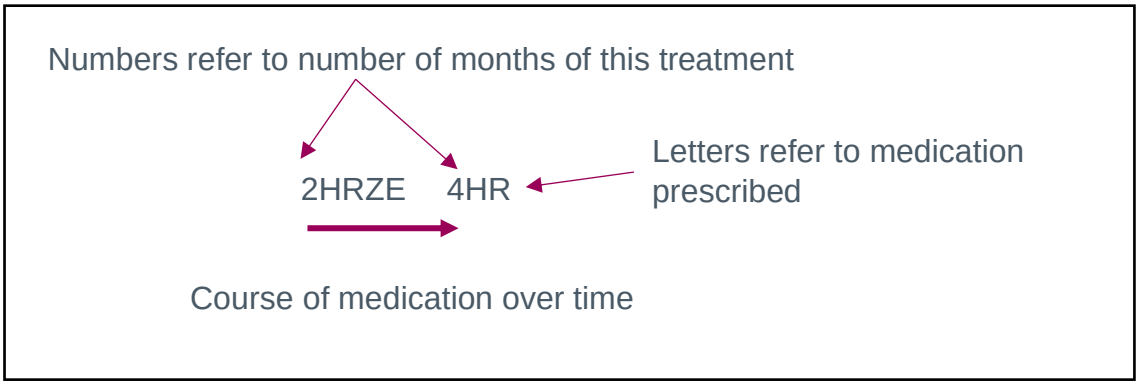


Figure 1: Annotation of TB medication regimes

2.1.5. Drug doses

It is recommended that daily dosing is used. Thrice weekly treatment is no longer recommended in WA based on randomised controlled trials (RCTs) that showed poorer outcomes and current WHO guidelines (WHO, 2022). An exception to this rule is in dialysis patients on TB treatment, which is discussed below.

To assist clinicians, Table 3 gives suggested medication doses based on body weight. This has been adapted from the WHO recommended dosing range of first line anti-TB drugs (WHO, 2022). Doses of TB drugs in children are detailed in section 4.2. Paediatrics. Adjustment of drug doses in patients with renal impairment is discussed in the following section.

Table 3: Tuberculosis medication dosing

Drug	Body Weight (kg)	Daily dose (mg)
Isoniazid 100mg tablets	≥ 40 < 40	300 5mg/kg
Rifampicin 150mg & 300mg capsules 10mg/kg daily Rifampicin 450mg is preferably given as 3 x 150mg capsules (rather than 300mg + 150mg)	≥ 50 < 50	600 450
Pyrazinamide 500mg tablets 25 mg/kg daily	>70 50 to 70 35 to 50 <35	2000 1500 1000 750
Ethambutol 400mg tablets 15mg/kg daily dose Round calculated dose of ethambutol up to nearest 200mg (half tablet)	>80 70 to 80 55 to 70 45 to 55 <45	1600 1200 1000 800 600

2.1.6. Treatment regimens

Standard treatment regimen

The preferred standard treatment regimen for TB is **2HREZ/4HR** (for explanation of abbreviation, see Figure 1 above). When susceptibility to first line drugs is known, ethambutol can be omitted, either at the commencement of treatment or subsequently, when the susceptibility results become available.

It is not recommended that ethambutol be omitted on the assumption of drug susceptibility because TB notifications in WA are at risk of drug resistance (>5% chance).

Patients who return a positive sputum smear at the completion of the intensive phase of this regimen, may be treated for an extended period. This will be discussed later in the chapter.

Fixed-dose combination formulations

Fixed-dose combination (FDC) are combinations, in the same tablet, of at least 2, and up to 4, of the first-line drugs used to treat TB. FDCs are recommended over single drug formulations in

the treatment of patients with drug susceptible TB (DS-TB) (WHO, 2022) and are routinely available worldwide. The use of FDCs have several advantages over individually formulated medications including:

- decreased pill burden
- improved adherence
- reduced risk of acquired drug resistance since one medication cannot be taken selectively.

In Australia, the use of FDCs has been limited by the formulations not being licensed by the Therapeutic Goods Administration (TGA), so having restrictions on supply and prescription. Treatment requires Special Access Scheme (SAS) approval.

FDC formulations for HREZ and HR have recently been introduced to routine use at the WATBCP for treatment of patients under the direct medical governance of WATBCP physicians. The WATBCP routinely supplies first line TB medication to patients cared for outside of Anita Clayton Centre according to the prescription of other physicians but, at this stage, this does not apply to FDC formulations.

Treatment of drug-susceptible tuberculosis using 4-month regimens

This regimen is recommended by WHO based on the evidence provided by a recent RCT (WHO 2022; Dorman et al., 2021) that showed the efficacy of a 4-month rifapentine-based regimen containing moxifloxacin in the treatment of TB.

Adults and children aged 12 years or older, weighing 40 kg or more with drug susceptible pulmonary TB are eligible for this regimen. However, due to cost, access issues and limited data associated with this therapy, the 6 months regimen is still preferred. This shorter 4-month regimen may be considered in select circumstances, on discussion with a TB physician.

The 4-month regimen of isoniazid, rifapentine (abbreviated ‘P’), moxifloxacin (abbreviated ‘M’) and pyrazinamide (2HPMZ/2HPM) is **not** recommended in the following circumstances:

- patients weighing less than 40 kg
- patients with severe extrapulmonary TB (e.g. tuberculous meningitis, disseminated TB osteoarticular TB or abdominal TB)
- co-infection with HIV with a CD4 count of less than 100 cells/mm^3
- children and adolescents aged under 12 years
- pregnant, breastfeeding, and postpartum women.

The study was based on the regimen with moxifloxacin; therefore, replacement of moxifloxacin by another fluoroquinolone cannot be recommended.

Extensive pulmonary tuberculosis

In cases of pulmonary TB with bilateral cavitary disease or extensive parenchymal damage on chest radiography, consideration should be given to extending the treatment course to 9 months (2HREZ/7HR) (WHO, 2022).

Extra pulmonary tuberculosis

Extension of the TB regimen should be considered in the following circumstances:

- bone and joint 9 - 12 months
- CNS 12 months.

Other forms of extra-pulmonary TB have been treated for longer than 6 months, but there is no evidence that extended regimens are more efficacious.

Relapsed tuberculosis

When there is a history of prior treatment for TB (not including preventive therapy) specimens for culture and drug susceptibility testing should be obtained prior to or at the start of treatment.

Previous TB, fully susceptible (or susceptibilities unknown): Treat with standard regimen. The drug regimen can be adjusted once drug susceptibilities are known (WHO, 2022).

Previous drug-resistant TB: consider adding at least 2 drugs that the patient has not previously received to the treatment regimen. Treatment should be discussed with a specialist TB physician.

HIV co-infection

There is good evidence that TB in the setting of immunodeficiency due to HIV infection does not require different (e.g. extended) treatment. Involvement of specialist TB and HIV physicians is essential. For further information on TB and HIV infection see section 4.5. HIV coinfection.

Liver impairment

TB treatment should be initiated according to the standard regimen in all but severe liver impairment. Liver function tests need to be monitored closely. Despite anti-tuberculous drugs commonly causing hepatitis, pre-treatment liver impairment often improves with TB treatment. It is not appropriate to reduce the dose of any TB drugs because of liver impairment. Adjustment of treatment when liver function deteriorates is detailed below, in the section Adverse drug effects.

Renal impairment

Table 4 below provides details of adjustments that should be made in renal impairment. Dose reduction is not recommended but the frequency of dosing should be reduced. Haemodialysis efficiently removes pyrazinamide and to a lesser extend isoniazid and ethambutol, so **TB drugs should only be given after haemodialysis**.

Table 4: Adjustment of Tuberculosis treatment in renal failure

		Change in dosing frequency	
Drug	**Risk**	**Estimated GFR* < 30mL/min**	**Haemodialysis#**
Isoniazid	Nil	Nil	Nil
Rifampicin	Nil	Nil	Nil

Ethambutol	Accumulation – optic neuropathy	Do not use daily Can be used 3x / week, but with close ophthalmological monitoring	Do not use daily Can be used 3x / week, but with close ophthalmological monitoring
Pyrazinamide	Accumulation of metabolites – gout	25 mg/kg, 3x / week in severe renal failure	25 mg/kg, 3x / week After dialysis

*Glomerular Filtration Rate

in patients receiving haemodialysis, all drugs should be given after dialysis.

Adapted from Table 12 'Dosing recommendations for adult patients with reduced renal function and for adult patients receiving haemodialysis' in Treatment of Tuberculosis, American Thoracic Society 2016

Pregnancy

No adjustment to TB regimen is required in pregnancy. Dosing is according to pre-pregnancy weight (see section 4.4. Pregnancy).

Infection with *M. bovis*

These organisms are innately resistant to pyrazinamide and thus a 9 month regimen should be used consisting of an initial 2 months of isoniazid, rifampicin and ethambutol therapy followed by a 7 month continuation phase of isoniazid and rifampicin (2HRE/7HR) (American Thoracic Society et al., 2017). Ethambutol can be ceased if phenotypic sensitivity to rifampicin and isoniazid is confirmed.

2.1.7. Adjuvant drugs

Pyridoxine (vitamin B6): Not required in most patients prescribed isoniazid. It should be given where there is a risk of vitamin B6 deficiency (e.g. malnutrition, alcoholism, renal impairment, pregnancy etc.) or in subjects at risk of peripheral neuropathy (e.g. diabetes, existing neuropathy, HIV infection etc.). The formulation that is used in WA is pyridoxine 25 mg daily.

Prednisolone: Indicated in tuberculous meningitis (prednisolone 1 mg/kg or equivalent for 6 – 8 weeks). In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (WHO, 2022). Prednisolone can also be considered for symptom control in the following circumstances:

- extensive TB (including miliary TB) with a severe inflammatory response
- extensive TB complicated by high persistent fever
- TB that constricts or compresses important structures such as the spinal cord, ureter, bronchus, pericardium or great vein
- large abscess formation
- in subjects suffering a paradoxical lymph node enlargement on appropriate TB treatment.

2.1.8. Treatment initiation

When treatment for TB is initiated in WA, the following should be completed (see Appendix 2.1 Checklist when starting tuberculosis treatment):

- **Drug chart:** each TB drug is prescribed on the TB Control Program Medication Chart (or equivalent in other settings), using generic drug names in full (no abbreviations). This prescription lasts until a cease date is charted i.e. the full course of treatment.
- TB Notification & Enhanced TB Data Surveillance form.
- Baseline blood tests:
  - Full blood count, urea & electrolytes, liver function tests.
  - HIV serology - mandatory in all TB cases, irrespective of apparent HIV risk.
  - Hepatitis B and C serology - consider in high-risk patients or if liver function tests are abnormal.
  - HbA1c in patients over 35 years old or with a first degree relative with diabetes.
- **Baseline visual acuity and colour vision testing** (Ishihara Chart) - if ethambutol is prescribed.
- **Baseline mental state assessmen**t: Kessler Psychological Distress Scale (K10 or K6) for all TB patients.
- **CXR:** If not done within the last 3 months e.g. extra pulmonary TB presentation, to exclude co-existent pulmonary TB.

Treatment initiation outside of the Western Australia Tuberculosis Control Program

Patients who are prescribed TB treatment by physicians outside of the WATBCP (private physicians, hospital patients, etc.) should still receive case management via the WATBCP. TB medication can be supplied through the WATBCP case manager according to the physician's prescription. A WATBCP doctor must prescribe these medications on the WATBCP Medication Chart, according to written instructions from the treating physician.

2.1.9. Follow-up

The treating physician should determine the follow-up frequency and tests. However, it is recommended that patients on TB treatment should be seen at least monthly. A suggested schedule for follow-up tests is given in Appendix 2.3 Recommended routine tests during treatment of tuberculosis disease.

Once TB treatment is completed, routine follow up occurs 2–3 months later. Further follow up is recommended when there has been concern regarding adherence to treatment or a non-standard regimen was used because of drug resistance or intolerance. It is also occasionally warranted in extensive, severe, or disseminated TB. Timeframes for follow up should be determined by the treating physician.

For drug-resistant tuberculosis, it is recommended that following completion of treatment patients be reviewed at 2-3 months, then 6 monthly for at least 2 years, with follow-up thereafter at the discretion of the treating physician.

2.1.10. Adverse drug effects

Drug reactions to TB medications occur commonly and are mostly mild and manageable without discontinuation of TB treatment. Patients should be warned about potential side effects, and they should be screened for these during follow up visits. The following are the common more serious adverse effects that the patient should be warned about:

- hepatitis (H,R,Z) – anorexia, malaise, nausea, vomiting, epigastric or right upper quadrant pain
- rash (H,R,Z) – macular, pruritic on trunk extending to limbs
- optic neuropathy (E) – loss of visual acuity, red/green colour blindness
- gout (Z) – joint pain, redness or swelling.

Other common, but less serious adverse effects are dyspepsia, tiredness, acne, dry skin and hair, red discolouration of the urine and staining of soft contact lenses.

Female patients taking the oral contraceptive pill should be warned that rifampicin reduces its contraceptive action, increasing the risk of inadvertent pregnancy. For details of other drug interactions see Appendix 2.2: Drug interactions with tuberculosis treatment.

2.1.11. Management of severe adverse drug effects

Drugs suspected of causing severe adverse effects should be ceased and the regimen adjusted as detailed below. In certain situations, it may be difficult to determine which is the causative agent. In this situation it is preferable to stop all drugs until the adverse event resolves and then reintroduce the drugs one at time in a stepwise drug challenge.

The exceptions to this approach may be in severely unwell TB patients or smear positive pulmonary TB patients who are infectious. In these circumstances the treatment should be revised to a minimum effective drug regimen not likely to be responsible for the adverse effect e.g. in severe hepatitis, use ethambutol, levofloxacin (Lfx) and amikacin.

Re-introduction of first line drugs as a drug challenge should still be attempted once the adverse effect has resolved.

Drug challenge

After a severe drug adverse effect has resolved, TB drugs should be re-introduced in a stepwise fashion to re-establish treatment and to identify which drug was responsible for the side effect(s). This should be individualised for the patient by a specialist TB physician.

The principles underpinning this include the following:

- re-introduction of the most effective drugs first (isoniazid and rifampicin)
- avoid treatment with a single drug class for more than 1 week
- start with low dose and increase to full dose as tolerated
- ensure appropriate tests (e.g. LFTs) are done frequently to be able to associate a recurrent adverse effect with a specific drug
- use a dosette box to ensure close adherence to the challenge regimen.

It is important to include rifampicin in the regimen, as it has important sterilising activity and there is no alternative drug with the same efficacy.

Adverse effects that absolutely contraindicate the re-introduction of a drug are unusual in TB treatment, but include the following:

- ethambutol optic neuropathy
- rifampicin or isoniazid induced thrombocytopenia, acute haemolytic anaemia and acute renal failure
- isoniazid-induced fulminant liver failure.

Rash

All TB drugs can cause rash. The severity of the rash determines its management.

If the patient complains of itch without other symptoms such as a significant rash, mucous membrane involvement or systemic signs like fever, the management is symptomatic with an antihistamine. All TB medications can be continued.

A petechial rash is more concerning and suggests thrombocytopenia from rifampicin. If thrombocytopenia develops, rifampicin is permanently stopped, and the platelet count closely monitored until definite improvement is noted.

If the patient has a generalised erythematous rash, fever and/or mucous membrane involvement, TB medications should be stopped. Once the drug reaction has completely resolved, stepwise introduction of TB medications is advised with close monitoring of hypersensitivity (rash, fever, raised transaminases, eosinophilia, pruritus, etc). If any of these develop, the last drug added to the regimen is stopped and eliminated from the regimen.

Systemic corticosteroids may be used to treat severe systemic reactions. The use of steroids in the treatment of systemic reactions, even in the setting of severe TB, has not been shown to worsen outcomes (Nahid et al., 2016).

Hepatotoxicity

Drug-induced hepatitis is the most frequent (3%) serious adverse reaction to first line TB drugs. Isoniazid, rifampicin, and pyrazinamide can cause drug induced hepatitis, which is considered significant when the alanine aminotransferase (ALT) serum level is ≥3 times the upper limit of normal in the presence of hepatitis symptoms, or ≥5 times the upper limit of normal in the absence of symptoms.

- Mild: ALT level is <5 times the upper limit of normal
- Moderate: ALT level 5–10 times normal
- Severe: >10 times normal (i.e. >500 U/L)

An asymptomatic increase in ALT occurs in nearly 20% of patients treated with standard TB treatment. In the absence of symptoms, therapy should not be altered because of modest asymptomatic elevations of ALT, but the frequency of clinical and laboratory monitoring should be increased. In most patients, asymptomatic ALT elevations resolve spontaneously.

If ALT levels are ≥5 times the upper limit of normal (with or without symptoms) or ≥3 times normal in the presence of symptoms and signs (nausea, vomiting, abdominal pain, jaundice), hepatotoxic drugs should be stopped immediately and the patient carefully evaluated. Significant increase in bilirubin and/or alkaline phosphatase may be seen with rifampicin induced hepatotoxicity.

It is also recommended to exclude alternative causes of abnormal liver function (e.g. viral hepatitis, alcohol, fatty liver) before diagnosing drug-induced hepatitis. If significant hepatitis develops, all hepatotoxic drugs must be stopped and serum ALT and prothrombin time or international normalised ratio (INR) measured (especially in severe cases) until levels return to baseline. Once the ALT level returns to <2 times the upper limit of normal, TB medications are restarted individually in a stepwise drug challenge. In patients with elevated baseline ALT (pre-existing liver disease) drugs are restarted when the ALT returns to near baseline levels.

The optimal approach to reintroducing TB treatment after hepatotoxicity is debateable. However, most TB programs use sequential reintroduction of drugs. As rifampicin is less likely to cause hepatotoxicity than isoniazid or pyrazinamide, it is restarted first. If there is no increase in ALT after a reasonable timeframe, isoniazid may be restarted and lastly pyrazinamide. If symptoms recur or the ALT increases, the last drug added should be stopped (Nahid et al., 2016; WHO, 2010).

Optic neuritis

Ethambutol related visual impairment in patients receiving standard doses is estimated to occur in 22.5 per 1000 persons (2.25%). The onset of optic neuritis is usually one month or more after treatment initiation but can occur within days of TB treatment starting. Expert opinion recommends that baseline visual acuity (Snellen test) and colour discrimination tests (Ishihara chart) followed by monthly colour discrimination tests are performed during ethambutol use. If optic neuritis is suspected, ethambutol should be stopped immediately and the patient referred for a specialist ophthalmologic opinion (Nahid et al., 2016).

2.1.12. Treatment in special situations

Tuberculous meningitis

Tuberculous meningitis remains a potentially devastating disease associated with high morbidity and mortality despite prompt initiation of adequate treatment. If this diagnosis is considered, treatment should be initiated prior to confirmation given the potentially devastating consequences. HIV-infected individuals are at increased risk of developing tuberculous meningitis. Complications of tuberculous meningitis that warrant neurosurgical review include hydrocephalus and tuberculous cerebral abscess.

A number of studies have examined the role of adjunctive corticosteroid therapy in the treatment of tuberculous meningitis. The WATBCP recommends adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks. Extension of the continuation phase of treatment for 10 months (total 12 months treatment) is also recommended (Nahid et al., 2016, WHO, 2010).

Spinal tuberculosis

Treatment of bone, joint, and spinal TB require 9-12 months regimens containing rifampicin. Trials have found no additional benefit from surgical debridement in addition to anti-TB treatment alone for spinal TB. Uncomplicated cases of spinal TB are managed with medical rather than surgical treatment. Consideration should be given to early use of corticosteroids if there is risk of spinal cord compression.

Surgery can be considered in situations where:

- there is poor response to anti-TB treatment with evidence of ongoing infection and/or clinical neurological deterioration
- cord compression evidenced by persistent or recurrent neurologic deficits
- there is instability of the spine (Nahid et al., 2016).

Renal tuberculosis

The pharmacokinetics of anti-TB drugs are altered in renal impairment. Therefore, dose adjustment in patients with renal insufficiency or end stage renal failure is required (see above,

Table 4.

Rifampicin and isoniazid are metabolised by the liver and conventional dosing for these drugs can be used in the setting of renal insufficiency. Pyrazinamide is primarily metabolized by the liver but its metabolites, pyrazinoic acid and 5-hydroxy-pyrazinoic acid, can accumulate in patients with renal insufficiency. Ethambutol is approximately 80% cleared by the kidneys and can accumulate in patients with renal insufficiency.

Experts suggest a longer interval between doses (i.e. thrice weekly) for pyrazinamide and ethambutol in patients with renal insufficiency. During haemodialysis, pyrazinamide and its metabolites are cleared to a significant degree, isoniazid and ethambutol are cleared to some degree, and rifampicin is not cleared by haemodialysis. The fluoroquinolones are also cleared variably by the kidneys. Levofloxacin undergoes greater renal clearance than moxifloxacin. Post dialysis administration of all TB medications is preferred to facilitate directly observed therapy (DOT) and to avoid clearance of drugs such as pyrazinamide during haemodialysis (Nahid et al., 2016; WHO, 2010).

2.1.13. Management of interrupted treatment

Interruption of treatment can occur for various reasons including adverse drug effects. Clinical decisions need to consider when the interruption(s) occurred and the duration of the interruption(s). In general, the earlier the interruption and the longer the duration of interruption, the more serious the effect and the greater the need to restart treatment from the beginning. The bacteriologic status of the patient prior to and after the interruption are also important considerations.

There is no evidence upon which to base detailed recommendations for managing interruptions in treatment, and no recommendations will cover all the situations that may arise. General guideline is summarised in Table 5 (adapted from ATS/CDC, 2016).

Table 5: Management of interrupted TB treatment

Time point of Interruption	Details of interruption	Approach
During intensive phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as

		long as all doses are completed within 3 months)
	Lapse is ≥ 14 days in duration	Restart treatment from the beginning.
During the continuation phase	Received ≥ 80% of doses and sputum was AFB smear negative on initial testing	Further therapy may not be necessary
	Received ≥ 80% of doses and sputum was AFB smear positive on initial testing	Continue treatment until all doses are complete
	Received <80% of doses and accumulative lapse was <3 months in duration	Continue treatment until all doses are complete (full course), unless consecutive lapse is >2 months
		If treatment cannot be completed within recommended time frame for regime, restart treatment from the beginning (i.e. restart intensive phase to be followed by continuation phase)
	Received <80% of doses and accumulative lapse was ≥3 months in duration	Restart treatment from the beginning, new intensive and continuation phases (i.e. restart intensive phase, to be followed by continuation phase)

Appendix 2.1: Checklist when starting tuberculosis treatment

Checklist when starting TB Treatment		
☐	AFB specimens	If no positive TB cultures, consider repeating AFB specimen collection prior to starting empiric TB treatment. ALL patients should attempt to have at least one set of 3 sputums for AFB microscopy and culture.
☐	CXR	All patients, including extra-pulmonary TB.
☐	Weight	Shoes & clothes on.
☐	Past TB treatment	Check history, obtain documentation.
☐	Other drugs	Check possible drug interactions. (see Appendix 2.2).
☐	Blood tests	U&E, LFT, FBC HIV serology (all patients irrespective of risk, assuming consent given). Hepatitis B and C serology (if high risk or abnormal LFT). Diabetic screen (HbA1c) if > 35 years old of first degree relative with diabetes. Pregnancy testing (serum beta hCG) in women of childbearing age
☐	Mental State Assessment	Kessler Psychological Distress Scale (K10 or K6).
☐	Medication Chart	Chart drugs using full generic name.
☐	Vision	Check baseline visual acuity & colour vision if starting ethambutol.
☐	TB Case Manager	Inform.
☐	TB Notification & TB Enhanced Surveillance Form.	

Appendix 2.2: Drug interactions with tuberculosis treatment

A list of the most common and important drug in product information. It is not exhaustive – it only includes first-line anti-TB drugs. Always check for drug interaction in production information.

Drug	TB Drug	Interaction	Action
Alcohol	H, R	↑ hepatotoxicity ↑ metabolism H	Minimise or avoid alcohol
Allopurinol	Z	↓ uric acid clearance	Adjust anti-gout treatment
Antacids	H, R, E	↓ absorption	Avoid coadministration
Amiodarone	R	↑ metabolism	Due to reduce effect of antiarrhythmic avoid combination
Amitriptyline	R	↑ metabolism	Use alternate or monitor levels
Anti-malarials	R	↑ metabolism	Don't rely on mefloquine, quinine, atovaquone
Azole antifungal	R	↑ metabolism	Use alternate anti-fungal
β blocker	R	↑ metabolism	Adjust dose based on clinical effect
Bupropion	R	↑ metabolism	Watch for reduced efficacy
Ca channel blocker	R	↑ metabolism	Adjust dose based on clinical effect
Carbamazepine	H	↓ metabolism ↑ hepatotoxicity	Adjust carbamazepine dose based on levels
Ciclosporin	R	↑ metabolism	Consider alternate to R, monitor levels
Clarithromycin	R	↑ metabolism	Use alternate antibiotic
Corticosteroid	R	↑ metabolism	Monitor efficacy, increase steroid dose
Digoxin	R	↑ metabolism	Increase digoxin dose based on clinical effect
Diuretic	Z	↑ risk of gout	Monitor uric acid levels
Doxycycline	R	↑ metabolism	Use alternate antibiotic

Drug	TB Drug	Interaction	Action
Fluvastatin	R	↑ metabolism	May need increased dose or alternate agent
Haloperidol	R	↑ metabolism	Use higher dose of haloperidol or alternate
Insulin	H	Antagonises action	Intensify BSL monitoring & adjust diabetic Rx
Levodopa	H	↓ metabolism	Watch for levodopa side effects
Lovastatin	R	↑ metabolism	May need increased dose or alternate agent
Methadone	R	↑ metabolism	Increase methadone dose
Morphine	R	↑ metabolism	Watch for reduced efficacy of morphine
NNRTIs	R	↑ metabolism	Rifampicin and efavirenz OK Low trough levels with nevirapine and risk of antiviral treatment failure
Ondansetron	R	↑ metabolism	Watch for reduced efficacy
Oral Contraceptive	R	↑ metabolism	Advise alternate contraceptive
Phenytoin	H	↓ metabolism	Adjust phenytoin dose based on levels
Phenytoin	R	↑ metabolism	Adjust phenytoin dose based on levels
Protease Inhibitors	H, R, Z	↑ hepatotoxicity	Monitor LFTs
Protease Inhibitors	R	↓ metabolism	Combination not recommended
Risperidone	R	↑ metabolism	Use higher dose of risperidone or alternate
Sertraline	R	↑ metabolism	Avoid coadministration
Simvastatin	R	↑ metabolism	May need increased dose or alternate agent

Drug	TB Drug	Interaction	Action
Sulfasalazine	R	↑ metabolism	Watch for reduced efficacy
Sulphonylureas	R	↑ metabolism	Intensify BSL monitoring & adjust diabetic Rx
Tacrolimus	R	↑ metabolism	Consider alternate to R, monitor levels
Tamoxifen	R	↑ metabolism	Consider alternate agents
Theophylline	H	↓ metabolism	Adjust theophylline dose based on levels
Theophylline	R	↑ metabolism	Adjust theophylline dose based on levels
Thyroxine	R	↑ metabolism	Monitor TSH and adjust dose
Trimethoprim	R	↑ metabolism	Use alternate antibiotic
Valproate	H	↑ valproate toxicity	Adjust valproate dose based on levels
Valproate	R	↑ metabolism	Adjust valproate dose based on levels
Vitamin D	R	↑ metabolism	Use higher dose of vitamin D
Warfarin	H	↓ metabolism	Monitor INR at start and finish of isoniazid
Warfarin	R	↑ metabolism	Monitor INR at start and finish of RIF

Refer to Table 2 for TB drug abbreviations.

BSL: blood sugar level
INH: isoniazid
INR: international normalised ratio
LFT: liver function tests
RIF: rifampicin
Rx: prescription
TSH: thyroid stimulating hormone

Appendix 2.3: Recommended routine tests during treatment of tuberculosis disease

Recommended Routine Tests During Treatment of TB Disease	
Baseline blood tests	Full blood count Liver function tests Urea and electrolytes HIV serology Beta hCG (consider for women of childbearing age) Vitamin D
Baseline other	Mental health assessment (K10/K6) CXR Visual acuity (Snellen) Colour discrimination (Ishihara)
2 weeks	Liver function tests Full blood count Colour vision & visual acuity – ethambutol treatment only
2 months	Sputum x 2 for AFB microscopy and culture (PTB) CXR (if initial CXR abnormal) Liver function & other tests if clinically concerned or initially abnormal Colour vision & visual acuity if still on ethambutol treatment
3 – 6 months	Sputum x 2 for AFB microscopy and culture if clinical or other concern that response is not satisfactory If 2-month test is positive repeat sputum x2 for AFB microscopy and culture at 3 months Blood tests – only if concerned or initially abnormal Consider repeat liver function testing if hepatitis B or C positive, HIV infection, pre-existing liver disease, alcohol use or older age group
6months / completion	CXR (all cases, even in extra pulmonary TB)

CXR: chest x-ray
AFB: acid-fact bacilli
PTB: pulmonary tuberculosis

2.2. Medical treatment of drug-resistant tuberculosis

2.2.1. Introduction

DR-TB is defined as TB disease caused by a strain of MTBC that is resistant to any TB medication. DR-TB is more difficult to treat than DS-TB and hence poses a greater challenge for patients, healthcare staff, and the healthcare system.

Additional drug susceptibility testing (DST) is recommended to be performed when rifampicin resistance is identified for first-line drugs, fluoroquinolones, and aminoglycosides. Drugs known or suspected to be ineffective based on *in vitro* phenotypic methods or molecular resistance should NOT be used.

2.2.2. Definitions

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of MTBC that is resistant to rifampicin and isoniazid.

Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of MTBC that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of MTBC that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other 'Group A' drug (bedaquiline or linezolid).

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of MTBC that is resistant to rifampicin. This should be treated as for MDR-TB.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of MTBC that is resistant to isoniazid but susceptible to rifampicin.

2.2.3. Regimen for rifampicin-susceptible, isoniazid-resistant TB (Hr-TB) or intolerance

Recent epidemiological evidence suggests that more than three quarters of the global burden of Hr-TB occurs among previously untreated TB cases. Resistance to fluoroquinolones should always be excluded in isoniazid-resistant TB. A six-month course of rifampicin, ethambutol, pyrazinamide, and levofloxacin **6REZ-Lfx** is the recommended regimen for patients with confirmed Hr-TB and rifampicin-susceptible TB (WHO, 2022). If low-level isoniazid resistance is confirmed (i.e. *inhA* mutation alone or resistance at 0.1 mg/L but not 0.4 mg/L concentration on phenotypic testing), the use of high dose isoniazid can be considered i.e. **6(Hh)REZ-Lfx**. In the presence of both *inhA* and *katG* mutations, addition of isoniazid (even at a high dose) is unlikely to add value to the regimen.

Levofloxacin is the preferred fluoroquinolone for 2 reasons. Firstly, exposure to moxifloxacin decreases markedly when it is combined with rifampicin (due to induction of the metabolism of moxifloxacin). This has not been reported for levofloxacin. Secondly, levofloxacin appears to cause less QT interval prolongation.

This regimen is recommended in patients with Hr-TB, except in the following situations:

- Resistance to rifampicin cannot be excluded (i.e. unknown susceptibility to rifampicin, or indeterminate or error results on GeneXpert MDR).
- Known or suspected resistance to levofloxacin.
- Known intolerance to fluoroquinolones.
- Known risk for prolonged QT interval.
- Pregnancy or during breastfeeding (not an absolute contraindication).

In patients with cavitary disease and with persistent positivity on sputum smear and culture, prolongation of (Hh)REZ-Lfx beyond 6 months should be considered on a case-by-case basis. If levofloxacin cannot be used because of toxicity or resistance, the patient may be given 6(H)REZ as an alternative, but consideration may be given to a longer treatment duration.

Treatment monitoring

A suggested schedule for follow-up tests as for DS-TB (see Appendix 2.3). Electrocardiography (ECG) for patients on 6(H)REZ-Lfx is not usually required unless there are other risk factors for QT interval prolongation (i.e. underlying structural heart disease, concomitant use of anti-depressant therapy or fluconazole).

Rifampicin mono-resistance (isoniazid susceptible)-RR-TB or intolerance

Even in the absence of isoniazid resistance, a patient should be treated with an MDR-TB regimen (see section 2.2.4. Multidrug-resistant tuberculosis).

Pyrazinamide mono-resistance or intolerance

Refer to section 2.1.6. Treatment regimens – Infection with *M. bovis*.

2.2.4. Multidrug resistant tuberculosis

It is now recommended that MDR-TB/RR-TB is treated with an all-oral short or long course regimen. The short course regimen should be considered first, providing criteria are met. The use of injectable agents is no longer recommended in either the short or long course regimens unless there is no suitable alternative. Drugs known or suspected to be ineffective based on *in vitro* growth based or molecular resistance should NOT be used. Patients who are commenced on a long regimen for 4 weeks or more are no longer recommended to switch back to the shorter regimen (WHO, 2022).

MDR/RR-, pre-XDR- and XDR-TB should be treated by a specialist physician with expertise and experience in treating this form of TB and either at, or in discussion with, the WATBCP. All cases should be discussed in the WATBCP case management meeting before or soon after starting treatment. Design of MDR-TB drug regimens and monitoring of response to treatment should be done in consultation with specialist TB physicians at regular case management meetings.

Treatment response should be monitored clinically, radiographically, and bacteriologically, with cultures obtained at least monthly for pulmonary TB. When cultures remain positive after 3 months of treatment, repeat susceptibility tests for drugs should be performed where available.

Drug-resistant (MDR/RR-, pre-XDR- or XDR-TB) infectious TB cases have significant public health implications. The role of patient isolation needs to be carefully considered in these

situations and should be discussed with the Medical Director of the WATBCP (i.e. whether isolation in the community or a hospital setting is most appropriate).

2.2.5. Regimens for treatment of multidrug-resistant tuberculosis

BPaLM regimen: 6-month (26 weeks) bedaquiline, pretomanid, linezolid and moxifloxacin (fluoroquinolone susceptible)

The 6-month / 26 weeks bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen is now the recommended regimen for MDR-TB over the 9 month shorter course or 18-20 month longer course regimens (WHO, 2022). DST for fluoroquinolones is recommended in all patients with MDR/RR-TB but should not delay initiation of the BPaLM. Results of the test should then guide a decision to retain moxifloxacin or remove it from the regimen (see BPaL regimen below).

BPaLM can be used in the following situations:

- Patients with MDR/RR-TB without resistance to fluoroquinolones.
- Patients with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
- Adults and adolescents aged 14 years and older.
- Patients that are HIV positive or negative.
- Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure to these agents has been for greater than 1 month, the regimens can be used if resistance to the drug(s) that have been used has been ruled out.
- Patients who are not pregnant or breastfeeding (there is limited evidence on the safety of pretomanid).

Doses of each drug are provided in Appendix 2.4.

The recommended dose of linezolid is 600 mg once daily. However, dose adjustment in response to therapeutic drug monitoring (TDM) is recommended in all cases to optimise the dose. If significant adverse events develop TDM is essential.

BPaL: 6-month (26 weeks) bedaquiline, pretomanid, linezolid (fluoroquinolone resistance)

In patients with pre-XDR-TB i.e. MDR-TB with fluroquinolone resistance, treatment is recommended for 6-9 months with BPaL, comprising bedaquiline, pretomanid and linezolid. Extension of treatment to 9 months may be considered if there is a slower but still favourable treatment response.

Eligibility criteria for this regimen are otherwise the same as for the BPaLM regimen.

Shorter, all-oral bedaquiline-containing regimen for MDR- or RR-TB

A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR-TB or rifampicin-resistant TB (RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1

month, and in whom resistance to fluoroquinolones has been excluded. This is typically in those patients not eligible or intolerant of the BPaLM regimen.

Regimen:

- Bedaquiline; used for 6 months, plus
- 4 months intensive phase; levofloxacin or moxifloxacin, ethionamide or prothionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine.
    - May be extended to 6 months if the patient remains sputum smear positive at the end of 4 months.
    - Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
- Followed by a 5 month continuation phase; levofloxacin or moxifloxacin, clofazimine, ethambutol and pyrazinamide.

See Appendix 2.4 for drug doses by weight.

Eligibility:

- No resistance or suspected ineffectiveness of a medicine in the shorter regimen (other than isoniazid resistance).
- No exposure to previous treatment with second-line drugs for more than 1 month.
- (unless susceptibility to these medicines is confirmed).
- No extensive TB disease and no severe extrapulmonary TB (e.g. miliary TB, tuberculous meningitis, osteoarticular or pericardial TB).
- Not Pregnant.
- 6 years of age or older.

Longer regimens for MDR- and RR-TB

Referring to Table 6, where possible, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective. If bedaquiline is ceased after 6 months, at least three agents are included for the remainder of treatment.

Total duration of treatment should be 18-20 months but can be adjusted according to treatment response determined by clinical, bacteriological and radiological parameters.

Table 6 Drugs used in longer regimens for MDR-TB and RR-TB

Groups and steps	Drug	Abbreviation
Group A Include all three medicines	Levofloxacin or Moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine or Terizidone	Cs Trd
Group C: Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or meropenem	Ipm-Cln Mpm
	Amikacin (or streptomycin)	Am (S)
	Ethionamide or Prothionamide	Eto Pto
	P-aminosalicylic acid	PAS

2.2.6. Monitoring drug adverse effects

Adverse events associated with TB drugs are presented in Table 7. The monitoring of adverse events for patients on DR-TB treatment follows similar principles to those that apply to other DS-TB regimens (see sections 2.1.10. and 2.1.11.). Monitoring schedules should include relevant clinical and laboratory investigations to detect, manage and prevent common and significant adverse events. Safety monitoring requirements will vary depending on the chosen treatment regimen, because some parameters apply to specific drugs (e.g. full blood counts during exposure to linezolid) whereas others (e.g. liver function tests) associated with a wider variety of anti-TB drugs.

Electrocardiography (ECG)

- Recommended for all patients before starting treatment.
- Not usually repeated in patients on REZ-Lfx regimen unless there are other risks for QT interval prolongation including structural heart disease, female sex, age >65 years, electrolyte disturbance and concomitant use of medications which prolong the QT interval (WHO 2022).
- Concomitant use of clofazimine, bedaquiline and high-dose moxifloxacin, all of which can cause QT interval prolongation, requires monitoring on regular basis e.g. monthly up to 24 weeks and 2 monthly thereafter.
- QTc >500 ms prior to commencement of therapy is a relative contraindication, seek expert medical advice
- If QTc >500 ms or QTc lengthening > 60 ms whilst on therapy, the suspected drug(s) should be ceased with correction of electrolytes if abnormal and ongoing ECG monitoring until normalised

Haematological assessment (Full blood count; FBC)

There is a risk of myelosuppression even with a short exposure to linezolid. Pre-treatment assessment of haemoglobin, neutrophils and platelets is recommended. Severe anaemia in patients with TB is a significant risk factor for poor treatment outcomes and patients with a low baseline haemoglobin may be at higher risk of severe linezolid-induced haematological toxicity. Linezolid should not be administered to patients with a pre-treatment serum haemoglobin below 8 g/dL that cannot be rapidly corrected. Similarly, owing to the morbidity associated with severe neutropenia and thrombocytopenia, treatment with linezolid is not suitable in patients with neutrophil levels below 0.75×10^9 /L or platelets below 150×10^9 /L before starting treatment (WHO, 2022).

During treatment haemoglobin must be checked fortnightly at least for the first month and then monthly for the duration of linezolid exposure.

TDM is recommended for patients receiving linezolid to optimise the dose for efficacy and reduced risk of adverse effects. Blood samples are collected approximately 12 hours after a dose, even with daily dosing.

Liver function tests (LFT)

Baseline LFTs and screening for viral hepatitis B and C is recommended in patients who receive regimens with hepatotoxic drugs, including bedaquiline, pretomanid, linezolid and moxifloxacin (BpaLM/BpaL). LFTs should be repeated at 2 weeks and at least 2 monthly thereafter.

Vision check

Baseline vision check (i.e. Ishihara and Snellen chart), then monthly and formal Ophthalmology review for those on prolonged ethambutol or linezolid.

Thyroid function test (TFT)

Para-aminosalicylic acid or ethionamide/prothionamide (or both) can cause hypothyroidism, which may be suspected during clinical assessment and should be screened for with TFTs.

