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

Guidelines for Tuberculosis Control in Western Australia

September 2019

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Acronyms and Abbreviations

TB = tuberculosis

LTBI = latent 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 LTBI 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.

3TC	lamivudine
ACH	air changes per hour
AFB	acid fast bacilli
AHPPC	Australian Health Protection Principal Committee
AIDS	acquired immunodeficiency syndrome
ARV	anti-retroviral
BCG	Bacille Calmette-Guerin vaccine
BFE	bacterial (3 micron) filtration efficiency
CDC	Centers for Disease Control and Prevention, United States of America
CDNA	Communicable Diseases Network of Australia
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CXR	chest x-ray
DMARS	disease-modifying anti-rheumatic drugs
DOT	directly observed therapy
E	ethambutol
ED	emergency department
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunospot assay
FTC	emtricitabine
H	isoniazid
HBC	high-burden countries
HCW	health care worker
HIV	human immunodeficiency virus
id	intradermal
IFN	interferon
IGRA	interferon gamma release assays
IRIS	immune reconstitution inflammatory syndrome
IU	international unit
IV	intravenous
LTBI	latent tuberculosis infection
Lfx	levofloxacin

MAC	mycobacterium avium complex
MDR-TB	multidrug resistant tuberculosis
Mfx	moxifloxacin
MMR	measles mumps rubella vaccine
MMRV	measles mumps rubella varicella vaccine
MRI	magnetic resonance imaging
MRL	Mycobacterium Reference Laboratory
MTB	Mycobacterium tuberculosis
NAA	nucleic acid amplification test
NATA/RCPA	National Accreditation and Testing Authorities, Royal College of Pathologists of Australia
NHMRC	Australian National Health and Medical Research Council
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside/nucleotide reverse transcriptase inhibitors
NTAC	National TB Advisory Committee
NTM	non-tuberculous mycobacterium
PCR	polymerase chain reaction
PFE	particulate (0.1 micron) filtration efficiency
PI	protease inhibitors
PPD	purified protein derivative (tuberculin)
PRP	personal respiratory protection
QIFN	QuantiFERON Gold-TB In-Tube test
RBT	rifabutin
RCT	randomised controlled trial
R	rifampicin
TB	tuberculosis (implies active disease, see note above)
TNF	tumour necrosis factor
T-Spot	T-SPOT.TB test
TST	tuberculin skin test
WA	Western Australia
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

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 WA Tuberculosis Control Program. 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. There is a variable number of suitable trained scientific and technical staff. Pathologist oversight and consultancy is 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 & 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 epidemiological typing (genotyping) by nationally-approved methods;
- Provision of specialised laboratory services for the investigation of clinically-significant non-tuberculous mycobacteria (NTM) infections;
- Participation in national quality assurance programs; and
- Training of clinical, public health and laboratory personnel to maintain expertise in mycobacterial diagnostics in both the public and private sectors.

This policy aims to outline the laboratory methods used in the diagnosis of tuberculosis disease in Western Australia (WA), in particular those performed at the Western Australia Mycobacterium Reference Laboratory.

Overview of the Mycobacteria Testing Process

A variety of clinical specimens are processed and cultured to 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, examined for acid-fast bacilli (AFB) and reported 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 *M. tuberculosis* (MTB) and the other *M. tuberculosis* Complex (MTBC) members such as *M.bovis*. Mycobacteria recovered from culture are fully identified by molecular means.

Susceptibility testing of *M. tuberculosis* complex, to first line anti-tuberculous drugs is undertaken for new cases and for suspected relapse cases, a process that may take 7-14

days from time of positive culture. Second line susceptibility testing is performed on strains of multi-drug resistant TB (MDR-TB), defined as resistance to at least isoniazid (INH) and rifampicin (RIF), or on the request of a TB Specialists. 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, in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines (Clinical and Laboratory Standards Institute, 2018).

Genotyping is performed on all new isolates of MTBC using Mycobacterial Interspersed Repetitive Unit - Variable Number Tandem Repeat (MIRU-VNTR) analysis (Supply et al 2000) and information is provided to WA TB Control for epidemiology purposes. The introduction of whole genome sequencing will provide additional information and supersede the use of MIRU-VNTR analysis.

Laboratory Services

The MRL is the only laboratory in Western Australia (WA) 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 performs both acid-fast microscopy and mycobacterial culture then refers isolates to the MRL for identification and susceptibility testing.