Psychosocial assessment

Several TB drugs are known to have neuropsychiatric adverse effects. TB medications, like clofazimine, can also have side-effects that are stigmatised, which can lead to distress. Additionally, patients may experience affective disorders during MDR/RR-TB treatment that is not directly related to a drug side effect, but due to an underlying psychiatric illness or the psychosocial stressor associated with the diagnosis and treatment of TB. The psychosocial aspects of the patient's circumstance should be carefully assessed as it can impact a patient's mental health and adherence to treatment. Regular use of a Kessler Psychological Distress Scale screening test (e.g. K6 2 monthly) is recommended. Patients receiving linezolid with concomitant other anti-depressants need careful review and monitoring for the potential development of serotonin syndrome.

Table 7: Adverse events associated with TB drugs

Adverse events	TB drug
Hearing problems	Am, Cs
Arthritis and arthralgia	Z, Bdq, Lfx, Mfx, H
CNS toxicity (dizziness, insomnia and headaches)	Lfx, Mfx, Dlm, Am, Trd/Cs, Mpm, Bdq, Eto/Pto, H, Pa
Depression, suicidal ideation	Trd/Cs, Dlm, Lfx, Mfx
Diarrhoea/or flatulence or bloating	PAS, Eto/Pto, Mpm, Amx/Clv, Lzd, Lfx, Mfx, Pa, S
Gastritis and abdominal pain	Eto/Pto, PAS, Cfz Lfx, Mfx, H, E, Z, Mpm, Dlm, Amx/clv
Gynaecomastia	Eto/Pto, H
Hypothyroidism	Eto/Pto, PAS
Metallic taste	Eto/Pto, H, Lfx, Mfx
Myelosuppression	Lzd, Mpm, H, Pa
Nausea and vomiting	Eto/Pto, PAS, Amx/Clv, Bdq, Lfx, Mfx, Mpm, H, E, Z, Cfz, Dlm, Imp/cln, Pa, Lzd, S
Nephrotoxicity (renal toxicity)	Am
Optic neuritis	Lzd, E
Ototoxicity (hearing loss, tinnitus and vertigo)	Am, S
Peripheral neuropathy	Lzd, H, Trd/Cs, Lfx, Mfx, Am
Psychotic symptoms (hallucinations and delusions)	Dlm, Trd/Cs, H, Lfx, Mfx
QT prolongation	Cfz, Bdq,Mfx, Dlm, Pa, Lfx

Adverse events	TB drug
Seizures	H, Trd/Cs, Mpm, Lfx, Mfx, Lzd, Imp/cln
Skin and sclerae hyperpigmentation	Cfz
Tendonitis or tendon rupture	Lfx, Mfx

Adapted from WHO operational handbook of Drug-resistant tuberculosis treatment Module 4, 2022.

Refer to Table 2 and Table 6 for drug abbreviations.

2.2.7. Multidrug-resistant tuberculous meningitis

The longer MDR-TB regimen is recommended. Treatment of MDR/RR-TB meningitis is best guided by drug susceptibility testing and based on knowledge of the properties of TB drugs in crossing the blood–brain barrier. Initial tuberculous meningitis treatment should be as for standard DS-TB, unless the patient is already known to have DR-TB from another site or rapid testing (i.e. GeneXpert MDR/TB).

In general:

- Levofloxacin and moxifloxacin penetrate the CNS well, as do ethionamide or prothionamide, cycloserine or terizidone, linezolid and imipenem–cilastatin.
- High-dose isoniazid and pyrazinamide can also reach therapeutic levels in the CSF, and they may be useful if the strains are susceptible.
- P-aminosalicylic acid and ethambutol do not penetrate the CNS well, and they should not be counted on as effective agents for MDR/RR-TB meningitis. Amikacin and streptomycin penetrate the CNS only in the presence of meningeal inflammation.

There is little data on CNS penetration of clofazimine, bedaquiline, and delamanid.

2.2.8. Surgery in the treatment of drug-resistant tuberculosis

Surgery has been employed in the treatment of TB since before the advent of chemotherapy. With the challenging prospect that more cases of MDR/XDR-TB are virtually untreatable with all available drugs or risk having serious sequelae despite drug treatment, there has been re-evaluation of the role of pulmonary surgery as a way to reduce the amount of lung tissue with intractable pathology and to reduce the bacterial load. Large case series have reported that resection surgery may be safe and an effective adjunct when skilled thoracic surgeons and excellent postoperative care are available. The updated WHO consolidated guidelines include a conditional recommendation for elective partial lung resection (lobectomy or wedge resection) as an adjunct to the chemotherapy of MDR/RR-TB patients with resistance to additional drugs. Radical pneumonectomy is not recommended (WHO, 2022).

Appendix 2.4: Dosage by weight band for medicines used in multidrug-resistant tuberculosis regimens

Patients aged 15 years and older

Group	Medicine	Dosing schedule	Formulation	Weight bands (kg)					Usual upper daily dose
				30-35	36-45	46-55	56-70	>70	
A	Levofloxacin		750 mg tab	1	1	1.5	1.5	1.5	1.5 g
	Moxifloxacin	Standard	400 mg tab	1	1	1	1	1	400 mg
		High dose	400 mg tab	1 - 1.5	1.5	1.5 - 2	2	2	800 mg
	Bedaquiline		100 mg tab	4 tabs daily for 2 weeks, then 2 tabs daily M/W/F for 24 weeks					400 mg
	Linezolid		600 mg daily	(<15y)	(<15y)	1	1	1	1.2 g
B	Clofazimine		100 mg cap or tab	1	1	1	1	1	100 mg
	Cycloserine or terizdone	10 – 15 mg/kg	250 mg cap	2	2	3	3	3	1 g
C	Ethambutol	15 – 25 mg/kg	400 mg tab	2	2	3	3	3	1600 mg
	Delamanid		50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 ng
	Pyrazinamide	20 – 30 mg/kg	500 mg tab	2	3	3	3	4	2 g
	Imipenem – cilastin		500 mg + 500 mg IV	2 vials (1 g + 1 g) bd Used with clavulanic acid					
	Meropenem		1g IVI	1 vial tds or 2 vials bd Used with clavulanic acid					
	Amikacin	15 – 25 mg/kg	500 mg in 2mL IVI	2.5 mL	3 mL	3 - 4 mL	4 mL	4 mL	1 g
	Streptomycin	12 – 18 mg/kg	1 g vial IMI	Calculate according to dilution used					1 g
	Ethionamide or Prothionamide	15 – 20 mg/kg	250 mg tab	2	2	3	3	4	1 g
	P-aminosali-cylic acid (PAS)	8 – 12 g/day 2–3 div doses	4 g sachet	1 bd	1 bd	1 bd	1 bd	1 - 1.5 bd	12 g
Other drugs	Isoniazid	Standard	100 mg tab	2	3	3	3	3	300 mg
		High dose	100 mg tab	3 – 4	4 – 5	6	6 - 7	7 - 8	-

Patients aged 15 years and older									
Group	**Medicine**	**Dosing schedule**	**Formulation**	**Weight bands (kg)**					**Usual upper daily dose**
				30-35	**36-45**	**46-55**	**56-70**	**>70**	
	Clavulanic acid		125 mg as Augmentin	1 bd	1 bd	1 bd	1 bd	1 bd	Only with carba-penems
	Gatifloxacin		400 mg tab	2	2	2	2	2	800 mg
	Pretomanid		200 mg tab	1	1	1	1	1	200 mg

Adapted from: WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022.

bd: twice a day
div: divide
IMI: intramuscular injection
IV: intravenous
IVI: intravenous injection
tds: three times per day

2.2.9. References

Dorman, S. E., Nahid, P., Kurbatova, E. V., Phillips, P. P. J., Bryant, K., Dooley, K. E., Engle, M., Goldberg, S. V., Phan, H. T. T., Hakim, J., Johnson, J. L., Lourens, M., Martinson, N. A., Muzanyi, G., Narunsky, K., Nerette, S., Nguyen, N. V., Pham, T. H., Pierre, S., Purfield, A. E., … Tuberculosis Trials Consortium (2021). Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *The New England Journal of Medicine, 384*(18), 1705–1718. https://doi.org/10.1056/NEJMoa2033400

Nahid, P., Dorman, S. E., Alipanah, N., Barry, P. M., Brozek, J. L., Cattamanchi, A., Chaisson, L. H., Chaisson, R. E., Daley, C. L., Grzemska, M., Higashi, J. M., Ho, C. S., Hopewell, P. C., Keshavjee, S. A., Lienhardt, C., Menzies, R., Merrifield, C., Narita, M., O'Brien, R., Peloquin, C. A., … Vernon, A. (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases, 63*(7), e147–e195. https://doi.org/10.1093/cid/ciw376

Nahid, P., Mase, S. R., Migliori, G. B., Sotgiu, G., Bothamley, G. H., Brozek, J. L., Cattamanchi, A., Cegielski, J. P., Chen, L., Daley, C. L., Dalton, T. L., Duarte, R., Fregonese, F., Horsburgh, C. R., Jr, Ahmad Khan, F., Kheir, F., Lan, Z., Lardizabal, A., Lauzardo, M., Mangan, J. M., … Seaworth, B. (2019). Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. *American Journal of Respiratory and Critical Care Medicine, 200*(10), e93–e142. https://doi.org/10.1164/rccm.201909-1874ST

World Health Organization. (2022). *Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis* (WHO/UCN/TB/2022/2). World Health Organization. https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2

World Health Organization. (2022). *WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment*. World Health Organization. https://www.who.int/publications/i/item/9789240063129

2.3. Case management

2.3.1. Introduction

Case management is the delivery of individualised nurse-led patient care, developed by a multidisciplinary team to achieve the successful completion of TB treatment (Global Tuberculosis Institute, 2012).

Case management is essential to the success of TB treatment. It involves education about TB and the development of a therapeutic relationship to ensure treatment is adhered to and completed satisfactorily. It also involves the identification and screening of TB contacts (described separately in 5.1. Tuberculosis contact tracing). When treating TB, it is never optimal to prescribe medication treatment alone. The prescription must always be accompanied by robust case management.

2.3.2. Rationale

The successful treatment and cure of TB requires patients to take numerous medications for extended periods of time. This is a difficult undertaking for many, particularly those who experience side effects. Medication adherence can be further hampered by both the stigma and potential visa implications associated with a TB diagnosis. Patients may also be reluctant to continue treatment once their symptoms of illness begin to resolve. Many TB patients are recent migrants with limited English and limited understanding of TB and associated treatments. Furthermore, even well-informed and well-intentioned patients can experience challenges with adherence, due to competing priorities.

Patients who face these challenges and are left unsupported, are more likely to miss doses and experience adverse outcomes or prolonged treatment. Case management primarily ensures the successful completion of TB treatment, but is also required as a public health measure to reduce TB transmission and the development of drug resistance caused by poor adherence.

Contact tracing further reduces TB disease by diagnosing secondary TB cases early and identifying and treating TBI.

All patients undergoing treatment for TB and TBI in WA have the support of a case manager at the WATBCP. This includes patients who are diagnosed and treated by physicians that work outside the WATBCP (refer to 2.3.17. Case management for tuberculosis patients treated by physicians external to WATBCP). The case manager works closely with medical staff and other professionals involved in the care of the patient to support the completion of TB treatment.

2.3.3. Components of case management

The components of case management include (Ross, Curry, & Goodwin, 2011):

- case detection, including contact tracing
- assessment and care planning of index
- care coordination
- medication management
- self-care support
- advocacy and negotiation

- psychosocial support
- monitoring and review
- case closure.

2.3.4. Case detection, including contact tracing

Case detection is the early identification of patients with TB disease to ensure that TB control activities can be initiated as soon as possible. This involves liaison with a wide range of stakeholders including, but not limited to, hospital-based and private physicians, infection control teams, staff health and workplace managers.

Coordination of timely contact tracing (see section 5.1. Contact tracing) is required to detect cases of TB related to the index case, to detect and treat TBI or TB (a secondary case) due to transmission from the index case, and to identify other cases that have TB acquired from a common, but unidentified source index case (cohort effect).

2.3.5. Patient assessment

Assessment involves gathering information about the patient's disease as well as their medical and social history to assist TB care planning. Information should be collected from the patient and/or their carer, other health care providers, community-based agencies, and other government departments e.g. housing, and schools.

Assessment should be initiated as early as possible after diagnosis either in an outpatient setting or during the patient's hospital admission. It may occur during the first clinic appointment or at the first home visit conducted by the case manager. During the assessment the case manager should aim to address and document the following:

- Previous medical history.
- Current medications (including dosage).
- The onset of TB symptoms (to determine infectious period and extent of contact tracing).
- The patient's knowledge and beliefs about TB.
- The prescribed TB medications.
- Potential barriers to treatment adherence that may indicate the need for DOT i.e. difficulty swallowing tablets, polypharmacy, drug and alcohol misuse, psychological factors.
- The patient's social circumstances that may impact treatment compliance or completion i.e. housing insecurity, employment, transport, education, residency status, welfare issues, cultural background.
- Enhanced surveillance data to complete statutory infectious disease notification that is forwarded to the WA Health Department.

Patient assessment should occur regularly in order to detect changes to the patient's circumstances before they negatively impact treatment e.g. social issues, communication and language difficulties, medication side effects or interactions, travel plans etc.

2.3.6. Care planning

The patient's care plan is pivotal to case management and should be developed with consideration of the individual's personal circumstances and health needs. The plan should be

developed in consultation with the patient, their medical team and the broader case manager team. The plan needs to be flexible to accommodate the patient's individual situation and requirements according to treatment progress.

2.3.7. Case management meeting

The team within the WATBCP meet fortnightly to discuss the care of TB cases. The purpose of these meetings is to document new TB cases, discuss challenging issues and barriers to effective care delivery, assess contact tracing and ensure that clinical outcomes are achieved.

2.3.8. Care coordination

The assigned case manager is the central point of contact for the duration of a patient's TB treatment. The case manager is responsible for the coordination of care and for communicating with the patient (via telephone, home visits and clinic attendances) throughout their treatment. An example of the care pathway for cases of drug susceptible uncomplicated TB is provided in Table 8.

For extended TB treatment and MDR-TB treatment, care is planned and provided in response with deviations to the pathway outlined in Table 8.

Table 8: Care pathway in uncomplicated TB case management

Treatment Milestone	Assessment and Care Planning
Start of treatment	Clinic visit – meet with TB physician and case manager, begin discussions on contact tracing, supply one month's medications
One week	Home visit – assess environment, complete management plan including contact tracing
2 weeks	Clinic visit – physician and case manager, supply one month's medications
4 to 6 weeks	Clinic visit – physician and case manager
2 months	Clinic visit – physician and case manager – drug sensitivities reviewed, treatment changed from intensive to continuation phase, supply one month's medications
3 months	Clinic visit – physician and case manager, supply one month's medications
4 months	Clinic visit – physician and case manager, supply one month's medications
5 months	Clinic visit – physician and case manager, supply one month's medications

Treatment Milestone	Assessment and Care Planning
6 months	Clinic visit – physician and case manager – treatment ceased and outcome reported.

2.3.9. Medication management

The goal of TB treatment is to see the patient successfully complete their treatment. Case managers play an integral role in this process by monitoring medication adherence, supporting patients through medication side-effects, and assisting patients to overcome barriers to treatment. TB medications can be self-administered or directly observed. The case manager should work closely with the medical team to ensure that the medication is being taken according to the prescription and policy standards.

Case managers are responsible for ensuring that all patients have a continued supply of TB medication, including for patients living in rural and remote areas. The medication should be supplied to the patient without any direct cost (see 8.1. Fees and charges).

The WATBCP has an Imprest store of TB medications at the Anita Clayton Centre. Whereas only first line TB medications were available from the TB clinic in the past, now all second-line TB medications and adjuvant medications likely to be required during TB treatment (e.g. pyridoxine, prednisolone, anti-emetics etc) are also available. This Imprest stock is maintained and overseen by the Sir Charles Gairdner Hospital Outpatient Pharmacy. SAS approval that is required for some TB medications (e.g. pyrazinamide, bedaquiline, clofazimine etc) can be obtained by the WATBCP online directly with the Therapeutic Goods Administration (TGA). Parenteral medication (e.g. intravenous amikacin), is managed through an ambulatory service such as Silver Chain, with case manager oversite.

The WATBCP will supply TB medication to any patient within WA, irrespective of who has medical governance. Patients who are treated by a physician outside of WATBCP can have medications supplied to them by a case manager, according to the physician's prescription and instruction. Generally, the patient does not need to attend the Anita Clayton Centre to collect these medications. The WATBCP provides all medications at no cost to the patient (see 2.3.17. Case management for tuberculosis patients treated by physicians external to WATBCP).

2.3.10. Non-adherence and directly observed therapy (DOT)

Case managers must encourage adherence to treatment. This can be facilitated by thorough education outlining the indication and importance of treatment, reporting and management of adverse effects, the use of dosette boxes or Webster packs as required, and ensuring an uninterrupted supply of medication.

Adherence should be checked regularly by directly questioning patients, performing pill counts and prompt contact when a patient does not attend a planned appointment. If there is evidence of non-adherence, this should be discussed with the treating physician as soon as possible, and a plan made for enhanced monitoring. Timelines for tolerance of unacceptable adherence and measures to be taken if this threshold is reached should also be discussed and planned.

DOT involves observing the patient swallow every dose of treatment. It is not utilised on all patients treated for TB in WA. It is used selectively in the following circumstances:

- Demonstrated consistent poor adherence to therapy.
- Relapsed TB where non-adherence is considered a possible reason for relapse.
- All MDR TB cases.
- All hospital inpatients.
- All patients within correctional or detention facilities.
- Any other patient where the case manager considers there to be a high risk of non-adherence.

If possible, DOT should be established at the start of TB treatment as patients who are switched to DOT can see this as a disciplinary measure resulting in increased resistance and non-adherence. The value of DOT should be reinforced by the treating physician and the case manager. DOT may also need to be introduced if a patient is clinically deteriorating while on treatment, they remain culture positive two months into treatment or experience adverse effects to the medication.

DOT is established and managed by the assigned case manager. DOT is commonly provided by the WATBCP case manager team, but with consent from the patient can be provided by a community nurse or service, local doctor, local pharmacist, correctional staff, or hospital staff. It is not recommended that family members observe therapy as they are not neutral or objective about the patient's health.

When DOT is required, the patient must complete a DOT Agreement (see Appendix 2.5: Directly observed therapy (DOT) agreement), which states the agreed time and location for DOT and includes the public health implications of not taking the treatment as prescribed. DOT can be arranged for any location convenient and safe to the patient and the provider. It is preferable for DOT to be provided at the clinic, but this may not be possible for all patients. Community based DOT can be provided more efficiently by establishing partnerships with community-based services.

The WATBCP advocates for daily DOT especially during the intensive phase of treatment. It is the responsibility of the assigned case manager to determine the most suitable method for DOT to occur and to seek the approval of the treating physician. Virtual or TeleDOT accessed via a URL link or app (i.e. Health Direct) is a convenient alternative to in-person DOT.

When a patient with infectious TB refuses treatment and cannot be managed by routine case management or DOT, there is provision in the Public Health Act (WA) 2016, Part 9 for the Chief Health Officer to issue a Public Health Order to isolate the patient. It is a measure of last resort and can only occur after all reasonable attempts have been made to counsel the patient to take TB treatment.

The Chief Health Officer can also issue a test order when there is reasonable suspicion of infectious TB, but the patient will not submit to testing. Failure to comply with the test order can lead to a financial penalty or detainment.

Incentives and enablers may assist with adherence. Incentives are small rewards given to patients to encourage them to take their medications or attend their allocated appointments. Incentives may include balloons, stickers, toys, books, movie tickets or personal care items.

Enablers such as taxi vouchers can assist clients to take treatment and attend appointments by overcoming barriers such as transportation issues.

2.3.11. Self-care support

The level of support offered to TB patients by their case manager will vary according to the needs of the individual. While patients are supported to manage their own condition, the case manager is expected to:

- Ensure the patient has a good understanding of his or her condition and provide continuous education regarding TB and its treatment.
- Provide and/or make referrals for general health education and advice e.g. diet, exercise, smoking cessation.
- Provide and/or make referrals for advice on health conditions specific to the patient's circumstances e.g. ensuring general practitioner involvement for diabetes management.
- Provide education on navigating the healthcare system and services to contact regarding non-urgent issues.

2.3.12. Advocacy and negotiation

A key role in case management is advocating for and negotiating on behalf of the patient for access to services for needs identified in the care plan. This may involve liaising with other government departments e.g. housing, social security; liaising with employers on behalf of the patient; ensuring appointments are made and attended for other providers; and, importantly, education of the patient's family, friends and colleagues regarding the nature of TB and its treatment.

The case manager also helps to advocate for the patient when liaising with the patient's TB physician. This is especially important if the physician works outside the WATBCP. The case manager is a crucial conduit, ensuring the physician is aware of any difficulties or non-adherence with treatment and, at the same time, the patient understands and complies with the physician's recommendations.

When TB treatment is prescribed by a physician outside the WATBCP and the case manager has concerns regarding the TB treatment regimen or treatment progress, these issues must first be raised with the treating physician. If the case manager remains concerned about a problem that is not being addressed, this should be raised with the Medical Director of the WATBCP who will contact the treating physician (see 2.3.17 Case management for tuberculosis patients treated by physicians external to WATBCP).

2.3.13. Psychosocial support

The case manager has the most contact with the patient and should provide continuity of care from the time of diagnosis to discharge from the program. This regular contact ensures support for the patient and promotes completion of treatment. Accepting a diagnosis of TB and the social stigma associated with the diagnosis can be a source of great distress for some patients. The case manager plays an important role supporting patients through this difficult time. As well as enabling the completion of TB treatment, TB case managers often provide considerable wrap-around support to rehabilitate patients to full health and function.

2.3.14. Clinical handover

It may be necessary for case managers to handover the care of their patients when they are on leave. The patient should be made aware of the handover and given contact details for the relieving case manager. The handover should be documented in the patient record according to The MHPHDS – PH Clinical Handover Procedure.

2.3.15. Monitoring and review

The case manager needs to determine if a patient is receiving and adherent with the TB treatment. The care plan may need revision as treatment progresses. The frequency of monitoring is dependent on the patient's circumstances and level of need. It may also vary during treatment (i.e. more frequently at the beginning of treatment) and need to increase in times of personal crisis or treatment issues (e.g. medication side effects). Monitoring may take place daily, weekly or monthly and may occur in a variety of forms (i.e. direct contact through clinic appointments, home visits or telephone contact). Email can be used, but only with the patient's consent and only according to local procedure. All episodes of patient care and patient-related interactions (i.e. with other care providers) should be recorded in the patient's record.

Home visiting is encouraged to evaluate the patient's home environment and social situation. It can also be important to provide support and promote adherence in a familiar environment. Not all patients require regular home visiting, but it is recommended that the case manager meets regularly patients on TB treatment, generally a minimum of every fortnight whether it be at home or in the clinic (refer to Table 8).

Pill counts should be performed regular to verify medication adherence.

2.3.16. Case closure

The goal of TB case management is for the patient to successfully complete their treatment. The point at which this occurs is ultimately the decision of the treating physician. The decision to discharge a patient from case management, however, should be determined by the case manager and the treating physician together. The process for discharge of patients from case management or 'case-closure' should be clear, defined in time and documented in the patient's record.

Case closure after routine TB treatment generally occurs 2-3 months after the successful completion of TB treatment. Prolonged follow-up may be required if there are concerns regarding adherence, a non-standard treatment regimen, the patient had extensive disease or has ongoing health issues. The decision on follow-up and case closure is made by the treating physician and the case manager together.

2.3.17. Case management for tuberculosis patients treated by physicians external to WATBCP

Introduction

Most patients treated for TB in WA are managed by physicians who work for the WATBCP based at the ACC. This is done in close collaboration with case management nurses. However,

about 24% of TB notifications are managed by respiratory and infectious diseases physicians in other clinics e.g. public hospital out-patient clinics or private rooms ('externally treated patients'). The WATBCP is supportive of this occurring as it often benefits the patient (continuity of care, maintenance of established therapeutic relationship, convenience), the physician (satisfactory completion of established therapeutic relationship, maintenance of skills and interest) and WATBCP generally (maintenance of widespread expertise). Even though these patients attend their physician outside of the Anita Clayton Centre it is the policy of the WATBCP that every patient treated for TB is supported by case management.

Case management is individualised, nurse-led patient care that aims to achieve successful completion of TB treatment and prevention of further cases through contact tracing (see section 2.3. Case management). Every patient receiving TB treatment in WA is assigned a WATBCP case management nurse, irrespective of who is responsible for prescribing and overseeing the treatment.

TB case manager services

Case management is individualised, so the scope and details of what a case manager does for an individual patient will vary according to requirement and the direction of the treating physician. Activities often include:

- **Medication supply:** WATBCP can supply all TB medications to externally treated patients directly to the patient at no cost. While TB drugs can also be dispensed from, teaching hospital/pharmacies, supply from Anita Clayton Centre is encouraged. This facilitates adherence to treatment by requiring less of the patient, ensuring they never run out of medication and allowing checks on adherence by the case manager. This is done strictly according to the prescription and directions of the treating physician.
- **Counselling and support:** e.g. at treatment initiation, psycho-social support, advocacy (e.g. in the workplace), ensuring ongoing maintenance of treatment, managing barriers to satisfactory adherence.
- **Feedback of issues to the treating physician:** e.g. side effects, poor adherence.
- **Directly observed therapy (DOT):** Arrangement and delivery.
- **Contact tracing:** In hospital, contacts are managed by the responsible institution with advice, as required, from WATBCP. All other contacts are identified and followed up by WATBCP case managers.
- **Notification dataset:** collection and recording of TB notification and enhanced surveillance.

Location of case management

WATBCP case managers are mobile and flexible in respect to where and when they deliver their care. TB patients are regularly visited at home (by appointment, at the patient's convenience) and can, when appropriate, be visited as in-patients, in outpatient clinics or private rooms, and in the workplace or school.

Referral of patients for case management

If a physician, who is treating a patient for TB outside of the WATBCP, wishes to maintain medical governance of that patient but have the support of case management, a referral for a medical appointment (e.g. through e-referral or the Central Referral Service) is not required.

However, before the patient attends or contacts the Anita Clayton Centre (e.g. to collect medication) two documents are requested:

- **TB notification** – please follow this link. Completed notification forms can be sent to the WATBCP by email or fax (see contact details below).
- **Written prescription of the TB treatment regimen** – in any format (e.g. correspondence, formal script, email) including drug, dose and patient's weight, sent by fax or email (see contact details below).

It is preferred that patients are not directed to attend at Anita Clayton Centre with these documents in-hand, but rather the documents are sent directly to the WATBCP with the patient's contact details, and the WATBCP will then arrange for the medication supply within 1 – 2 days. The TB drugs prescribed for externally treated patients are formally charted and dispensed by a WATBCP physician according to the instruction from the external physician and then delivered by the case manager. If there is any concern or uncertainty regarding the treating physician's instruction this will be clarified by the WATBCP physician directly with the treating physician.

Relationship between the treating physician and case manager

The medical governance of TB patients always remains with the treating physician. Case managers take instruction from this physician regarding drug prescription, directions for changes to and length of treatment, management of side effects and poor adherence. All TB cases are discussed at a fortnightly case management meeting at the ACC, but WATBCP physicians will not direct case managers regarding externally treated patients unless requested by the treating physician.

Treating physicians are encouraged to share clinic correspondence or review summaries with case managers to ensure the case managers are up to date with the treatment plan and other instructions. Case managers will also be pleased to be contacted at any other time by phone or email. Case managers are allocated to patients according to Health Service Areas (Metro North, South and East, and WA Country Health Service). Therefore, it is likely that the same case manager will be caring for all TB patients under the care of an individual physician. The WATBCP encourages physicians to establish a working relationship and rapport with the case manager for their area.

The only aspect of the management of externally treated patients that the WATBCP physicians will be involved in is oversight of the adequacy and completeness of contact tracing. This is a requirement of the Public Health role of the WATBCP. Any concerns that the treating physician has regarding contact tracing, together with decisions around this and outcome data, can be shared with the Medical Director of the TB Control Program if required.

What happens if issues arise?

Contact details for the WATBCP are given below.

1. Treating physician has concerns regarding TB patient

When a physician treating a patient with TB from outside of the WATBCP has concerns e.g. non-adherence to treatment, non-attendance at follow-up appointments, drug side effects etc., the case manager should be seen as a potential resource. The WATBCP encourages

physicians to contact case managers by phone or email. The TB physicians working at the Anita Clayton Centre are also available to discuss TB patient management and will be pleased to provide consultative advice without necessarily seeing the patient. All new and problematic TB cases are discussed in a fortnightly TB Case Management Meeting at the ACC, including externally treated patients. Physicians from outside the WATBCP are welcome to join this meeting when their patient is discussed, either in person or by video or telephone. If the treating physician is not present at the Case Management meeting, any concerns or recommendations that arise from the meeting will always be shared by the case manager with the treating physician.

2. Treating physician has concerns regarding case management

If a physician treating a patient with TB has concerns regarding the activity or involvement of the case manager, these should be, in the first instance, taken up with the case manager directly. Case managers welcome contact and feedback from physicians treating their patients.

If the concerns are unresolved after discussion with the case manager or relate to the public health activities for the TB patient (e.g. contact tracing, surveillance data collection), the Medical Director or Clinical Nurse Manager of the program should be contacted (see contact details below).

3. Case manager has concerns regarding an externally treated TB patient

When a case manager has concerns regarding an externally treated TB patient, these will always be taken up with the treating physician directly, in the first instance. physicians from outside the WATBCP are encouraged to let the relevant case manager know how they would prefer to be contacted (mobile, voicemail, email, message with room's secretary etc.).

If a case manager is unable to contact the treating physician after at least 2 attempts, or the case manager feels the concern is unresolved after making contact, the case manager will take these concerns up with a physician at the WATBCP. The WATBCP physician will then attempt to resolve the concern with the treating physician. WATBCP physicians will not give instruction to case managers on the management of externally treated patients unless there is a significant and immediate risk to the patient.

WATBCP Contact

General
Business hours: 8.15 – 4.15, Monday to Friday
Phone: 9222 8500 Fax: 9222 8501
Email: ACCadmin@health.wa.gov.au

Medical Director
Dr Alison Keed
Phone: 0407 445 120 or 9222 8500
Email: alison.keed@health.wa.gov.au

Clinical Nurse Manager
Brenda Kamau
Phone: 9222 8530
Email: Brenda.Kamau@health.wa.gov.au

Appendix 2.5: Directly observed therapy (DOT) agreement

Government of **Western Australia**
North Metropolitan Health Service
Mental Health, Public Health and Dental Services

Directly Observed Therapy Agreement - Active Tuberculosis (TB) Disease

AFFIX PATIENT IDENTIFICATION LABEL HERE

UMRN:
Family Name:
Given Name:
Address:

DOB: Sex M F

PATIENT INFORMATION – TO BE COMPLETED BY THE PATIENT

Tuberculosis (TB) is a curable and preventable disease.

I have been told that I have TB and that I need to take medications for _____ months.

PATIENT DECLARATION – TO BE COMPLETED BY THE PATIENT

I understand that a TB nurse or _____ will watch me take my medicine.

To take my medicine I will:

☐ Come to the Anita Clayton Centre at _____ hours on:
Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday ☐

☐ Attend _____ at _____ hours on:
Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday ☐

☐ Dial into health direct via the link provided by my case manager at _____ hours:
Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday ☐

☐ Take my medication unsupervised at the following time _____ and then send a video SMS message to the following phone_____ confirming I have taken my medication on:
Monday ☐ Tuesday ☐ Wednesday ☐ Thursday ☐ Friday ☐ Saturday ☐ Sunday ☐

I have been told that if I do not take my medicine my TB may get worse and I could spread the disease to my friends and family.

Patient / Guardian signature…….. Date……..

INTERPRETER'S DECLARATION – TO BE COMPLETED BY THE INTERPRETER

Interpreter services required ☐ Yes ☐ No Language provided: _____

I declare that I have interpreted the dialogue between the patient / guardian and health professional to the best of my ability and understanding.

Interpreter's full name ……

Interpreter signature …… Date……

HEALTH PROFESSIONAL WHO FACILITATED THE CONSENT PROCESS

I have informed this patient / guardian as detailed above, including the nature, likely results and relevant foreseeable risks of the treatment.

TB nurse signature…….. Date……

Copy for patient and scan to notes

Chapter 3: Tuberculosis infection

3.1. Tuberculosis infection – Diagnosis

3.1.1. Introduction

The WHO estimates that one quarter of the world's population is infected with *M. tuberculosis*. In the infected individual, the immune system successfully contains the infection but usually fails to clear it. A state of persistent immune response to the stimulation by *M. tuberculosis* antigens develops without evidence of TB disease. This is known as tuberculosis infection (TBI), formerly termed latent tuberculosis infection (LTBI) and is likely to represent a dynamic spectrum condition rather than a distinct state. (WHO, 2018; Stock & NTAC, 2017).

A person withTBI with a normal immune response that has not receive treatment for TB infection has an estimated life-time risk of active TB of 5%-10%. About half these cases of TB reactivation occur within 2 years of the initial infection (refer to CDC webpage - TB Risk Factors | TB | CDC)

3.1.2. Rationale for testing for TBI

Most TB notifications in Australia are in the overseas-born population (92% of 2021 cases in WA). This, combined with evidence of low local transmission, indicates that most of TB cases in Australia are the result of reactivation of TBI acquired prior to immigration to Australia. (Stock & NTAC, 2017; Tuberculosis notifications in Western Australia, 2021). This highlights the importance of diagnosing and treating TBI in high-risk populations as a fundamental strategy in TB control to achieve the goal of TB elimination.

3.1.3. Indications for TBI testing

Testing for TBI should be performed with the intention to offer preventive treatment. It aims to identify individuals with high pre-test probability of TBI and increased risk of progressing to TB (Stock & NTAC, 2017; Marais et al., 2009).

Risk factors for high pre-test probability of tuberculosis infection

Certain subgroups in the general population are at higher risk of TB infection (Mazurek et al., 2010) and include:

- A contact of TB.
- Individuals born, or who have lived for prolonged periods of time (> 3 months), in countries that have a high incidence of TB (>40/100 000 per year). For country-based TB incidence refer to WHO interactive site (https://worldhealthorg.shinyapps.io/tb_profiles/) (WHO, 2023).

Amongst immigrants, TBI testing should be a priority for the following groups (without necessarily precluding other migrants from testing):

- immigrants that migrated within the last 5 years
- immigrants who have been granted permanent residency
- Immigrants with a history of TB contact within the last 2 years, (irrespective of the country of origin)
- younger immigrants, as future life protection from TBI treatment is likely to be longer and treatment is better tolerated,
- older immigrants with risk factors for reactivation (see next section).
- Aboriginal Australians, especially if resident in communities where local transmission of TB has been demonstrated (for further information, please consult the WATBCP directly)
- certain occupational groups or residential settings (refer to Table 9).

Table 9: Groups with increased risk of TB exposure

Occupational or residential settings with increased risk of TB exposure
Healthcare workers
Individuals in residential care facilities
Individuals in prisons and detention centres
Mycobacteriology laboratory personnel and mortuary staff performing autopsies

Risk factors for progression of tuberculosis infection to tuberculosis disease

Once infected with *M. tuberculosis* most people do not develop disease. However, there are certain subgroups of the population who are at higher risk of progression to TB (WHO, 2018; Stock & NTAC, 2017; Mazurek et al 2010; American Thoracic Society, 2000).

These include:

- individuals recently infected with *M. tuberculosis* (within 2 years)
- infants and children < 5 years old, especially if they are contacts of TB patients
- individuals with a history of untreated or previously inadequately treated TB, including persons with fibrotic changes or upper lobe infiltrates on CXR consistent with prior TB
- individuals with associated medical conditions or treatments (refer to Table 10).

Table 10: Co-morbid conditions that increase the risk of TB disease

Co-morbid condition (References given as superscripts)	Estimated relative risk of reactivation*
HIV infection (untreated) – see chapter 4.5	20 – 37[1]
Treatment with anti-TNFα agent – see chapter 5.4	6[2]
Treatment with other immunosuppressive therapy equivalent to prednisolone 15mg/day for > 1 month – see chapter 5.4	2-3
Solid organ transplant	20 - 74[3]
Dialysis & chronic renal failure	8[4]
Diabetes (especially if poorly controlled)	2 – 4[5]
Excess alcohol intake	3[6]
Cigarette smoking	2.5[7]
Under weight, malnutrition	4[8]
Silicosis	4[9]
Haematological malignancy	2 - 40[10]
Cancers of the head, neck or lung	25 - 50[11]
Individuals who have had gastrectomy or jejunoileal bypass	2[12]

* Relative risk refers to multiple of normal risk or reactivation without given risk factor.

1. Getahun et al. *Clinical Infectious Diseases*, Volume 50, Issue Supplement_3, May 2010, Pages S201–S207
2. Aydin et al. J Clin Pharm Ther. 2019 Aug;44(4):553-560.
3. Alizadeh et al. Tanaffos. 2016; 15(3): 124–127
4. Dobler, McDonald & Marks. PLoS One. 2011; 6(12): e29563
5. Jeon & Murray PLoS Med. 2008 Jul; 5(7): e152
6. Imtiaz et al. Eur Respir J. 2017 Jul; 50(1): 1700216
7. Bates et al. *Arch Intern Med.* 2007;167(4):335-342
8. Gupta et al. Lung India. 2009 Jan-Mar; 26(1): 9–16
9. Ehrlich et al *BMC Public Health* **volume 21**, Article number: 953 (2021)
10. Anibarro et al. Mediterr J Hematol Infect Dis. 2014; 6(1): e2014026
11. Cheon et al. J Thorac Dis. 2020 Sep; 12(9): 4950–4959
12. Jung et al. World J Gastroenterol. 2016 Feb 28; 22(8): 2585–2591

ALWAYS test for TBI in the following patients with a view to treatment of TBI if diagnosed:

- HIV infected
- preparing for any solid organ transplant
- preparing for haemodialysis
- starting anti-TNF treatment.

3.1.4. Tests for TBI

The screening tests available for TBI in WA are:

- tuberculin skin test (TST), also called the Mantoux test
- QuantiFERON-TB Gold test (QFT).

Both tests are indirect and reflect cellular immune response to previous sensitisation with mycobacterial antigens. Neither test can distinguish between individuals with TBI, TB disease or past TB infection.

A positive TST or QFT test suggests TB infection. It does not indicate the presence or absence of TB disease. A positive TST or QFT does not indicate disease and a negative result does not rule out disease.

The result of either TST or QFT must be interpreted with the patient's history, clinical presentation, and reason for testing in mind. TB disease needs to be excluded before a diagnosis of TBI can be made based on a positive screening test.

If TB disease is suspected, additional testing is needed. (Refer to sections 1.1. Diagnosis of tuberculosis - Laboratory and 1.2 Diagnosis of tuberculosis - Clinical).

3.1.5. Tuberculin skin test (TST)

The TST has been used in the management of TB since the 19th century. The form of tuberculin used in WA is 'Tubersol', a tuberculin purified protein derivative (PPD), which is a mix of proteins derived from cultures of *M. tuberculosis*. Tuberculin does not contain viable organisms and is safe to use in pregnancy, children and in immunocompromised individuals. When injected into the skin of a person previously infected with *M. tuberculosis*, a hypersensitivity reaction occurs at the injection site. It is this hypersensitivity reaction that is measured. A dose of 5 International Units (IU) of human PPD in 0.1 ml is used.

Indication for TST

Refer to section 3.1.3. Indications for tuberculosis infection testing.

Contraindications for TST

- Individuals with a history of severe skin reaction following a previous TST (vesiculation, ulceration, necrosis).
- Individuals with a history of a severe immediate hypersensitivity reaction following a previous TST.
- Confirmed TB disease or infection.

- Individuals previously treated for TB disease.

Recent immunisation with measles mumps rubella (MMR), varicella or yellow fever vaccines within the last month as the risk of a false negative result increases.

In addition, caution should be used in the following situations:

- Short-term immunosuppressant therapy (may cause a false negative reading).
- Documented prior positive reaction (reconsider the need for a repeat test).

Administration of the TST

All health professionals performing a TST should be trained and accredited to administer and interpret the TST. A dose of **5 IUs of human PPD in 0.1 ml** is injected intradermally. Informed consent should first be obtained from the patient. Recording and documentation of the TST should include as a minimum:

- age
- dates and result of any previous TST
- previous adverse reactions
- date of any previous BCG vaccination
- reason for testing.

Reading of the TST

The reaction to the TST begins 5-6 hours after injection and produces maximum induration at 48-72 hours, at which time it should be read. A reading up to 96 hours (4 days) is considered valid in circumstances when this is necessary. The measurement should be in millimetres; the diameter of induration across the transverse axis of the forearm. Any surrounding erythema IS NOT included in the measurement. Absence of induration should be recorded as 0 mm rather than as ‘negative’ as this can cause confusion. Any blistering, if present, should be noted.

Adverse reactions to the TST

Potential reactions to the TST include:

- vaso-vagal reactions
- immediate flare with a local rash
- strong positive reactions of blistering, ulceration and necrosis at the site of injection. This can be alleviated with cold packs and topical corticosteroids. Such reactions may result in scarring.
- lymphadenitis and regional adenitis
- anaphylaxis or life-threatening hypersensitivity reactions are rare, but the TST should be performed where access to adrenaline and resuscitation equipment are available.

Interpretation of the TST

The TST result should be interpreted in conjunction with the reason for testing, clinical features and medical history of the patient. The cut offs listed below (Table 11) may be increased or reduced to improve specificity and sensitivity respectively. Cut off values may also change in specific circumstances e.g. mass screening exercises.

Table 11: TST Diameter considered indicative of infection with TB

TST ≥ 5mm	TST ≥ 10mm

• HIV positive patients (should be referred for medical assessment regardless of TST reading).
• Child <5 years old AND significant TB risk e.g. contact of TB, abnormal chest x-ray, born or resident for >3 months of a high prevalence TB country (defined as >40 cases/100 000 population per year).
• Significant immunosuppression AND significant TB risk e.g. Contact of TB, abnormal chest x-ray, born or resident for >3 months of a high prevalence TB country. Examples of immunosuppression include:
  ○ individuals with organ transplants
  ○ individuals on immunosuppressant therapy or prednisolone 15mg/day for > 1 month
  ○ TNFα treatment
  ○ dialysis patients
	All others

Effect of BCG vaccination

Most people vaccinated with BCG develop a TST reaction within 2 months but this wanes with time).

BCG vaccination given in infancy is unlikely to affect TST test interpretation in adults. Where BCG has been given in the preceding 5 years, or more than one BCG has been given; then the interpretation of the TST reading needs to be undertaken by a physician with experience in TB medicine. A QFT test may be used for clarification. Prior BCG vaccination is not considered significant when setting TST cut off points.

False negative TST

Causes of false negative TST i.e. negative test in the presence of *M. tuberculosis* infection include (Northern Territory Centre for Disease Control, 2016):

- PPD out of date or improperly handled
- subcutaneous injection or unrecognized leakage at the time of administration
- reading of the test <48 hours or >5days after injection
- test performed too soon after TB infection; The TST may need to be repeated 8 -12 weeks following exposure
- acute viral or bacterial infections, including TB
- impaired cellular immunity e.g. HIV, immunosuppression
- live virus vaccination within 4 weeks.

False positive TST

Causes of a false positive TST i.e. positive test in the absence of *M. tuberculosis* infection include (Northern Territory Centre for Disease Control, 2016):

- rupture of a small venule at time of injection
- trauma to the site e.g. scratching
- failure to distinguish erythema from induration at time of TST reading
- past BCG vaccination or exposure to NTM
- sensitivity to preservative in PPD.

Booster reaction and two step testing

The ability to mount an immune response to mycobacterial antigens can wane with time in individuals with previous TB exposure. Such individuals may not react when tested with the TST. However, the TST itself may boost immunological memory and a repeat TST shortly after the initial one may produce a much larger response (a boosted response). The initial test result should be considered a false negative result, and the second result considered the true reading.

Two-step testing is performed when there is a need to establish a true baseline TST reaction. It is performed to distinguish boosting from conversion in people who have serial TSTs. The second test is needed only if the initial reading is negative. The second TST of a two-step TST should be performed 1-5 weeks after the initial negative TST with the second reading taken as the true result.

Two-step TST may be useful in pre-employment screening HCWs who are likely to have subsequent testing following exposure to a TB case. In practice two-step testing might not be practicable as it requires four visits by the patient.

TST conversion

TST conversion is the change in reactivity of the TST with:

- a change from a negative to a positive reaction
- an increase of 5mm in the TST diameter (Menzies, 1999).

TST conversion indicates the development of a hypersensitivity reaction to infection with *M. tuberculosis* or NTM, including BCG vaccination. A TST used to document conversion following infection should be done at least 8 weeks after the last date of suspected exposure to TB.

3.1.6. Interferon gamma release assays (IGRA)

IGRAs are blood tests that detect cell mediated immune responses to TB specific antigens secreted by *M. tuberculosis*. The QFT is used in WA. This test measures the gamma interferon (IFN) secretion by T cells in response to *in-vitro* exposure to TB specific antigens. These antigens are present in all *M. tuberculosis* but are absent from BCG vaccine strains and most NTM with the exception of *M. kansasi*, *M. szulgai* and *M. marinum*.

QFT is an *in-vitro* test with the measurement of the immune response to TB antigens done according to a manufacturer-specified, standardised method in the laboratory. The test is reported positive based on gamma IFN measurement above a standardized cut-off in response

to TB antigen in either of 2 tubes. The test has 2 additional tubes that act as negative (saline) and positive (mitogen) controls. If either of these controls fails, the test is reported 'indeterminant'. This result is not useful in the assessment for TBI, and either the QFT must be repeated or an alternative test for TBI used.

An alternative IGRA is the T-Spot TB Test (Oxford Immunotech®). The T-Spot TB test is, in most circumstances, an equivalent test to QFT, with the main difference being the method of gamma IFN measurement in the laboratory. It is not routinely available in WA but can be requested in specialized circumstances through consultation with a TB physician at the WATBCP.

IGRAs should not replace the standard diagnostic investigations of TB disease (See section 1.1. Diagnosis of tuberculosis – laboratory). A positive QFT may not indicate disease, and a negative result does not rule out disease.

3.1.7. Selection of TBI test

Both TST and QFT are acceptable for the diagnosis of TBI (WHO. 2018; Stock & NTAC, 2017); therefore, either test can be used in most circumstances. QFT is usually preferred because of the convenience of doing the test (simple blood draw with minimal expertise required and patient does not need to return to measure result). The advantages and disadvantages of each test are described in Table 12. There are two exceptions where QFT is not preferred, which are described below.

The selection of a test to diagnose TBI infection should consider the reason for testing, the context of testing, the test availability and the logistics of administering the test or getting the blood sample to the laboratory (in WA, QFT specimens need to reach the laboratory in Perth within 16 hours of collection).

Table 12: Advantages and disadvantages of TST verses QFT

	Tuberculin Skin Test	QuantiFERON-TB Gold test
Advantages	Has been used for >100 years and it's use is better understood from experience and research, particularly from longitudinal data.	Convenience in administration. Improved specificity: the test is minimally affected by previous BCG or sensitisation to non-tuberculous mycobacteria (Pai & O'Brien, 2008). This is especially useful in low incidence populations. Less inter-reader variability than TST. No boosting effect from previous QFT-Plus testing (Pai & O'Brien, 2008). Results are recorded and easily retrieved from a results database.

	Tuberculin Skin Test	QuantiFERON-TB Gold test
Disadvantages	Requires 2 visits. Requires skilled practitioners to administer the test. Reduced specificity: cross reactions may occur, giving false positive results in subjects who have had prior BCG vaccination or who have had exposure to non-tuberculous mycobacteria.	Time limitations: blood samples need to be collected and processed within limited time frames. This can be a problem for samples collected outside the metropolitan area. Lack of longitudinal studies that inform us how the test performs over time, especially conversion from negative to positive (Mazurek et al, 2010). Indeterminate tests (Denkinger et al, 2011). Uncertainty about the significance of threshold results (positive or negative results that are near the cutoff) and fluctuations in the interferon gamma response over time (Mazurek et al, 2010).

Exceptions where TST remains preferable to QFT.

In both exceptions serial testing is required and TST is preferred because the dynamics of conversion are better understood, whereas QFT is recognized to “flip-flop” around the cut-off threshold giving false positive conversions. The 2 exceptions are below.

- Screening of household contacts: Testing performed immediately and if negative, repeated after 8 – 12 weeks.
- Serial surveillance testing of HCWs with high probability of TB exposure (Refer to section 5.3 Health Care Workers).

In both circumstances a TST conversion as well as a positive result are indications for TBI treatment (refer to Interpretation of the TST).

3.2. Tuberculosis infection – Treatment

3.2.1. Introduction

The treatment of TBI (previously referred to as LTBI), also known as preventive treatment (or therapy), reduces the risk of developing TB by up to 90% (WHO, 2020). One person can be prevented from developing TB for every 35 people taking isoniazid for six months (Smeja et al.,1999).

3.2.2. Rationale for TBI Treatment

The rationale for treating TBI is to kill dormant bacilli to prevent later reactivation and consequent TB disease. Treatment for TBI can either be (NICE, 2016):

- **Primary:** To prevent the acquisition of infection after exposure. Examples are in the treatment of neonates exposed to parents with sputum smear positive TB or people with significant immunosuppression e.g. HIV, that are exposed to TB.
- **Secondary:** Treatment after TBI has occurred.

3.2.3. Indications for TBI Treatment

The decision to treat TBI should be made by balancing the person's lifetime risk of developing TB with the risk of developing treatment side effects, adherence to treatment, and the individual's preference.

3.2.4. Precautions for TBI Treatment

Caution should be exercised in prescribing preventive treatment in certain groups of patients with increased risk of treatment side effects. This includes patients with pre-existing hepatic impairment, alcoholism, viral hepatitis, and patients of an older age.

Although isoniazid hepatotoxicity increases with age and underlying disease, most international guidelines recommend no absolute age limit for treatment of TBI because the risk of severe or fatal hepatotoxicity is considered low, with an acceptable risk-benefit ratio even in those aged over 35. (Alvarez et al., 2022; NICE, 2016; CDC, 2000). The greatest risk of hepatotoxicity is observed in patients 65 and older with co-morbidities; those without co-morbidities under the age of 65 have low rates of hepatotoxicity (Alvarez et al., 2022).

In pregnant women treatment can be delayed until after delivery unless there is a high risk of progression to TB disease (see section 4.4. Pregnancy).

These are no absolute contraindications to preventive treatment, but the risk of treatment side effects should be weighed against the benefit of treatment. Patients at risk of side effects should be reviewed more regularly with more frequent liver function tests.

3.2.5. Contraindications for TBI treatment

Preventive treatment is not recommended for patients:

- with a history of previously completed treatment for TB

- who have previously completed treatment for TBI. CXR follow up for 2 years is preferred in this group
- with suspicion of TB disease.

3.2.6. Primary preventive therapy

Individuals at high risk of developing primary TB following exposure to an infectious case require special consideration. Commencement of preventive therapy immediately following the exposure to prevent the development of primary TB should be considered in the following at risk groups:

- children under the age of 2 years exposed to TB
- a neonate whose mother has pulmonary TB
- immunosuppressed individuals (e.g. HIV infection, transplant recipients).

3.2.7. Pre-treatment investigations

Treatment of TBI should only be considered once TB has been excluded by CXR and clinical assessment. The following should be performed prior to the commencement of preventive treatment:

Chest x-ray

The CXR needs to be current i.e. within 6 months, or within 1 month if the patient is symptomatic or in cases of recent TB exposure.

In pregnancy CXR is not performed until after delivery unless there is a strong clinical suspicion of pulmonary TB.

If the CXR is abnormal and suggestive of TB disease, then other investigations including sputum AFB examination are required and preventive treatment should not be commenced until TB disease is excluded.

If the CXR is abnormal but represents old TB changes, then preventative therapy can be commenced if there is no history of previous completed TB treatment.

Baseline blood tests

LFTs are recommended prior to treatment commencement. If abnormal at baseline, a viral hepatitis screen should be performed. Follow up LFT is recommended within 2 to 4 weeks of commencing treatment, with further testing after this as indicated (e.g. abnormal baseline LFTs, high risk of hepatotoxicity, advanced age).

3.2.8. Treatment Regimens

The doses for drugs used in preventive treatment are provided in Table 13.

Table 13: Doses of drugs used in treatment of TB infection

Drug	Dose
Isoniazid (H)	> 40kg body weight: 300mg daily
	≤ 40kg body weight: 5mg/kg daily
Rifampicin (R)	≥ 50kg body weight: 600mg daily
	< 50kg body weight: 450mg daily NB. Rifampicin 450mg is preferably given as 3 x 150mg capsules.
Rifapentine (P)	900mg weekly

The regimens used at the WATBCP are provided below. The treatment used is at the discretion of the treating physician in consultation with their patient. Factors that should be taken into consideration in this decision include:

- length of treatment
- pill burden
- potential adverse effects
- drug interactions
- risk of inadvertent monotherapy in TB.

Rifampicin Monotherapy (4R)

A 4 month course of rifampicin monotherapy has equivalent efficacy to 9 months isoniazid (Menzies et al 2018, WHO 2020). Rifampicin is generally not recommended in HIV infected individuals, due to the potential for interaction with certain antiretroviral drugs, but may be used in specific circumstances e.g. isoniazid resistance in index case, intolerance to isoniazid. Joint management with an HIV specialist is essential.

Isoniazid Monotherapy (6H)

Single agent isoniazid has been used to treat TBI for at least 35 years (Smeja et al, 1999). In most instances isoniazid monotherapy for 6 months is adequate treatment for TBI in adults (including children >12 years old) with efficacy in the order of 60% to 90% depending on adherence (Smeja et al, 1999). Isoniazid treatment longer than six months has slight additional efficacy, but the small extra benefit is outweighed by the poorer adherence associated with prolonged length of treatment. There is also a small increased risk of hepatic toxicity.

Rifampicin plus Isoniazid Therapy (3HR)

Combination treatment with rifampicin and isoniazid for 3 months (3HR) has been shown to be equivalent to isoniazid monotherapy in terms of effectiveness and safety (Zenner et al., 2017; NICE, 2016, WHO 2020).

Other treatment regimens

A short-course combination regimen of once-weekly isoniazid and rifapentine for 12 weeks (3HP) or daily isoniazid and rifapentine for one month (1HP) have been shown to be non-inferior to 9 months of daily self-administered isoniazid treatment in a large RCTs and are acceptable regimens for TBI treatment (WHO, 2020). The 3HP weekly regimen is well established in other countries, especially the USA where it is often a first preference. In WA it has not been available until recently due to the difficulty with supply of rifapentine but has become available in 2023. The 1HP regimen is not routinely used yet.

3.2.9. Drug Side Effects

Side effects of isoniazid and rifampicin are presented in detail in section 2.1. Medical treatment of drug-susceptible TB.

3.2.10. Pyridoxine administration

(25 mg daily) should be given concurrently with isoniazid in patients that are predisposed to neuropathy e.g. persons with diabetes, chronic renal impairment, malnutrition, HIV infection, and those with seizure disorders or with high nutritional demands such as pregnancy and breastfeeding. It is not required for otherwise healthy adults on preventive treatment.

3.2.11. Special Treatment Groups

HIV Co-Infection

Co-infection with HIV increases the lifetime risk of progression of TBI to TB disease from 5-10% in non-HIV infected individuals to a10% annual risk in HIV positive individuals (WHO, 2018). Preventive treatment with 6-9 months of isoniazid monotherapy is the preferred treatment regimen, and pyridoxine 25 mg daily should be prescribed concurrently. For further details on TB in HIV-affected individuals see section 4.5. HIV co-infection.

Pregnancy

The preferred regimen in pregnancy is isoniazid 300 mg daily for 6 months with pyridoxine 25 mg daily. Isoniazid is a category A drug and is safe to use in pregnancy. Treatment should be encouraged during pregnancy when there is a high risk of progression to TB disease (see below) but the decision to treat TBI should be made in conjunction with the patient's preference. High risk of progression to TB disease occurs in the following scenarios:

- recent close contact with TB
- HIV infection or severe immunocompromise
- medical conditions that increase the risk of reactivation of TBI.

If preventive treatment is to be deferred until after delivery, then the pregnant woman should be closely monitored for signs of TB disease.

Neonates and children

Refer to sections 4.2. Paediatrics and 4.4. Pregnancy.

Isoniazid resistance

Contacts of individuals with isoniazid resistant TB should be offered 4 months of rifampicin (4R).

Multidrug-resistant TB (MDR-TB)

Contacts of MDR-TB should be given preventive treatment if they are household or close contacts at high risk of developing TB (e.g. children, people receiving immunosuppressive therapy and people living with HIV). The choice of drug depends on the susceptibilities of the *M. tuberculosis* isolate of the index case. Consultation with a specialist physician experienced in TB management should be sought. (Stock & NTAC, 2017; WHO, 2020)

3.2.12. Preventive therapy not given: Refusal or otherwise

Patients who are eligible for treatment of TBI but decline treatment should be given information regarding TB symptoms. Follow up with a CXR every 6 months for at least 2 years, should be offered to those who have had recent TB contact or have risk factors for reactivation (see section 3.1.3. Indications for TBI testing).

3.2.13. Clinic management and follow up

Follow up is essential to ensure adherence and to manage side effects. After patients have been assessed as suitable for preventive treatment and baseline investigations have been performed, they are assigned a case manager who will provide support, education and guide the patient through the duration of their treatment.

Patients should be followed up 2-4 weeks after commencing treatment and subsequently every 4-8 weeks while on treatment. At each visit, patients should be monitored for side effects, adherence with medication and review of blood chemistry as appropriate. LFTs should be checked at least once after starting preventive treatment. More frequent biochemistry should be considered in HIV-infected individuals, pregnant women or women within 3 months of giving birth, individuals with chronic liver disease, those who consume alcohol regularly, individuals with co-morbidities and on other medications likely to interact with isoniazid, and those over 50 years of age. An end-of-treatment CXR is only needed if the pre-treatment CXR was abnormal (Guidelines for Tuberculosis Control in New Zealand, 2010) or where there have been concerns with adherence.

3.2.14. Treatment completion

Treatment for TBI would be considered complete when a minimum 80% of the intended doses have been administered within the allocated timeframe (Table 14). The duration of treatment may be extended within reason if doses have been missed or treatment interrupted temporarily.

Table 14: Criteria for completion of treatment of TB infection

Treatment Regimen	Criteria for Completion
4 months daily rifampicin	120 doses within 6 months
6 months daily isoniazid	180 doses within 8 months
3 months daily isoniazid + rifampicin	90 doses within 4 months
9 months daily isoniazid	270 doses within 12 months
3 months weekly isoniazid + rifapentine	12 doses in 15 weeks

When restarting treatment for patients who have interrupted treatment, clinicians may continue the regimen originally prescribed if the criteria for completion mentioned above are achievable. If interruptions were frequent or prolonged, the entire regimen needs to be restarted. In either situation, when treatment is restored after an interruption of more than 2 months, a medical examination to rule out TB is indicated (American Thoracic Society, 2000).

3.2.15. Follow-up after TBI treatment and management of re-exposure

No follow up is required after completion of a satisfactory course of preventive treatment. If a patient who completed adequate preventive treatment is exposed to a case of infectious TB, a second course of TBI treatment is not recommended as there is good evidence that a first episode of TB infection provides 80% protection against development of disease following re-exposure. However, if there is uncertainty about adherence to a prior course of TBI treatment or in an immunocompromised individuals (e.g. HIV-infected, children < 5 years); then it is prudent to recommend a full course of TBI treatment (Alvarez et al., 2022).

3.2.16. References

Alvarez, G. G., Pease, C., & Menzies, D. (2022). Chapter 6: Tuberculosis preventive treatment in adults. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 6*(sup1), 77–86. https://doi.org/10.1080/24745332.2022.2039498

American Thoracic Society. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine*, *161*(4), S221-247. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600

Behr, M., Jarand, J., & Marras, T. K. (2014) *Canadian tuberculosis standards 7th edition*. Public Health Agency of Canada. https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition.html

Borisov, A. S., Morris, S. B., Njie, G. J., Winston, C. A., Burton, D., Goldberg, S., Woodruff, R. Y., Allen, L., LoBue, P., & Vernon, A. (2018). Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *MMWR. Morbidity and mortality weekly report, 67*(25), 723–726. https://doi.org/10.15585/mmwr.mm6725a5

Centers for Disease Control and Prevention. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR. Morbidity and mortality weekly report, 49*(RR-6).

Centers for Disease Control and Prevention. (2011). Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR. Morbidity and mortality weekly report, 60*(48), 1650–1653.

Centre for Disease Control, Northern Territory Department of Health. (2016). *Guidelines for the Control of Tuberculosis in the Northern Territory* (5th Ed.). Northern Territory Department of Health. https://digitallibrary.health.nt.gov.au/entities/publication/e34e3849-3f49-4829-a50d-fe6fea7f95fe/details

Denkinger, C. M., Dheda, K., & Pai, M. (2011). Guidelines on interferon-γ release assays for tuberculosis infection: concordance, discordance or confusion?. *Clinical Microbiology and Infection, 17*(6), 806–814. https://doi.org/10.1111/j.1469-0691.2011.03555.x

Department of Health New South Wales. (2009). *Tuberculin Skin Testing Policy Directive* (PD2009_005). https://www1.health.nsw.gov.au/pds/Pages/doc.aspx?dn=PD2009_005

Marais, B. J., Schaaf, H. S., & Donald, P. R. (2009). Pediatric TB: issues related to current and future treatment options. *Future microbiology, 4*(6), 661–675. https://doi.org/10.2217/fmb.09.39

Marais, B., Schaaf, H., & Donald, P. (2009). Management algorithms for paediatric tuberculosis. In H. Schaaf, & A. Zumla, Tuberculosis: A comprehensive clinical reference (pp. 323-331). Elsevier.

Mazurek, G. H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., Castro, K., IGRA Expert Committee, & Centers for Disease Control and Prevention (2010). Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports, 59*(RR-5), 1–25.

Menzies D. (1999). Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *American Journal of Respiratory and Critical Care Medicine, 159*(1), 15–21. https://doi.org/10.1164/ajrccm.159.1.9801120

Menzies, D., Adjobimey, M., Ruslami, R., Trajman, A., Sow, O., Kim, H., Obeng Baah, J., Marks, G. B., Long, R., Hoeppner, V., Elwood, K., Al-Jahdali, H., Gninafon, M., Apriani, L., Koesoemadinata, R. C., Kritski, A., Rolla, V., Bah, B., Camara, A., Boakye, I., … Benedetti, A. (2018). Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *The New England journal of medicine, 379*(5), 440–453. https://doi.org/10.1056/NEJMoa1714283

Ministry of Health. (2010). *Guidelines for Tuberculosis Control in New Zealand 2010*. Ministry of Health. https://natlib.govt.nz/records/21759152

National Institute for Health and Clinical Excellence. (2016). Tuberculosis (NG33). https://www.nice.org.uk/guidance/ng33

Pai, M., & O'Brien, R. (2008). New diagnostics for latent and active tuberculosis: state of the art and future prospects. *Seminars in respiratory and critical care medicine, 29*(5), 560–568. https://doi.org/10.1055/s-0028-1085707

Smieja, M. J., Marchetti, C. A., Cook, D. J., & Smaill, F. M. (2000). Isoniazid for preventing tuberculosis in non-HIV infected persons. The Cochrane database of systematic reviews, 1999(2), CD001363. https://doi.org/10.1002/14651858.CD001363

Stock, D., & National Tuberculosis Advisory Committee. (2017). National position statement for the management of latent tuberculosis infection. *Communicable diseases intelligence quarterly report, 41*(3), E204-E208.

Western Australian Tuberculosis Control Program, North Metropolitan Health Service. (2021). *Tuberculosis notifications in Western Australia 2021*. https://www.health.wa.gov.au/~/media/Corp/Documents/Health-for/Tuberculosis/Tuberculosis-notifications-in-Western-Australia-2021.pdf

World Health Organization. (2020). *WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment*. https://www.who.int/publications/i/item/9789240001503

Zenner, D., Beer, N., Harris, R. J., Lipman, M. C., Stagg, H. R., & van der Werf, M. J. (2017). Treatment of latent tuberculosis infection: an updated network meta-analysis. *Annals of internal medicine*, *167*(4), 248–255. https://doi.org/10.7326/M17-0609

Chapter 4: Tuberculosis in Special Populations

4.1. Tuberculosis in Aboriginal People

4.1.1. Introduction

Rates of TB in Aboriginal and Torres Strait Islander people are significantly higher than Australian born non-indigenous people, and transmission continues in some Aboriginal communities in Western Australia. Social determinants of health are the primary drivers of disparity in risk and outcomes of TB, with complex historical, social, cultural and geographic factors also contributing (Devlin et al., 2019).

The principles of cultural respect as outlined in the Cultural Respect Framework for Aboriginal and Torres Strait Islander Health form the foundation of guidance for managing TB in Aboriginal people in WA. The WATBCP is committed to improving access to TB healthcare for Aboriginal people and addressing inequities in outcomes through provision of a high quality culturally aware and sensitive service. Involvement of Aboriginal people and organisations in all aspects of service design, delivery and evaluation is essential.

While the majority of Aboriginal people in WA reside in metropolitan regions, historically TB has occurred more frequently Aboriginal people in regional and remote areas of the state. For cases in areas outside metropolitan areas, unique challenges arise related to geographic isolation, requiring close collaboration and communication between WATBCP and relevant regional public health units and Aboriginal Community Controlled Health Services.

The National Aboriginal and Torres Strait Islander Health Protection Committee (NATSHIP) in partnership with the National Tuberculosis Advisory Committee (NTAC) aims to reduce TB transmission and support improved TB services for Aboriginal people in Australia. NATSHIP, with support of NTAC, have committed to a project to develop an evidence-based national guideline for the prevention and control of TB in Aboriginal communities. The aim is to provide clear, practical guidance for health services and to ensure a culturally safe and acceptable approach to TB management, whilst aligning with the Priority Reforms of the National Agreement on Closing the Gap, specifically with regard to formal partnerships and inclusion of Aboriginal people in decision making. The guideline is expected to be completed in the latter part of 2025.

4.1.2. Presentation of TB

Aboriginal people are more likely to present with advanced TB and have poorer outcomes compared with non-Aboriginal people for several reasons including higher rates of smoking, malnutrition, diabetes, coexistent respiratory illness and barriers to accessing healthcare. TB must be considered as a differential for chronic cough in Aboriginal people, and a high index of suspicion must be maintained for features of extrapulmonary TB.

4.1.3. Diagnosis and management of TB in Aboriginal people

The diagnosis, medical treatment and case management of TB in Aboriginal people follows the general principles outlined in this guideline, however consideration of cultural perspectives is essential. Aboriginal people and organisations must be central to planning and delivery of care. The diversity of Aboriginal people and communities in WA necessitates guidance of processes at a regional level to ensure delivery of culturally safe services. The approach to care and contact tracing is collaborative involving Aboriginal people and organisations as well as primary carecand regional public health units, with strategic oversight, governance and medical expertise provided by the WATBCP.

Aboriginal people view health in terms of the social, emotional and cultural wellbeing of the community, rather than the physical wellbeing of the individual alone. When providing care, consideration must be given to this broader concept of wellbeing, incorporating connection to country, traditional practices and knowledge, as well as sensitivity around social equity and rights.

Provision and supervision of medication must be done in a culturally appropriate way, ensuring a wholistic approach focused on overall wellbeing and building of trust.

4.1.4. Contact tracing

Guidance must be sought from Aboriginal people and organisations, in collaboration with the WATBCP to plan and implement contact tracing which are appropriate and acceptable.

The following considerations are essential to ensure effective and culturally safe contact tracing for TB in Aboriginal people:

- Uniqueness of Aboriginal family structure and kinship system which is characterised by a broader understanding of the family unit
- Contact tracing activities directed primarily toward a nuclear family structure are generally not applicable or appropriate
- Sensitivity toward potential for stigma and perceived discrimination in conducting contact tracing activities
- Understanding Aboriginal concepts of health which often focus on community rather than the individual

Decisions regarding activation and stand down of an Aboriginal TB outbreak response are made through multiagency consultation between WATBCP, WACHS and the ACCHS Sector.

4.1.5. References

Devlin, S., MacLaren, D., Massey, P. D., Widders, R., & Judd, J. A. (2019). The missing voices of Indigenous Australians in the social, cultural and historical experiences of tuberculosis: a systematic and integrative review. BMJ global health, 4(6), e001794. https://doi.org/10.1136/bmjgh-2019-001794

4.2. Paediatrics

4.2.1. Introduction

This chapter addresses differences in the clinical features and approach to the assessment and treatment of TB in the paediatric setting, particularly in young children.

Clinical, diagnostic, and management differences between TB in children and TB in adolescents and adults include the following:

- Children are at higher risk of TB disease following primary infection compared with adults, especially in very young (<5 years) and immunocompromised children.
- Children <5 years are at higher risk of developing severe disseminated forms of TB (e.g., miliary and meningeal TB) compared with adults.
- Paediatric TB is usually paucibacillary with a lower risk of TB transmission unless lung cavities are present. The risk of transmission in older children and adolescents (>10 years), many who present with lung cavitation, is akin to adults.
- TB disease in children usually occurs within 6-12 months of infection (Marais et al., 2009). Paediatric TB is an indicator of recent transmission in the community.
- Most children are infected by a household index case, usually one of the parents, but extended family members and other caregivers should also be considered as possible sources.
- Diagnosis of active TB in children should be based on the exposure risk and clinical and/or radiological signs of TB. Microbiological confirmation of disease is not always found owing to the paucibacillary nature of disease. Negative molecular diagnostics and/or mycobacterial culture on diagnostic samples should not be used to exclude TB in a child.

4.2.2. Presentation of TB

The type of TB disease in children is dependent on the effectiveness of the immune response to contain a recent *M. tuberculosis* infection. The immune response improves with age as the immune system matures (Graham et al., 2009). Therefore, infants and younger children are at higher risk of developing TB disease and more severe disease (tuberculous meningitis and disseminated disease) after primary infection.

Pulmonary TB is the most common form of TB in children accounting for about 75% of presentations. Extra-pulmonary TB accounts for around 25% of cases in children and includes cervical lymphadenitis, spinal, pleural, abdominal, miliary TB and tuberculous meningitis (Graham et al., 2009).

Most children with TB infection do not develop disease.

4.2.3. Signs and symptoms of TB

Early in the disease, most children with TB have few symptoms and signs. They can present with a range of clinical symptoms and signs that depend on the major site of disease involvement. Diagnosing TB in children can be difficult because the symptoms and signs are often non-specific, children are often unable to express their symptoms, and diagnostic

confirmation of disease is often not achieved. The most important clue to suggest TB as a possible diagnosis is recent exposure to an infectious TB case.

Symptoms in children suggestive of TB disease include (Marais et al., 2006; Marais et al., 2004):

More common symptoms:

- a persistent cough, often non-productive, > 2 weeks' duration
- weight loss or failure to thrive
- reduced playfulness, fatigue, or increased tiredness
- enlarged, non-tender cervical lymph nodes (> 2 cm x 2 cm) with/without overlying skin changes or fistulae.

Less common symptoms:

- respiratory distress (uncommon and more likely in neonates and infants, or in those with a large pleural effusion)
- haemoptysis (uncommon and more likely in older children and adolescents)
- unexplained, persistent fever
- excessive night sweats
- lethargy, headache, irritability +/- progressive neurological signs (suggestive of tuberculous meningitis).

A high index of suspicion is required due to the non-specific nature of TB in children. This is particularly important in children with recent exposure to an infectious TB case or extended travel to a high-incidence country (>40 cases /100,000 people). Up to date TB data, including the Global TB report, and country, regional and global profiles, is available on the WHO website: Global Tuberculosis Programme (who.int) .

Many children and adolescents may appear surprisingly well despite a diagnosis of TB.

The risk of progressing from infection with *M. tuberculosis* to disease is greater in children than adults. The risk of developing tuberculous meningitis or miliary TB is highest in infancy (refer to Table 15).

Table 15: Age specific risk for development of TB following primary infection

Age at primary infection	Disease presentation	Risk of disease following primary infection (%)
<1 year	No disease	50
	Pulmonary disease	30-40
	TB meningitis or miliary disease	10-20
1-2 years	No disease	70-80
	Pulmonary disease	10-20
	TB meningitis or miliary disease	2-5
2-5 years	No disease	95

Age at primary infection	Disease presentation	Risk of disease following primary infection (%)
	Pulmonary disease	5
	TB meningitis or miliary disease	0.5
5-10 years	No disease	98
	Pulmonary disease	2
	TB meningitis or miliary disease	<0.5
>10 years	No disease	80-90
	Pulmonary disease	10-20
	TB meningitis or miliary disease	<0.5

4.2.4. Differential diagnosis of TB

The differential diagnosis of TB is broad. Discussion with a paediatric infectious disease specialist is recommended.

4.2.5. TB assessment

The main objective of TB assessment is to distinguish children with **TB infection (TBI)** (positive screening test and normal CXR without signs/symptoms of active disease) versus **TB disease** (children with TB infection with signs and symptoms suggestive of disease +/- supporting radiological +/- microbiological evidence).

Most children seen at the WATBCP have TBI **without** active disease. The aim of identifying and treating TBI is to:

- Prevent progression to TB disease (the risk of progression is 10-15% over the course of an individual's lifetime; this risk is highest in the first 6-12 months following infection).

The aim of identifying and treating **TB disease** is to:

- Cure the patient of TB.
- Prevent death from TB or its late effects.
- Prevent relapse of TB
- Prevent the development and transmission of drug-resistant TB.
- Reduce transmission of TB to others
- Minimise toxicity.

4.2.6. Infection risk

TBI is NOT transmissible, and no infection prevention control measures are required.

Pulmonary TB disease is potentially infectious to others. However, young children with TB are generally less contagious than adults because they:

- rarely produce sputum

- experience less lung cavitation
- have low concentration of organisms in bronchial secretions
- lack the tussive force necessary to suspend infectious particles of the correct size in the air (Starke, 2004).

Children and adolescents are as infectious as adults if they exhibit lung cavities or are sputum smear positive. As the age of a child increases and their social interaction expands, community acquisition and transmission of TB becomes more relevant.

TB diagnosed in a young child usually indicates recent infection and the most likely source of infection is a close family member or close contact of the child. Contact tracing procedures should begin with the immediate family and expand as necessary.

Each case should be considered individually regarding the risk of infecting others based on the site of infection, disease burden and resistance profile. School exclusion is not needed unless the child is smear positive. If smear positive, the child should remain at home and avoid new contacts for 2 weeks following commencement of therapy, or until smear negative; whichever is longer.

4.2.7. TB screening

TB screening in children is usually performed in the context of immigration or contact tracing (see section 5.1 Contact Tracing). Children who undergo offshore immigration screening are referred for a Health Undertaking Assessment, while children undergoing onshore assessment are referred for a BUPA assessment (this is the organisation contracted by the government to coordinate this process). A small proportion of children reviewed at WATBCP are referred by their GP or other medical practitioner. As outlined in section 5.1 Contact Tracing, household/close contacts are those with prolonged or extensive contact (>8 hours cumulative exposure to the index case). Casual contacts are those who have had intermittent exposure to the index case, but the total cumulative exposure time is still estimated to be greater than 8 hours.

If the index case is diagnosed with pulmonary TB, there is a risk of transmission and a need for prompt screening, as outlined in Table 16 below. The risk of transmission is higher if the index is smear positive.

TST or QFT can be used to test for TBI at any age (Buonsenso et al., 2023; Andrews et al., 2017). Tests performed after receipt of a BCG vaccine (especially within ~2 years of BCG vaccination) may result in a false-positive result and for this reason, QFT is the test of choice in this context (Buonsenso et al., 2023). Please see Table 11 for TST thresholds considered indicative of infection and section 5.1 Contact Tracing for further information on contact tracing. Of particular note, children at high risk of TB exposure/infection (<5 years, prior residence in a country of high TB incidence and/or HIV+ or severe malnutrition), the threshold for a positive TST result is 5 mm. In other groups, the threshold is 10 mm.

Pulmonary TB index case

Children identified as contacts of a case of pulmonary TB (culture positive and/or MTB PCR positive irrespective of smear status), should be screened as follows:

- Assess for symptoms of TB disease.

- Assess history including previous tuberculin skin test (TST) result, previous TB exposure or treatment, BCG immunisation, and co-existing medical conditions.
- TST/IGRA testing is recommended for all children as soon as practicable except if there has been a previous positive result or documented past TB.
- CXR should be performed (or repeated if not performed within preceding 3 months) for:
  - Children >10 years of age
  - Any child, regardless of age, with symptoms compatible with TB disease.
  - Any child, regardless of age, with a positive TST/IGRA result.
  - Any child, regardless of age, who has had a **previous** positive TST/IGRA.
  - Immunocompromised children and/or those with severe malnutrition (Kwashiorkor or marasmus)
  - Children who are prescribed primary preventive therapy (even with a negative baseline TST/QFT).
- Book for clinical review as outlined in Table 16 below. The paediatric Infectious Diseases service (on call Registrar) at Perth Children's Hospital can also be contacted to triage children as required.

Table 16 Approach to contact tracing in child contacts of pulmonary TB cases

	Household/close contact	Casual contacts	Timing of clinic review^
<5 years	TST/QFT 2 rounds*	1-round TST/QFT**	Household contact: next scheduled paediatric clinic within 2 weeks.
			Casual contact: within 4 weeks
5-10 years	TST/QFT 2 rounds*	1-round TST/QFT**	Household contact: within 4 weeks
			Casual contact: if the TST/QFT is positive or if parental concerns
>10 years	TST/QFT 2 rounds* AND CXR	1-round TST/QFT**	Household contact: if the TST/QFT and/or CXR is abnormal or if parental concerns
			Casual contact: if the TST/QFT is positive or if parental concerns
*2-rounds: TST/QFT at baseline & 8-12 weeks after last exposure (if initial screen negative)			
**1-round: single TST/QFT 8-12 weeks after last exposure to index			
^Any child with concerning symptoms or active TB or CXR changes should be discussed with the on-call paediatric infectious diseases registrar/consultant at Perth Children's Hospital			

Extrapulmonary TB index case

Children identified as close or household contacts of extrapulmonary TB (**without** pulmonary involvement) should be screened with TST/QFT. Symptomatic children, or those with a positive TST/QFT should be referred to the Paediatric clinic for review.

4.2.8. Primary preventative therapy (PPT)

Following exposure to an infectious case of TB, young children (<5 years) and immunocompromised children are at high risk of developing primary TB infection. Infected children may initially have a negative TST/QFT and a normal CXR. These children may rapidly develop TB before a contact tracing visit and before a TST/QFT test can become positive.

All children under 5 years old and those who are immunocompromised and/or severe acute malnutrition who have had household exposure to an infectious TB case (adult or adolescent with bacteriologically confirmed pulmonary TB), should be screened for TB disease.

Commencement of preventive treatment immediately following the exposure aims to prevent the development of primary TB infection.

If TB is excluded, children under 5 years old and children who are immunocompromised and exposed to an index case with smear positive pulmonary TB should be started on PPT. Options for therapy include those used for treatment of TBI.

These children should be reviewed at 2 weeks after commencement of therapy for a repeat clinical assessment and liver function testing. Subsequent review is recommended at 4–6-week intervals. Children who require 2-stage TST/QFT testing (see Table 16) should be tested as soon as possible. If the initial test result is negative, testing should be repeated 8-12 weeks after their last exposure to the index case. If the TST/QFT result is negative at this time, and the child remains well, PPT can be ceased.

4.2.9. Perinatal TB

Perinatal TB encompasses TB acquired by the baby while i) in-utero, ii) intrapartum or iii) during the postnatal period.

TB acquired by the foetus in-utero from haematogenous spread via the umbilical cord, or in-utero via aspiration or ingestion of infected amniotic fluid, is rare. TB in the infant should be considered if the mother has inadequately treated pulmonary TB at the time of delivery of their infant (<2 months treatment and/or persistent smear positivity) or disseminated/miliary/TB meningitis/primary pleural and/or pelvic/genital TB. TBI after delivery occurs via respiratory transmission from an infected mother, an adult family carer, or another infectious adult with whom the infant has had contact (including health care workers).

Our approach to risk stratification and management of the infant aligns with the Queensland guidelines, which can be accessed here. All pregnant women with TB should be discussed with the paediatric on-call registrar/consultant to allow appropriate risk stratification and management of the infant. The registrar can be contacted via the Perth Children's Hospital switchboard on (08) 6456 222.