The National Tuberculosis Advisory Committee (NTAC) published set of guidelines for Mycobacteriology Laboratories in 2006. This extensive document, Guidelines for Australian Mycobacteriology Laboratories (National Tuberculosis Advisory Committee Australia, 2006), actively promotes high standards of laboratory testing 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 *M. tuberculosis* complex (MTBC) within an average of 10-14 days, and reporting of 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 as basis for the analysis of TB and MDRTB samples.

After hours services

Currently, PathWest sites at Queen Elizabeth II Medical Centre (QEII), Fiona Stanley Hospital (FSH) and Royal Perth Hospital (RPH) offer an urgent, after-hours AFB (Ziehl-Neelsen) microscopy service. This 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 report will always be followed up by a final microscopy report from the MRL, who perform microscopy on processed samples, i.e. samples subjected to mucolytic decontaminating agents and high-speed centrifugation or, if required, review of direct smear.

The larger two PathWest metropolitan sites (QEII & FSH) also offer an after- hours molecular TB detection service utilizing the GeneXpert® 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.

Specimen Collection

Laboratory guidelines exist that ensure optimal recovery of mycobacteria from samples. Generally speaking, mycobacteria are robust organisms and tolerate transport and delays in culture quite well. Issues with specimen collection include:

- Ensuring an adequate sample is provided to capture the low numbers of mycobacteria often present, notably in body fluids. Generally the more organisms present the sooner cultures become positive;
- Overgrowth by commensal flora, particularly when a highly enriched broth-culture mycobacteria medium is used or when there is delayed transfer of samples to the laboratory, presents technical problems and delays in laboratory turn-around time. A high quality specimen is therefore important and specimens should reach the laboratory within 24 hours.

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 mycobacteria per millilitre of sample.

Despite this, 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; and
- Affect the patient's discharge back into the community.

Both fluorochrome (using ultra violet 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 area of the smear to be scanned. Whilst the ZN method remains the reference standard for AFB microscopy, fluorochrome microscopy is the recommended screening method (GLI 2013).

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 that appropriate cultures 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 Western Australia. 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 ultra violet light (typically 366 nm). Tubes with oxygen depletion emit a bright orange fluorescence.

In general, cultures from smear-positive specimens become positive at 37^{o}C 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 30^{o}C.

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 non-tuberculous mycobacteria (NTM) by nucleic acid amplification testing (NAAT) using a multiplex real time PCR system. Gene sequencing may be used to further identify NTM isolates, with results generally available within a few days. There are limitations associated with gene sequencing and a whole genome analysis approach is currently under development. The additional resource demands involved in this may limit its use to significant isolates and an adequate clinical history is therefore essential.

All MTBC isolates (and NTM isolates of clinical significance) are stored frozen at -80^{o}C 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 Australia (NATA) requirements.

Specimen-direct nucleic acid amplification testing (NAAT)

Significant improvements in NAAT methods, including automation, have moved these methods from a research environment into routine clinical laboratories. PathWest routinely operates an in-house Real-Time PCR test with results available within 24 hours, but can also offer a rapid result (approximately 2 hour turn-around time) using Cepheid GeneXpert (see below).

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

One important factor in NAAT is the smear status of specimens that are culture-positive for MTBC. Although NAAT is very sensitive and can theoretically detect a single bacterial cell, in practice organism load, sample volume and quality are important. The cut-off sensitivity threshold for the in-house test is the same as for microscopy, i.e. ~10^4 AFB/ml. A further consideration for NAAT is inhibitors sometimes found in a clinical sample. Assays used at PathWest detect their presence and this may cause delays in reporting when re-testing is required.

The GeneXpert MTB/RIF is a sensitive cartridge-based, automated real time assay that can detect MTB and resistance to rifampicin, a surrogate marker for MDR strains, within

approximately 2 hours from receipt in laboratory. It is said to have similar sensitivity to culture (98-100% in smear-positive cases, 73-91% in smear negative cases). Specificity is >98%, giving very good positive and negative predictive values, for detection of both MTB presence and rifampicin resistance. The test is available at QEII and FSH PathWest sites. It should be noted that the GeneXpert assay is currently only accredited for use on respiratory samples and there is a lack of a true positive control for every assay. Confirmatory methods are therefore needed for both MTB and rifampicin resistance detections and comments to this effect are made at the time of reporting.

Issues of when and how often to test have been addressed and the following is the NTAC and CDC recommended algorithm for NAAT that is also applied at PathWest (Centers for Disease Control, 2009 and 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; and
- Selected 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;
- When a patient is respiratory smear-positive and has a very high probability of TB; and
- Paucibacillary non-respiratory specimens (e.g. pleural fluid, ascitic fluid).