The diagnosis of perinatal TB is difficult and frequently delayed. If the neonate exhibits any signs or symptoms of TBI, then a thorough assessment and investigation(s) should be undertaken (refer to section 4.2.7. TB Screening).

4.2.10. Diagnostic TB tests

No single test for TB is robust to exclude TB in childhood. Microbiological or molecular detection of TB is confirmatory for TB, but in most circumstances a combination of exposure history, clinical features, and radiological findings are used to confirm or exclude a diagnosis of active TB in the absence of microbiological/molecular detection of TB.

A TST/QFT is not a helpful discriminatory test for ruling active TB in/out.

Molecular diagnostic methods

In children with signs and symptoms of pulmonary TB, *M. tuberculosis* and rifampicin resistance by molecular testing (PCR) is performed as the initial diagnostic test for TB on sputum, nasopharyngeal aspirate, gastric aspirate, or stool. Xpert Ultra is the preferred platform for molecular testing in our setting. This molecular diagnostic assay has a lower limit of detection (greater analytic sensitivity) than the Xpert MTB/RIF assay and includes a 'trace' semi-quantitative result. 'Trace' results are common with the use of Xpert Ultra in a paediatric specimen type, reflecting the paucibacillary nature of TB disease in children. Positive Xpert Ultra trace results are considered as bacteriological confirmation of TB. Trace results will, however, have indeterminate results for rifampicin resistance.

The diagnostic accuracy of Xpert Ultra TB testing methods is summarised in Table 17 (WHO, 2022). These estimates apply for high-quality samples only.

Table 17: Sensitivity and specificity of Xpert Ultra diagnostic tests in children

Xpert Ultra	Sensitivity	Specificity
Sputum	0.73	0.97
Gastric aspirate	0.64	0.95
NPA*	0.46	0.98
Stool	0.53	0.98

*NPA: nasopharyngeal aspirate

Smear for AFB/microscopy and culture of respiratory specimens

Smear for AFB microscopy, culture and DST on respiratory samples will be conducted on all children with a suspicion or request for TB diagnostics after *M. tuberculosis* PCR. This is recommended for children in WA. Optimal methods for collection of specimens in children depends on their age, location, and the skillset of healthcare staff assisting with the collection of clinical specimens.

Respiratory samples

Respiratory samples should be collected in any child or adolescents with symptoms concerning for active TB and/or with abnormal CXR findings and a positive screening test.

Respiratory samples may be obtained in a variety of settings:

1. WATBCP: expectorated sputa may be obtained at the WATBCP for children >6 years of age.
2. Hospital: as an inpatient or an outpatient (via the emergency department or day treatment unit at Perth Children's Hospital).

A minimum of two **early morning** respiratory samples are ideally obtained. It may be pragmatic to collect both samples on the same day. Potential sampling types include:

1. Induced sputa: performed with the assistance of the respiratory physiotherapist in children >3 months of age. Pre-treatment with inhaled bronchodilators (to protect against bronchospasm) and hypertonic saline (to encourage sputum expectoration) should be given as follows:
    - salbutamol: 6 puffs x100 mcg (<6 years) or 12 puffs x100 mcg (≥6 years) via spacer OR 2.5 mg neb (<6 years) or 5 mg neb (≥6 years)
    - 3% or 6% Hypertonic saline neb (10 mLs).
2. Gastric aspirates: In young children, sputum is swallowed rather than expectorated. Consecutive early morning gastric aspirates obtained via a nasogastric or orogastric tube may be collected as an alternative to induced sputa. Early morning gastric aspirates need to be obtained while a child is fasting and before a child is ambulant. These are most frequently performed in the early morning upon waking in hospitalised children.
3. Bronchoalveolar lavage (BAL): BAL samples may be indicated in specific situations, however BALs should be performed by an experienced operator with appropriate infection control precautions, ideally at the end of a procedural list.
4. Stool samples: stool samples may be considered for AFB and mycobacterial culture.

Extrapulmonary diagnostic tests

The diagnosis of extrapulmonary TB is usually based on exposure history, clinical presentation, radiology, and microbiological sampling. Obtaining specimens for microscopy and culture (e.g., CSF in suspected tuberculous meningitis or lymph node in suspected tuberculous lymphadenitis) should be undertaken where possible. Infants <1 year with suspected TB should have 5 mL CSF collected to check for pleocytosis, and sent for Xpert Ultra, as well as AFB microscopy and mycobacterial culture, and if positive, arrangement of neuroimaging. Abdominal ultrasound in infants <1 year is also recommended to exclude disseminated TB.

An HIV test should be performed in all children with probable or confirmed TB.

Imaging

CXR

CXR is useful in the diagnosis of pulmonary TB in children. A posterior-anterior (PA) CXR should be requested for all patients suspected of having TB whether the primary site is pulmonary or extra-pulmonary, as the two forms of the disease may co-exist. A lateral CXR is not routinely performed in children to minimise radiation exposure to the child.

CXR appearances suggestive of pulmonary TB in children include (International Union against Tuberculosis and Lung Disease, 2010):

- hilar and mediastinal lymphadenopathy
- parenchymal infiltrates
- lobar or segmental collapse/consolidation; and pleural or pericardial effusions (forms of extrapulmonary TB which tend to occur in older children)
- lung cavitation is unusual in children but more common in adolescents and adults with pulmonary TB.

No radiological features are pathognomonic for pulmonary TB in children, and there is overlap with radiological abnormalities due to other causes of lung disease in children. Nevertheless, if

there are characteristic CXR changes of TB in a patient considered at high risk for TB, then TB should be assumed until an alternative diagnosis is proven.

CT imaging

In circumstances where the CXR is abnormal, but the diagnosis is uncertain, a chest CT may be useful to confirm the diagnosis of pulmonary TB. A chest CT may show a Ghon foci, small cavitation(s) and/or hilar adenopathy that may not be seen on CXR. Discuss with a radiologist to confirm the benefit of organising a chest CT.

4.2.11. Management of TB infection

TBI treatment

If the TST/QFT is positive in the absence of symptoms and CXR changes, TBI treatment should be commenced.

Recommended treatment regimens for TBI in children at the WATBCP, in order of preference, are listed in Table 18Table 18.

Combination therapy with 3HR is equivalent to isoniazid monotherapy in terms of effectiveness and safety (Fox et al., 2017; National Institute for Health and Clinical Excellence [NICE], 2011; Ena & Valls, 2005). Rifampicin monotherapy has better compliance and less toxicity compared to 9 months of isoniazid monotherapy (Diallo et al., 2018). Therefore, where there are concerns regarding compliance or toxicity, using 4R over 3HR might be considered (Menzies et al., 2018). Isoniazid monotherapy for 6 months is considered in children with chronic comorbidities and concurrent administration of medications that may interact with rifampicin (e.g., antiretroviral medications; immunosuppressants).

Children and their families should be counselled about potential adverse events of therapy prior to commencing TBI treatment. Table 19 provides an overview of potential adverse events related to TB medicines and a suggested approach to management.

Table 18: TBI treatment regimens for children

Treatment regimen	Drug dose mg/kg	Weight-banded dosing								
3HR	Isoniazid tablet (100mg; this is dispersible)									
	•Age <10 years: 10mg/kg/day (range 7-15mg)									
	•Age ≥10 years: 5mg/kg/day									
	MAX DOSE =300mg daily									
	Rifampicin (150mg or 300mg capsules or liquid 100mg/5mL)									
	•Age <10 years: 15mg/kg/day (range 10-20mg)									
	•Age ≥10 years: 10mg/kg/day									
	MAX DOSE =600mg daily									
	Fixed drug combinations (FDCs)	4-<8kg	8-<12kg	12-<16kg	16-<25kg	25-<30kg	30-<35kg	35-<50kg	50-<65kg	≥65kg
	Isoniazid 50mg/Rifampicin 75mg FDC dispersible tablet	1	2	3	4	-	-	-	-	-
	Isoniazid 75mg/Rifampicin 150mg FDC tablet	-	-	-	-	2	3	4	4	5
4R	Age <10 years: 15mg/kg/day (range 10-20mg)									
	Age ≥10 years: 10mg/kg/day									
1HP	Age ≥13 years (regardless of weight band)									
	•Isoniazid 300mg/day (100mg tablets)									

	•Rifapentine 600mg/day (150mg tablets)					
3HP	**Age 2-14 years**	**10-<16kg**	**16-<24kg**	**24-<31kg**	**31-<34kg**	**≥34kg**
	•Isoniazid 100mg/day (100mg tablets; this is dispersible)	**3**	**5**	**6**	**7**	**7**
	•Rifapentine 150mg tablet once weekly	**2**	**3**	**4**	**5**	**5**
	Age >14 years	**30-<36kg**	**36-<46kg**	**46-56kg**	**56-70kg**	**≥70kg**
	•Isoniazid 300mg/day tablet	**3**	**3**	**3**	**3**	**3**
	•Rifapentine once weekly (150mg tablets)	**6**	**6**	**6**	**6**	**6**
6H	**Age <10 years; 10mg/kg/d (range 7-15mg)**					
	Age ≥10 years: 5mg/kg/d					
	MAX DOSE=300mg daily					
	WEIGHT BAND	**4-<8kg**	**8-<12kg**	**12-<16kg**	**16-<25kg**	**≥25kg**
	100mg tablet (this is dispersible)	**0.5**	**1**	**1.5**	**2**	**3**

Table 19 Adverse events relating to TB medicines and a suggested approach to management

System	Medicine	Adverse event	Frequency	Management	Caution
Systemic	Rifampicin	Orange discolouration of urine, tears, saliva & other body secretions	Common	Not harmful; continue therapy	
		Hypersensitivity; flu-like symptoms	Rare with daily dosing	Typically develops after several months of treatment	If severe reaction, may have to be stopped
	Levofloxacin	Vasculitis, arthralgia, myalgia, fever	Rare	Symptomatic management	
	Prothionamide	Metallic taste, vomiting, abdominal pain, anorexia, diarrhoea		Symptomatic management	
Hepatic	Isoniazid, rifampicin, pyrazinamide, levofloxacin, prothionamide	Hepatitis, nausea, decreased appetite and vomiting may appear before jaundice	Rare in most children; more common in children with HIV	Discontinue all drugs if >5x upper limit of normal or >3 times upper limit of normal with hepatitis symptoms	Rifampicin is more commonly associated with cholestatic pattern
				If <5 times upper limit of normal or <3 times upper limit of normal with symptoms of hepatitis, monitor closely	Discontinue medicine for: systemic symptoms, fever, urticaria, mucous membrane involvement, blistering of skin, oedema of lips or eyes, wheezing or compromised airway

System	Medicine	Adverse event	Frequency	Management	Caution
Renal	Levofloxacin	Interstitial nephritis, acute renal failure	Very rare	Cease drug	Consider alternative agent in children with a history of renal impairment
Ophthalmic	Ethambutol, isoniazid	Optic neuropathy, neuritis	Very rare	Refer if concerns about decreased visual acuity or colour discrimination	Conduct baseline visual acuity and colour vision assessment in older children
					Observe fixation and tracking in infants
Neurotoxicity	Isoniazid, levofloxacin, prothionamide	Peripheral neuropathy: paraesthesia, hypoesthesia, weakness, pain, burning, tingling, refusal to walk	Common in severely malnourished children and children living with HIV, otherwise rare	Check and correct electrolyte disturbances, exclude other medicines contributing, assess pyridoxine dose, trial low-dose non-steroidal anti-inflammatories or aspirin	Isoniazid-related peripheral neuropathy generally improves after discontinuation
					Monitor extremity reflexes and gait in all infants and children
	Levofloxacin	Tendinitis/tendon rupture	Very rare	Discontinue if patient experiences pain, swelling m inflammation or rupture of tendon	Can occur at any stage of use
	Levofloxacin	CNS: seizures, increased intracranial pressure, tremors, light-headedness, anxiety, depression, suicidal thoughts,	Very rare	Discontinue if symptoms occur	Consider alternative agent if history of mood disorder

System	Medicine	Adverse event	Frequency	Management	Caution
		hallucinations, psychoses, nightmare, memory impairment			
	Prothionamide	Depression/anxiety, encephalopathy headache, psychoses			
Haematological	Isoniazid, rifampicin, levofloxacin	Marrow suppression, which may result in decreased haemoglobin, platelets and white blood cells	Rare	Consider discontinuation for severe anaemia, leukopenia or thrombocytopaenia	Children with TB may have depressed cell lines at the commencement of treatment
Dermatological	Rifampicin, isoniazid, ethambutol, pyrazinamide, levofloxacin	Maculopapular rash, pruritis	Common	Antihistamines, hydrocortisone cream, low-dose prednisolone if other measures fail	Discontinue medicine for: systemic symptoms, fever, urticaria, mucous membrane involvement, blistering of skin, oedema of lips or eyes, wheezing or compromised airway
	Rifampicin, pyrazinamide	Transient flushing reactions	Rare	Antihistamines	
	Pyrazinamide	Photosensitivity	Common	Sunscreen, coverage of exposed areas	
	Rifampicin, isoniazid,	Severe urticaria or anaphylaxis	Rare	Referral for evaluation of possible re-challenge or desensitisation	Management requires controlled environment

System	Medicine	Adverse event	Frequency	Management	Caution
	pyrazinamide, ethambutol				with capacity for resuscitation
Metabolic	Prothionamide	Hypothyroidism, gynaecomastia, hypoglycaemia	Rare	Consider discontinuation of drug	Consider alternative agent in children with history of metabolic disorders

MDR TB exposure

For treatment of TBI in the setting of an MDR-TB positive index, 6 months of levofloxacin is recommended as first line therapy (WHO, 2022) and may be modified depending on DST results in the index case is known. Please see Table 20 for dosing recommendations.

Table 20: Levofloxacin dosing recommendations for suspected MDR-TB TBI

	Dose by age and weight band
6Lvx*	**Age <15 years (approximate range 15-20 mg/kg/day)**
	• 5-10 kg: 150 mg/day • 10-<16 kg: 200-300 mg/day • 16-<24 kg: 300-400 mg/day • 24-<35 kg: 500-750 mg/day
	Age >14 years, by body weight
	• <46 kg: 750 mg/day • >45 kg: 1 g/day

*Lvx: Levofloxacin

Children and their families should be counselled about potential adverse events of therapy prior to commencing treatment. Table 19 provides an overview of potential adverse events related to levofloxacin and a suggested approach to management. If TBI treatment is declined, children should be follow-up according to the recommendations outlined in Table 24.

4.2.12. Treatment for drug-susceptible TB in children and adolescents

Combination regimens are used to treat children with TB, and treatment is divided into an intensive phase to rapidly eliminate organisms and prevent drug resistance, followed by a continuation phase using fewer drugs to eradicate dormant organisms.

The WATBCP's treatment recommendations for TB in children align with those of WHO. Recommended treatment regimens for pulmonary TB and extrapulmonary TB are presented in Table 21 and Table 22.

.

Table 21 Recommended treatment options for drug-susceptible pulmonary and extrapulmonary TB

		Intensive phase	Continuation phase	Isoniazid (H)	Rifampicin (R)	Rifapentine (P)	Pyrazinamide (Z)	Ethambutol (E)	Prothionamide (Pro)	Moxifloxacin (Mfx)
Pulmonary TB	Infants <3 months or <3kg	2HRZ or 2HRZE*	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥3 months to <12 years – non severe	2HRZ or 2HRZE*	2HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥3 months to <12 year – severe	2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥12 years to <16 years – non severe	2HRZ or 2HRZE*	2HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥12 years to <16 years - severe	2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	12 years to <16 years – any severity and >40kg	2HPZMfx	2HPMfx	300mg		1200mg	40-<65kg: 1500-1600mg ≥65kg: 2000mg			400mg

		Intensive phase	Continuation phase	Isoniazid (H)	Rifampicin (R)	Rifapentine (P)	Pyrazinamide (Z)	Ethambutol (E)	Prothionamide (Pro)	Moxifloxacin (Mfx)
	16 years to <20 years – any severity	2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	16 years to <20 years -any severity and >40kg	2HPZMfx	2HPMfx	300mg		1200mg	40-<65kg: 1500-1600mg			400mg
							≥65kg: 2000mg			
Extrapulmonary TB – peripheral lymph node TB	Infants <3 months or <3kg	2HRZ	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)			
		2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥3 months to <16 years	2HRZ	2HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)			
		2HRZE	2HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		
	≥16 years	2HRZ	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)			
		2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35mg/kg (30-40)	20mg/kg (15-25)		

		Intensive phase	Continuation phase	Isoniazid (H)	Rifampicin (R)	Rifapentine (P)	Pyrazinamide (Z)	Ethambutol (E)	Prothionamide (Pro)	Moxifloxacin (Mfx)
Extrapulmonary TB	0-19 years – TB meningitis	6HRZPto		15-20mg/kg	22.5-30mg/kg		35-45mg/kg		17.2-22.5mg/kg	
	0-19 years – TB meningitis	2HRZE	10HR	10mg/kg (7-15)	15mg/kg (10-20)		35-45mg/kg	20mg/kg (15-25)		
	0-19 years – Osteoarticular	2HRZE	10HR	10mg/kg (7-15)	15mg/kg (10-20)		35-45mg/kg	20mg/kg (15-25)		
	0-19 years – other	2HRZE	4HR	10mg/kg (7-15)	15mg/kg (10-20)		35-45mg/kg	20mg/kg (15-25)		

H = I = isoniazid, R = rifampicin, Z=pyrazinamide, E = ethambutol, Mfx = moxifloxacin, Pto = Prothionamide

* Ethambutol only recommended in settings with high HIV prevalence defined as ≥5% people with TB and isoniazid resistance

** It may be prudent to substitute ethambutol for moxifloxacin in cases of extrapulmonary TB in conjunction with a paediatric TB specialist

Table 22 Dispersible fixed drug combination treatments for TB in children

Weight	Number of tablets		
	Intensive phase (HRZ 50/75/150mg)	E 100mg	Continuation phase (HR 50/100mg)
4-<8kg	1	1	1
8-<12kg	2	2	2
12-<16kg	3	3	3
16-<25kg	4	4	4

Weight	Number of tablets	
	Intensive phase (HRZE^{+} 75/150/400/275mg)	Continuation phase (HR*** 100/150mg)
25-<30kg	2	2
30-<35kg	3	3
35-<50kg	4	4
50-<65kg	4	4
>65kg	5	5

$^{+}$HRZE: Isoniazid, rifampicin, pyrazinamide, ethambutol

The use of ethambutol in the first 2 months of treatment is generally recommended in settings with a high prevalence of HIV (Kabir et al., 2021) or isoniazid resistance (Institut National de la Santé Et de la Recherche Médicale, 2021) and for extrapulmonary TB and severe forms of pulmonary disease.

There is now evidence to support short-course treatment for children aged between 3 months and 16 years with non-severe TB (see Table 21) (Turkova et al., 2022). This includes children:

- with isolated peripheral lymph node disease
- with smear-negative pulmonary TB confined to one lobe of the lung without cavitation, complicated pleural effusion, or clinically significant airway obstruction
- without suspicion or evidence of disseminated TB
- without suspicion or evidence of MDR-TB or RR-TB.

The shorter intensive regimen for tuberculous meningitis (6HRZPto) is suitable for children and adolescents without HIV who have low likelihood/evidence of DR-TB (WHO, 2022).

The mycobacterial load in children is usually less than in adults. As such, the treatment of susceptible TB in children is successful in >99% of cases (Starke, 2004).

Dosing should be rounded to the nearest appropriate tablet/capsule size/volume (to the nearest ¼ tablet or 0.5 mL).

2 dispersible fixed drug regimens are now available for use in Australia based on weight-bands for dosing. Recommended dosing regimens are listed in Table 22.

Dispersible fixed frug combination options require SAS approval. WATBCP/Sir Charles Gairdner Hospital may need to order stock so please advise as soon as possible, to ensure continuity of stock.

Alternative options include:

- Isoniazid (H) **(max dose 300 mg/day)** comes as:
  - extemporaneously prepared 10 mg/mL solution*
  - 100 mg tablets (can be split into halves or quarters with a tablet cutter or crushed and mixed with food or rifampicin syrup). The 100 mg tablets also disperse within 5 minutes (recommended volumes to disperse are 5 to 20 mL).
- Rifampicin (R) **(max dose 600 mg/day)** comes as:
  - syrup 100 mg/5 mL in 60 mL bottle
  - capsules: 150 mg or 300 mg (can be opened and mixed with crushed isoniazid and/or food).
- Pyrazinamide (Z) **(max dose 2000 mg/day)** comes as:
  - 500 mg tablets
  - extemporaneously prepared 50mg/mL suspension*.
- Ethambutol (E) **(max dose 1600 mg/day)** comes as:
  - 100 mg or 400 mg tablets
- Prothionamide (or Protionamide - Pto) **(max dose 1000 mg/day)** comes as:
  - 250 mg tablets

*Only available at Perth Children's Hospital Pharmacy. Where possible, consider using tablet formulations.

Adjuvant corticosteroids

In patients with TB meningitis, initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks is recommended.

In patients with TB pericarditis, adjuvant corticosteroids may be used at the discretion of the treating clinician (WHO, 2022).

Management of adverse events from TB medicines in children

Children and their families should be counselled about potential adverse events of therapy prior to commencing treatment. Table 19 provides an overview of potential adverse events related to TB medicines and a suggested approach to management.

Processes for prescribing TB medications:

- Doctors are responsible for assessing patients, prescribing TB treatment if needed, and discussing potential side-effects of therapy and the treatment plan with the child and their guardian/parent(s).
- A case manager will be assigned to every child prescribed TB treatment. The case manager (or a nursing staff member) will provide education and provide the relevant medications to the child.

- All care is available with no financial cost to the patient from the WATBCP under the WA Health Fees and Charges Manual.
- Directly Observed Therapy (DOT) is offered for MDR-TB and XDR-TB.
- A SAS Form MUST be filled out by the prescriber for any fixed drug and for the following medications:
    - FDCs (see Table 22)
    - Bedaquiline (Cat A)
    - Clofazamine (Cat C)
    - Cycloserine (Cat A)
    - Levofloxacin (Cat C)
    - Pretomanid (Cat A)
    - Prothionamide (Cat A)
    - Pyrazinamide (Cat C)
    - Rifapentine (Cat A)
- The SAS form can be accessed here via the TGA website. A separate form is required for induction and continuation therapy for all FDCs. SAS forms should ideally be completed prior to supply.

Treatment issues to consider:

- Doses should be calculated according to the child's weight.
- The child's weight should be monitored frequently during treatment and medication doses adjusted accordingly (for example as the child gains weight as they clinically improve).
- The method of delivery needs to be considered in young children and advice provided to ensure the child can take medications (e.g., crushed pills, suspensions).
- Children are dependent on caregivers for treatment adherence. If concerns with adherence exist, discuss with case manager whether there is a role for DOT.
- If there is no TB isolate available from the patient, then treatment regimens should be based on proven or probable drug susceptibilities of the index case.

Treatment interruptions for drug-susceptible TB

Treatment interruptions may require recommencement of therapy or consideration of additional doses, depending on when the interruption occurs and how many doses are missed. Recommendations for an approach to managing treatment interruptions are summarised in Table 23.

Table 23 Treatment interruptions for drug-susceptible TB disease in children

Treatment phase	Details of interruption	Management
Intensive phase		
Applies to 4- and 6-month regimens	≤14 days	Continue treatment and complete all intensive phase doses
	≥14 days	Restart intensive phase
Continuation phase – 4-month 2HRZ(E) / 2HR		
4-month regimen	Completed ≥80% doses within 8 weeks	Further treatment not necessary
	Completed <80% doses and cumulative interruption <1 month	Complete remaining doses of treatment
	Completed <80% doses and cumulative interruption >1 month	Restart treatment from beginning of intensive phase
Continuation phase – 6-month 2HRZE / 4HR		
6 month and bacteriologically negative at initiation	Completed ≥80% doses within 16 weeks	Further treatment not necessary
6 month and bacteriologically positive at initiation	Completed ≥80% doses within 16 weeks	Complete remaining doses of treatment. If consecutive lapse >2 months, use clinical judgement
6-month regimen	Completed <80% doses and cumulative interruption <2 months	Complete remaining doses of treatment
6-month regimen	Completed <80% doses and cumulative interruption ≥2 months	Restart treatment from beginning of intensive phase, particularly if interruption was consecutive

MDR and XDR-TB treatment

DR-TB should be managed by a paediatrician familiar with efficacy and side effects of treatment regimens. Oral regimens are now available for drug-resistant TB, including for use in children. For more information, please see section 2.2 Medical treatment of drug-resistant tuberculosis.

Pyridoxine supplementation

Pyridoxine (vitamin B6) supplementation is recommended in children and adolescents living with HIV, breastfed children, and in malnourished children and adolescents who are treated for

TB at a dosage of 0.5-1 mg/kg/day (WHO, 2022). It is also recommended in the treatment of TB for children who are vegetarian/vegan. Pyridoxine deficiency manifests as peripheral neuropathy, characterised by pain, burning, or tingling in the hands or feet, numbness or loss of sensation or muscle cramps/twitching. Pyridoxine dosages may be increased to 2-5 mg/kg/day if peripheral neuropathy develops.

Recommended pyridoxine dosages are:

- Birth (at term) to 1 month - 6.25 mg daily.
- 1 month to 12 years - 6.25-12.5 mg daily.
- 12 to 18 years - 12.5-25 mg daily.

HIV co-infection

Several HIV-related diseases may present in a similar way to TB in children e.g., viral, or bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, and *Pneumocystis jirovecii* pneumonia. There may be multiple and concurrent opportunistic infections so the presence of one of the above infections does not exclude TB (WHO, 2014). The clinical assessment and investigation of TB in an HIV-infected child should be the same as in an HIV-uninfected child. The interpretation of TST in the presence of HIV infection is less reliable. An immunocompromised child may have a negative TST despite having TB disease.

HIV-infected children with all forms of pulmonary and extra-pulmonary TB should be treated with 4 drugs in the initial intensive phase of TB treatment (Cotton et al., 2010) and followed by at least 4 months of rifampicin and isoniazid in the continuation phase. A longer continuation phase may be needed if there has not been complete resolution of TB after 6 months of therapy. Daily therapy is preferred to intermittent therapy in HIV infected patients. It is important to check for drug interactions (https://www.hiv-druginteractions.org) when initiating TB therapy in patients with HIV who are on concomitant antiretroviral therapy (ART). Certain antiretroviral drugs may also require dose adjustment when administered with TB treatment.

The risk of immune reconstitution inflammatory syndrome (IRIS) is highest in patients with TB-HIV co-infection and who are not on ART. ART should be initiated within the first 2 weeks of TB treatment with CD4 cell counts <50/mm^3 and by 8 weeks of TB treatment for patients with CD4 cell counts >50/mm^3. However, patients with tuberculous meningitis **should not** start ART before 8-10 weeks of TB treatment is completed, regardless of CD4 count (Nahid et al., 2016). For patients already on ARVs, these should be continued, and TB treatment can be commenced without delay. Signs and symptoms of IRIS may include a paradoxical worsening of clinical or radiological features and consideration of corticosteroids may be appropriate if severe, after excluding other differential diagnoses along with expert advice.

Recommended clinical follow-up

Children and adolescents receiving TBI or TB disease treatment are reviewed after 2 weeks of commencement for clinical assessment and liver function testing. Subsequent reviews are scheduled every ~6 weeks until treatment is completed. The suggested duration of follow-up is outlined in Table 24.

Radiological follow-up is recommended in children with pulmonary TB. In most children with clinical improvement on therapy, this can be done at the end of therapy. In children with severe

disease, persistent symptoms, or drug resistance, earlier radiological follow-up may be considered.

Once appropriate, children and adolescents can be discharged from the WATBCP with a letter to their local doctor. Patients and their families should be advised on discharge that their risk of developing TB is now <2% providing they do not return to an endemic country. If symptoms occur in the future of cough for >2 weeks, weight loss, night sweats or persistent fevers, they should be reassessed for TB.

Table 24 Recommended duration of follow-up for children and adolescents

Disease type	Duration of follow-up
TBI	
Drug-susceptible	Treated: until completion of therapy; untreated: 6-monthly for 2 years
Confirmed or suspected drug-resistant	Treated: until completion of therapy; untreated: CXR and clinical review 6-monthly for 2 years.
Active TB disease (treated)	
Drug-susceptible	Until 3 months following cessation of treatment (one appointment after completion of therapy is recommended)
Confirmed or suspected drug-resistant	Clinical follow-up 6-monthly for 2 years, clinical follow-up thereafter to be decided at the discretion of the treating clinician.

4.2.13. BCG disease

BCG disease can be categorised as (Hesseling et al., 2006):

- Local disease: This involves a local process at the site of vaccination e.g., BCG injection site abscess or severe BCG scar ulceration.
- Regional disease: Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site e.g., ipsilateral axillary gland enlargement, suppuration, or fistula.
- Distant disease: Involvement of any site beyond a local or regional ipsilateral process e.g., BCG isolated from pulmonary secretions, CSF, urine etc.
- Disseminated disease: BCG confirmed from >1 remote site and/or at least blood or bone marrow culture.

Medical and/or surgical treatment of local and regional disease is influenced by the severity of disease, age of the patient and degree of immunosuppression. Distant and disseminated disease requires BCG-specific therapy. BCG immune reconstitution syndrome (BCG-IRIS) is defined as BCG disease that presents in an HIV-infected child within 3 months after the initiation of ART (Hesseling et al., 2006). It can occur with local, regional, distant, or disseminated disease as described above.

The management of BCG disease is specialised, and children with BCG disease should be referred to a paediatrician experienced in TB treatment. *M. bovis* (including all BCG strains) is inherently resistant to pyrazinamide and treatment may require higher doses of other first-line TB or additional medications (WHO, 2016).

4.2.14. BCG vaccination

BCG vaccine is the only vaccine available for TB. BCG vaccination does not prevent transmission of TB infection to an individual but in immune competent neonates and infants, BCG reduces the likelihood of TBI progressing to disease. If TB disease occurs, it lessens the chance of a severe outcome.

BCG vaccination is not offered routinely in WA because of the low incidence of TB in Australia. However, it may be indicated based on an assessment of increased risk. For more information on BCG vaccination, including the indications for use, please see section 6.1 BCG vaccination.

4.2.15. Other information about caring for children and adolescents in WA

Clinics

The weekly paediatric clinic is held on Tuesday mornings at the Anita Clayton Centre. Adult clinics are held on most days of the week. Occasionally adolescents will be seen by adult physicians.

When children and adults in the same family need follow-up, facilitation of appointments for the adults to be seen on the same day as the children in the paediatric clinic can be arranged.

When emailing staff relating to patients or clinic, please use the generic TB clinic for communications.

The email is: ACCadmin@health.wa.gov.au

Video conferences

For rural and regional patients, clinical consults may occur via video conference. It is important to keep the case manager for rural and regional patients involved in the management of these patients.

4.2.16. References

Andrews, J. R., Nemes, E., Tameris, M., Landry, B. S., Mahomed, H., McClain, J. B., Fletcher, H. A., Hanekom, W. A., Wood, R., McShane, H., Scriba, T. J., & Hatherill, M. (2017). Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study. *The Lancet. Respiratory medicine, 5*(4), 282–290. https://doi.org/10.1016/S2213-2600(17)30060-7

Buonsenso, D., Seddon, J. A., Esposito, S., & Barcellini, L. (2023). QuantiFERON-TB Gold Plus performance in children: A narrative review. *The Pediatric infectious disease journal, 42*(5), e158–e165. https://doi.org/10.1097/INF.0000000000003877

Cotton, M., Graham, S., Jaspan, H., Hesseling, A., Marais, B., Mehtar, S., Rabie, H., Schaaf, H. S., & Zar, H. (2010*). Guidance for national tuberculosis and HIV programmes on the management of tuberculosis in HIV-infected children: Recommendations for a public health approach.* International Union against TB and lung disease.

Cruz, A., & Starke, J. (2014). Tuberculosis. In Cherry, J., Harrison, G. Kaplan, S., Hotez, P. & Steinbach, W., *Feigin and Cherry's textbook of pediatric infectious diseases seventh edition* (96, 957-988.e12). Elsevier/Saunders.

Diallo, T., Adjobimey, M., Ruslami, R., Trajman, A., Sow, O., Obeng Baah, J., Marks, G. B., Long, R., Elwood, K., Zielinski, D., Gninafon, M., Wulandari, D. A., Apriani, L., Valiquette, C., Fregonese, F., Hornby, K., Li, P. Z., Hill, P. C., Schwartzman, K., Benedetti, A., … Menzies, D. (2018). Safety and side effects of rifampin versus isoniazid in children. *The New England journal of medicine, 379*(5), 454–463. https://doi.org/10.1056/NEJMoa1714284

Ena, J., & Valls, V. (2005). Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clinical Infectious Diseases*, *40*(5), 670–676. https://doi.org/10.1086/427802

Fox, G. J., Dobler, C. C., Marais, B. J., & Denholm, J. T. (2017). Preventive therapy for latent tuberculosis infection-the promise and the challenges. *International Journal of Infectious Diseases*, *56*, 68–76. https://doi.org/10.1016/j.ijid.2016.11.006

Graham S. M. (2011). Treatment of paediatric TB: revised WHO guidelines. *Paediatric respiratory reviews, 12*(1), 22–26. https://doi.org/10.1016/j.prrv.2010.09.005

Graham, S., Marais, B., & Gie, R. (2009). Clinical features and index of suspicion of tuberculosis in children. In A. Schaaf, & H. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 154-163). Elservier.

Hesseling, A. C., Rabie, H., Marais, B. J., Manders, M., Lips, M., Schaaf, H. S., Gie, R. P., Cotton, M. F., van Helden, P. D., Warren, R. M., & Beyers, N. (2006). Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. Clinical Infectious Diseases, *42*(4), 548–558. https://doi.org/10.1086/499953

Institut National de la Santé Et de la Recherche Médicale (2019) Evaluation of four stool processing methods combined with Xpert MTB/RIF Ultra for diagnosis of intrathoracic paediatric TB. Retrieved December 1, 2021, from https://clinicaltrials.gov/study/NCT04203628.

International Union Against Tuberculosis and Lung Disease (2010). *Desk guide for the diagnosis and management of TB in children*. https://www.tbonline.info/media/uploads/documents/desk-guide_for_diagnosis_and_management_of_tb_in_children_%282010%29.pdf

Kabir, S., Rahman, S. M. M., Ahmed, S., Islam, M. S., Banu, R. S., Shewade, H. D., Thekkur, P., Anwar, S., Banu, N. A., Nasrin, R., Uddin, M. K. M., Choudhury, S., Ahmed, S., Paul, K. K., Khatun, R., Chisti, M. J., & Banu, S. (2021). Xpert ultra assay on stool to diagnose pulmonary tuberculosis in children. *Clinical Infectious Diseases, 73*(2), 226–234. https://doi.org/10.1093/cid/ciaa583

Marais, B. J., Gie, R. P., Hesseling, A. C., Schaaf, H. S., Lombard, C., Enarson, D. A., & Beyers, N. (2006). A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics, 118*(5), e1350–e1359. https://doi.org/10.1542/peds.2006-0519

Marais, B. J., Gie, R. P., Schaaf, H. S., Hesseling, A. C., Obihara, C. C., Starke, J. J., Enarson, D. A., Donald, P. R., & Beyers, N. (2004). The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *The international journal of tuberculosis and lung disease, 8*(4), 392–402.

Marais, B., Schaaf, H., & Donald, P. (2009). Management algorithms for paediatric tuberculosis. In H. Schaaf, & A. Zumla, Tuberculosis: A comprehensive clinical reference (pp. 323-331). Elsevier.

Marais, B., Wright, C., Gie, R., et al (2006). Tuberculous lymphadenitis as a cause of persistent cervical lymphadenopathy in children from a tuberculosis endemic area. *Paediatric Infectious Disease Journal, 25*(2), 142-146. https://doi.org/10.1097/01.inf.0000199259.04970.d1

Menzies, D., Adjobimey, M., Ruslami, R., Trajman, A., Sow, O., Kim, H., Obeng Baah, J., Marks, G. B., Long, R., Hoeppner, V., Elwood, K., Al-Jahdali, H., Gninafon, M., Apriani, L., Koesoemadinata, R. C., Kritski, A., Rolla, V., Bah, B., Camara, A., Boakye, I., … Benedetti, A. (2018). four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *The New England journal of medicine, 379*(5), 440–453. https://doi.org/10.1056/NEJMoa1714283

Nahid, P., Dorman, S. E., Alipanah, N., Barry, P. M., Brozek, J. L., Cattamanchi, A., Chaisson, L. H., Chaisson, R. E., Daley, C. L., Grzemska, M., Higashi, J. M., Ho, C. S., Hopewell, P. C., Keshavjee, S. A., Lienhardt, C., Menzies, R., Merrifield, C., Narita, M., O'Brien, R., Peloquin, C. A., … Vernon, A. (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases*, *63*(7), e147–e195. https://doi.org/10.1093/cid/ciw376

National Institute for Health and Clinical Excellence. (2011). *Tuberculosis: Clinical diagnosis and management of tuberculosis and measures for its prevention and control*. National Institute for Health and Clinical Excellence. https://www.nice.org.uk/guidance/cg117

Starke, J. (2004). Tuberculosis in children. *Seminars in Respiratory and Critical Care Medicine , 25*(3), 353-64. https:doi.org/10.1055/s-2004-829507

Turkova, A., Wills, G. H., Wobudeya, E., Chabala, C., Palmer, M., Kinikar, A., Hissar, S., Choo, L., Musoke, P., Mulenga, V., Mave, V., Joseph, B., LeBeau, K., Thomason, M. J., Mboizi, R. B., Kapasa, M., van der Zalm, M. M., Raichur, P., Bhavani, P. K., McIlleron, H., … SHINE Trial Team (2022). shorter treatment for nonsevere tuberculosis in African and Indian children. *The New England Journal of Medicine, 386*(10), 911–922. https://doi.org/10.1056/NEJMoa2104535

World Health Organization. (2010). *Rapid advice: treatment of tuberculosis in children.* World Health Organization: http://apps.who.int/iris/bitstream/10665/44444/1/9789241500449_eng.pdf

World Health Organization. (2010). *Treatment of tuberculosis: guidelines* (4th ed.). World Health Organization. https://iris.who.int/handle/10665/44165

World Health Organization. (2014). *Guidelines for national tuberculosis programs on the management of tuberculosis in children* (2nd ed.). World Health Organization. https://iris.who.int/handle/10665/112360

World Health Organization. (2016). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach* (2nd ed.). World Health Organization. http://www.who.int/hiv/pub/arv/arv-2016/en/

World Health Organization. (2022). *WHO operational handbook on tuberculosis. Module 5: management of tuberculosis in children and adolescents*. World Health Organization. https://www.who.int/publications/i/item/9789240046832

4.3. Prisoners and immigration detainees

4.3.1. Introduction

TB can be more difficult to manage in a correctional or detention facility due to the high turnover of prisoners and detainees, the background risk factors of the prisoners and detainees, closer living conditions and more complex contact tracing of TB. The aim of this chapter is to highlight important aspects in TB management within a prison or detention facility. It acknowledges that specific correctional facilities and immigration detention centre procedures may differ from these guidelines.

Effective TB control activities in this setting include:

- The early identification of persons with TB.
- Targeted screening for TBI (formerly termed LTBI) in those at risk of reactivation while in the correctional or detention facility.
- Completion of treatment for TB and TBI.
- Appropriate infection control measures used when a case of TB is suspected and/or diagnosed.
- Timely contact tracing when a case of TB is diagnosed.
- Effective transfer of medical care and follow up when a prisoner or detainee is released into the community.

The clinical diagnosis, investigations, and treatment for TB in prisoners and immigration detainees does not differ from that of the general population. Details are provided in other chapters.

4.3.2. Background

A disproportionate number of prisoners are derived from population groups without access to adequate medical treatment in civilian life and are at higher risk of TB infection and disease (e.g. those addicted to alcohol or illicit drugs, the homeless, the mentally ill, Aboriginal Australians).

As well as sentenced prisoners, the prison population consists of around 18% remand prisoners, which contributes to a high turnover. Initial health assessments are conducted on adult prisoners and juvenile detainees as they enter a correctional facility.

A survey of 194 prisoners in WA in 2011 showed approximately 8% of inmates to be positive for a test for TBI. Similar results have been reported from NSW. This is higher than the estimated 1-3% in the general population (Arellano, 2012).

Prison populations may have higher levels of TB because transmission of TB infection is facilitated through prolonged and repeated exposure to *M. tuberculosis* as a result of:

- Late case detection, and the lack of respiratory isolation and inadequate treatment of infectious cases.
- High turnover of prisoners through repeated transfers within the prison system, release and recidivism increasing the risk of potential exposure to long-term inmates.
- Overcrowding and close living arrangements.

- Restricted ventilation.

Prisoners are also at risk of rapid progression to TB disease following recent infection or reactivation of TB infection through:

- co-existing pathology, particularly HIV and intravenous (IV) drug use
- poor nutritional status.

4.3.3. Early identification of TB

Early identification and treatment of TB is the most effective means to prevent transmission of TB, and any prisoner or detainee with symptoms suggestive of TB should be identified and treatment established before they are integrated into the general prison or detention facility population (CDC, 2006).

4.3.4. Health assessment on entry – active surveillance

It is recommended that all persons upon entry to a prison facility or immigration detention facility be screened for TB. This is currently a part of the first nurse assessment made in WA prisons. All prisoners are also routinely booked for a doctor admission assessment within 90 days that includes specific questions relating to TB, with the urgency of this assessment determined by the nurse assessment of risk. Those at highest risk include persons with recent close contact with TB, immigrants from TB endemic countries within the last 5 years, and Aboriginal Australians.

Prisoners and detainees should be questioned about symptoms of pulmonary TB which include:

- prolonged cough (lasting more than 3 weeks)
- haemoptysis
- unexplained fever
- night sweats
- unexplained weight loss.

Prolonged cough has a low specificity (35%) but high sensitivity (95%) in detecting TB. The addition of a CXR after symptom screening increases the sensitivity to 98% (WHO, 2013).

Therefore, if an individual reports symptoms suggestive of TB, a thorough medical evaluation should follow, which includes a CXR and if TB is likely, a sputum collection for TB microscopy and culture should be performed. In addition to the initial investigations, infection control measures should be instituted. A suspected case of TB should be discussed without delay by telephoning a TB Physician at the WATBCP on 08 9222 8500 or 0407 445 120.

Other information that should be gathered includes:

- Any previous diagnosis of or treatment for TB (disease or latent).
- A family history / or recent contact history of TB.
- Previous investigations for TB, including a TST, QFT, or CXR.
- Medical conditions that increase the risk of TB e.g. HIV infection, immunosuppression, diabetes, chronic renal failure and blood borne virus infections.
- A history of being born or prolonged residence in a TB endemic country.

4.3.5. Self-presentation – passive surveillance

Health care professionals should have a high index of suspicion for TB disease in prisons or detention facilities if any prisoner or immigration detainee presents with any of the symptoms mentioned above. This is especially pertinent in those persons from groups with an increased risk of TB i.e. recent contact with TB, immigrants from a TB endemic country within the last 5 years or Aboriginal Australians.

4.3.6. Immediate management of suspected TB

Any prisoner or detainee with symptoms suggestive of pulmonary TB should be identified and infection control precautions instituted immediately (see below; section 4.3.8 Infection control). The prisoner or detainee needs to be isolated from the general facility population until results of the following investigations are known:

- CXR.
- Sputum specimen examination for TB microscopy and culture.

In addition, the WATBCP should be contacted as soon as possible when there is a suspicion of a case of TB in the facility for further advice on management. Contacting the WATBCP does not need to wait until a positive test result is obtained. See Appendix 4.1 Flow chart for the management of a prisoner suspected of active tuberculosis).

4.3.7. Effective treatment of TB

The medical management of TB is discussed in detail in Chapter 2: Tuberculosis treatment.

It is important that the full duration of treatment is completed for TB control and the prevention of drug resistance. In a prison or detention setting, treatment via DOT is imperative and should be documented. This is necessary to ensure adherence and for vigilance regarding side effects.

Management in conjunction with the WATBCP is important to ensure the medical management is guided by a TB physician, to assist with maintaining adherence, for education and support for the prisoner or detainee; and for prompt intervention if side effects occur. A medical review should take place within 2 weeks after commencement of treatment and monthly thereafter, or as recommended by the TB Control Program. Appointments can take place either at a booked time at the WATBCP in Perth or via telemedicine.

If a prisoner or detainee is to be released from detention before treatment for TB is completed, then provisions need to be made for the continuation of therapy in the community (see below; section 4.3.11 Planning for released prisoners).

4.3.8. Infection control

Infection control precautions should begin immediately if TB is suspected. Persons who have suspected or confirmed pulmonary or laryngeal TB should be placed immediately in a negative-pressure room while being investigated for TB. The person usually requires transfer to hospital where negative pressure isolation is available.

If this is not possible, health staff from the detention or correctional facility should seek advice from the WATBCP regarding management of the case. TB isolation procedures can be discontinued if the TB physician deems the prisoner or detainee is non-infectious.

4.3.9. Transfer of prisoners and immigration detainees

Prisoners or detainees suspected of having infectious TB who are required to be transferred between facilities or to hospital should, wherever possible, reside in a different compartment of the vehicle, separate from the rest of the vehicle occupants. If this is not possible, the prisoner or detainee should be in the rear of the vehicle and the ventilation system for the vehicle should bring in as much fresh air as possible; and be set to non-recirculating.

Drivers or other individuals transporting prisoners or detainees with suspected TB in an enclosed vehicle should wear a particulate N95/P2 “duck bill” mask during transfer. Consideration should be given for the prisoner or detainee to wear a mask during transport, in waiting areas, or when others are present (CDC, 2006).

Once a diagnosis of TB is established, the prisoner or detainee should remain in negative-pressure isolation until they have had enough treatment to satisfy the treating TB physician that they are deemed non-infectious.

If the diagnosis of TB is made by the detention or correctional facility health staff, the WATBCP should be alerted as soon as possible to coordinate admission to hospital for initiation of treatment and to begin contact tracing activities.

4.3.10. Contact tracing

Contact tracing can be difficult in a prison or detention setting due to:

- Transfer of inmates within and between prisons and detention facilities increasing the potential number of contacts.
- Daily and weekly schedules of inmates that can affect TB exposure.
- Rapid turnover of inmates.
- Crowding.
- Release of contacts from prison or detention facility before contact tracing is initiated.

The WATBCP coordinates contact tracing activities. Close cooperation is needed to access facility records for the location and movements of inmates and detainees to determine contact lists, exposure periods and prioritising contact tracing. Unless there are accurate facility records that show exposure to the index TB case was brief (<8 hours), then all known contacts should be followed up including prison or detention centre staff. (CDC, 2006).

The assessment and investigation of contacts is given in section 5.1. Contact Tracing.

4.3.11. Planning for released prisoners

Effective transfer of medical care and follow up when a prisoner or detainee is released into the community is an important final step in the management of a case of TB.

Individuals still receiving TB treatment at release

If individuals are still undergoing TB treatment at the time of discharge from a prison or detention facility, involvement of the WATBCP should already be in place.

Health facility staff should ensure that the patient has sufficient supply of medications (at least one month) until the next medical review and forward relevant referral or discharge paperwork

to the WATBCP prior to the appointment. Up to date patient contact information is particularly important if the individual fails to attend a booked appointment.

A summary of the individual's TB treatment and other medical issues needs to be provided by the prison or detection facility to the service taking over the care of the individual (e.g. Other detention facility or prison, community case worker, TB service in another State or Territory). Copies of this documentation need to be sent to the WATBCP to facilitate ongoing TB case management within WA, interstate or overseas.

Individuals who have completed TB treatment at release

Individuals who finish TB treatment whilst in prison or a detection facility, upon discharge, need a summary of TB and other medical management to be provided to the individual, the individual's GP or case worker and the WATBCP.

Routine follow up after completion of TB treatment requires a CXR and medical review 3 months post therapy. This can be organised via the WATBCP in Perth or via telemedicine with a regional health centre.

Prisoners or detainees moving interstate during or after TB treatment need to be referred to the appropriate TB service in that State or Territory. The WATBCP can assist with this process.

4.3.12. Screening for tuberculosis infection

The management of TBI is discussed in detail in section 3.2. Tuberculosis infection - Treatment. The following comments are specific to TBI screening in correctional facilities and detention centres.

Universal screening for TBI at the entry health assessment is not warranted. However, certain groups have an increased risk of developing TB and the entry health assessment is an opportune time to undertake screening for TBI in these targeted groups.

A prisoner or detainee should only be screened for TBI when the intention is to offer treatment with preventive therapy if the diagnosis of TBI is made.

4.3.13. Employee screening

It is recommended that all Department of Corrective Services employees (HCWs, non-clinical staff, custodial staff, etc.) in WA and staff working with immigration detainees have a TB risk assessment (e.g. pre-employment) and be screened for TB as appropriate. However, whether and how this occurs in specific facilities is determined by the facilities administration based on risk assessment and capacity for such screening. A possible schedule for this assessment and which employees should be screened can be taken from what is recommended for HCWs (see section 5.3 Health Care Workers).

Appendix 4.1 Flow chart for the management of a prisoner suspected of active tuberculosis

Person suspected of having active TB

- Cough >3 weeks duration
- Unexplained fevers
- Night sweats

See section *Health assessment on entry*

Urgent medical assessment

- History
- Examination
- Collect sputum AFB
- **Immediate isolation of prisoner at the facility from others**

See sections *Immediate management of suspected active TB case* and *Infection Control*

Contact Anita Clayton Centre (WATBCP)

- Advice on management of suspected case
- If required, Staff will assist coordination for admission to hospital for investigations

Contacts: ph: 08 9222 8500, fax: 08 9222 8501, 1/311 Wellington Street, Perth, WA 6001

Transfer between facilities or to hospital

- Prisoner to wear N95/P2 mask
- Escorting staff to wear N95/P2 mask

See section *transfer of prisoner and immigration detainees*

Hospital Management

- CXR
- Sputum AFB/bronchoscopy
- Isolation in negative pressure room
- Other relevant investigations

Diagnosis of active TB

- Initiation of anti-tuberculous treatment in consultation with WATBCP staff
- Monitor for side effects
- Two weeks of therapy prior to discharge to correctional facility (patient no longer infectious)

Prisoner returns to facility

- Case management from Anita Clayton Centre
- Contact tracing coordinated by staff at Anita Clayton Centre
- Directly Observed Therapy (DOT)
- Shared care between facility doctor and Anita Clayton Centre doctor
- Appointment at Anita Clayton Centre at end of treatment
- Documentation of completion of therapy

4.4. Pregnancy

4.4.1. Introduction

TB in pregnancy can lead to adverse consequences for the mother as well as cause infection in the neonate during the antenatal, intrapartum and post-partum periods.

The neonate can acquire TB through haematogenous spread via the placenta, aspiration/ingestion of infected amniotic fluid or maternal genital secretions; or by airborne transmission from an infected mother in the post-partum period (Adhikari & Jeena, 2009). Most cases of neonatal TB are due to airborne spread after delivery. Breast milk does not transmit TB.

Transmission from mother to baby is more likely to occur if the mother has TB with sputum smear positive disease, miliary or untreated TB, or when maternal disease is diagnosed late (Adhikari & Jeena, 2009).

If left untreated, TB in pregnancy has a mortality rate of 30-40%. Pregnancy-related complications such as a higher frequency of miscarriage, pre-eclampsia and pre-term labour are seen more frequently in TB infected mothers (Adhikari & Jeena, 2009; Ormerod, 2001). Effects on the foetus include higher rates of perinatal mortality, prematurity and poor foetal growth. The risk of complications is greater when TB is diagnosed late.

4.4.2. Tuberculosis disease in pregnancy

Clinical presentation

The clinical presentation of TB in pregnancy is similar to that in non-pregnant women, but diagnosis may be delayed because nonspecific symptoms such as malaise and fatigue may be attributed to the pregnancy (Ormerod, 2001). Delay in diagnosis and treatment increases the risk of obstetric and perinatal complications.

Diagnosis of tuberculosis

The clinical assessment and investigations of a suspected case of TB in pregnancy are the same as the general population (see section 1.2 Diagnosis of tuberculosis – clinical). The placenta delivered from a mother with TB, especially if disseminated or miliary, should be examined microbiologically and histologically for evidence of TB disease.

The diagnosis of TB may be delayed when CXR is postponed or omitted due to concerns of radiation exposure to the developing foetus.

Radiation exposure to the unborn child from maternal chest x-ray

A CXR is required if TB is suspected to look for asymptomatic but radiologically pulmonary TB.

The radiation risk to the foetus from a maternal CXR during pregnancy is very small. Radiation to the foetus below 50 mGy is not associated with significant health risks and the amount of exposure to the foetus from a maternal two-view CXR is <0.01 mGy. This is comparable to 10 days of natural background radiation (Screening patients for pregnancy prior to chest x-ray at Anita Clayton Centre, Mental Health, Public Health and Dental Services, March 2023 [intranet]).

Therefore, if TB is strongly suspected, the benefit of a CXR outweighs the small risk to the foetus from radiation exposure as it leads to an early diagnosis and treatment of TB. This includes during the first trimester, though consideration may be given to deferring an x-ray very early in pregnancy.

Lead shielding of the abdomen is no longer considered warranted as the small radiation exposure received by a foetus is through scatter radiation through the mother's trunk, rather than direct radiation that would be prevented by a lead shield.

Medical treatment

If TB is diagnosed in a pregnant woman, treatment must commence as soon as possible to ensure the best health outcome for the woman, the foetus and the neonate; as well as limiting the infectiousness of the woman.

First-line treatment of TB in pregnant women is no different to non-pregnant women. For details of drug doses and circumstances in which this regimen may be altered see sections 2.1.5 Drug doses and 2.1.6 Treatment regimens.

Pyrazinamide

Although in some jurisdictions (American Thoracic Society et al., 2016) pyrazinamide (PZA) is not recommended for routine treatment of TB in pregnancy because of a lack of published teratogenicity data, WHO and the International Union Against TB & Lung Disease Management of Tuberculosis, support the use of pyrazinamide. In Australia it has an Australian Category B2 classification for risk of drug use in pregnancy.

Given the lack of reported adverse outcomes in pregnancy and the importance of pyrazinamide in short-course TB chemotherapy, it is recommended for routine use in pregnant patients in WA (Therapeutic Guidelines, 2014). This discrepancy in recommendation should be discussed with the patient at the beginning of therapy and in gaining the patient's informed consent to use an unlicensed product.

If pyrazinamide is not included in the treatment regimen, a 9-month course consisting of an initial 2 months of isoniazid, rifampicin and ethambutol therapy followed by a 7-month continuation phase of isoniazid and rifampicin should be used (2HRE7HR) provided the *M. tuberculosis* isolate is fully susceptible. (American Thoracic Society et al., 2016).

Rifampicin

Bleeding attributable to hypoprothrombinaemia has been reported in newborn infants and in mothers after the use of rifampicin during late pregnancy. This is a rare adverse outcome. The TB physician should ensure the midwife and/or obstetrician managing the delivery is aware of this possibility. MIMS© recommends the mother and the newborn receive vitamin K (MIMS, 2017), but there is no evidence to support this, and in WA it is not routine management. This rare possibility is not a reason to stop or withhold treatment with rifampicin.

Drugs contraindicated in pregnancy

The following drugs are contraindicated in pregnancy:

- aminoglycosides (amikacin, streptomycin, capreomycin, kanamycin)

- prothionamide, ethionamide (CNS defects)
- cycloserine (can be used if absolutely necessary)
- bedaquiline (some preliminary recent evidence indicates that it may be safe, but the lack of data suggests it should used only if absolutely necessary)
- pretomanid (there is a lack of data to determine the risk in pregnancy at this stage).

Liver function should be monitored frequently due to the increased risk of drug-associated liver toxicity during pregnancy and the early peri-partum period.

Pyridoxine

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid (WHO, 2009). Isoniazid-induced peripheral neuropathy usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women. The dose of pyridoxine is 25 mg per day (CDC, 2016).

4.4.3. Labour

Women with fully susceptible pulmonary TB on first-line treatment are generally no longer infectious after 2-4 weeks of commencement of TB therapy and should be allowed to deliver as normal. If delivery occurs prior to two weeks of TB therapy and the mother has sputum smear positive TB, then delivery should be conducted in a negative pressure room and appropriate infection control measures taken. The neonate will require PPT. Contact tracing procedures are followed as per usual.

4.4.4. Breastfeeding

Breast-feeding should not be discouraged if a woman is on treatment for TB. The concentration of TB medications found in breast milk is not associated with toxicity in the neonate and all breastfeeding mothers who are receiving isoniazid should continue to take pyridoxine supplementation (WHO, 2009; CDC, 2008). The concentration of TB medications found in breast milk is too small to be an effective treatment for TB or TBI in the nursed baby. Neonates born to mothers with TB should receive their own treatment for either TB or preventive therapy, with pyridoxine supplementation.

4.4.5. Perinatal tuberculosis

Transmission of TB from a mother to the foetus or neonate is most likely to occur when the mother has untreated or disseminated TB, sputum smear- positive TB or when TB is diagnosed late in the pregnancy. Perinatal TB encompasses TB acquired by the baby while in-utero, intra-partum and in the postnatal period.

TB acquired by the foetus in-utero from haematogenous spread via the umbilical cord, or in-utero aspiration or ingestion of infected amniotic fluid is rare. It should be considered if the mother has been diagnosed with genital tract TB, especially late in the pregnancy, and if the neonate develops signs of sepsis.

TB can be spread to the neonate during delivery by aspiration or ingestion of infected amniotic fluid or cervicovaginal secretions. TB infection acquired after delivery occurs from

airborne infection from the mother, an adult family carer or another infectious adult with whom the infant has had contact with (including HCWs).

Medical management

A paediatric specialist should always be involved in the management of children at risk of or suspected to have neonatal TB. The diagnosis of perinatal TB is difficult and frequently delayed. If the neonate exhibits any signs or symptoms of TB infection, a thorough assessment and investigation should be undertaken for bacterial confirmation of *M. tuberculosis* infection.

Symptoms and signs that should raise suspicion of TB in a neonate are fever, respiratory distress, hepatosplenomegaly, jaundice, lymphadenopathy or an abnormal CXR. The clinical features can be subtle and difficult to differentiate from other congenital or neonatal infections.

Standard TB therapy should be commenced after appropriate specimens have been collected. Paediatric drug regimens and doses are discussed in more detail in section 4.2 Paediatrics.

After TB has been excluded in the baby, the neonate should receive preventive therapy. Infants exposed to a mother with fully susceptible TB should be offered preventive therapy (WHO, 2010).

During treatment, medication dosages need to be checked regularly as they may require adjustment to reconcile the effect of age, weight gain and possible toxicity in young infants. The decision to adjust dosages should be made by a clinician experienced in managing paediatric TB.

If the infant receiving preventive therapy develops clinical symptoms or signs or radiological appearances suggestive of TB, then appropriate investigations should be undertaken to exclude TB and a course of treatment for TB considered.

Standard contact tracing of family members and other contacts applies. See section 5.1 Contact tracing for details.

4.4.6. Tuberculosis infection in pregnancy

Screening

Routine screening for TBI in pregnancy is not necessary, however, it is warranted in selected groups:

- Close contacts of infectious TB.
- Recent arrivals from countries with TB incidence rate of >40 per 100,000 population. Individual country incidence rates for TB can be found through the WHO TB country profile website.
- HIV infected patients (and other profoundly immunocompromised patients).

The TST or an IFN gamma release assay such as the QFT are both safe and validated in pregnancy. Thus, the choice of test is based on the same parameters as for a non-pregnant patient (see section 3.1. Tuberculosis infection – diagnosis). There is evidence that the pregnancy associated immune changes are likely to reduce the immunological response to antigens used in either test (LaCourse et al., 2017). This may reduce the sensitivity for diagnosis of TBI in pregnancy.

It is recommended that asymptomatic pregnant women with positive TST or QFT *and* at risk of progressing to disease e.g. recent contact of TB, HIV co-infection, should have a CXR after 12 weeks gestation to exclude asymptomatic but radiological pulmonary TB.

Treatment

The preferred regimen for preventive therapy in pregnant women is isoniazid 300 mg daily for 6 months with pyridoxine 25 mg per day. Isoniazid is a category A drug and is safe to use in pregnancy. Treatment should be encouraged during pregnancy in situations when there is a high risk of progression to disease, such as:

- recent close contact with TB
- HIV infection or is severely immunocompromised
- known medical condition, which increases the risk of reactivation of TBI.

If preventive treatment is to be deferred until after delivery, then the pregnant woman should be closely monitored for signs of disease.

4.5. Human immunodeficiency virus (HIV) co-infection

4.5.1. Introduction

This chapter addresses differences in the approach to the assessment and treatment of TB in patients co-infected with HIV.

Untreated HIV infection leads to progressive immunodeficiency and increased susceptibility to opportunistic infections, including *M. tuberculosis* infection. HIV co-infection is a risk factor for progression of *M. tuberculosis* infection to disease. The risk of progression from TBI to active TB in people with HIV is approximately 5 to 8% per year, in contrast to a 10% lifetime risk in HIV-negative people (Australasian Society for HIV Medicine, 2019). The risk of developing active TB increases 2-3-fold after HIV seroconversion, with ongoing increase in risk with decline in CD4+ T cell counts. Treatment of TBI and use of combination antiretroviral therapy (ART) are important interventions to decrease the incidence of TB in HIV infected populations. (Cohen et al., 2019)

4.5.2. Diagnosis

Clinical features

The clinical presentation of TB in HIV infected persons is influenced by the:

- degree of immunosuppression
- rate of HIV disease progression.

Pulmonary TB is the most common form of TB with clinical features dependent on the degree of immunosuppression. TB progresses more rapidly in immunocompromised patients, which increases the imperative for TB to be diagnosed, and treatment initiated with minimal delay. Assessment for pulmonary TB in a patient known to be infected by HIV should begin if cough persists for more than 1 week rather than 3 weeks (Nachega & Maartens, 2009).

As HIV infection progresses, the CD4+ T-lymphocytes decline in number and function. This compromises the immunological suppression of *M. tuberculosis*, and patients may be more likely to present with sputum smear negative TB, disseminated and extra-pulmonary TB disease (Australasian Society for HIV Medicine, 2019).

Radiographic features

CXR changes in TB and HIV co-infected patients reflect the degree of immunocompromise. In HIV-infected individuals with relatively preserved immunity, pulmonary TB presents in the typical adult pattern of upper lobe predominance and cavitation. In the severely immunocompromised, the appearance is often atypical and may include non-cavitary lower or mid zone infiltrates, hilar and/or mediastinal lymphadenopathy (CDC et al., 2017; Nachega & Maartens, 2009). Patients with clinical features suggestive of pulmonary disease with a normal CXR should still submit sputum specimens for examination.

Investigations

The investigation of TB disease in HIV infected persons should not differ from non-HIV infected individuals. All patients, regardless of HIV status, with clinical features suggestive of pulmonary TB should submit sputum specimens for microscopy, culture, and NAAT.

Patients who are highly immunocompromised may return a negative result on sputum microscopy despite clinical and/or radiological appearances suggestive of TB. NTM infections may be present in patients with advanced immunodeficiency and NAAT can help to differentiate these from TB and the need for respiratory isolation.

Disseminated and extrapulmonary TB may be present and specimens from extrapulmonary sites should be examined for *M. tuberculosis* by microscopy, culture and NAAT. For a list of suitable clinical specimens see section 1.2 Diagnosis of tuberculosis - clinical. Patients with a relatively intact immune system will have a more typical granulomatous histological picture on tissue specimens. In advanced immunodeficiency, granulomas are poorly formed, due to a decrease in CD4+ T cell function (CDC et al., 2017).

Table 25 Features of TB for degrees of immunosuppression (CDC et al., 2017)

	CD4 count >200 cells/μL	CD4 count <200 cells/μL
Clinical picture	Similar to non-HIV infected persons. Majority have disease limited to the lungs.	Extrapulmonary or disseminated TB, with or without pulmonary involvement are more common.
Pathology	Often sputum smear positive. Histopathology shows typical granulomatous inflammation.	Sputum smear-negative TB common. Granulomas poorly formed or absent. Nucleic acid amplification useful to distinguish TB from non-tuberculous mycobacterial infections.
Chest x-ray	Common changes are upper lobe infiltrates with or without cavities.	Infiltrates with no predilection for the upper lobes. Cavitation is uncommon. May be normal.

4.5.3. Treatment of TB in HIV infected patients

The principles of TB treatment are the same irrespective of HIV status. However, there are specific issues related to the treatment of TB in HIV infected patients which include:

- the timing of ART
- drug interactions between TB medication and ART
- IRIS after ART initiation
- complexities in case management and integration of HIV and TB treatment.

Collaboration between TB and HIV physicians is essential as the medical management of TB should be planned in conjunction with the HIV treating physician.

Tuberculosis medication

The standard treatment of TB in HIV infected individuals does not require different drugs or duration of treatment than HIV unaffected persons (WHO, 2010; Australasian Society for HIV Medicine, 2019).

Therefore, standard short-course therapy for TB is 2 months intensive phase of isoniazid, rifampicin, ethambutol and pyrazinamide followed by a 4 month continuation phase of isoniazid and rifampicin (2HREZ 4HR). If there is evidence of slow response to treatment and/or extensive disease, prolongation of the continuous phase to 7 months should be considered. Total length of therapy of 9 months is recommended for individuals with a positive 2 month sputum culture (CDC et al., 2017). Similar to patients without HIV co-infection, the continuation phase is extended in specific situations with increased risk of relapse as well as selected extrapulmonary disease e.g. tuberculous meningitis, bone or joint disease spinal TB. For further information on various drug regimens and drug doses please see sections 2.1.5 Drug doses and 2.1.6 Treatment regimens.

Daily TB treatment should be used, rather than intermittent therapy, as intermittent regimens are associated with a higher rate of relapse and failure (WHO, 2010; CDC et al., 2017).

Other considerations in the management of TB and HIV co-infected patients include:

- Patients with tuberculous meningitis should be cautiously initiated on ART early, as high rates of adverse events and deaths have been reported (Department of Health and Human Services, 2017).
- All HIV infected patients receiving isoniazid should also be given supplemental pyridoxine to minimise the risk of peripheral neuropathy (Australasian Society for HIV Medicine, 2016).
- Adjuvant steroid treatment can be used in HIV-positive patients and steroids are likely to be of benefit in the following indications (CDC et al., 2017; Department of Health and Human Services, 2017; Nahid et al., 2017)
    - tuberculous meningitis
    - severe TB-IRIS.

Although the evidence is weak and not routinely recommended, adjuvant steroids can be considered in:

- TB pericarditis (with large pericardial effusion or early signs of constriction)
- TB laryngitis (with life-threatening airway obstruction)
- severely ill patients with pleural TB
- severe hypersensitivity reactions to anti-TB drugs
- hypoadrenalism (TB of adrenal glands)
- massive lymph node enlargement with pressure effects.

The use of adjuvant steroid therapy in TB and HIV co-infected patients is at the discretion of the treating physician.

Timing of TB treatment with ART

ART is recommended in all HIV infected individuals with TB. For ART naïve patients, ART should be started within 2 weeks after TB treatment initiation when the CD4 T-cell count is <50cells/mm^3 and, within 8 weeks of starting anti-TB treatment in those with higher CD4 T-cell counts (CDC et al., 2017). The exception is in HIV infection and tuberculous meningitis. Caution is needed in patients with tuberculous meningitis where early initiation of ART is associated with more severe adverse events than delayed ART therapy (WHO, 2016).

The timing of initiation of TB treatment with ART treatment should always be made in consultation with the patient's HIV physician, taking into consideration the patient's clinical features, CD4+ count, severity of TB disease, presence of TB drug resistance and age (Australasian Society for HIV medicine, 2019; WHO, 2016). Early initiation of ART is important to reduce morbidity and mortality.

Physicians managing patients being treated for both TB and HIV infection should be aware of, and monitor the:

- risk of the development of TB associated IRIS (TB-IRIS);
- drug interactions
- compliance with a large pill burden.

Drug interactions

Significant drug interactions can occur between TB medications and ART. A key interaction is between rifamycin antibiotics (rifampicin, rifapentine and rifabutin) and antiretroviral drugs including all protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc, raltegravir and fostemsavir. Rifamycins induce the synthesis of several drug transporting and drug metabolising enzymes, the most common being the liver cytochrome P450 enzyme system. Rifampicin and rifapentine are more potent inducers than rifabutin (CDC, 2013). Induction of drug metabolising enzymes can lead to reduced plasma concentrations of co-administered antiviral drugs with the associated risks of HIV treatment failure and emergence of antiviral drug resistance (CDC, 2013).

However, rifamycins are important for the success of TB treatment and should not be eliminated from therapy except in cases of drug resistance or intolerance. Patients with HIV and TB should receive a rifamycin antibiotic for the full course of treatment.

The preferred treatment regimen for HIV related TB disease is rifampicin-based TB therapy and effective ART that has minimal interaction with TB drugs. Expert HIV physician management in conjunction with a TB physician is required to prescribe the best treatment combination. This should be individualised.

For further information on the use of alternative rifamycins and detail on the interactions between the drugs used to treat TB and HIV please see the references given and consult http://www.hiv-druginteractions.org.

Tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS)

TB-IRIS is a frequent early complication of ART in patients with recently diagnosed or undiagnosed TB and it is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis*. TB-IRIS is characterised by excessive local

or systemic inflammation and may result in either a deterioration of the treated infection or the new presentation of a previously subclinical infection. Two forms of TB-IRIS are recognised: paradoxical TB-IRIS and unmasking TB-IRIS (CDC, 2017).

Paradoxical tuberculosis associated IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with TB prior to starting ART. Typically, these patients have had clinical improvement on TB treatment prior to starting ART. Within the first weeks of ART (though sometimes later), patients may develop new or recurrent symptoms as well as new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include fevers, return of a cough, new or enlarging lymph nodes, and new or worsening pulmonary infiltrates (CDC, 2017). CNS TB-IRIS can be severe and in patients with profound immunosuppression and TB-IRIS can involve multiple sites (Australasian Society for HIV medicine, 2019).

Paradoxical TB-IRIS typically occurs within the first 1 to 4 weeks after ART is initiated and lasts for 2 to 3 months. Patients at highest risk are those with advanced HIV disease and low CD4+ counts, high HIV viral load prior to ART, disseminated and extrapulmonary forms of TB, a shorter time between the start of TB treatment and ART and a significant response to ART (CDC, 2017).

Most cases of paradoxical TB-IRIS are self-limited though patients may require treatment for symptom relief e.g. analgesia, anti-emetics or corticosteroids for severe cases. Corticosteroids should be avoided in patients with Kaposi's sarcoma, as life-threatening exacerbations can occur. They should also be avoided where the diagnosis of paradoxical TB-IRIS is not certain. Aspiration and drainage of large abscesses or effusions may provide relief, but re-accumulations often occur (CDC, 2017).

TB therapy and ART should both be continued if a patient develops TB-IRIS.

Alternative reasons for clinical deterioration should be excluded such as:

- failure of TB treatment due to drug resistance
- non-compliance with TB medications
- alternative diagnosis e.g. other infection, neoplasm, or drug toxicity or reaction.

TB paradoxical reactions can also occur in HIV negative individuals and in HIV positive patients not receiving ART but this occurs less frequently compared to those on ART.

Unmasking tuberculosis associated IRIS

Unmasking TB-IRIS may occur in patients who have unrecognised TB at the start of ART. TB is diagnosed after the initiation of ART and may be the result of a missed diagnosis prior to ART, due to low sensitivity of TB testing prior to immune system restoration e.g. sputum smear microscopy, or the presence of subclinical TB disease becoming symptomatic after ART is started.

Unmasking TB-IRIS can present with heightened intensity of clinical manifestations. A common presentation is pulmonary TB with rapid symptom onset and clinical features similar to bacterial pneumonia with high fever, respiratory distress, sepsis syndrome, and consolidation on CXR (CDC, 2017). Standard TB treatment should continue. Corticosteroids may be used if the

manifestations are life-threatening, although there is no clinical trial evidence to support steroid use (CDC, 2017).

Monitoring during treatment

Patients should be monitored closely for response to TB treatment and for the development of drug adverse effects and drug interactions. Further detail on TB treatment monitoring can be found in the section 2.3 Case management.

4.5.4. TB infection in HIV

Diagnosis

The TST relies on a competent immune response to identify people with TBI and therefore in HIV infected patients, a lower cut-off of a 5 mm diameter reaction is deemed a positive result (versus 10 mm in the general population). HIV related immunosuppression can be associated with false negative results. False negative and indeterminate QFT results increase with advancing immunodeficiency and low CD4+ counts (WHO, 2011).

On balance QFT is the preferred test for TBI in HIV patients. The routine use of both a TST and QFT test to screen for TBI is not recommended.

All individuals should be tested for TBI at the time of HIV diagnosis, regardless of their epidemiological risk (CDC, 2017). Patients with advanced HIV infection (CD4+ count <200 cells/µL) may initially return a negative screening test for TBI and should be retested once ART commences and the CD4+ count increases above 200 cells/µL (CDC, 2017).

All individuals returning a positive screening test for TBI should be assessed for TB disease with a CXR as well as by screening for symptoms including cough, fever, sweats, weight loss. Once TB has been excluded, all HIV infected persons with a positive screening test for TBI should receive treatment for TBI. If there is a history of TB exposure, then treatment for TBI should be offered regardless of the result of screening tests.

Treatment

Preventive therapy should be offered to all HIV infected individuals, once TB has been excluded, who fulfil one of the following criteria (Australasian Society for HIV Medicine, 2019):

- Have a TST reaction of ≥5 mm in diameter or positive QFT test and no prior history of treatment for TB or TBI.
- Negative TST or QFT test but is a close contact of infectious TB.
- Radiological evidence of past TB infection (e.g. fibrotic change on chest radiography).

There is insufficient data to clearly determine the optimal duration of preventive therapy in people living with HIV. The treatment recommended by the WATBCP is 6 - 9 months of isoniazid monotherapy, at a dose of 5-10 mg/kg to a maximum of 300 mg daily. WHO guidance is for 6 months isoniazid monotherapy in both adults and children in high and low incidence TB settings. For adults living with HIV living in settings with high TB incidence and transmission, the WHO recommendation is for at least 36 months of Isoniazid, irrespective of whether they are taking ART (WHO, 2018). Pyridoxine at a dose of 25 mg daily should be given concurrently to minimise the risk of peripheral neuropathy.

Rifampicin monotherapy for preventive therapy is not recommended in HIV infection because of drug interactions. Expert opinion should be sought.

Primary preventative therapy

Individuals with HIV infection are at high risk of developing primary TB infection following exposure to an infectious case. Commencement of TBI treatment immediately following the exposure aims to prevent the development of primary TB infection. These patients should be offered PPT regardless of TST or QFT result. For individuals who are a contact of infectious DR-TB, the choice of medication should be made in conjunction with a TB physician.

4.5.5. Pregnancy

The investigations and principles of management of TB and TBI in HIV infected pregnant women are no different from that in HIV negative women. However, the following should be considered (CDC, 2017):

- HIV infected pregnant women who do not have documentation of a prior negative TB screening test or who are at risk of exposure to TB should be screened during pregnancy.
- If TBI is diagnosed in pregnancy and TB is ruled out, preventive treatment should be considered during pregnancy.
- The choice of antiretroviral drugs in pregnant women should be made by the patient's HIV physician.
- Pregnancy can alter the pharmacokinetics of a number of drugs.
- Hepatotoxicity from isoniazid may occur more frequently in pregnancy and the postpartum period and should be monitored. Supplemental pyridoxine should be prescribed.
- If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months.
- DR-TB in pregnant women should be managed in consultation with a specialist experienced in the management of TB.

The management of pregnant women with HIV and TB co-infection should be discussed with a specialist in HIV medicine.

4.5.6. Paediatrics

The approach to diagnosing TB in children infected with HIV should be the same for HIV negative children with the following considerations (WHO, 2014):

- Several HIV-related diseases may present in a similar way to TB including viral or bacterial pneumonia, lymphocytic interstitial pneumonitis, bronchiectasis, *Pneumocystis jirovecii* pneumonia and Kaposi's sarcoma.
- There may be multiple and concurrent opportunistic infections and the presence of these infections does not exclude TB being present as well. Lymphoid interstitial pneumonitis is the most difficult condition to distinguish from TB, due to radiological similarities.
- TST is less sensitive in children with HIV than in HIV-negative children; induration of >5 mm is considered positive if the child has HIV co-infection. An immunocompromised

child may have a negative TST despite having TB and so caution is needed in interpreting results.
- BCG vaccination should **NOT** be given to HIV-infected children due to the increased risk of disseminated BCG disease.

If TB is suspected in a HIV infected child, the child should be referred to and be managed by clinicians familiar with both paediatric TB and HIV (see section 4.2 Paediatrics)

4.5.7. BCG disease

BCG is a live attenuated vaccine derived from *M. bovis* and is used in areas of high prevalence to reduce the likelihood of TB infection progressing to severe disease in infants and children. BCG disease is a rare complication of BCG administration and the presentation can be the same as TB. BCG disease can be categorised as (Hesseling et al., 2006):

- Local disease – This involves a local process at the site of vaccination e.g. BCG injection site abscess or severe BCG scar ulceration.
- Regional disease – Involvement of any regional lymph nodes or other regional lesions beyond the vaccination site e.g. ipsilateral axillary gland enlargement, suppuration or fistula.
- Distant disease - Involvement of any site beyond a local or regional ipsilateral process e.g. BCG isolated from pulmonary secretions, CSF, urine etc.
- Disseminated disease – BCG confirmed from >1 remote site and/or at least blood or bone marrow culture.

The management of BCG disease is specialised, and HIV-infected children suspected of having BCG disease should be referred to a paediatrician experienced in TB treatment. *M. bovis* is inherently resistant to pyrazinamide and treatment may require higher doses of other first-line TB medications (WHO, 2014).

BCG-IRIS is defined as BCG disease that presents in an HIV infected child within 3 months after the initiation of ART (Hesseling et al., 2006). It can occur with local, regional, distant or disseminated disease as described above.

4.5.8. Non-tuberculosis mycobacteria

Other NTM infections may also be common in the setting of advanced HIV. When microscopy demonstrates AFB, but TB PCR (GeneXpert) is negative, these should be considered. Expert opinion from an Infectious Disease or Respiratory Physician should be sought.

4.6. Patients living in regional Western Australia

This guideline relates to the care of patients that are resident outside of Perth metropolitan area who are referred to the WATBCP. There are between 10 – 15 notifications of TB in WA annually that are resident outside of Perth metropolitan area, which represents 8-14% of all notifications. This is at a rate usually lower than that for Perth e.g. in 2022 the rate for regional and metropolitan TB notifications was 2.5 and 3.8 per 100 000 population respectively. The WATBCP also receives referrals for management of TBI and active surveillance, such as a pre- and post-migration surveillance in people living outside of Perth.

In principle, patients that are resident in regional WA should receive the same standard of TB care as metropolitan patients and as recommended throughout these guidelines. However, there is obviously a risk of delayed or impaired delivery of care due to remoteness, lack of local expertise and experience, lack of local resources, distance for patients to travel and distance for delivery of resources such as medication. It is stressed that the WATBCP is a statewide service. With the collaboration of local clinicians and WA Country Health Service (WACHS) Public Health Units, and in particular the regular use of telehealth, the highest standard of TB care can be provided irrespective of where a patient lives.

The overarching document for the process of delivering TB and leprosy care to patients in regional WA is the *Memorandum of Agreement* between the WATBCP and WACHS which came into effect in May 2017 and was revised in May 2022. The Memorandum of Agreement is in place to ensure that patients within regional WA receive equivalent TB and leprosy care to that of metropolitan patients. For details of the roles and responsibilities of the WATBCP and WACHS refer to this *Memorandum of Agreement*.