NAAT should not be used to monitor patients on anti-tuberculosis treatment. Tests may remain positive for an extended period of time regardless of whether DNA or RNA is the target for amplification.

Susceptibility Testing

Any new MTBC isolate has susceptibilities performed to first-line antimycobacterial agents isoniazid, rifampicin, ethambutol & 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 to this is bacille Calmette-Guérin (BCG) associated *M. bovis*, which is a standardized strain of known lineage. MTB strains that show low-level resistance to INH (at 0.1 µg/ml) are retested at a higher concentration (at 0.4 µg/ml) before classifying the strain as INH resistant. MTB strains showing any resistance to INH are routinely tested for fluoroquinolone susceptibility (at least) in accordance with NTAC guidelines. *M.bovis* is intrinsically resistant to pyrazinamide.

If an isolate demonstrates multiple resistance to first-line drugs, additional susceptibility testing is performed in accordance with WHO guidelines for drug susceptibility testing of medicines used in the treatment of drug-resistant tuberculosis (WHO, 2018). These tests are also performed using the automated MGIT 960 system.

Progress in understanding the genetic mechanisms of drug resistance in MTB has resulted in the development of molecular methods for rapid determination of susceptibility profiles. Resistance to rifampicin is a useful predictor of MDR-TB and molecular methods have demonstrated greater than 90% correlation with established phenotypic methods. Molecular methods have a much poorer correlation with traditional methods for isoniazid, pyrazinamide, and ethambutol. Establishment of whole genome sequencing will enable additional resistance information to be available.

Some non-tuberculous mycobacteria (e.g., *M.marinum*) have such uniform susceptibility patterns that there is little to be gained from testing individual isolates. Clarithromycin susceptibility testing of *Mycobacterium avium complex* can be performed using the automated MGIT system. 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 Clinical and Laboratory Standards Institute (CLSI) guidelines (2018).

Molecular Epidemiology

Repetitive DNA elements present within the genome of mycobacteria undergo genetic rearrangements. DNA typing methods exploit genetic movement or drift in *M. tuberculosis* and *M. bovis* and therefore provide an important laboratory tool for understanding the epidemiology of their infections.

Automated MIRU-VNTR genotyping is performed on all isolates of MTBC. Twenty four loci are examined in real-time to allow determination of exogenous reinfection versus endogenous reactivation, laboratory cross-contamination, and whether the change in an isolate's drug resistance profile is due to a reinfection or an acquisition of resistance determinants. Data is added to a comparative (local) database that is forwarded to the Medical Director of the WA Tuberculosis Control Program, whenever new data is added. The genotyping result does not form part of the laboratory report.

Implementation of whole genome sequencing will provide improved epidemiological information for strain comparison and assist significantly in cluster analysis.

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.

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 WA TB Control Clinic are phoned directly to the duty Doctor. 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, Western Australia TB Control Program. This is done initially by fax, and then followed with a copy of the report.

Conclusion

The key roles of the MRL are rapid detection of MTB, 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 tuberculosis 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 WA TB Control Program.

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1.2 Diagnosis of Tuberculosis – Clinical

Introduction

The highest priority for tuberculosis (TB) control is the identification and cure of infectious cases of TB. Therefore, any person with symptoms suggestive of TB, particularly cough for more than three weeks, should be investigated.

The primary test should always be sputum microscopy and culture for acid-fast bacilli (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.

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.

Extra-pulmonary TB is disease involving any other part of the body and includes lymph node, 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. Conversely, the risk to community from extra-pulmonary TB is minimal (Hoffman & Churchyard, 2009).

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

Presentation of TB

TB usually has a subacute presentation. Disease can be detected in an asymptomatic patient, for example, through 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 website http://who.int/tb/country/data/profiles/en/index.html (WHO 2018). About a 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, being an Aboriginal Australian or being born prior to 1950.

Special Situations

Human Immunodeficiency Virus (HIV) Infection

The clinical presentation of TB in 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 present atypically e.g. with non-cavitatory 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 TB 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 4.4 HIV Coinfection.

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, Gershon, & Wise, 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 Therapy.

Investigations for Tuberculosis

Direct microscopy ZN examination and AFB culture of clinical specimens (e.g. sputum, fine needle aspiration, tissue biopsy, cerebrospinal fluid, pleural/pericardial and peritoneal cavity fluid or urine) are the first line investigations for tuberculosis.