In general, the following applies:

- Referrals are received and triaged in the usual way. Regional patients are offered telehealth review or, alternatively, can attend the TB clinic in person.
- A TB physician is available during business hours, Monday to Friday, at the WATBCP (Anita Clayton Centre) to give immediate advice and support to regional clinicians at the time that they are assessing patients e.g. regional hospital emergency departments. The TB physician can be contacted on 9222 8500 or directly on 0407 445 120. For calls outside of business hours, a message can be left that will be answered the following business day, or the caller is re-directed to the on-call respiratory registrar or consultant at RPH for more urgent enquiries.
- TB treatment for both active and TBI, is largely directed by a physician at the WATBCP through telehealth consultation. This can be done in consultation with a local primary care provider (such as GP/Aboriginal Medical Service/Nurse Practitioner/District Medical Officer) where *on-the-ground* service is required. Details of a patient's treatment and progress are shared by correspondence to relevant local care providers in all cases, irrespective of the level of their involvement in the TB treatment.
- TB medication is usually supplied from the WATBCP. A WATBCP case manager arranges for delivery of the medication to the patient often through a relevant local agency e.g. pharmacy, local hospital, public health unit.
- All services for the diagnosis, treatment and management of TB in patients in regional WA are provided free of financial cost to the patient (see section 8.1 Fees and Charges).

However, this only applies to services provided by the WA Health Department, and does not include private practices, including primary care practices.

- Public health activity is shared between the relevant regional WACHS Public Health Unit and the WATBCP. This includes case management of patients with active TB, including DOT when required, and contact tracing. This activity is coordinated by a WATBCP Case Manager with local activities done by a WACHS Public Health Unit designated local case worker. Early in the course of the TB case management the WATBCP Case Manager arranges a video conference to establish contact with the local case worker and to provide direction and support for the public health actions.

4.6.1. References

Adhikari, M., & Jeena, P. (2009). Tuberculosis in pregnancy and in the neonate. In H. Schaaf, & A. zumla, *Tuberculosis: a comprehensive clinical reference* (pp. 572-580). Saunders Elsevier.

American Thoracic Society, CDC, & Infectious Diseases Society of America (2003). Treatment of tuberculosis. *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports, 52*(RR-11), 1–77.

American Thoracic Society, Centers for Disease Control and Prevention, & Infectious Diseases Society of America (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis clinical infectious diseases. *Clinical Infectious Diseases,* 63(7), e147-e195. https://doi.org/10.1093/cid/ciw376

Arellano, A. (2012). *Latent tuberculosis infection (LTBI) screening in Western Australian correctional facilities* [Poster presentation]. 2012 Annual Scientific Conference of the Australasian Society for Infectious Diseases, Fremantle, WA.

Australasian Society for HIV medicine. (2016). HIV Management in Australasia: a guide for clinical care. Retrieved on October 12, 2017, from http://hivmanagement.ashm.org.au/

Caminero, J. (2003). *A Tuberculosis Guide for Specialist Physicians*. International Union against Tuberculosis and Lung Disease.

Centers for Disease Control and Prevention (2013). *Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis* [online]. Retrieved on October 4, 2019, from: https://stacks.cdc.gov/view/cdc/25866

Centers for Disease Control and Prevention, National Institute of Health, & HIV medicine Association of the Infectious Diseases Society of America. (2017). *Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America*. Retrieved on November 29, 2017, from https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf

Centers for Disease Control and Prevention. (2006). Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *Morbidity and Mortality Weekly Report, 54 (*RR-15), 1-37.

Centers for Disease Control and Prevention. (2006). Prevention and control of tuberculosis in correctional and detention facilities: Recommendations from CDC. *Morbidity and Mortality Weekly Report, 55*(RR-9), 1-54.

Centers for Disease Control and Prevention. (2014). *Tuberculosis and pregnancy*. CDC. Retrieved February 27, 2017, from http://cdc.gov/tb/publications/factsheets/specpop/pregnancy.htm

Cohen, A., Mathiasen, V. D., Schön, T., & Wejse, C. (2019). The global prevalence of latent tuberculosis: a systematic review and meta-analysis. *The European respiratory journal*, *54*(3), 1900655. https://doi.org/10.1183/13993003.00655-2019

Department of Corrective Services Western Australia. (2015). *Annual Report 2014/2015*. Retrieved September 2016, from www.correctiveservices.wa.gov.au

Department of Health and Human Services. (2017). *Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*. Retrieved December 5, 2017, from https://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Hesseling, A. C., Rabie, H., Marais, B. J., Manders, M., Lips, M., Schaaf, H. S., Gie, R. P., Cotton, M. F., van Helden, P. D., Warren, R. M., & Beyers, N. (2006). Bacille Calmette-Guérin vaccine-induced disease in HIV-infected and HIV-uninfected children. *Clinical Infectious Diseases*, *42*(4), 548–558. https://doi.org/10.1086/499953

Jensen, P. A., Lambert, L. A., Iademarco, M. F., Ridzon, R., & CDC (2005). Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care settings, 2005. *MMWR. Recommendations and reports: Morbidity and mortality weekly report. Recommendations and reports, 54*(RR-17), 1–141.

LaCourse, S. M., Cranmer, L. M., Matemo, D., Kinuthia, J., Richardson, B. A., Horne, D. J., & John-Stewart, G. (2017). Effect of pregnancy on interferon gamma release assay and tuberculin skin test detection of latent TB infection among HIV-Infected women in a high burden setting. *Journal of acquired immune deficiency syndromes (1999)*, *75*(1), 128–136. https://doi.org/10.1097/QAI.0000000000001298

Levy, M. H., Butler, T. G., & Zhou, J. (2007). Prevalence of Mantoux positivity and annual risk of infection for tuberculosis in New South Wales prisoners, 1996 and 2001. *New South Wales Public Health Bulletin, 18*(8), 119-124. https://doi.org/10.1071/NB07051

Mental Health, Public Health and Dental Services. (2023). *Screening patients for pregnancy prior to chest x-ray at Anita Clayton Centre*. North Metropolitan Health Service [intranet].

MIMS online. (2017). *Rifampicin: Full product information*. Retrieved February 27, 2018, from MIMS online: [Department of Health, WA intranet].

Nachega, J., & Maartens, G. (2009). Clinical aspects of tuberculosis in HIV-infected adults. In Schaaf, H.S. and Zumla, A. (Eds) *Tuberculosis: A comprehensive clinical reference.* (pp. 524-531). Suanders/Elsevier.

Nahid, P., Dorman, S. E., Alipanah, N., Barry, P. M., Brozek, J. L., Cattamanchi, A., Chaisson, L. H., Chaisson, R. E., Daley, C. L., Grzemska, M., Higashi, J. M., Ho, C. S., Hopewell, P. C., Keshavjee, S. A., Lienhardt, C., Menzies, R., Merrifield, C., Narita, M., O'Brien, R.,…Vernon, A. (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases, 63*(7), e147-e195. https://doi.org/10.1093/cid/ciw376

Nahid, P., Dorman, S. E., Alipanah, N., Barry, P. M., Brozek, J. L., Cattamanchi, A., Chaisson, L. H., Chaisson, R. E., Daley, C. L., Grzemska, M., Higashi, J. M., Ho, C. S., Hopewell, P. C., Keshavjee, S. A., Lienhardt, C., Menzies, R., Merrifield, C., Narita, M., O'Brien, R., Peloquin, C. A., … Vernon, A. (2016). Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: Treatment of drug-susceptible tuberculosis. *Clinical Infectious Diseases*, *63*(7), e147–e195. https://doi.org/10.1093/cid/ciw376

North Metropolitan Health Service. (2022). *Memorandum of Agreement between the WA TB Control Program and WA Country Health Service*. Department of Health.

Ormerod P. (2001). Tuberculosis in pregnancy and the puerperium. *Thorax, 56*(6), 494–499. https://doi.org/10.1136/thorax.56.6.494

Therapeutic Guidelines. (2014). *Therapeutic Guidelines: Antibiotic. Version 15. Tuberculosis in pregnancy and breastfeeding*. eTG complete [Internet].

Toms, C., Stapledon, R., Waring, J., Douglas, P., & National Tuberculosis Advisory Committee, for the Communicable Diseases Network Australia, and the Australian Mycobacterium Reference Laboratory Network (2015). Tuberculosis notifications in Australia, 2012 and 2013. *Communicable diseases intelligence quarterly report, 39*(2), E217–E235.

World Health Organization. (2008). Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. World Health Organization. https://iris.who.int/bitstream/handle/10665/43792/9789241546676_eng.pdf?sequence=1

World Health Organization. (2010). *Rapid advice: treatment of tuberculosis in children.* World Health Organization: http://apps.who.int/iris/bitstream/10665/44444/1/9789241500449_eng.pdf

World Health Organization. (2010). *Treatment of tuberculosis: guidelines* (4th ed.). World Health Organization. https://iris.who.int/handle/10665/44165

World Health Organization. (2011). *Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings*. World Health Organization. https://iris.who.int/bitstream/handle/10665/44472/9789241500708_eng.pdf?sequence=1

World Health Organization. (2013). *WHO Global TB Report: spotlight on TB in prisons*. World Health Organization.

World Health Organization. (2014). Guidelines for national tuberculosis programmes on the management of tuberculosis in children (2nd ed.). World Health Organization. https://www.who.int/publications/i/item/9789241548748

World Health Organization. (2016). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach* (2nd ed.). World Health Organization. http://www.who.int/hiv/pub/arv/arv-2016/en/

World Health Organization. (2021). *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach.* World Health Organization. https://www.who.int/publications/i/item/9789240031593

World Health Organization. (2024). *Tuberculosis country profiles.* Retrieved from https://worldhealthorg.shinyapps.io/tb_profiles/

Chapter 5: Active Surveillance for Tuberculosis

5.1. Contact Tracing

5.1.1. Introduction

Effective contact tracing is an important strategy for TB control in Australia (Communicable Diseases Network Australia, 2002). The aims of contact tracing are to detect:

- another individual with TB disease that transmitted TB to the index case (source case)
- TBI or TB disease due to transmission from the index case (secondary case)
- other cases of TB infection acquired from an un-identified source that is shared with the index case (cohort effect).

The risk of infection and disease is highest within 2 years of exposure to TB.

5.1.2. Background

Governance

TB contact tracing is undertaken by the WATBCP. Primary oversight is provided by the TB case manager for the index case, who in turn reports to and seeks advice from the physician that has clinical governance of the index case. Occasionally, contact tracing is undertaken by other care providers, in which case it is carried out in consultation with the WATBCP. This is especially important when contact tracing is required in a hospital (see below Hospitals and other Health Care Settings) or for index cases living in regional WA, where it is coordinated between the WACHS regional Public Health Unit and the WATBCP (see section 4.6 Patients Living in Regional Western Australia).

Principle of contact tracing

Contact tracing for TB is conducted based on the ‘stone in the pond’ principle (see Figure 2) where contacts are identified and tested in a logical (in time and space) order of decreasing closeness to the index case, which form concentric circles. Screening of contacts is performed starting with the closest contacts (household) and expanding outwards in a stepwise fashion through the more distant or casual contacts until minimal cases of TB infection (as determined by TB case management meeting) are found from screening results (TST or QFT).

The degree to which this is extended depends on the factors affecting infectiousness described below, and most importantly the sputum smear result of the index case.

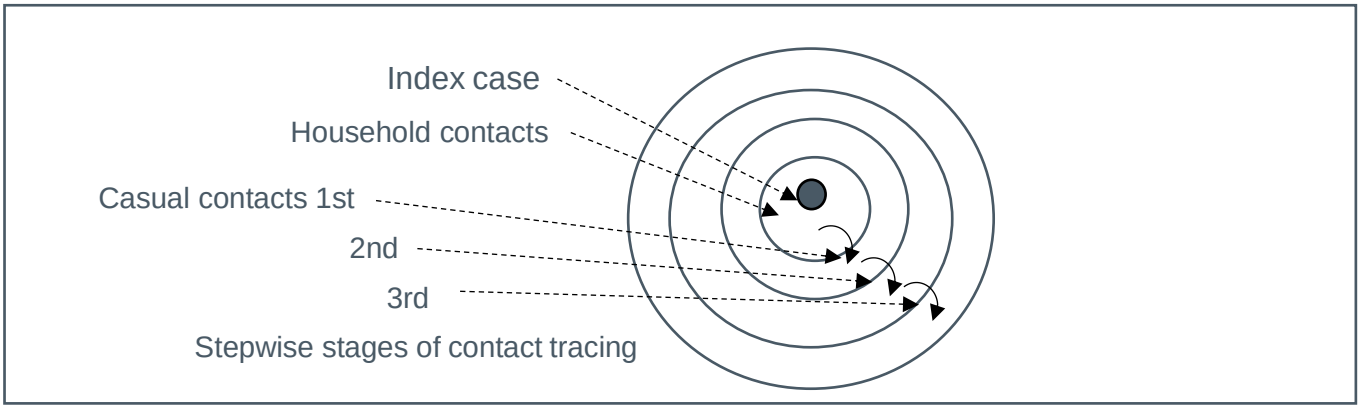


Figure 2: Stone-in-a-pond Principle of Contact Tracing

5.1.3. Definitions

Index case

The index case is the person diagnosed with TB that leads to the contact tracing. If the contact tracing identifies a new case of TB, this then becomes a new index case that requires independent (though often overlapping) contact tracing.

Household / close contacts

Household or close contacts are people who have had prolonged exposure to the index case. Prolonged exposure is arbitrarily set at a cumulative total exposure of about 8 hours or more. Exposure is defined as sharing the same air space and does not imply the index case and the contact being in the room at the same time. This exposure is predominantly in the household where the index case lives but can also include other enclosed areas where the exposure time is greater than 8 hours (e.g. shared hospital room, dormitory, other residential institution, but not a school room or workspace). These individuals need to be included in the contact tracing exercise in addition to household contacts (NICE, 2011).

Casual contacts

Casual contacts are those who have less exposure to the index case, but the total cumulative exposure time is still estimated to be greater than 8 hours. These tend to be people who have contact with the index case outside their primary place of residence and include work or school contacts. Employees who have left the workplace but who had a significant exposure to the index case may be omitted from current employee lists but should also be offered screening.

5.1.4. Factors influencing the infectiousness of TB

Characteristics of the index case

The characteristics of the index case that influence the TB infectiousness and the subsequent risk to contacts are presented in Table 26)

Table 26: Characteristics of the index case that influence TB infectiousness (CDC, 2005)

Name	Description
Site of infection	Patients with pulmonary or laryngeal TB transmit TB. Extra-pulmonary TB only, including pleural TB, and with no evidence of pulmonary TB (i.e. no respiratory symptoms, normal CXR and negative sputum AFB smear or culture), has a negligible risk of TB transmission. Contact tracing is performed primarily to identify a source case and others infected by the same source case.
Sputum microscopy	Sputum smear positive TB indicates higher infectiousness. Sputum smear negative, but culture positive, pulmonary TB is infectious, but less so. Other respiratory specimens such as bronchial washings and bronchoalveolar lavage are regarded the same as sputum.
Radiographic findings	Cavitation observed on CXR is associated with higher infectiousness than non-cavitating pulmonary disease.
Age of index case	Transmission of TB from children aged <10 years is unusual.
HIV status	TB patients who are also infected with HIV that is not controlled can have CXR findings that are not typical of pulmonary TB (e.g. less likely to have upper lobe infiltrates and cavities). Atypical x-ray findings may contribute to a delay in diagnosis, which increases transmission.
Patient behaviour	Frequent coughing and sneezing are associated with increased risk of TB transmission. Singing is also associated with TB transmission risk. Close social networks of the index case may have an increased risk of infection depending on the intensity of exposure. The lifestyle of the index case may reveal close contacts other than in the household or workplace (e.g. aircraft travel, itinerant cases, prostitution). Certain lifestyles and behaviours can create difficulties in identifying contacts of the index case and in ensuring compliance with treatment and follow up of the index case (e.g. IV drug use, homelessness, chronic alcoholism and mental health problems).
Medical procedures	Aerosolizing medical procedures that increase respirable droplet production can increase the risk of transmission of TB (e.g. chest physiotherapy, nebulization, intubation, airway suction, sputum induction, cardiopulmonary resuscitation, post-mortem examination).

Characteristics of contacts

The characteristics of individuals identified as contacts that can influence the risk of TB infection and the development of TB disease are given in Table 27.

Table 27: Characteristics of contacts that influence risk of TB infection and disease

Name	Description
Age of the contact	The risk of disease progression after infection is higher in children <5 years old (Marais, Schaaf, & Donald, 2009).
Co-morbid conditions of contacts	Contacts who have risk factors that increase their risk of developing tuberculosis should be considered and screened at a lesser level of exposure time (at the discretion of those conducting the contact tracing). The risk factors include: • HIV infection • Immunosuppressive therapy such as anti-tumour necrosis factor alpha (TNFα), post organ transplantation, and immunosuppressant therapy equivalent to prednisolone 15 mg/day for > 1 month • Silicosis • Chronic renal failure and haemodialysis • Leukemia or lymphoma • Cancers of the head, neck or lung • Persons who have had gastrectomy or jejunoileal bypass
Proximity to index case	The amount of time in contact with the index case and the environment in which the contact occurred. A higher risk of TB infection is found in: • Household contacts • Exposure within a confined space • > 8 hours cumulative exposure
Occupation	Occupational groups more likely to be in contact with an index case and the production or respiratory droplets are at higher risk e.g. TB clinic staff, anaesthetist, chest physiotherapist, mortuary staff.

5.1.5. Extent of contact tracing

Timeframe

Contact tracing should begin as soon as possible after an index case has been diagnosed with TB. Contacts of an index case should be included from the time of the index case's first

symptom onset, with the focus being on the duration of the cough and spanning the time until the index case is no longer thought to be infectious.

Who to contact trace

All household or close contacts of pulmonary TB should be considered and assessed. Screening should extend to casual contacts if the initial screen of close contacts results in a high number of positive cases or the factors influencing infectiousness described above (see above section Factors Influencing the Infectiousness of TB) indicate a higher risk of transmission. The most important factor determining the extent of screening of casual contacts is the sputum smear result of the index case. Therefore, the priority for extensive contact tracing is sputum smear positive index cases. However, sputum smear negative, but culture positive, pulmonary TB index cases also warrant contact tracing beyond the household. Other factors that will influence the extent of contact tracing are as listed in Table 26 and Table 27 above.

In cases of extra-pulmonary TB, with no evidence of pulmonary TB (i.e. no respiratory symptoms, normal CXR and negative sputum AFB smear or culture), contact tracing is performed on household or close contacts primarily to identify a possible source case or to identify others who may also have been recently infected from the same (possibly un-identified) source as the index case (this is termed 'the cohort effect'). Contact tracing is usually not extended beyond the household or close contacts in extra-pulmonary TB cases.

Other considerations in determining the extent of contact tracing include:

- perception and public relations, and duty of care to employees
- DR-TB in the index case: the infectivity does not differ from a susceptible case of TB, but the consequences of transmission are potentially greater, so the imperative to identify infected contacts is greater.

5.1.6. Procedure for contact tracing

The procedure for contact tracing in household contacts and casual contacts of TB is summarised in the flowcharts in Appendix 5.1 *and* Appendix 5.2 respectively.

Review of index case

The index case should be interviewed to determine lists of contacts requiring screening. In addition, the characteristics of the index case that influence infectiousness should be reviewed (see above Table 26).

Stratification of contact list

Contacts should be stratified into groups according to the "stone in a pond" principle (see above Figure 2) i.e. household contacts and different levels of casual contacts based on the extent of contact; forming widening circles around the index case. This stratification should be pre-determined to at least 3 levels before contact screening is commenced.

Contact screening

Once a group of contacts is identified they should undergo the following:

Interview

Contacts can be questioned for symptoms of TB. This usually includes at least all household/close contacts. Other relevant history should include any previous TST or QFT result, previous TB exposure or treatment, history of BCG vaccination scar, and co-existing medical conditions.

CXR

- All household contacts over 10 years old (irrespective of result of test for TBI).
- All contacts with positive test for TBI regardless of age.
- All contacts with symptoms suggestive of TB disease.
- All contacts starting preventive treatment (a CXR within the preceding 3 months is adequate).

Test for TBI

The preferred screening tool when sequential testing is required is the TST. This applies to household/close contact tracing where contacts with an initially negative result are usually tested a second time after 8 – 12 weeks to look for conversion. Casual contacts usually only require a single test performed 8-12 weeks after exposure to detect new TB infection. This is preferred from an individual, logistic and public health point of view (CDC, 2005; Menzies, 1999). Therefore, for casual contacts the TST or QFT are considered equivalent tests and either can be used.

A detailed summary of the pros and cons of the TST and QFT can be found in section 3.1 Tuberculosis infection - Diagnosis and section 5.3 Health care workers.

More detail on the standard operating procedure of contact tracing can be obtained from the WATBCP. See Appendix 5.1 for the investigation pathway for household or close contacts and Appendix 5.2 for the investigation pathway for casual contacts.

Physician review

The following contacts should be reviewed by a physician with expertise in TB management:

- all contacts with CXR abnormalities
- all contacts with symptoms suggesting TB disease
- all contacts with a positive TST result or TST conversion (consider preventive treatment irrespective of age)
- all contacts with a positive QFT (consider preventive treatment irrespective of age)
- all contacts <5 years old are referred for paediatrician review (see section 4.2 Paediatrics).
- high -risk contacts e.g. HIV positive and other immunocompromised people.

Follow up

If preventive treatment is initiated, follow up is according to section 3.2 Tuberculosis infection – Treatment. Individuals who decline or cannot take preventive treatment are followed up with CXRs every 6 months for 2 years. Contacts of MDR-TB with a positive test for TBI should be followed up in the same way, but for at least 5 years, even if preventive therapy is given.

Contact tracing report

When contact tracing is completed the responsible Case Manager completes a report summarising the extent and results of the contact tracing. The details of this reporting are described in the WATBCP contact tracing standard operating procedure.

5.1.7. Special situations

Aircraft

The risk of infection is related to the infectiousness of the source case, the susceptibility of those exposed, the duration of exposure, the proximity to the source case, and the efficiency of cabin ventilation (WHO, 2008). The risk of transmission of *M. tuberculosis* on board aircraft is generally low and limited to persons in close contact with an infectious case flight times of 8 hours or longer.

The decision to initiate contact tracing in this setting in influenced by the following:

- Infectiousness of the index case: pulmonary or laryngeal TB, sputum AFB smear positive, presence of cavitation on CXR, existing documented transmission to close contacts, symptomatic at time of flight i.e. coughing, haemoptysis.
- Duration of exposure: if an index case was infectious at the time of travel, then contact tracing is required for travellers in close contact with the index case for at least 8 hours duration. The exposure time incorporates the total duration of the flight including ground delays after boarding, flight time and ground delays after landing.
- Context: the susceptibility of those exposed, the proximity of travellers to the source case and consequence of transmission (MDR-TB, XDR-TB).
- The time elapsed between the flight and the notification of the case: Contact tracing should be considered where the time between notification of the index case with TB and the flight are within 3 months of each other.

If contact tracing is to be performed, information should be obtained on passengers sitting in the same row as the index case and in the two rows in front of and behind the index case. Any travelling partners of these contacts or the index case can also be considered for contact tracing, irrespective of where they sat.

The procedure of identifying passengers that require contact tracing and conduction of the necessary tests is organised by the National Incident Room, who are contacted in turn by the Clinical Nurse Manager of the WATBCP. Tuberculosis and Air Travel: guidelines for prevention and control (WHO, 2008) contains relevant information on this process.

Educational Institutions

Contact tracing following the notification of TB in a student or teacher attending an educational institution should follow the procedures and steps for the assessment of TB risk discussed in earlier sections. Some issues to be addressed are:

- Estimating the duration of exposure and prioritising contact lists. This may involve gathering information on class lists, academic schedules and extra-curricular activities.
- Communication with students, parents, guardians and teachers, including to alleviate anxiety and obtain consent for contact tracing.
- Communication with facility officials and relevant government department.

- Addressing publicity and media attention. All media enquiries should be directed to the Medical Director of the WATBCP.
- Ensuring the privacy and confidentiality of the index case.

Hospitals and other Health Care Settings

When pulmonary TB is diagnosed in a hospital or other health setting where a patient has not been adequately isolated or HCWs are exposed, contact tracing is necessary. This is conducted according the same principles as above. Specific details on definitions of significant exposure and procedures are given separately in section 5.3 Health care workers. Infection Control Officers are also encouraged to discuss planned contact tracing with the WATBCP before it is initiated.

MDR-TB index case

The assessment of risk for contacts of MDR-TB cases and screening procedures should be the same as for drug susceptible cases. However, treatment of individuals infected with MDR-TB is more difficult. Contacts who have been assessed as high risk and those with a high risk of progression to TB should be referred to a clinician with experience in TB management (NTAC, 2007).

Importantly, the contact and the contact's family doctor must be made aware of the seriousness of MDR-TB and the need to assess the contact for disease if ever that contact presents with symptoms suggestive of TB.

Children

All children < 5 years old, who are close contacts of pulmonary TB, are at higher risk of progression to disease (Marais et al., 2009). All children and especially neonates born to mothers with TB, should be referred to a paediatric physician experienced in the management of TB for consideration of empiric preventive treatment. Please see the WATBCP section 4.2 Paediatrics for further details regarding TB management in children.

5.1.8. Other Considerations

Maintaining confidentiality of the index case

The name of the index case should never be disclosed to contacts without the consent of the index case. Health professionals (including public health authorities) have a duty to maintain the confidentiality of all information that comes to them in the course of providing medical treatment and care to patients. Inadvertent disclosure of a patient's diagnosis of TB to a third party could have adverse consequences for the patient both at home and in the workplace.

Further information regarding confidentiality and divulging patient information to third parties is provided in the Department of Health Patient Confidentiality fact sheet. This fact sheet supersedes the previous mandatory policy MP 0010/16 (now rescinded).

Clients declining tests or treatment

Clients who refuse to be tested for TB should be informed of the signs and symptoms of TB and advised to seek medical attention if they become symptomatic. If a patient refuses

preventive therapy, once TB has been excluded, follow up with CXR every 6 months for 2 years should be offered as an alternative to medication.

Large scale contact tracing in public places

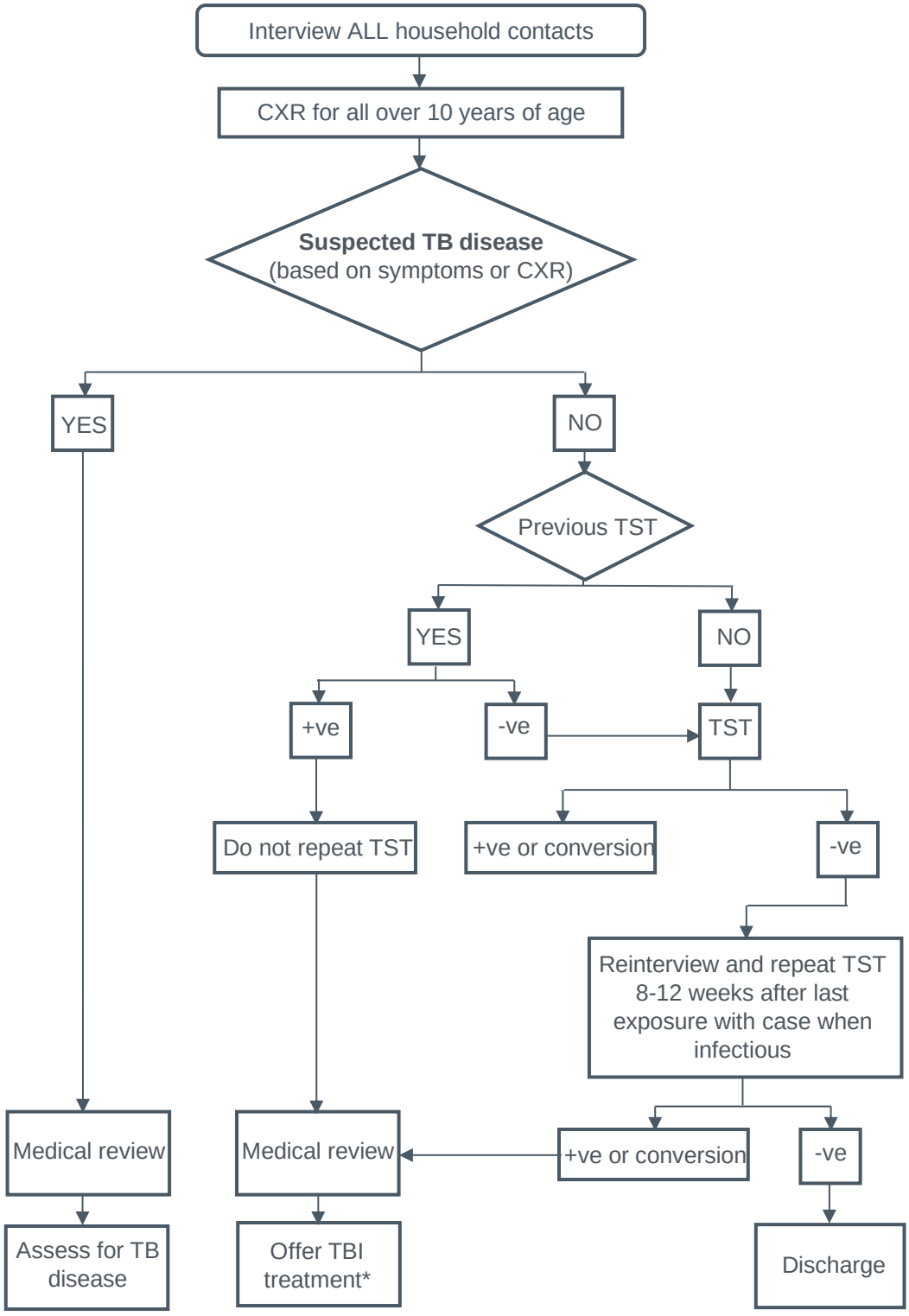
Any large-scale TB contact tracing (arbitrarily set at greater than 20 contacts) in a public setting (e.g. workplace, education institution, detention centre or gaol, nursing home etc.) should be discussed with the Clinical Nurse Manager or Medical Director of the WATBCP on the day that the necessity for large scale contact tracing is first recognised.

If a decision is reached to proceed with a large-scale contact tracing exercise that is not within the North Metropolitan Health Service area a Health Service Notification Report may be required to ensure timely communication to the relevant Health Service Board via the Chief Executive NMHS to the Chief Executive of the relevant Health Service.

Media attention

Media attention may develop when TB involves schools, childcare centres, hospitals, detention facilities or other public settings. This is most likely to arise through contacts speaking to the media. Contact tracing procedures and priorities should not be any different in this situation. Attention should be paid to clear and prompt communication with contacts to alleviate anxiety and concerns that may prompt erroneous media reporting. Any media enquiry should be addressed as soon as possible to ensure accurate reporting. However, pre-emptive media statements in the setting of contact tracing are not recommended. All media enquiries should be referred to the Medical Director of the WATBCP and/or the Clinical Nurse Manager and are managed by the NMHS Media Relations.

Appendix 5.1 Algorithm for Investigation of Household/Close Contacts of TB (TRIM D/24/228560)

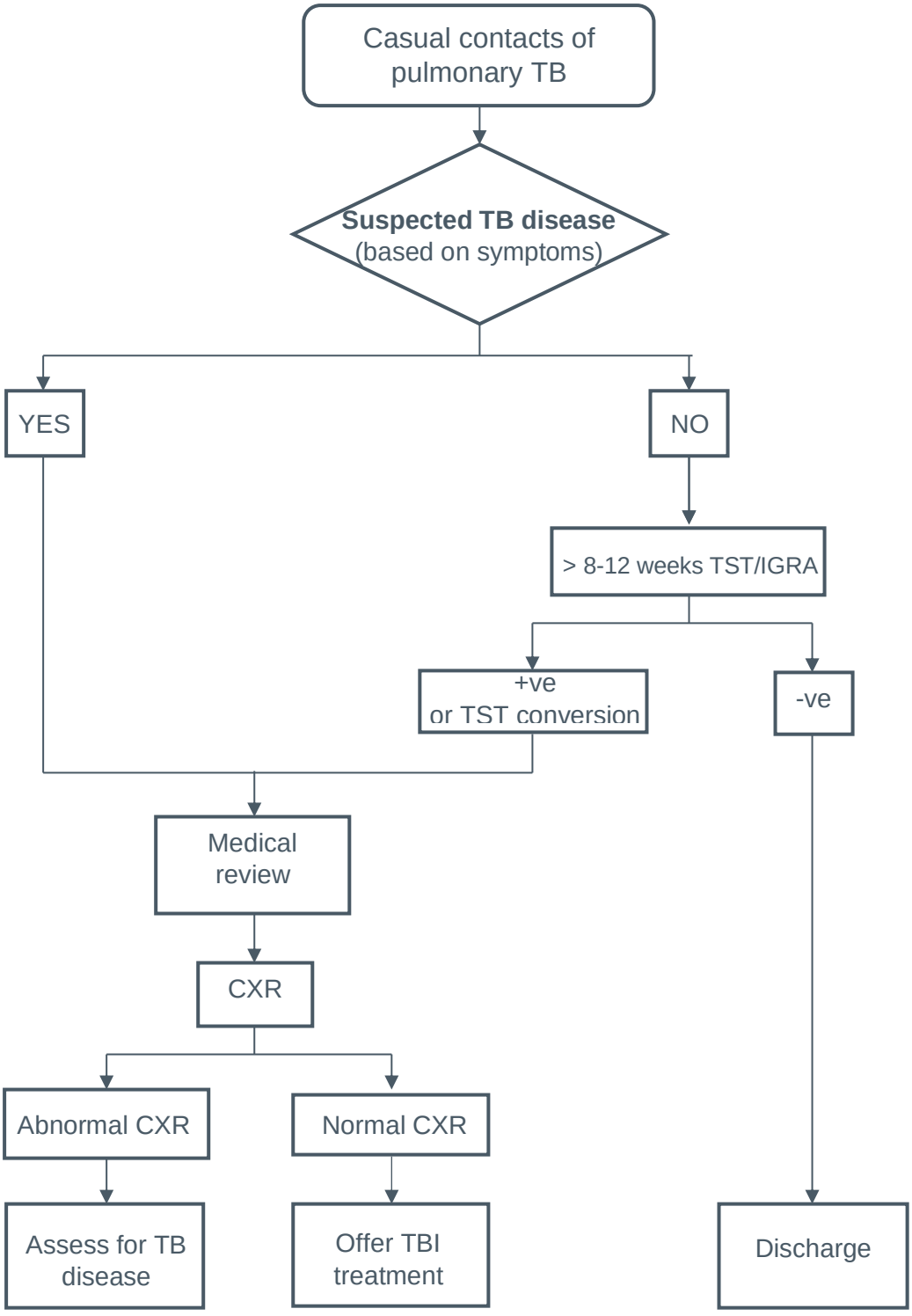


NOTE:

For age > 5 years # In high-risk contact, a highly infectious index case or pre-disposing conditions in the contact, consider treatment for TBI.
* For those who decline treatment for TBI, then follow up for 2 years.
CXR = chest x-ray TST = tuberculin skin test TBI = TB infection

Appendix 5.2 Algorithm for Investigation of Casual Contacts of TB

(TRIM D/24/228558)



CXR = chest x-ray
IGRA = Interferon gamma release assay test
TST = tuberculin skin test
TBI = TB infection

5.1.9. References

American Thoracic Society. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine, 161*(4), S221-247. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600

Centers for Disease Control and Prevention. (2005). Guidelines for the investigation of contacts of persons with infectious tuberculosis: recommendations from the National Tuberculosis Controllers Association and CDC. *Morbidity and Mortality Weekly Report, 54*(RR-15), 1-37.

Communicable Diseases Network Australia. (2002). National strategic plan for TB control in Australia beyond 2000. *Communicable Diseases Intelligence, 26*(2), 238-241.

Department of Health New South Wales. (2009). *Tuberculin Skin Testing Policy Directive* (PD2009_005). https://www1.health.nsw.gov.au/pds/Pages/doc.aspx?dn=PD2009_005

Marais, B., Schaaf, H., & Donald, P. (2009). Management algorithms for paediatric tuberculosis. In H. Schaaf, & A. Zumla, *Tuberculosis: A comprehensive clinical reference* (pp. 323-331). Elsevier.

Menzies D. (1999). Interpretation of repeated tuberculin tests. Boosting, conversion, and reversion. *American journal of respiratory and critical care medicine, 159*(1), 15–21. https://doi.org/10.1164/ajrccm.159.1.9801120

National Institute for Health and Clinical Excellence. (2011). *Tuberculosis: Clinical diagnosis and management of tuberculosis and measures for its prevention and control* (CG117). National Institute for Health and Clinical Excellence. https://www.nice.org.uk/Guidance/CG117

National Tuberculosis Advisory Committee. (2007). Multi-drug resistant tuberculosis. *Communicable Diseases Intelligence*, *31*(4), 406-409.

World Health Organization. (2008). *Tuberculosis and air travel: guidelines for prevention and control* (3rd ed.). World Health Organization. https://www.who.int/publications/i/item/9789241547505

5.2. Migrant Screening

5.2.1. Introduction

Most TB diagnosed in Australia occurs in immigrants. Between 2015 and 2018, the majority of cases across the 4-year period were in people reported as overseas-born: 89% (n = 1,276) in 2018; 89% (n = 1,270) in 2017; 89% (n = 1,215) in 2016; and 87% (n = 1,082) in 2015. Between 2015 and 2018, the incidence rate of TB in the overseas-born population was considerably higher than in the Australian-born population, by a factor of 17 to 20 times, consistent with historical trends. (Communicable Diseases Network Australia, 2020)

Reducing the burden of TB in overseas-born people and other high-risk groups is a priority of the National Strategic Plan for Control of Tuberculosis in Australia 2021- 2025. Strengthening migrant TB screening programs is an area of particular focus. Secondary and tertiary students from TB endemic countries as well as HCWs born overseas are important subgroups to target.

New migrants have the highest burden of TB disease among the overseas born population with 36% diagnosed within two years and 55% within five years of arrival (Figure 3). Therefore, screening for TB in this population must be done in a timely fashion.

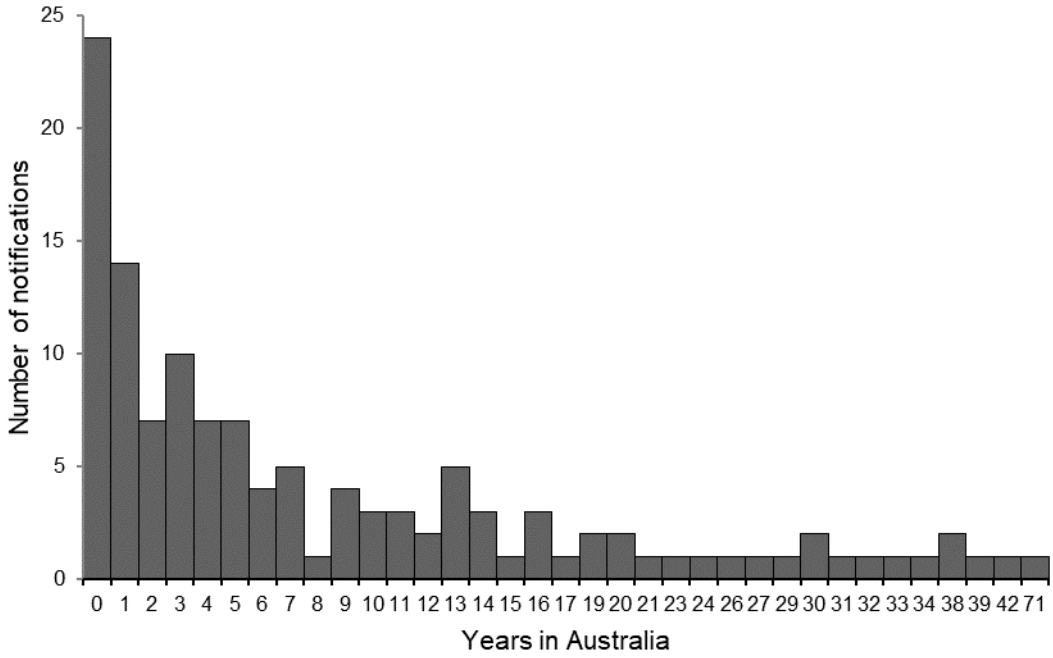


Figure 3: Tuberculosis notifications in the overseas-born population in Western Australia, 2020 by number of years since arrival in Australia

5.2.2. Rationale

The purpose of screening recently arrived migrants from TB endemic countries is to detect:

- individuals with TB disease who require treatment and to prevent those individuals transmitting TB
- TBI in order to offer TBI treatment, especially in younger migrants.

Screening, investigation and treatment for both TB and TBI in migrants should be provided at no cost to the patient regardless of their visa status.

5.2.3. Target groups

Individuals born, or who have lived for prolonged periods of time, in countries with a high incidence of TB (defined as >40/100 000 per year) should be screened for TB within 5 years of arrival in Australia. (For country based TB incidence refer to WHO TB incidence profiles.

TBI testing should be prioritised for migrants:

- from any country with a history of TB contact within the last 2 years or
- countries with a high incidence of TB as stated above.

5.2.4. Screening

Pre migration

Migrants, refugees, irregular maritime arrivals and long-term visitors to Australia are screened for evidence of TB prior to being granted a visa. TB is the only condition where automatic exclusion from entry into Australia is regulated. Pre migration screening for TB is undertaken by the Department of Home Affairs and may take place offshore, where the testing and assessment is delegated to authorised physicians; or onshore, where the process is contracted to non-government health assessment companies.

Not all immigrants are screened. Whether an immigrant is screened is determined by Department of Home Affairs regulations that are based on how long a visa is for and the incidence of TB in the country of origin. Thus, for example, visitors for < 3 months (tourists, visiting family) are not screened, whereas all immigrants seeking permanent residency are screened, regardless of their origin. Temporary visas for longer than 3 months e.g. a 2 year student or work visa, may require screening if the applicant is from a country with high TB incidence.

Screening is primarily for active pulmonary TB. Exceptions to this are detailed below, but generally the screening is not intended to detect active extra-pulmonary TB or TBI. This means that it is certainly still possible for immigrants to have active TB, or to develop it, after migration, despite appropriately performed pre-migration screening. In particular, an immigrant can reactivate asymptomatic TBI after migration that was acquired prior to migration but would never be detected by the usual screening tests. In short, a history of pre-migration screening for TB should never preclude a diagnosis of active TB, even shortly after arrival in Australia.

Applicants who require TB screening and are over 10 years of age have a clinical assessment for symptoms and signs of TB, and a CXR. If either is suggestive of TB, applicants are required to submit 3 sputum samples for AFB smear and culture and are then reassessed clinically with a repeat CXR and the TB culture result after 3 months. For on-shore applicants in WA, the initial clinical and CXR screening is done by BUPA (under contract with the Department of Home Affairs), but if there is evidence of possible TB, subsequent sputum collection and reassessment to rule out (or diagnose) TB is done by the WATBCP (Anita Clayton Centre).

Children under 10 years of age have a TST or QFT instead of CXR, and CXR (as well as sputum tests) are only required if there is clinical evidence of TB or a positive TBI test. If the test

for TBI is positive, but TB is otherwise ruled out, the child is referred for post-migration follow up with a view to preventive therapy being offered via TB Health Undertaking (TBU) (see below).

TBI is not tested for in applicants over 10 years of age, apart from HCWs. Immigrants declaring an intent to study or work in the health industry are also required to have a test for TBI, either QFT or TST. As for children, if other screening rules out active TB, but TBI is diagnosed with a positive QFT or TST, the applicant is referred for post-migration follow up under a TBU, with a view to offering preventive therapy for TBI.

Pre-migration screening does not deliberately look for extra-pulmonary TB as the aim is to exclude infectious or pulmonary TB. If evidence of extra-pulmonary TB is found clinically e.g. cervical lymph node enlargement, further investigations to rule out TB are required.

Diagnosis of TB in pre-migration screening precludes further visa processing. The applicant's visa application is reconsidered for processing once TB is treated and adequate evidence of successful completion of therapy is provided. If TB is diagnosed onshore, applicants are not obliged to leave Australia, even if their existing visa expires. However, their visa application is on-hold for the duration of TB treatment and a bridging visa is issued for medical purposes until TB treatment is completed. It is important to reassure individuals in this situation and mention that they can continue to stay, and work or study in Australia, despite the TB diagnosis.

Post migration

Post migration screening is carried out in conjunction with jurisdictional TB Prevention and Control Services. In WA this is performed by the WATBCP in the following circumstances:

- TBU: A TBU is required for individuals identified on offshore pre-migration screening to be at risk of TB but where active TB has been ruled out. This includes, for example, applicants with a history of TB (treated or untreated), those who have a suspicious CXR (but no proven TB microbiologically), those not fully screened (e.g. due to pregnancy), applicants with a history of recent TB contact, or applicants with a diagnosis of TBI (e.g. children under 10 years old or HCWs). The TBU, although not legally binding, requires the migrant to contact the Department of Home Affairs soon after their onshore arrival and to declare their residential address. This prompts referral to the nearest jurisdictional TB service (in WA, the WATBCP). The further assessment and management, including any subsequent follow up is entirely at the discretion of the physician seeing the migrant at the WATBCP. The primary objective remains exclusion of post-migration TB but testing and treatment for TBI should be considered.
- Post BUPA referral follow-up: Applicants referred by BUPA to the WATBCP for further assessment and sputum culture as part of pre-migration screening, may be followed up by the WATBCP after this pre-migration screening is completed. This may be for the same reasons as those given above that are referred under a TBU from offshore screening. However, onshore screened applicants are not referred with a TBU and the post-migration screening is entirely at the discretion of the physician that performs the pre-migration screening in the WATBCP.
- Humanitarian Entrant Health Service (HEHS): Assessment for TB is a part of the health screen of recently arrived refugees. This includes review of pre-migration screening, clinical assessment and a QFT in all individuals with an intention to offer preventive

therapy for TBI. Those with a history or CXR changes of possible or treated TB, or a positive QFT; are referred to the WATBCP for further assessment and TBI treatment.

- Opportunistic screening: Any migrants referred to the WATBCP should be assessed for TB and TBI, regardless of the reason for referral. This may include, for example, those referred for pre-employment screening, those referred because of co-morbidity (e.g. immunosuppressed etc) or those with a suspicion of TB.

Beyond these specific circumstances, active surveillance for TB, including testing for TBI, is not currently done systematically in WA, apart from in refugees attending HEHS.

5.2.5. Clinical assessment

Assessment of TB risk in immigrants from high incidence countries includes the following:

- country of origin and recent residency
- history of TB
- history of TB treatment
- contact with TB cases
- recent tests, including pre-migration TB screening e.g. CXR, sputum culture, TST, IGRA
- symptoms of TB.

5.2.6. Investigations

Tuberculosis

It is routine to repeat a CXR on all migrants attending for post-migration screening, unless it was last done within 3 months. This is irrespective of whether they present with symptoms of TB (they usually don't). It is to find early, asymptomatic abnormalities of pulmonary TB, especially changes in the CXR appearance compared with pre-migration x-rays.

Otherwise, if TB is suspected in an immigrant, the clinical assessment, investigation and treatment of the disease should not differ from the general population (refer to section 1.2 Diagnosis of tuberculosis - clinical).

TB infection

Children and HCWs may be referred specifically for a diagnosis of TBI from pre-migration screening, as detailed above. However, all immigrants referred for post-migration screening should be considered for TBI risk and counselled accordingly. An immigrant that is interested to consider preventive therapy if TBI is diagnosed, should be offered a test for TBI with appropriate follow up.

Both TST and IGRAs, such as the QFT, are acceptable for the diagnosis of TBI in migrants (refer to section 3.1 Tuberculosis infection – Diagnosis).

5.2.7. Management

The treatment and management of TB or TBI in migrants is no different than for any patient with these diagnoses. For more detail on the management, treatment and follow up of TB or TBI please see the relevant preceding sections.

Management of immigrants around the time of migration should be opportunistic. Irrespective of the screening, diagnostic tests or treatment that is required, all migrants should be counselled about the possibility of TB. This includes, where relevant, explaining the individual's future estimated risk of TB, the opportunity for prevention through TBI treatment, symptoms of TB, what action to take if symptoms develop, that attendance for assessment and treatment of TB (within WA Health) is free of charge and how the individual can recontact the WATBCP if required.

A key element of the management of TB in migrants is the recognition and attention to minimising language and cultural barriers to effective care. If required, all migrants receiving the above assessment or management should preferably have a face-to-face interpreter using their primary language. If this is not possible, then a telephone interpreter may be used. TB management using family members as interpreters or without an interpreter should be minimised, with consultation deferred to when an interpreter is available. The provision and access of competent interpreters and translators is addressed in the WA Health System Language Services Policy.

5.2.8. References

Bright, A., Denholm, J., Coulter, C., Waring, J., & Stapledon, R. (2020). Tuberculosis notifications in Australia, 2015-2018. *Communicable diseases intelligence, 44,* 10.33321/cdi.2020.44.88. https://doi.org/10.33321/cdi.2020.44.88

National Tuberculosis Advisory Committee of Communicable Diseases. (2012). The strategic plan for control of tuberculosis in Australia: 2011-2015. *Communicable diseases intelligence quarterly report, 36*(3), E286–E293.

National Tuberculosis Advisory Committee. (2017). The strategic plan for the control of tuberculosis in Australia: 2016-2020: Towards disease elimination. *Communicable Diseases Intelligence, 43*, 10.33321/cdi.2019.43.10. https://doi.org/10.33321/cdi.2019.43.10

Stock, D., & National Tuberculosis Advisory Committee (2017). National position statement for the management of latent tuberculosis infection. *Communicable diseases intelligence quarterly report, 41*(3), E204–E208.

Toms, C., Stapledon, R., Coulter, C., & Douglas, P. (2017). Tuberculosis notifications in Australia, 2014. *Communicable diseases intelligence quarterly report, 41*(3), E243–E259.

5.3. Health Care Workers

5.3.1. Background

TB is uncommon in Australia and rare in HCWs working in a clinical setting. However, occasional exposure is inevitable and there is reliable evidence demonstrating the increased risk of acquiring TB infection and disease amongst HCW (Menzies et al., 2007; Stuart et al., 2001). In addition, increasing numbers of personnel recruited from high TB incidence countries means there is an increased risk that these workers have acquired TB infection before arrival and may develop TB in Australia. Among TB notifications in health care staff, the proportion of overseas born increased from 50% (10 of 20 cases) in 2001 to 92.9% (26 of 28 cases) in 2007 (NTAC, 2009). The most recent national TB notification report for Australia described 144 cases in HCW in 2018, of which 44 were working in health care at the time of diagnosis (NTAC, 2020).

5.3.2. Pre-employment / placement surveillance for tuberculosis

Rationale

- HCW may be exposed to TB in the course of their work. Baseline assessment of TB status is useful in the post-exposure assessment.
- HCW may have TBI, especially if they come from, or have worked in, high incidence countries; and are therefore at increased risk of developing TB. This group should be considered for preventive therapy.
- HCW may have TB.

Risk Assessment

All HCW, should be assessed for risk of TB prior to exposure in a clinical area. This includes volunteers, honorary employees, externally employed personnel, students undertaking tertiary education that involves clinical work, who are often referred to as under ‘placement’, but for the purposes of this guideline all are included with HCW undertaking ‘pre-employment’ assessment. This assessment determines which TB tests are required and what action should be taken if the tests are positive.

Pre-employment assessment, with or without screening, does not need to be repeated. For example, if a HCW with written documentation of prior TB assessment moves to a new health care facility or returns to a position in health, pre-employment TB assessment does not need to be repeated. Repeat TB assessment may be considered if a HCW has had TB exposure after the original assessment (e.g. from work, travel to TB endemic areas) and this should be considered on a case-by-case basis.

A proforma for collecting relevant information for a pre-employment TB risk assessment is given in Appendix 5.3 Proforma for pre-employment TB risk assessment

The procedure for using this information to determine the tests required and action to be taken is summarised in an algorithm given in Appendix 5.4 Algorithm for pre-employment TB screening tests. A fact sheet that can be provided to all new HCW at the time of TB screening is given in Appendix 5.5. This explains the reason for testing and the nature of TB risk for HCW in health care facilities.

Pre-employment TB risk assessment includes three components:

3. Assessment for Risk of prior TB infection, which includes:
   - having been born in a high TB incidence country (rate > 40 / 100 000 population, for TB country profiles see WHO - country profiles)
   - residence and/or work in a high incidence country for more than 6 months
   - history of TB disease or treatment
   - history of contact with TB (work or personal).

HCW who have any of the above in their history are considered to have high risk for TBI and referred to as Group 2 in the Proforma (see Appendix 5.3 and Appendix 5.4). HCW who have none of these have a low risk for TBI and are referred to as Group 1 in the Proforma (see Appendix 5.3 and Appendix 5.4).

4. Predicted probability of future occupational exposure

The probability of future TB exposure should be categorised according to HCW's likely contact with TB (see Table 28). Note that this does not refer to the risk of TBI in any particular individual (assessed in #1 above), or the risk of transmission of TB when contact tracing is undertaken (discussed in section 5.1 Contact tracing). Rather it is an assessment of the likelihood of exposure to TB from patients in particular HCW roles. High and medium probability groups are distinguished because the HCW in the high probability group must also be considered for routine follow up screening in addition to pre-employment screening. While medium and low risk groups are screened by the health care facility or institution that is employing them, the high probability group has recurrent screening done by the WATBCP at the Anita Clayton Centre (see Routine follow-up tests below).

Table 28 Predicted probability of future occupational TB exposure

High probability	Medium Probability	Low probability
HCW in the following roles who may have regular or higher risk contact with patients that have TB: • TB clinics, • Microbiology laboratories dealing with TB specimens, • Bronchoscopy or sputum induction, • Post-mortem examinations.	HCW with regular contact with patients that are not in a high probability category.	HCW who do not usually have contact with patients (e.g. clerical, administrative, non-microbiological laboratory).

5. Other useful information, which includes:
   - previous TST results
   - medical history and medications that may compromise immune response
   - residency status and, if temporary, expected duration of stay in Australia.

Screening test

If written documentation of a prior TB screening test (TST, Mantoux or QFT) is available, tests do not need to be repeated. Results from a prior employer are transferable to all subsequent workplaces. There is no time limit on this.

Screening tests for TB are indicated in the following HCWs:

- Persons assessed as low risk of prior TB exposure (Group 1 in the algorithm – see Appendix 5.4) but predicted probability for future exposure to TB is high or medium.
- **All** persons assessed at high risk of prior TB exposure (Group 2 in the algorithm – see Appendix 5.4) regardless of future occupational exposure.

Individuals who are likely to have minimal or no contact with patients (low probability of future occupational exposure), and do not have any history indicating a risk for prior TB infection, are not required to have any test. However, if these non-clinical HCWs do have high risk for prior TB infection, a screening test is indicated, with the aim of diagnosing the possible TBI and offering preventive treatment.

There should be no financial impediment to HCW undertaking TB screening or any necessary treatment. Institutions should provide these free of charge to HCW as outlined in section 8.1 Fees and charges.

The result of the test must be given in written form to the HCW. A record of the pre-assessment and results of tests must be kept by each health service provider or institution.

Which screening test for TBI should be used?

Tuberculin skin test (TST)

Advantages:

- Cut-offs for a positive result and conversion are well supported by research data.
- Longitudinal data is available to validate the predictive value of results.

Disadvantages:

- Reduced specificity: cross reactions may occur, giving false positive results in subjects who have had prior BCG vaccination or who have had exposure to environmental mycobacteria.
- Requires 2 visits to obtain a result. Compliance with return visit to obtain the result is usually about 60%.
- Reduced sensitivity: co-morbidity or medication may render a subject anergic resulting in false negative results.
- Requires skilled practitioners that regularly administer and read the test.
- Booster effect: pre-employment TST can boost the result causing false positive conversion on subsequent testing.

QuantiFERON-TB Gold Test (QFT)

Advantages:

- Convenience: a blood sample for QFT testing can be taken at the same time as other blood sampling. This substantially improves compliance.
- Improved specificity: the test is minimally affected by previous BCG or sensitisation to NTM (Pai & O'Brien, 2008). This is especially useful in low incidence populations (Group 1 in Appendix 5.4).
- Less inter-reader variability than with the TST (Pai & O'Brien, 2008).
- No boosting effect from previous QFT testing (Mazurek et al., 2005).

Disadvantages:

- Uncertainty about the significance of threshold results (positive or negative results that are near the cut-off) and the phenomenon of "flip-flopping" (threshold results that change from positive to negative or vice-versa between two tests) (Mazurek et al., 2010). This is especially important in HCW that have routine follow up screening (see below subsection Routine follow-up tests).
- Time limitations: blood samples need to be collected and processed within a limited time frame. This can be a problem for samples collected outside the metropolitan area.

Provision of TST for health care workers

The WATBCP does not routinely provide pre-employment screening testing, however this can be provided in certain circumstances and only by prior arrangement with the TB Clinical Nurse Manager.

WATBCP nursing staff are available to train practitioners in the provision of TST testing. This training can be arranged through the TB Clinical Nurse Manager. Alternatively, TST is available through some private pathology providers or Regional Public Health Units.

General considerations:

- Informed consent must be obtained from the HCW.
- A record of the TST (including date of the test and the reading) must be kept by the health service provider or institution, with a copy given to the HCW.
- Tuberculin skin testing should only be undertaken by appropriately trained health care providers.

Management of abnormal results

The procedure for management of abnormal screening results, including what further tests are indicated (e.g. CXR) and whether preventive therapy is recommended, is summarised in the algorithm given in Appendix 5.4.

HCW with a positive TST, or a positive or indeterminate QFT, require a CXR and medical evaluation by a medical practitioner experienced in TB management. The WATBCP is available for management or advice. Alternative practitioners for medical evaluation are Infectious Disease Physicians, Respiratory Physicians or Public Health Physicians with expertise in TB, and the clearance given by these physicians is equally valid.

5.3.3. Management of tuberculosis in a health care setting

A HCW suspected of, or diagnosed with, active TB should be urgently referred (appointment within 1 week) to a TB physician at the WATBCP, or a suitable alternative specialist, for assessment and treatment. If possible, arrangements should be made for the individual to submit 3 sputum samples collected on consecutive days for AFB smear and TB culture.

In addition:

- Informed consent must be obtained from the HCW before disclosure of details of the disease to the health service provider or institution.
- The practitioner making the diagnosis is required, under the *Public Health Act 2016,* to notify the Communicable Disease Control Directorate (CDCD).
- The HCW is to be excluded from the workplace, if diagnosed with pulmonary TB, until cleared by a medical supervisor nominated by the institution in consultation with a medical practitioner experienced in TB management.
- The HCW must complete a satisfactory course of treatment and follow up, with appropriate certification provided to the institution by the treating doctor.

5.3.4. Post exposure follow-up

When a hospital inpatient, other health facility resident or HCW is diagnosed with TB, follow up of other HCW and patients that have had contact, or exposure, to the index case may be necessary. While specific details relevant to contact tracing in a clinical setting are given here, this section of the guideline must be read in conjunction with section 5.1 Contact tracing where routine contact tracing principles are detailed.

Significant exposure

Post-exposure follow-up is not always necessary. Whether it is required depends on whether there has been “significant exposure”, which in turn should be assessed on a case-by-case basis. Significant exposure is defined more fully below but in simple terms it is contact with a patient with pulmonary TB and sputum that is smear positive for AFB who has not been isolated or where a breach of airborne precautions has occurred. See also section below on Significant contact.

Post-exposure follow-up is not routinely required for:

- Contact with patients that have been isolated with uninterrupted implementation of airborne precautions throughout their admission even when the sputum smear is positive.
- Contact with patients with pulmonary TB that is smear negative (follow-up only for other patients that have shared their room for more than 8 hours). It is therefore important to be certain of the sputum AFB smear result.
- Contact with patients who have extra pulmonary TB only.

Significant contact

Significant contact includes:

- Contact, on a single occasion or cumulatively, for more than 8 hours (refer to section 5.1 Contact tracing). It is important to appreciate that contact does not mean direct patient care, but rather time spent in the same air space as the patient e.g. a routine shift of 8 hours on a ward with an infectious TB patient that has not been isolated would be considered significant; and/or
- Contact involving a procedure that confers increased risk (e.g. sputum induction, bronchoscopy, intubation, post-mortem examination) where airborne precautions had not been implemented; and/or
- Contact where physical containment requirements in a microbiological laboratory are breached.

The above definitions broadly define the circumstances that require contact tracing. However, there will be occasions when contact tracing is deemed necessary outside these requirements (e.g. sputum smear negative index case) and the decision to do this should be made by the responsible infection control officer in consultation with a physician with expertise in TB in the given institution and the Medical Director of the TB Control Program.

As described in detail in section 5.1 Contact tracing, the extent and timing of screening when contact tracing is undertaken is critically dependent on whether contacts are identified as close ("household") or casual contacts. In general:

- Patients whohave shared a room with an index case for more than 8 hours are considered close ("household") contacts. This applies to contacts of all index cases with pulmonary TB, whether smear positive or negative, but not extra-pulmonary TB.
- Patients who have contact with an index case (either patient or HCW) in areas other than a shared room are classified as casual contacts and are stratified according to the estimated time and/or closeness of contact.
- HCW who have contact with an index case (patient or another HCW) are considered casual contacts.
- All contacts of a HCW with sputum smear positive TB are considered casual contacts.

As can be seen from these definitions, most contacts from a hospital-based index case are considered "casual".

Notification and testing

Casual contacts generally only need one test after 8 – 12 weeks, in accordance with general principles as outlined in section 5.1 Contact tracing.

To make the above principles and definitions clear, an algorithm for the broad process that should be followed is given in Appendix 5.6 Procedure for TB contact tracing in health care setting.

Post exposure follow up should also include:

- Informing contacts in writing of the possible exposure as soon as possible. A standard template letter that can be used for this purpose is given in Appendix 5.7.
- Uniform TB testing: If a QFT was performed on pre-employment screening, a repeat QFT should be done; if the baseline test was a TST or there is no baseline, a TST should be done.

- If the TB test is positive or converts (as compared to the baseline test), a CXR is required, and the HCW should be referred to a medical practitioner experienced in TB management (as described above).

The responsibility for contact tracing of HCW and patients from a health setting rests primarily with the hospital or other place in which it is to occur. It should, however, be conducted in consultation with the WATBCP and, in particular, screening should not be initiated until the index case details and the stratification of the contact list has been reviewed by the TB Control Program. Screening tests are generally done by the hospital, but some responsibilities may be handed over to the TB Control Program e.g. follow up of patients that have been discharged, medical review of contacts with positive test results.

Other issues to address in post-exposure contact tracing in a clinical setting include:

- Clear and prompt communication with patients and staff, especially to alleviate anxiety or unfounded fear. A template for informing HCW of possible occupational TB exposure is given in Appendix 5.7.
- Communication with senior health service executive or another responsible executive. This is recommended for all hospital-based contact tracing.
- Addressing the possibility of publicity and media attention. It is not recommended that this be done pre-emptively. Any media enquiries should be referred to the Medical Director of the WATBCP through the Communications Department, NMHS.
- Ensuring the privacy and confidentiality of the index case.

5.3.5. Routine follow-up tests

Repeat TB screening tests or CXR are not recommended routinely. However, testing is warranted in certain HCW specifically, those who:

- Have ‘significant’ exposure (defined above in subsection Post exposure follow-up) more than once in a calendar year.
- Are regularly in a role identified as ‘high probability’ for future occupational exposure (see above Table 28).

In these HCWs the preferred baseline screening test is the TST, rather than a QFT test, for reasons described above. If the baseline TST is negative, these HCW should be offered an annual TST. If the TST is positive, then annual CXR can be considered.

This recurrent annual screening is usually done by the WATBCP at the Anita Clayton Centre. The Anita Clayton Centre has a more detailed in-house procedure document describing this process, which is available upon request.

5.3.6. BCG vaccination

BCG vaccination is not recommended for HCW in WA.

5.3.7. Responsibilities for TB infection prevention and management

Health care facilities

Health care facilities should:

- Periodically review a TB infection control policy for the facility and ensure that all HCW are updated on current policy on a regular basis.
- Have protocols to ensure the rapid detection, isolation and treatment of patients with infectious TB.
- Manage patients with known or suspected TB as outpatients wherever possible.
- Have respiratory isolation rooms for patients with known or suspected infectious TB that require inpatient management. These rooms must have appropriate engineering controls including negative pressure ventilation separated from general air conditioning and exhausted to the outside of the building. The ventilation of the rooms should achieve at least 12 air changes per hour. A mobile HEPA filtration unit is not considered adequate for TB infection control.
- The Australian standard is that all hospitals, irrespective of their size, should have at least one respiratory isolation room and should aim to provide between 1% and 3% of all available beds for respiratory isolation. For further information on respiratory isolation rooms and facility requirements refer to *Standards Australia, HB 260: Hospital acquired infections-Engineering down the risks* (NTAC, 2016).
- Promptly transfer of inpatients with known or suspected TB to a facility with an appropriate respiratory isolation room if inpatient management is required and isolation as described above is not available (the size or function of the facility may make the provision of such a room impractical). On rare occasions where immediate transfer is impractical, patients should at least be managed in a single room with an ensuite that is as isolated from other patients.
- Educate the TB patient to wear a surgical mask when not in a single room or if air from the single room recirculates to other areas of the building, until advised to remove it by attending staff; if not wearing a surgical mask, cough etiquette should be used (covering mouth when coughing using disposable tissues, or hand followed by hand hygiene).
- Supply appropriate personal respiratory protection (PRP). Use of correctly fitted P2 or N95 particulate filter masks is required to prevent airborne transmission for staff caring for patients with known or suspected pulmonary TB. Surgical masks are inadequate for those HCW.
- Ensure HCW receive appropriate training on donning of, and performing a fit check for, a fit-tested P2 or N95 respirators available at the health care facility. The fit check procedure is the appropriate minimum standard for staff using P2 and N95 masks and must be performed every time a mask is donned.
- Maintain microbiological laboratory protocols that ensure minimal risk of transmission of TB from potentially infectious specimens (NTAC, 2006).
- Educate HCW about TB that is appropriate to their work category. It should be emphasised that the most effective way to control TB is early detection and commencement of treatment of active TB.

Exclude HCW staff who are immune-compromised or immunosuppressed, from work in an environment with known or suspected infectious TB patients.

Western Australian TB program

The WATBCP can be contacted for further information on any aspect of TB management, and to provide:

- Specific advice to the Health Service Provider or institution about pre-employment screening, post-exposure contact tracing and maintenance of infection prevention and management infrastructure and policy.
- Training in TB infection prevention and management and HCW TB risk management. This includes training in TST if this is the screening test chosen by the institution.
- A consultative service for review of HCW with positive tests for TBI or suspicion or evidence of TB.
- WA TB Control Guidelines.

Appendix 5.3 Proforma for pre-employment TB risk assessment

Surname: _____

First name: _____

Date of Birth: _____

Address: _____

Telephone contact: _____

_____

What is the risk of TB infection?

1. Have you been treated for TB in the past? _____
2. Have you had contact, personally or at work, with somebody that suffered from TB? _____
3. Country of Birth? _____
4. What countries have you lived or worked in for more than 6 months, other than your country of birth?

_____

_____

_____

Office Use Only

Y ☐ N ☐

Y ☐ N ☐

TB incidence > 40 / 100 000*

Y ☐ N ☐

TB incidence > 40 / 100 000 *

Y ☐ N ☐

Y ☐ N ☐

Y ☐ N ☐

If "Y" to ANY of the above, then go to Group 2 (yellow) in Algorithm for the Management of TB Risk (see Appendix 5.4)

* *For country-based TB incidence refer* to https://worldhealthorg.shinyapps.io/tb_profiles/ (WHO 2023)

What is the risk of TB contact from work?

What is the proposed area in which you will be working, placed or studying in the health system?

Specify: 1) position (e.g. doctor, RN, physio, student etc.) _____

2) speciality area (e.g. medical, surgical, paediatric etc.) _____

Other information

Have you had a Tuberculin skin (Mantoux) test before? ☐ No ☐ Yes - Result: _____

Have you had a Quantiferon blood test before? ☐ No ☐ Yes - Result: _____

Do you have a medical history of immune deficiency, ☐ No ☐ Yes

or take medicines that reduce immune response? ☐ No ☐ Yes

Are you a permanent resident / citizen of Australia? ☐ **N**o - Visa expiry date: ☐Yes

Office Use Only

Past history of TB treatment: ☐ No ☐ Yes Refer to TB specialist for assessment

Risk of Latent TB infection? ☐Low Group 1 (blue) in algorithm

☐High Group 2 (yellow) in algorithm

Predicted risk of future occupational exposure: ☐ High ☐Medium ☐Low

Test for Latent TB Infection: Date: _____

Test used: ☐TST – result: _____ mm

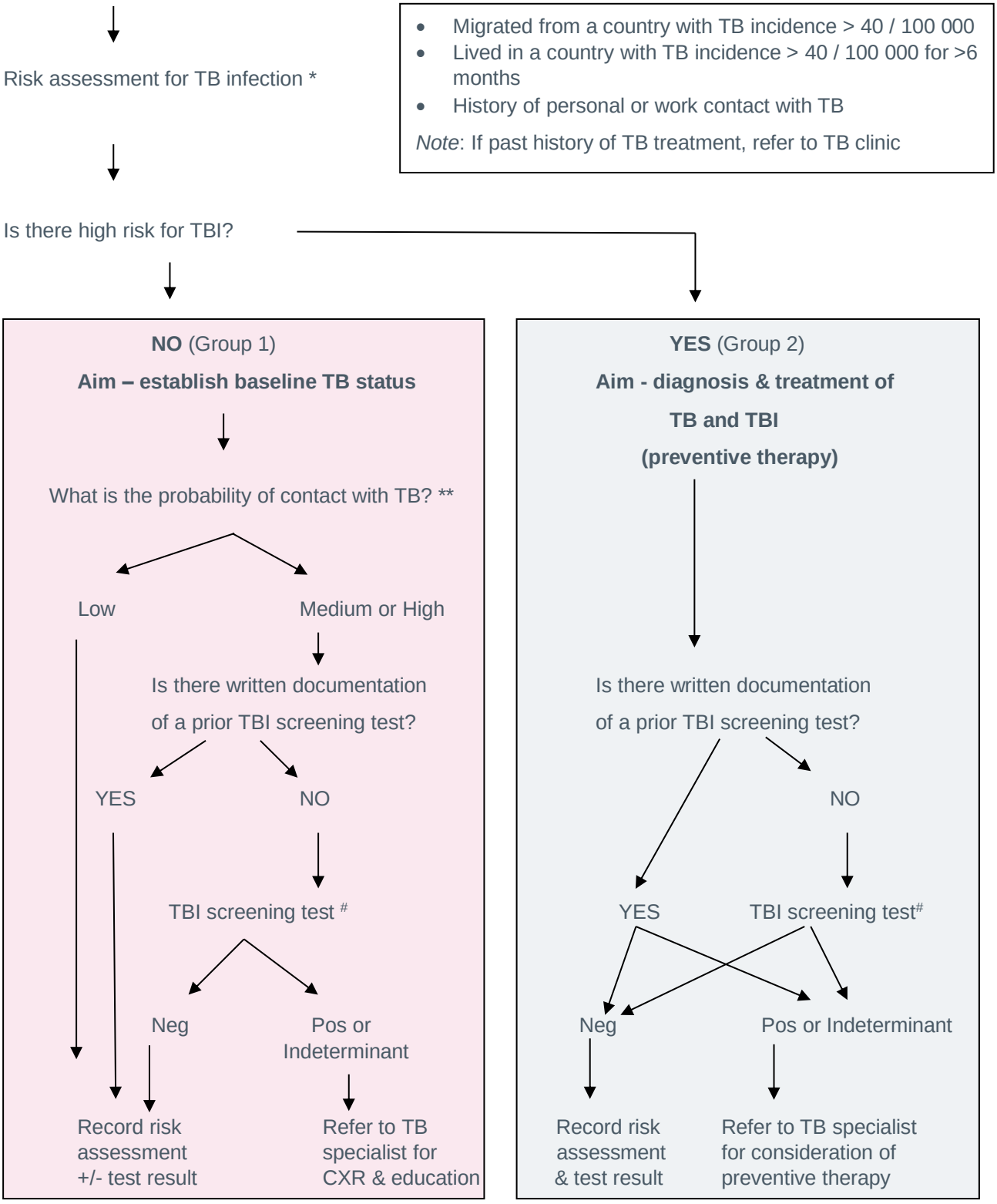
☐QuantiFERON – result: _____

CXR done? ☐ No ☐Yes Result: _____

Referred to TB specialist? ☐ No ☐Yes Where: _____

Appendix 5.4 Algorithm for pre-employment or student placement TB screening tests

All Health Care Workers & Tertiary Students in Health Care



Notes				
	*	See text for definition	CXR	Chest x-ray
	**	See text for definition	#	TST or QFT
	TBI	TB Infection		

Appendix 5.5 TB fact sheet for health care workers or students

Pre-employment tuberculosis screening fact sheet for health care workers and students

You have been asked to undergo screening for tuberculosis (TB) as part of your pre-employment and pre-engagement surveillance for TB. This is a routine requirement of all personnel working in clinical settings. The following are answers to commonly asked questions:

Why do we do screening?

There are two reasons:

- To check for dormant (latent) TB infection and, if this is found, to offer you the opportunity to have preventive therapy to protect your future health.
- To act as a baseline, which helps in the interpretation of future screening that may be required if you come into contact with a patient with TB.

What is the risk you will get TB from your work?

TB is uncommon in WA and TB is not a highly contagious disease, so the risk is very low. Usually, patients with TB are appropriately isolated and / or on treatment so that the TB cannot be transmitted to you. Occasionally, when this is not the case, you may be asked to have further screening tests (see below), because you are identified as a contact of the patient with TB.

What screening tests are done?

You will be asked to complete a simple, single page questionnaire that is designed to assess the risk that you have already had contact with TB. You may also be asked to have a tuberculin (Mantoux) skin test or QuantiFERON TB assay (blood test). These tests measure whether you have been infected with TB.

What if the test is positive?

A positive test does not usually mean you have tuberculosis, but rather that you may have been infected in the past. A positive test indicating dormant infection (called TB infection or latent TB) means that there is no immediate risk to your health and you cannot pass the TB on to anyone else. If you have a positive test, arrangements will be made for you to have a CXR (to make sure there is no active TB) and to see a TB specialist doctor who will discuss with you what the result means and what can be done about it.

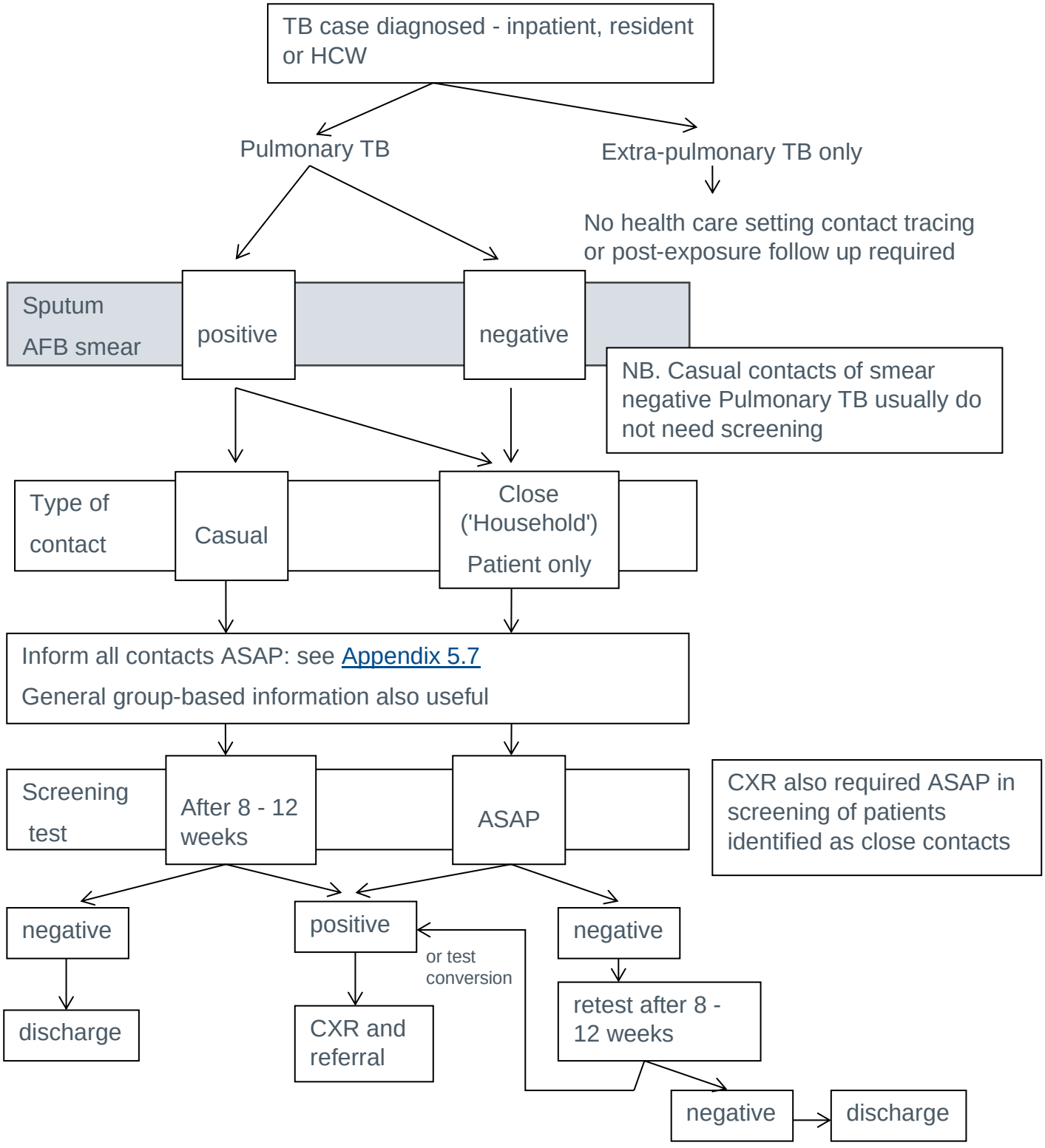
What if you think you have TB?

TB usually affects the lungs and causes a cough lasting for more than 3 weeks, possibly together with phlegm production, low grade fever and weight loss. If you are worried you have TB you should contact an Occupational Health Officer in your place of your employment or the TB clinic (see below) as soon as possible.

Contact:

If you have queries regarding this advice, please feel free to contact the WA TB Control Program:
P: 08 9222 8500 or E: ACCADMIN@health.wa.gov.au | Hours of operation: Mon – Fri 8:15 – 4:00pm

Appendix 5.6 Procedure for TB contact tracing in a health care setting



Note: Follow this algorithm with reference to details given in the text, section *Post exposure follow-up*

Appendix 5.7 Template letter to inform of occupational exposure to TB

Dear

We have reason to believe you have been in contact with someone who has been diagnosed with tuberculosis (TB). This is an airborne infection which may be passed on from person to person by coughing, sneezing, etc. Although the risk of acquiring TB from occupational exposure is low we recommend you undergo routine screening.

We recommend you have a [*insert screening test: Tuberculin Skin Test (Mantoux test) / Quantiferon TB Assay*], which can be provided at the [*insert name of health care facility*]. The test will be available to you free of charge. It is important that you have the test 8 weeks after exposure, rather than immediately, and therefore you will need to have your test done after the [*insert date*]

In Australia TB is an easily treatable disease. It is preferable to detect the infection early as often preventive treatment can be given to stop the development of the disease. Even if screening tests show that the exposure to TB has led to infection in you, this does not result in you being infectious and you cannot pass the bacteria onto other people.

It is normal practice to keep the name of the person with TB confidential. All information relating to your visit will also be confidential.

If you have already had TB screening or do not want to undergo the tests, please complete the slip below and return it to [*insert location*].

Please bring this letter with you when you attend the clinic. If you have any queries please telephone the WA Tuberculosis Control Program on 9222 8500 and ask to speak to a Nurse. Further information can be found at http://healthywa.wa.gov.au/Articles/S_T/Tuberculosis

Yours sincerely

_____

Name……. Position…….

I do not wish to undergo screening tests following my exposure to a TB patient.

I have already undergone the screening tests following my exposure to the TB patient.

Signed…….. Date……..

5.4. Testing prior to TNFα antagonist therapy or other immunosuppressive therapy

5.4.1. Introduction

Tumour necrosis factor alpha (TNFα) antagonist therapies are increasingly being used in multiple medical specialities, including immunology, rheumatology, gastroenterology, dermatology, and respiratory medicine for a wide variety of inflammatory conditions. Whilst these are associated with the highest rate of reactivation of TBI other immunosuppressive agents including small molecule inhibitors, immune checkpoint inhibitors, and non-targeted immunosuppressive agents are also associated with increased risk. (Laundy et al., 2022; Cantini et al., 2017).