Mycobacterial culture remains the gold standard for a definitive TB diagnosis. When microscopy for AFB and nucleic acid amplification testing (NAAT) are both positive, the diagnosis of tuberculosis is established.

The diagnosis is strongly supported by the histological appearance of granulomatous inflammation with caseation in tissue specimens within the appropriate clinical 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 for *M.tuberculosis* isolates ensures the appropriateness of treatment.

Sputum collection for microbiological examination should be performed 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. This is because of the potential for asymptomatic co-existent pulmonary TB and the public health implications of a positive result.

Sputum Microscopy

Sputum smear microscopy is the most reliable and cost effective method of diagnosing infectious cases of pulmonary TB. Whenever pulmonary or extra-pulmonary tuberculosis is suspected in a patient, three sputum samples should be collected and examined by microscopy for acid-fast bacilli. They are best collected in the early morning but patients who are very productive can have three specimens collected 8 hours apart within 24 hours.

Sputum Culture

Culture of sputum for acid-fast bacilli is more sensitive and specific than direct smear microscopy and it is useful in detecting cases where the number of organisms are 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 Tuberculosis

- A patient with at least two sputum smears positive for AFB by microscopy OR
- A patient with at least one sputum smear positive for AFB by microscopy and CXR abnormalities consistent with pulmonary TB as determined by a clinician, OR
- A patient with at least one sputum smear positive for AFB by microscopy and sputum culture positive for *M.tuberculosis*.

Smear Negative Tuberculosis

- A patient with at least three sputum smears negative for AFB by microscopy and CXR abnormalities consistent with pulmonary tuberculosis, OR
- A patient whose initial sputum smear was negative for AFB, but whose sputum culture is positive for *M.tuberculosis*.

Nucleic Acid Amplification Testing (NAAT)

Microscopy is rapid but an insensitive test requiring approximately 104 organisms /ml for it to be reliably positive and it is not specific for *Mycobacterium tuberculosis*.

Culture is the most sensitive method for diagnosis, but can take 2-4 weeks to yield a positive result. Microscopy and culture for tuberculosis however, remain the first line tests for TB detection.

Nucleic acid amplification testing is usually laboratory-initiated following consultation with a consultant Clinical Microbiologist. All new smear-positive clinical samples, regardless of specimen origin and clinical presentation are considered for NAAT.

NAAT is very sensitive and can theoretically detect the presence of a single organism but in practice organism load and sample volume come into play to influence its sensitivity. The cut-off threshold for the sensitivity of the test is approximately the same as for microscopy, i.e. ~10^4 AFB/ml.

Automated PCR for TB DNA, and specifically Xpert MTB/RIF (Cepheid GeneXpert system), is routinely used in WA. It is highly sensitive even in single sputum samples that are smear

negative (Boehme et al. 2010) and also reliably detects mutations of the rpoB gene indicating rifampicin resistance. Xpert MTB/RIF (Cepheid GeneXpert system) has a rapid turnaround with a result available 2 hours after sample reception.

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 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 paucibacilliary small volume samples like cerebrospinal fluid or post hoc examination of fixed histological samples. It should not take preference over microscopy and culture for tuberculosis, especially if there is a limited amount of sample.

NAAT should not be used to monitor patients on anti-tuberculosis treatment. Tests may remain positive for an extended period of time regardless of whether DNA or RNA is the target for amplification. 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.

A rapid diagnosis of *M. tuberculosis* is possible using Cepheid GeneXpert, which is a sensitive cartridge-based, automated real time assay that detects MTB and resistance to rifampicin (a surrogate marker for MDR strains) within approximately 2 hours from receipt in the laboratory. The test is available at Royal Perth Hospital, Fiona Stanley Hospital 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 MTB and rifampicin resistance detection at the time of reporting.

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

Chest Radiograph or X-ray (CXR)

Diagnosis of tuberculosis by means of CXR alone is unreliable, because it lacks specificity. Abnormalities seen on a CXR, even when characteristic of pulmonary tuberculosis, 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 is 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.

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).
- “Soft” opacities that fluctuate over time suggest active disease.
- Cavities are usually thin-walled and if present indicate active and infectious disease.

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

Computed Tomography (CT) Scan Chest

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 milary TB and TB exclusively involving mediastinal lymph nodes.

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 latent TB infection, TB disease or past TB infection.

A positive TST result suggests tuberculosis 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.

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 4.1 Paediatrics) or pauci-bacilliary extra-pulmonary TB (e.g. TB meningitis). If TB disease is suspected then additional microbiological testing is needed to confirm a diagnosis.

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 In-Tube Plus test (QIFN) is used in Western Australia. The antigens tested are present in all *M. tuberculosis* but absent from BCG vaccine strains and most non-tuberculous mycobacteria; with the exception of *M. kansasii*, *M. szulgai* and *M. marinum* (Mazurek et al, 2010).

Like the TST, a positive QIFN 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 QIFN test should not replace the standard diagnostic investigations of TB disease.

Compared to the TST, IGRAs have been in use for a short period of time. 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.

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

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 1.1* provides examples of common specimens for mycobacterial investigation according to disease site.

Table 1.1 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
TB meningitis	Cerebrospinal fluid
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 raises the possibility of TB) Renal biopsy Bladder biopsy 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 three consecutive days and early morning samples are preferable. Patients should be advised to collect sputum following deep inspiration and coughing. 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 two 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, therefore it is less expensive.

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 WA TB Control Program located at the Anita Clayton Centre. Induced sputum collection should only be performed by suitably trained physiotherapist or registered nurse, and in accordance with approved standard operating procedures (refer to WA TB Control Program if required).

An audit of the first 2 years of induced sputum collection at the WA TB Control Program 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 pauci-bacilliary and fine needle aspiration can miss the pathology yielding 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 three consecutive mornings and sent for smear AFB microscopy and culture.

Pleural and Other Serosal Membrane TB

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 pauci-bacilliary 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 Abhram'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.

CNS TB

TB involving the CNS, and especially TB meningitis, can be rapidly progressive and a catastrophic illness. Therefore, if CNS TB is strongly 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 pauci-bacilliary 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.

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Chapter 2: Tuberculosis Treatment

2.1 TB Treatment – Medical

Introduction

This chapter describes the drug treatment for TB in adults. Treatment of latent TB infection is described separately in section 3.2. Latent TB Infection - Treatment. The management of TB in children, including drug treatment, is described in section 4.1. Paediatrics. There are also separate sections on the management of TB in specific circumstances such as in prisoners and detainees (section 4.2.), and in pregnancy (section 4.3.).

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 2.2. TB Treatment – Case Management.

Principles of Drug Treatment of TB

Principles that underpin the drug treatment of TB include:

Standardized 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 World Health Organisation (WHO) international agreed strategy for TB control (World Health Organisation, 2017).

Multi-drug Regimens

Single drug therapy 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 latent TB infection (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.

Pre-Treatment Considerations

Assessment prior to TB treatment initiation must include the following considerations (See *Appendix 2.1A: Checklist When Starting TB 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 central nervous system 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 & clothes on. In cases of fluid overload, the patient's 'dry' weight should be used (e.g. in renal dialysis patients the patient's weight *after* dialysis).

Other Drug Treatment

Particular consideration should be given to potential drug interactions with TB drugs, especially with rifampicin. (See *Appendix 2.1B: Drug Interactions with TB treatment*).

Drugs Used to Treat TB

Table 2.1 below shows agents used for the treatment of TB in WA according to drug group. Common abbreviations are shown. The majority (>95%) of TB cases are adequately and most appropriately treated with standard regimens using Group 1 drugs.

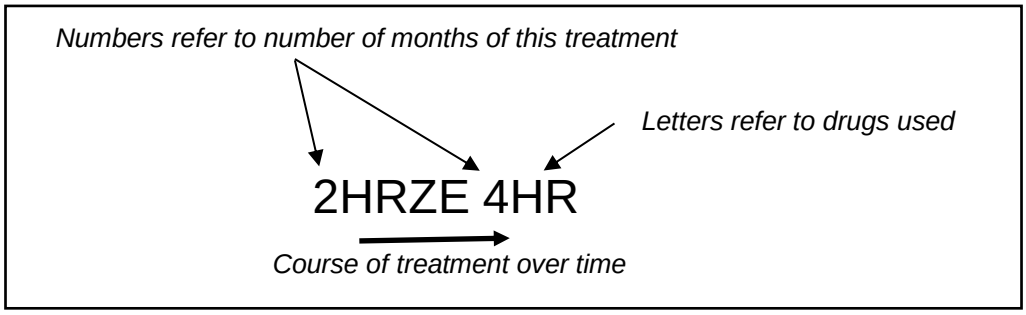
Drugs in Groups 2, 3, 4 and 5 should only be used in the treatment of drug resistant TB or in cases of drug intolerance. Combination regimens are well established but require expert management from a specialist TB physician. Some agents used in the treatment of drug resistant TB are not listed as their use is only appropriate in highly specialised circumstances.