Many of these agents are sufficiently novel that data on actual risk of reactivation is unknown, but international guidelines continue to recommend screening for TB because of potential risk, given mechanisms of action (Evangelatos et al., 2020; Nogueira et al., 2020). Some agents with no direct potential risk (i.e. immune checkpoint inhibitors) instead confer risk due to the potential need for further immunosuppression as a consequence of their use, and thus screening is recommended internationally prior to use of biological agents, albeit with limited evidence or where trials have excluded patients with TBI disease (Davis, 2020).

Standard chemotherapeutic regimens for solid organ malignancies are not thought to convey significant risk of TB reactivation beyond that of the underlying malignancy and are not included in this list.

A limited summary of categories, common agents and relative risks (where known) are presented in Table 29. This list is not exhaustive but endeavours to cover common categories. The subsequent discussion and recommendations, while written largely with reference to TNFα antagonist therapy, can, in principle be applied to other agents, with reference to the estimated risk of TB reactivation.

Table 29 Immunomodulatory and Immunosuppressant agents that may confer increased risk of TB reactivation.

Immunomodulatory therapies	Risk (see footnote)
Anti-TNF therapy	
Adalimumab Certolizumab Etanercept Golimumab Infliximab	High
Other Biologicals / Small Molecule Inhibitors (SMI)	
JAK inhibitors Baricitinib Tofacitinib	Moderate
Anti-T lymphocyte agents Abatacept	Low

Immunomodulatory therapies	Risk (see footnote)
Anti-B lymphocyte agents Rituximab Ocrelizumab	Low
Combination lymphocyte-depleting agents Alemtuzumab	Low
IL-6 pathway inhibitors Tocilizumab	Moderate
IL-12/IL-23 pathway inhibitors Guselkumab Ustekinumab	Low
IL-17 inhibitors Secukinumab	Low
Integrin inhibitors Vedolizumab	Low
Immune checkpoint inhibitors Atezolizumab Nivolumab Pembrolizumab	Low
Non-Biological Immunosuppressants	
Glucocorticoids If > 20mg/day prednisolone-equivalent for > 1 month	High
Low-risk agents Methotrexate Leflunomide	Low
High risk agents Azathioprine Cyclophosphamide	Moderate
Calcineurin inhibitors Tacrolimus Cyclosporine	Moderate

Risk of developing active TB:

High: OR > 4
Moderate: OR 2 – 4
Low: OR < 2 or unknown

TNFα antagonist therapy is associated with a significantly increased risk of TB acquisition and reactivation of TBI, but TB, either disease or latent infection, is not a contraindication to TNFα antagonist therapy or other significant immunosuppression if required for control of the underlying disease process. However, patients with TB should be referred promptly for treatment, and patients who are at risk of reactivation of TB while on TNFα antagonist therapy, should be identified prior to the commencement of biological agents and considered for TB preventive therapy.

The risk of TB reactivation should still be considered in other patients treated with non- anti-TNF immunosuppressive agents.

5.4.2. Role of TNFα

The release of TNFα in response to mycobacterial infection increases the ability of macrophages to phagocytose and kill mycobacteria, and TNFα production is a requirement for the formation of granulomas, which wall-off mycobacteria and prevent their dissemination (Wolfe et al., 2004; Gardam et al., 2003). The presence of granulomas is protective to the host and limits tissue damage. Therefore, inhibition of this process has the potential to increase the susceptibility to *M. tuberculosis*.

While TNFα production is required for effective immune responses, excessive production increases host tissue sensitivity to the cytokine, causing necrotising reactions and damage to tissues and organs (Gardam et al., 2003). TNFα mediates systemic inflammation, which manifests clinically as cachexia.

5.4.3. Tuberculosis and TNFα antagonist therapy

Patients on TNFα antagonists have an increased risk of reactivation TBI and an increased susceptibility for acquisition of primary TB (Keane et al., 2001). TNFα antagonist therapy also increases the risk of reactivation of Hepatitis B infection (Carroll & Forgione, 2010) and has been associated with candidiasis, histoplasmosis, aspergillosis and listeriosis (Perlmutter et al., 2009).

TB may develop soon after the initiation of TNFα antagonist therapy with the median time to onset being 3 months (Keane et al., 2001). Patients who develop TB have a higher proportion of extra-pulmonary and disseminated forms of TB compared to the non- immunosuppressed population (Keane et al., 2001). This difference in TB presentation may contribute to delays in investigation and diagnosis of TB in patients undergoing TNFα antagonist therapy, as well as increased morbidity and mortality from TB.

5.4.4. Active surveillance

Patients should be assessed for TB risk and screened prior to the commencement of TNFα antagonist therapy. Certain subgroups of patients are at higher risk of TB infection and therefore of reactivation when treated with TNFα antagonist therapy. These include:

- a contact of TB
- persons born, or who have lived for at least 3 months, in countries that have a high incidence of TB
- Aboriginal Australians
- elderly patients (date of birth prior to 1940) born in a low prevalence country (e.g. Australia) in which rates of TB were higher in the past
- certain occupational or residential settings e.g. HCWs.

5.4.5. Screening procedure for TB

Exclude TB disease

A history of prior TB or symptoms of current TB needs to be elicited. All patients should have a CXR if one has not been performed in the 2 months prior to starting the TNFα antagonist. Further examination and investigation for TB should be directed by the history (refer to section 1.2 Diagnosis of tuberculosis – clinical).

Exclude TB infection

The assessment of a patient for TB infection involves:

- Taking a good history to assess risk of TB infection and exclude TB disease.
- A TBI screening test if indicated.
- A recent CXR, which while primarily to exclude TB, can also show evidence of TB infection (e.g. calcified nodular lesions, apical fibrosis, pleural scarring).

Who to test for TBI?

The Australian Rheumatology Association and other guidelines (Gupta, Street, & Macrae, 2010) recommend a test for TBI in all patients starting TNFα antagonist therapy. The American Thoracic Society (2011) recommends that a screening test for TBI be done only if there is an identifiable risk factor for TBI. The American College of Rheumatology recommend screening for TBI in all patients before starting biological agents regardless of risk factors, and for all agents including non-TNFα antagonist therapies. Most biologic agents similarly carry guidance for screening for TBI prior to use in their drug information pamphlets, independent of evidence of risk (Davis, 2020), though this often relates to the exclusion of these patients from trials of these agents.

The WATBCP recommends testing for TBI in all patients starting TNFα antagonist therapy because of the potential serious consequences of TB reactivation in this immunosuppressed population if TBI is not treated. Screening is also recommended in the setting of significant immunosuppression for treatment of COVID-19 pneumonitis (i.e. with tocilizumab or baricitinib). Some patients with a positive screening test will receive preventive therapy unnecessarily and this is acceptable to ensure all individuals with reactivation risk are covered. It is worth noting that TBI testing should only be done with the intention to give preventive therapy.

If a patient has been treated in the past for TB, the screening test in this circumstance is likely to remain positive, and the management is not influenced by the test result (see below Previous TB treatment). A possible exception to this rule is a person who has been previously treated and subsequently had a close contact with infectious TB, in which case the treating physician may elect to give empiric preventive therapy.

Which test for TBI?

Either TST or QFT can be used, but the WATBCP recommends the QFT. This test has an in-built positive control that reduces the chance of false negative results due to anergy, which is more common in patients with autoimmune conditions or other co-morbidity receiving immunosuppressive therapy. A falsely negative TST due to anergy is indistinguishable from a genuinely negative TST, whereas a QFT test will be indeterminate in a strongly anergic patient.

5.4.6. TB management and TNFα antagonist therapy

Any patient with symptoms or signs of TB or those with a positive or indeterminate QFT test, should be referred to a physician experienced in the management of TB for assessment, investigation and treatment.

Treatment of TB during or prior to TNFα antagonist therapy

If a patient becomes unwell with fever and weight loss while on TNFα antagonist therapy, the possibility of TB disease should be considered even if an initial TBI screening test was negative or treatment for TBI has been given. Clinical assessment and discussion with a TB physician is suggested, including sputum assessment if productive or changes on thoracic imaging suggestive of TB are identified.

Management of ongoing biological therapy in patients with TB detected after the commencement of TNFα antagonist therapy or other significant immunosuppression is complex. Decisions around cessation or adjustment of immunosuppression should be a joint action between the treating TB physician and physician managing their underlying immunosuppression. It is preferable to delay further TNFα therapy if possible, though withdrawal of significant immunosuppression carries a risk of TB-IRIS. (Quinn et al., 2020).

This is a complex area, and specialist involvement and discussion is recommended in these cases.

Previous TB treatment

Patients with a history of previous TB treatment should be appropriately investigated for the presence of TB disease. Once disease has been ruled out, patients who give a good history of previous adequate treatment for TB are able to start TNFα antagonist therapy but should be monitored closely, and investigated promptly with a CXR and sputum AFB smear and cultures, if respiratory symptoms develop (British Thoracic Society Standards of Care Committee, 2005). Every effort should be made to obtain independent documentation of the prior treatment to assess its adequacy.

A test for TBI should not be performed in patients previously treated for TB, as the test is likely to remain positive, even if the treatment was adequate. Giving routine treatment for TBI e.g. isoniazid monotherapy in this circumstance is not recommended. If the prior treatment was adequate there is no need for further TBI treatment.

If prior TB treatment is considered inadequate but there is no current evidence of TB, assessment for further treatment prior to the starting the TNFα antagonist therapy should be made by a physician experienced in TB.

TB infection

Patients with TBI should be given standard preventive treatment before commencing TNFα antagonist therapy (see section 3.2 TB infection - Treatment). Preventive therapy can decrease the incidence of TB by more than 80% (Tymms, 2009) though guarantee of complete prevention is not possible (Sichletidis et al., 2006).

TNFα antagonists can be commenced in patients with TBI once they are established on preventive therapy and does not need to be delayed until the preventive therapy is completed.

Patients are established on preventive therapy once they have demonstrated steady adherence, have not manifested significant side effects requiring treatment interruptions and have had at least one follow up liver function test that is satisfactory. This usually takes 2 – 4 weeks.

Exposure to TB whilst on TNFα antagonist therapy

Patients exposed to an infectious case of TB whilst on TNFα antagonist therapy should be managed according to the usual contact tracing protocol (see section 5.1 Contact tracing). However, decisions regarding TBI screening and requirement for preventive therapy should be individualised in light of the patient's immunosuppression. For example, in a high-risk exposure situation, empiric preventive therapy irrespective of TBI test results would be reasonable, as is the case in HIV infected individuals.

In patients who were initially negative on screening for TBI (I.e. TST or QFT) and who return to a TB endemic area for a prolonged period (i.e. > 3 months) whilst on immunosuppression, repeat screening for TBI should be considered. If a patient converts, i.e. QFT becomes positive, from prior negative, then it should be discussed with a TB physician and assessment for active disease should be undertaken before considering TBI treatment.

TB re-infection after preventive therapy whilst on TNFα antagonist therapy

Re-infection after prior treatment for TB or TBI is rare in Australia. A patient on TNFα antagonist therapy is at higher risk of re-infection if exposed, because of immunosuppression, and, if re-infected, is again at risk of TB activation and dissemination because of the TNFα antagonist.

There is currently no testing algorithm for re-infection as the TST or QFT are likely to be positive from previous TB infection, so will be uninformative if repeated. Thus, in this situation consideration should be given to empiric preventive therapy once TB has been ruled out, with the decision being based on clinical grounds and the circumstances of the contact.

5.4.7. References

American Thoracic Society. (2000). Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine*, *161*(4), S221-247. https://doi.org/10.1164/ajrccm.161.supplement_3.ats600

British Thoracic Society Standards of Care Committee (2005). BTS recommendations for assessing risk and for managing *Mycobacterium tuberculosis* infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax, 60*(10), 800–805. https://doi.org/10.1136/thx.2005.046797

Cantini, F., Nannini, C., Niccoli, L., Petrone, L., Ippolito, G., & Goletti, D. (2017). Risk of Tuberculosis Reactivation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Receiving Non-Anti-TNF-Targeted Biologics. Mediators of inflammation, 2017, 8909834. https://doi.org/10.1155/2017/8909834

Carroll, M. B., & Forgione, M. A. (2010). Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. *Clinical rheumatology, 29*(9), 1021–1029. https://doi.org/10.1007/s10067-010-1523-2

Evangelatos, G., Koulouri, V., Iliopoulos, A., & Fragoulis, G. E. (2020). Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors. *Therapeutic advances in musculoskeletal disease, 12*, 1759720X20930116. https://doi.org/10.1177/1759720X20930116

Fehily, S. R., Al-Ani, A. H., Abdelmalak, J., Rentch, C., Zhang, E., Denholm, J. T., Johnson, D., Ng, S. C., Sharma, V., Rubin, D. T., Gibson, P. R., & Christensen, B. (2022). Review article: latent tuberculosis in patients with

inflammatory bowel diseases receiving immunosuppression-risks, screening, diagnosis and management. *Alimentary pharmacology & therapeutics, 56*(1), 6–27. https://doi.org/10.1111/apt.16952

Gardam, M. A., Keystone, E. C., Menzies, R., Manners, S., Skamene, E., Long, R., & Vinh, D. C. (2003). Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *The Lancet. Infectious diseases, 3*(3), 148–155. https://doi.org/10.1016/s1473-3099(03)00545-0

Gupta, A., Street, A. C., & Macrae, F. A. (2008). Tumour necrosis factor alpha inhibitors: screening for tuberculosis infection in inflammatory bowel disease. *The Medical journal of Australia, 188*(3), 168–170. https://doi.org/10.5694/j.1326-5377.2008.tb01565.x

Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., Siegel, J. N., & Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *The New England journal of medicine, 345*(15), 1098–1104. https://doi.org/10.1056/NEJMoa011110

Laundy N, Colley S, Fawcett J, Ryder L, Video A, Cohgen D, Collini P. (2022). Assessment of latent tuberculosis infection pre-immunomodulatory therapy; 5 year experience in a UK centre. *Clinical Infection in Practice, 13*, 100136. https://doi.org/10.1016/j.clinpr.2022.100136

Mazurek, G. H., Jereb, J., Lobue, P., Iademarco, M. F., Metchock, B., Vernon, A., & Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention. (2005). Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports, 54*(RR-15), 49–55.

Mazurek, G. H., Jereb, J., Vernon, A., LoBue, P., Goldberg, S., Castro, K., IGRA Expert Committee, & Centers for Disease Control and Prevention (CDC) (2010). Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR. Recommendations and reports : Morbidity and mortality weekly report. Recommendations and reports, 59*(RR-5), 1–25.

Menzies, D., Joshi, R., & Pai, M. (2007). Risk of tuberculosis infection and disease associated with work in health care settings. *The international journal of tuberculosis and lung disease*, *11*(6), 593–605.

National Tuberculosis Advisory Committee (2006). Guidelines for Australian mycobacteriology laboratories. *Communicable diseases intelligence quarterly report, 30*(1), 116–128.

National Tuberculosis Advisory Committee (2009). Tuberculosis notifications in Australia, 2007. *Communicable diseases intelligence quarterly report, 33*(3), 304–315.

National Tuberculosis Advisory Committee Australia. (2009). Position statement on interferon gamma elease immunoassays in the detection of latent tuberculosis infection. *Communicable Diseases Intelligence, 41*(4), E322-E336.

Nogueira, M., Warren, R. B., & Torres, T. (2021). Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis - time for a paradigm change. *Journal of the European Academy of Dermatology and Venereology, 35*(4), 824–834. https://doi.org/10.1111/jdv.16866

Pai, M., & O'Brien, R. (2008). New diagnostics for latent and active tuberculosis: state of the art and future prospects. *Seminars in respiratory and critical care medicine, 29*(5), 560–568. https://doi.org/10.1055/s-0028-1085707

Perlmutter, A., Mittal, A., & Menter, A. (2009). Tuberculosis and tumour necrosis factor-alpha inhibitor therapy: a report of three cases in patients with psoriasis. Comprehensive screening and therapeutic guidelines for clinicians. *The British journal of dermatology, 160*(1), 8–15. https://doi.org/10.1111/j.1365-2133.2008.08891.x

Quinn, C. M., Poplin, V., Kasibante, J., Yuquimpo, K., Gakuru, J., Cresswell, F. V., & Bahr, N. C. (2020). Tuberculosis IRIS: Pathogenesis, presentation, and management across the spectrum of disease. *Life (Basel, Switzerland), 10*(11), 262. https://doi.org/10.3390/life10110262

Saliu, O. Y., Sofer, C., Stein, D. S., Schwander, S. K., & Wallis, R. S. (2006). Tumor-necrosis-factor blockers: differential effects on mycobacterial immunity. *The Journal of infectious diseases, 194*(4), 486–492. https://doi.org/10.1086/505430

Sichletidis, L., Settas, L., Spyratos, D., Chloros, D., & Patakas, D. (2006). Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. *The international journal of tuberculosis and lung disease*, *10*(10), 1127–1132.

Singh, J. A., Saag, K. G., Bridges, S. L., Jr, Akl, E. A., Bannuru, R. R., Sullivan, M. C., Vaysbrot, E., McNaughton, C., Osani, M., Shmerling, R. H., Curtis, J. R., Furst, D. E., Parks, D., Kavanaugh, A., O'Dell, J., King, C., Leong, A., Matteson, E. L., Schousboe, J. T., Drevlow, B., … McAlindon, T. (2016). 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis & rheumatology (Hoboken, N.J.), 68*(1), 1–26. https://doi.org/10.1002/art.39480

Stuart, R. L., Bennett, N. J., Forbes, A. B., & Grayson, M. L. (2001). Assessing the risk of tuberculosis infection among healthcare workers: the Melbourne Mantoux Study. Melbourne Mantoux Study Group. *The Medical journal of Australia, 174*(11), 569–573. https://doi.org/10.5694/j.1326-5377.2001.tb143437.x

Tymms, K. (2009). *Screening for latent tuberculosis infection prior to use of biological agents in Australia.* Retrieved October 18, 2011, from http://www.rheutamology.org.au

Wolfe, F., Michaud, K., Anderson, J., & Urbansky, K. (2004). Tuberculosis infection in patients with rheumatoid arthritis and the effect of infliximab therapy. *Arthritis and rheumatism, 50*(2), 372–379. https://doi.org/10.1002/art.20009

Zaemes, J., & Kim, C. (2020). Immune checkpoint inhibitor use and tuberculosis: a systematic review of the literature. *European journal of cancer,132*, 168–175. https://doi.org/10.1016/j.ejca.2020.03.015

Chapter 6: BCG Vaccination

6.1. BCG vaccination

6.1.1. Introduction

BCG vaccine is a suspension of a live attenuated strain of *M. bovis.* BCG vaccination does not prevent transmission of TB infection to an individual, but it is an important strategy in TB prevention in countries with a high burden of TB. In immune competent neonates and infants, BCG reduces the likelihood of TB infection progressing to disease and there is strong evidence that BCG vaccination in infancy provides up to 85% protection against severe disseminated forms of TB including miliary TB and tuberculous meningitis (WHO, 2018).

BCG protection against leprosy varies in studies between 20% and 90%. Study design and features of the target population are likely the most significant factors influencing observed vaccine efficacy (Merle et al., 2010).

6.1.2. BCG indications

BCG vaccination should not be offered routinely to Australian residents. However, it is indicated in the following groups:

- Children less than 6 years of age who are going to live in a country with high TB incidence (annual incidence of > 40 / 100 000 population) for more than 3 months (once off or cumulatively). Ideally, BCG should be given 2 – 3 months prior to departure. For country specific incidence rates see the WHO TB country profile website https://worldhealthorg.shinyapps.io/tb_profiles/ (WHO, 2024)
- Newborn children of migrants who have arrived from countries with a high TB incidence in the last 5 years, or newborn children who have close contact with people who have arrived from a high incidence country in the last 5 years.
- Newborn children of parents with Leprosy.
- Children less than 6 years of age who have not previously been vaccinated with BCG and are household contacts of newly diagnosed Leprosy.
- Infant household contacts of TB after empiric prophylaxis if TST remains negative.

BCG can be considered for children not included in these indications. However, care should be taken to adequately inform individuals (or their guardian) of the potential risks and low efficacy of the vaccine, especially in adults.

WA Health sites should consider a Structured Administration and Supply Arrangement (SASA) for BCG that list the indications for BCG vaccine. It is recommended that BCG administration outside the above indications should be discussed with a medical officer and a written medication order obtained. The WATBCP Medical Director or Clinical Nurse Manager can be contacted to assist.

6.1.3. BCG contraindications

Immunisation service providers should undertake a comprehensive pre-vaccination health screen on all individual's pre- vaccination. Refer to the Australian Immunisation Handbook for a detailed explanation of the required pre-vaccination checklist. Specific contraindications and precautions to consider for BCG vaccination include:

- Prior BCG vaccination.
- Anaphylaxis following any component of BCG vaccine.
- Infants with a body mass < 2.5kg.
- Individuals who are immunocompromised (increased risk for disseminated BCG infection), including but not necessarily limited to:
    - Those with known or suspected HIV infection; including newborn children of mothers infected with HIV until this infection is ruled out in the child.
    - Those on corticosteroid or other immunosuppressive therapy.
    - Those undergoing radiation or chemotherapy.
- Pregnancy (live vaccines are not recommended during pregnancy).
- Individuals who are known to have had TB in the past.
- Individuals with a positive TST > 5mm diameter induration.
- Individuals with generalised infective skin disease such as furunculosis, eczema, dermatitis or psoriasis. Vaccination should be deferred until the condition clears.
- Individuals who have received a live vaccine (MMR, varicella, yellow fever) within the prior 28 days, unless they are given the same day as BCG vaccine. Oral rotavirus vaccines are an exception to this - no delay is required for BCG administration.

6.1.4. Tuberculin skin testing and BCG vaccination

Universal TST prior to BCG is no longer recommended; instead, all children presenting for BCG vaccination should be assessed for their risk of TB infection. Pre-BCG vaccination TST is only recommended if a child meets one or more of the following criteria:

- Born in a country with an annual TB incidence >40 cases per 100000 population per year (see reference webpage https://worldhealthorg.shinyapps.io/tb_profiles/ (WHO, 2024).
- Has lived or travelled to a TB endemic country or region (>40 cases per 100000 population per year).
- Had exposure to a close contact with TB or who is under investigation for TB.
- Symptoms compatible with TB disease including persistent (>3 weeks) cough, weight loss, fever or night sweats.

In individuals with TBI or TB disease, BCG can be associated with an increased risk of an accelerated reaction with development of induration at the injection site of 5 mm or more within 24 – 72 hrs. (Ritz et al., 2012).

The use of IGRA, such as QFT as pre-BCG screening is not recommended as there is insufficient data in the setting of screening prior to BCG vaccination and QFT will not be positive after prior BCG vaccination.

6.1.5. General considerations

- Repeat BCG vaccination is not recommended.
- BCG vaccination should only be administered by appropriately trained health care providers. The WATBCP can assist with training health care providers in BCG administration.
- Children who have travelled to a high incidence country should delay BCG vaccination until a TST undertaken 8 weeks after arrival back in Australia with a result of < 5 mm induration.

6.1.6. BCG vaccine administration

- The vaccine should not be exposed to direct sunlight or heat and should be stored between 2^{0}C and 8^{0}C.
- BCG vaccine must be reconstituted by adding the entire contents of the diluent to the vial and mixing until the powder is completely dissolved.
- BCG is given as a single dose by intradermal injection at the level of the humeral deltoid muscle insertion.
- Reconstituted vaccine is unstable and must be stored between 2^{0}C and 8^{0}C and discarded (depending on the brand) after 4 – 8 hours.
- A record of the BCG vaccination (including name, date of birth, date of vaccination, dose, and batch number of vaccine) must be kept, with a copy given to the recipient and the details entered into the Australian Immunisation Register (AIR).
- Please refer to WATBCP - Intradermal BCG Injection Guideline for further information on how to administer BCG.

6.1.7. Adverse reactions and complications

- Approximately 95% of vaccine recipients experience a reaction at the vaccination site 2 – 4 weeks after vaccination, characterised by a papule which may become ulcerated and heal after 2 – 5 months leaving a superficial scar. This is normal.
- Severe ulceration or suppurative lymphadenitis can occur but is usually caused by inadvertent injection of the vaccine sub-dermally (WHO, 2018). In the event of an accelerated or ulcerating reaction, expert advice from the WATBCP should be sought.
- Anaphylactic reactions can occur but are rare.
- Accelerated BCG reactions are seen in TST positive individuals with the response occurring within 2 – 5 days after the vaccine is administered.
- Keloid scars can result from vaccination with or without an accelerated reaction.
- Very rarely a potentially fatal disseminated infection can occur, especially when BCG vaccination is given to an immunocompromised individual.
- BCG-IRIS occurs in association with HIV infection (WHO, 2018).

Adverse reactions and complications from BCG are rare but if they occur, they should be discussed with the patient and/or guardian and they should be recorded. Advice regarding adverse events and how to report to the Western Australian Vaccine Safety Surveillance (WAVSS) system can be found at: Western Australian Vaccine Safety Surveillance (WAVSS)

6.1.8. Recommendation in the event of a failure of BCG supply

In the past there have been a number of interruptions to the supply of BCG worldwide.

If BCG is unavailable the following procedures should be considered:

- All children under 6 years of age travelling to high TB burden countries for extended periods (> 3 months) should be provided with education on TB risk factors and TB disease and offered follow up TST 8 -12 weeks after their return to Australia.
- Those with evidence of recent TB infection will be referred to the WATBCP Paediatric TB clinic for medical review and consideration for preventive therapy to minimise the risk of progression to TB disease.

6.1.9. References

Barth-Jaeggi, T., Steinmann, P., Mieras, L., van Brakel, W., Richardus, J. H., Tiwari, A., Bratschi, M., Cavaliero, A., Vander Plaetse, B., Mirza, F., Aerts, A., & LPEP study group. (2016). Leprosy Post-Exposure Prophylaxis (LPEP) programme: study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. *BMJ open, 6*(11), e013633. https://doi.org/10.1136/bmjopen-2016-013633

Bothamley, G. H., Cooper, E., Shingadia, D., & Mellanby, A. (2003). Tuberculin testing before BCG vaccination. *BMJ (Clinical research ed.), 327*(7409), 243–244. https://doi.org/10.1136/bmj.327.7409.243

Department of Health and Aged Care. (2013). *The Australian Immunisation Handbook* (10th Ed.), p 410.

Hennessy B. (2008). Is tuberculin testing before BCG vaccination necessary for children over three months of age? *Irish medical journal, 101*(3), 72–74.

Merle, C. S., Cunha, S. S., & Rodrigues, L. C. (2010). BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. *Expert review of vaccines, 9*(2), 209–222. https://doi.org/10.1586/erv.09.161

National Tuberculosis Advisory Committee. (2013). The BCG vaccine: information and recommendations for use in Australia. *Communicable Diseases Intelligence*, *37*(1), 65-72.

Ritz, N., Tebruegge, M., Camacho-Badilla, K., Haeusler, G. M., Connell, T. G., & Curtis, N. (2012). To TST or not to TST: is tuberculin skin testing necessary before BCG immunisation in children? *Vaccine, 30*(8), 1434–1436. https://doi.org/10.1016/j.vaccine.2011.11.099

World Health Organization. (2018). BCG vaccines: WHO position paper – February 2018. *Weekly Epidemiological Record, 93*(8), 73-96. https://www.who.int/publications/i/item/who-wer9308-73-96

World Health Organization. (2024). *Tuberculosis country profiles.* Retrieved from https://worldhealthorg.shinyapps.io/tb_profiles/

Chapter 7: Notification of tuberculosis and enhanced surveillance

7.1. Tuberculosis notification and enhanced surveillance

7.1.1. Introduction

It is a legal requirement for clinicians and laboratories to notify TB cases in children and adults to the WA Department of Health. TBI does not need to be notified. This chapter is a guide for clinicians on the process of mandatory notification of TB and enhanced surveillance requirements.

7.1.2. Statutory medical notifications

The statutory requirement to notify communicable diseases is specified in Part 9 of the *Public Health Act 2016* and the associated *Public Health Regulations 2017*. Section 94 of the Act requires that medical doctors, nurse practitioners and pathology laboratories are legally required to report the diagnosis of notifiable infectious diseases, including TB, and related conditions to the Chief Health Officer.

Section 97 of the Act describes the obligations of the diagnosing practitioner to advise the patient that the disease or condition is notifiable and to provide them with information about the disease or condition and their rights and responsibilities, including how to minimise the risk of transmission to other people.

Normally, notification is the responsibility of the medical doctor or nurse practitioner who makes the diagnosis and is in charge of the patient's management. Notification should be made using the approved Department of Health Notification Form, by post, fax or telephone, depending on urgency. In situations where 2 or more practitioners are involved in the patient's management, and it is not clear if the case has already been notified, the case should still be reported. This ensures optimal ascertainment of all cases. The Department of Health undertakes checks that will detect duplicate notifications.

7.1.3. Case definition of tuberculosis

Only confirmed cases of TB should be notified to the Department of Health. A confirmed case of TB is defined by the Communicable Diseases Network Australia (CDNA) for state and national surveillance in Table 30 below.

TB should be notified whenever diagnosed, even if it is not proven microbiologically. This means any TB that is diagnosed on clinical, radiological or histological grounds must be notified.

If TB treatment is started, notification is required in **ALL** cases.

A notified case can be readily removed from the register if subsequently found to not be a case of TB.

Table 30 National tuberculosis case definition

A **confirmed case** requires a diagnosis accepted by the Director of Tuberculosis Control (or equivalent) in the relevant jurisdiction, based on either: 1. Laboratory definitive evidence OR 2. Clinical evidence. <u>Laboratory definitive evidence</u> 1. Isolation of *M. tuberculosis* complex (excluding *M.bovis* var BCG) by culture OR 2. Detection of *M. tuberculosis* complex by nucleic acid testing EXCEPT where this is likely to be due to previously treated or inactive disease. <u>Clinical evidence</u> A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis, including follow–up assessment to ensure a consistent course.

7.1.4. Notification and Surveillance Process

Western Australia notification

Under the Public Health Act 2016, the Chief Health Officer must be notified of infectious diseases that are of public health significance. Notifications are sent to the Director of the CDCD for cases diagnosed in the Perth metropolitan area, and to the appropriate Public Health Unit for cases diagnosed in country areas.

The information that is required by the Department of Health is specified in the Department of Health Notification Form, which is available here. Reply paid envelopes are provided to clinicians with notification forms to facilitate mailing, and a fax number is provided on the form if faxing is preferred.

Pathology laboratories provide notifications by automated electronic downloads directly to the CDCD.

Core notifiable disease data from both paper-based clinician notifications and electronic or paper-based laboratory notifications are stored in the Western Australian Notifiable Infectious Diseases Database (WANIDD), which is accessible to a limited number of authorised users, including designated staff of the WATBCP. Notifications are entered into WANIDD within 24

hours of receipt at CDCD. The database provides real-time surveillance capacity on a statewide basis.

The responsibility for entry of notifications into WANIDD is with designated staff in CDCD. Notifications are often generated by, or sent directly to, the WATBCP. These are immediately faxed to CDCD for data entry. Conversely, notifications received by CDCD, once entered into WANIDD are faxed to the WATBCP to ensure the program is aware of the newly identified case. The fax is received and processed by the Clinical Nurse Manager at the WATBCP or their delegate. The MRL, in addition to sending electronic notifications to CDCD, also notifies the WATBCP of all new positive *M. tuberculosis* microbiology results by fax and email.

TB notifications are made according to the patient's state of residence. If a resident from WA returns to live in WA during the course of their treatment, a notification should be completed. In this scenario, communication should occur with the other relevant jurisdiction to avoid duplicate notifications. The WATBCP is responsible for providing this surveillance data to the WA Health Department.

Enhanced surveillance

For TB, additional information such as risk factors for infection, site of disease and antibiotic susceptibility are collected subsequent to the original notification using a specific enhanced surveillance form. The enhanced surveillance form is completed by the medical and case management staff of the WATBCP. The definitions of the data fields for enhanced surveillance are provided by the Australian Government Department of Health and Aged Care (DoHA).

Enhanced surveillance data for TB are maintained as a separate module in WANIDD, with staff of the WATBCP updating patient records on a regular basis as data become available. A paper copy of the enhanced surveillance data collection form is attached to the medication chart at the WATBCP. This acts as a prompt to doctors and case managers to review enhanced surveillance data as and when the case is reviewed. CDCD provides assistance with quality control and analysis and reporting via its Data Manager and a designated Senior Project Officer.

One element of enhanced surveillance is documentation of treatment outcome of cases of TB. Treatment outcome is classified according to Table 31 below.

Table 31 Tuberculosis treatment outcome classification

Outcome	Definition
Cured	A patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the local policy, with evidence of bacteriological response and no evidence of failure.
Treatment completed	A patient who completed treatment as recommended by the local policy but whose outcome does not meet the definition for cure or treatment failure.

Outcome	Definition
Died	A patient who died (for any reason) before starting treatment or during the course of treatment.
Treatment failed	A patient whose treatment regimen needed to be terminated or permanently changed[b] to a new regimen or treatment strategy.
Lost to follow-up	A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome was assigned.[c]
Treatment success	The sum of all patients cured and treatment completed.

[a] "Bacteriological response" refers to bacteriological conversion with no reversion:

- "bacteriological conversion" describes a patient with bacteriologically confirmed TB where at least 2 consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are negative; and
- "bacteriological reversion" is where at least 2 consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only) taken on different occasions at least 7 days apart are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.

[b] Reasons for the change include:

- no clinical response or no bacteriological response, or both (see note 'b');
- adverse drug reaction; or
- evidence of additional drug-resistance to medicines in the regimen

[c] This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown; however, it excludes those lost to follow-up.

Treatment outcome should be documented on the enhanced surveillance form and reported no later than 12 months after initial notification. For purposes of national surveillance, CDNA recommends that if a person transfers from one jurisdiction to another, information regarding treatment and conversion at three months should be sent from the receiving jurisdiction back to the jurisdiction that originally notified the case. The WATBCP is responsible, as far as possible, for following up with the receiving jurisdiction in obtaining outstanding enhanced surveillance data information on cases of TB that transfer out of WA.

Data cleaning of the initial notification for TB is performed on a fortnightly basis by designated staff at CDCD who then request staff of the WATBCP to complete missing data fields for all patients diagnosed with TB.

Enhanced surveillance data for TB are reviewed for completeness by designated staff at CDCD every quarter prior to submission of the data to the Commonwealth DoHA and the NTAC. Requests to complete missing data fields are emailed to the WATBCP prior to submission.

In May each year, TB notifications reported during the entire previous 12 months are reviewed at the WATBCP, for completeness and accuracy prior to submission of the surveillance data to the Commonwealth. The WA TB notification dataset is analysed and reported annually by the WATBCP. This report is presented to the WA Tuberculosis and Leprosy Advisory Council (WATLAC) and made available to WATBCP clinical staff and other relevant stakeholders on the Department of Health website.

National Notifiable Diseases Surveillance System (NNDSS)

The National Notifiable Diseases Surveillance System (NNDSS) was established in 1990 and is maintained by the Australian Government DoHA. Under this scheme, de-identified core information on cases of infectious diseases that are notified to State or Territory health authorities, under the provisions of the public health legislation in the respective jurisdictions, are forwarded electronically to DoHA daily for incorporation in the NNDSS database. CDNA comprises representatives from DoHA and State/Territory Departments of Health, co-ordinates national surveillance of the agreed list of communicable diseases that are maintained in the NNDSS. Sharing of notifiable disease data across jurisdictions is covered under the terms of the National Health Security Act 2007.

The NTAC, a sub-committee of CDNA, has representatives from State and Territory TB control programs. It provides strategic guidance on public health management and surveillance of TB in Australia and has oversight of the enhanced surveillance data collection. In addition to the daily electronic transmission of core surveillance data on notified TB cases from WANIDD to the NNDSS, CDCD provides DoHA with additional enhanced surveillance data which is also transmitted electronically to the Commonwealth on the day the information is entered or amended on WANIDD.

7.1.5. Access to data outside the WATBCP

Occasionally individuals or groups that do not work within CDCD or the WATBCP will request access to TB data from WANIDD or the enhanced surveillance dataset. These individuals are required to provide a written submission to CDCD, which in turn is reviewed by the Medical Director of TB, detailing specifically the data required and how it will be used. Access is granted at the discretion of the Medical Director of TB, and after review by the Medical Epidemiologist at CDCD.

7.1.6. References

Department of Health and Aged Care. (2007). *National Health Security Act 2007*. Australian Government. Retrieved November 22, 2017, from https://www.legislation.gov.au/Series/C2007A00174

Department of Health Western Australia. (2016). *Public Health Act 2016.* Government of Western Australia. Retrieved October 4, 2019, from https://www.legislation.wa.gov.au/legislation/statutes.nsf/main_mrtitle_13791_homepage.html

Department of Health Western Australia. (2017). *Public Health Regulations 2017*. Government of Western Australia. Retrieved October 4, 2019, from https://www.legislation.wa.gov.au/legislation/statutes.nsf/law_s49088.html

World Health Organization. (2022). *WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment*. World Health Organization. https://www.who.int/publications/i/item/9789240050761

Chapter 8: Fees and charges

8.1. Fees and charges related to the diagnosis and management of tuberculosis and leprosy

It is WATBCP policy that individual patients should not incur any financial cost for the investigation of possible TB or leprosy, or the management of proven TB or leprosy.

A key strategy in the control of chronic infectious mycobacterial diseases (TB and leprosy) is prompt and effective, free treatment. Ensuring that there is no financial barrier to the individual to investigate or treat these infections enables attendance and adherence; and thereby reduces the risk of delayed diagnosis or poorly treated infection, and transmission within the community.

This policy is in line with *The Strategic Plan for Control of Tuberculosis in Australia: 2021 - 2025* (National Tuberculosis Advisory Committee).

All fees and charges associated with TB and leprosy management that may be incurred by a patient cared for in WA health facilities are *non-chargeable* by the Health Service. The principle is that the patient has no out-of-pocket expense, as an individual. Fees and charges may be payable if a third party is liable to meet the cost of TB or leprosy management on behalf of an individual patient (for example, a State or Commonwealth Government department or a commercial entity, such as an insurance company). These invoices may include fees and charges for radiology, pathology, pharmacy, outpatient consultation and inpatient services, but this is not an exclusive list. This policy applies to any service that can be reasonably associated with the possibility (investigation for) or proven diagnosis of TB or leprosy.

All WA Health public hospital pharmacies are required to provide drugs used for the treatment of TB or leprosy free of any charge to the individual patient. The treating physician should annotate prescriptions to indicate that the drugs are for the treatment of TB or leprosy. Conversely, medication for the treatment of TB or leprosy can be supplied to patients free-of-charge anywhere in WATBCP (Anita Clayton Centre).

This policy applies especially to patients that are not Medicare eligible. It is preferable, for accounting reasons, that patients are not charged for services (“non-chargeable” services, as above). However, if a patient receives accounts for these services, they should be advised not to pay them, and the treating physician should apply to the Director of Clinical Services in the relevant Health Service for the account to be waived.

In the event of differing medical opinions as to whether a particular condition (for which an account is raised) is related to a patient’s TB or leprosy, and in the absence of any local policy or procedures establishing a decision-making pathway, the Director of Clinical Services (or equivalent) of the relevant site should determine whether the condition is to be treated as related to a TB diagnosis for the purposes of this policy. The Director of Clinical Services (or equivalent) of the relevant site should seek the opinion of the Medical Director of TB for Western Australia in making such a decision.

The WA Medical Director of TB can be contacted directly or through the Anita Clayton Centre (Mon – Fri, business hours, T: 92228500, E: ACCadmin@health.wa.gov.au). If the Medical Director is not available advice can be sought from a TB expert physician in the Centre.

Individual patients may be referred to the WATBCP for free investigation, drug therapy or management for TB and leprosy.

This policy is mandated in the WA Department of Health Patient Fees and Charges Manual 2024/25 under section 8.2 Treatment of Patients with Tuberculosis or Leprosy.

8.1.1. References

Department of Health. (2024). *WA Health patient fees and charges manual 2024/2025.* Government of Western Australia. https://www.health.wa.gov.au/~/media/Corp/Documents/Reports-and-publications/Fees-and-charges/WA-Health-Fees-and-Charges-Manual.pdf

National Tuberculosis Advisory Committee. (2022). The Strategic Plan for Control of Tuberculosis in Australia, 2021–2025. *Communicable Diseases Intelligence, 46,* 10.33321/cdi.2022.46.48. https://doi.org/10.33321/cdi.2022.46.48

This document can be made available in alternative formats on request for a person with a disability.