The full name of a medication should be always used when drugs are prescribed in a medication chart. Otherwise, drug abbreviations can be used according to the standard format illustrated in *Figure 2.1*.

Table 2.1 Tuberculosis Drugs

Group	Drug Name	Abbreviation
1	**First line oral agents**	
	Isoniazid (INH)	H
	Rifampicin (RIF)	R
	Pyrazinamide (PZA)	Z
	Ethambutol (EMB)	E
2	**Injectable agents**	
	Capreomycin	Cm
	Amikacin (or Kanamycin)	Am (Km)
3	**Fluoroquinolones**	
	Moxifloxacin	Mfx
	Levofloxacin	Lfx
4	**Second line oral bacteriostatic agents**	
	p-aminosalicyclic acid	PAS
	Cycloserine	Cs
	Prothionamide (or ethionamide)	Pto (Eto)
5	**Drugs of unclear role**	
	Clofazimine	Cfx
	Linezolid	Lzd
	Bedaquiline	Bdq
	Delamanid	Dlm
	Imipenem/cilastatin	Ipm/Cln
	Meropenem	Mpm
	High-dose isoniazid	High dose H
	Clarithromycin	Clr
	Amoxicillin/ clavulanate	Amx/Clv

Figure 2.1 Annotation of TB Drug Regimens



Drug Doses

The recommended doses for drugs in of Group 1 are detailed in Table 3. Doses for drugs in Groups 2, 3, 4 and 5 should be determined by a specialist TB physician on an individual basis. Doses of TB drugs in children are detailed in section 4.1. Paediatrics

It is recommended that daily dosing is used. Thrice weekly treatment is no long recommended in WA based on randomised controlled trials that showed poorer outcomes and current WHO guidelines (WHO, 2017). An exception to this rule is in dialysis patients on TB treatment, which is discussed below.

To assist clinicians, *Table 2.2* gives suggested drug doses based on body weight. This has been adapted from the WHO recommended dosing range of first line anti TB drugs (World Health Organisation, 2017). Adjustment of drug doses in patients with renal impairment is discussed in the following section.

Table 2.2 Tuberculosis Drug Doses

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

Treatment Regimens

The standard treatment regimen for TB is **2HREZ 4HR** (for explanation of abbreviation, see *Figure 2.1 above*). Circumstances when this regimen may be altered are:

Fully Drug Susceptible Isolate of *M. tuberculosis*

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 for ethambutol be omitted on the assumption of drug susceptibility because the majority (>85%) of TB notifications in WA are at risk of drug resistance (>5% chance).

In patients with drug susceptible pulmonary TB, 4-month fluoroquinolone containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen.

Drug Resistance

See section below: *Adjustment of TB Drug Regimen in Drug Resistance or Intolerance*.

Extensive Pulmonary TB

In pulmonary TB involving more than 2 CXR zones and where sputum smears are highly positive for acid-fast bacilli, consideration should be given to extending the treatment course to 9 months (2HREZ 7HR). There is no strong evidence to support this practice, but it is recommended in some guidelines e.g. American Thoracic Society (*Nahid et al., 2016)*

Extra Pulmonary TB

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

- Bone & joint 9 – 12 months
- Central nervous system 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 TB

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 (World Health Organisation, 2017).
- Previous drug resistant TB: consider adding at least two 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 4.4. 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-tuberculosis 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 2.3 below gives 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 2.3 Adjustment of TB 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	25mg/kg, 3x / week in severe renal failure	25mg/kg, 3x / week 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

*Glomerular Filtration Rate

in patients receiving haemodialysis, all drugs should be given intermittently, after dialysis.
Data currently is not available for patients receiving peritoneal dialysis. Until data becomes available, begin with doses recommended for patients receiving haemodialysis and verify adequacy of dosing using serum concentration monitoring.

Pregnancy

No adjustment to TB regimen is required in pregnancy. Dosing is according to pre-pregnancy weight (see section 4.3. TB in Pregnancy).

Infection with *M. bovis*

These organisms are almost always 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 (2HRE7HR) (American Thoracic Society, CDC and Infectious Diseases Society of America, 2017).

Adjuvant Drugs

Pyridoxine (vitamin B6): is 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 Western Australia is pyridoxine 25mg daily.

Prednisolone: is indicated in TB meningitis (prednisolone 1mg/kg or equivalent for 6 – 8 weeks). In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (WHO 2017). 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 or great vein;
- Large abscess formation; or
- In subjects suffering a paradoxical lymph node enlargement on appropriate TB treatment.

Treatment Initiation

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

- Drug chart: each TB drug is prescribed on the TB Control Program Medication Chart, 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 or prothionamide is prescribed.
- Baseline mental state assessment: e.g. Kessler Psychological Distress Scale (K10 or K6) for all TB patient and on regular basis for MDR TB and for others where appropriate.
- 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 WA TB Control Program

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

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 TB 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.

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 commonest 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 aches and pains

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 TB treatment*.

Management of Severe Adverse Drug Effects

Drug(s) suspected of causing the severe adverse effect should be ceased and the regimen adjusted as detailed below. However some adverse effects in TB drug treatment can be due to any of the TB drugs. In this situation it is preferable to stop all treatment 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, moxifloxacin 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:

- 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 the 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:

- Ethambutol optic neuropathy.
- Rifampicin or isoniazid induced thrombocytopenia, acute haemolytic anaemia and acute renal failure.

Rash

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

If the patient complains of itch without a significant rash, mucous membrane involvement or systemic signs such as 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 identified as the offender, eliminating it 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 tuberculosis, 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 suspected when the alanine aminotransferase (ALT) 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 normalized ratio (INR) level 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 tuberculosis treatment after hepatotoxicity is not known. However, most tuberculosis 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).

Adjustment of TB Drug Regimen in Drug Resistance or Intolerance

Table 2.4 is provided as a guide to treatment regimens for mono and poly drug resistance (other than Multidrug Resistant TB) or drug intolerance. Treatment of drug resistant tuberculosis should be guided by a specialist TB physician.

Table 2.4 Drug Regimens in Drug Resistance or Intolerance

Drug resistance	Suggested drugs	Minimum duration (mns)	Comments
H (± S)	R, E, Z & Lfx	6	
H & Z	R,E & Lfx	6 - 9	Use longer duration in extensive disease
H & E	R, Z & Lfx	6 - 9	Use longer duration in extensive disease
R	H, E Mfx + 2mn Z	12 - 18	#Injectable agent may strengthen the regimen in extensive disease
R & E (± S)	H, Z, Mfx + 2-3mn	18	# Use 6mn injectable in extensive disease
R & Z (± S)	H, E, Mfx + 2-3mn	18	# Use 6mn injectable in extensive disease
H, E, Z (+ S)	R, Lfx, + oral second line + 2-3mn	6 - 9	Use 6mn injectable in extensive disease

Adapted from Table 6.1 'Treatment regimens for the management of mono- and poly-resistant TB, WHO 2014

WHO recommends full MDR-TB regimen plus H, but WA TB control program does not consider injectable are mandatory

** Supplement to the WHO treatment guidelines for drug-resistant tuberculosis 2018, the addition of levofloxacin to REZ is recommended in all patients with isoniazid resistant TB, with exception of the following:

- known or suspected resistance to levofloxacin or intolerence
- known or suspected risk for prolonged QTc interval
- pregnancy or during breastfeeding (not an absolute contraindication). In INH resistant TB cases in whom a fluoroquinolone cannot be used, the patient may still be treated with 6(H)REZ

Multidrug Resistant (MDR) and Extensively Drug Resistant (XDR) TB

MDR TB is defined as TB bacteria that are resistant to at least isoniazid and rifampicin. Extensively drug-resistant TB (XDR TB) is resistant to at least isoniazid and rifampicin plus any fluoroquinolone and at least one of three injectable second-line injectable drugs (capreomycin, kanamycin, and amikacin).

MDR and XDR TB should be treated by a specialist TB physician with expertise and experience in treating this form of TB. Drug regimens are designed on an individual basis, according to WHO guidelines and based on drug sensitivities. An MDR regimen must include at least 5 active agents included in the intensive phase, one chosen from groups A and B and at least 2 from group C with the remainder made up from group D – see *Table 2.5* below (World Health Organisation, 2016). If diagnostic specimens are culture negative, then susceptibility results of the index case should guide treatment.

New recommendations for prioritization of candidate drugs in the treatment of MDR and XDR TB outlined in the WHO rapid communication (World Health Organisation, 2018) have not been adopted by the WATBCP at this stage, but will be considered once the final guidelines are released.

Design of MDR and XDR TB drug regimens and monitoring of response to treatment should be done in consultation with other specialist TB physicians at regular case management

meetings. Hospitalisation is usually required for the initiation of MDR and XDR TB treatment to ensure infection control and to manage early adverse effects.

Table 2.5 Anti-tuberculosis Drugs used in MDR TB

Group A: Fluoroquinolones	Group B: Second line injectables	Group C: other core second line agents	Group D: Add on Agents (not part of the core MDR-TB regiment)
Moxifloxacin	Amikacin	Ethionamide	Pyrazinamide (D1)
		Prothionamide	Ethambutol (D1)
		Cycloserine	High dose Isoniazid (D1)
		Linezolid	Bedaquiline (D2)
		Clofazamine	Delamanid (D2)
			p-aminosalicylic acid (PAS) (D3)
			Imipenem (D3)
			Meropenem (D3)
			Amoxicillin-clavulanate (D3)

* **D1 drugs followed by D2 and D3 in order of preference.**

Importantly, the index and the index's family doctor must be made aware of the seriousness of MDR-TB and the need to assess the contact for TB disease whenever that contact presents with symptoms suggestive of TB.

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. 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 WA TB Control Program 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 TB

Treatment of bone, joint, and spinal tuberculosis require 6-9 month regimens containing rifampicin. Some experts favour the 9-month duration. Trials found no additional benefit from surgical debridement in addition to anti TB treatment alone for spinal tuberculosis.

Uncomplicated cases of spinal tuberculosis are managed with medical rather than surgical treatment.

Surgery can be considered in situations where:

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

Renal Disease

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 2.3 Adjustment of TB Treatment in Renal Failure*).

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 (ie, 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 and to avoid clearance of drugs such as pyrazinamide during haemodialysis. (Nahid et al., 2016, WHO, 2010).

Appendix 2.1 *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.
☐	**Mental State Assessment**	Kessler Psychological Distress Scale (K10 or K6)
☐	**Medication Chart**	Chart drugs using full generic name.
☐	**TB Notification & TB Enhanced Surveillance Form.**	
☐	**Vision**	Check baseline visual acuity & colour vision if starting ethambutol.
☐	**TB Case Manager**	Inform.

Appendix 2.2 *Drug Interactions with TB Treatment*

This is a list of the most common and important drug interactions. It only includes Group 1 drugs. Always check for drug interactions in product information

Drug	TB Drug	Interaction	Action
Alcohol	H, R	↑ hepatotoxicity ↑ metabolism H	Minimize or avoid alcohol
Allopurinol	Z	↓ uric acid clearance	Adjust anti-gout treatment
Antacids	H, R, E	Reduced absorption	Avoid co-administration
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
ß 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

Drug	TB Drug	Interaction	Action
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
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.

Drug	TB Drug	Interaction	Action
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 co-administration
Simvastatin	R	↑ metabolism	May need increased dose or alternate agent
Sulfasalazine	R	↑ metabolism	Watch for reduced efficacy
Sulphonyureas	R	↑ metabolism	Intensify BSL monitoring & adjust diabetic Rx
Tacrolimus	R	↑ metabolism	Consider alternate to R, monitor levels
Tamoxifen	R	↑ metabolism	Consider alternate agents

Drug	TB Drug	Interaction	Action
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
Trimethroprim	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 Vit. D
Warfarin	H	↓ metabolism	Monitor INR at start & finish of INH
Warfarin	R	↑ metabolism	Monitor INR at start & finish of RIF

Appendix 2.3 Recommended Routine Tests During Treatment of TB Disease.

Baseline blood tests:	Full blood count, liver function tests, urea and electrolytes, HIV serology.
Baseline other:	Mental health assessment (K10), 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 x2 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
2 - 6 months:	Sputum x2 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 CXR (if initial CXR abnormal) 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 tuberculosis)

2.2 TB Treatment – Case Management

Introduction

Case management involves the 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. In the treatment of TB it is never optimal to prescribe drug therapy alone. The prescription must always be accompanied by case management.

Rationale

The successful treatment and cure of TB requires a large number of medications to be taken for extended periods of time. This is a difficult undertaking and adherence to prescribed drug regimens can be further hampered by the stigma and sometimes immigration VISA implications associated with a TB diagnosis. Patients may also not want to continue treatment once symptoms resolve. Many patients are recently arrived migrants with limited English and poor understanding of TB and TB treatments, and side effects from medications can also lead to poor adherence. Some well informed and well-intentioned, but busy people with competing priorities can also have problems with adherence.

Patients who are left to take TB treatment unsupervised are therefore likely not to adhere to the treatment prescribed. Case management primarily ensures the successful completion of TB treatment but it is also required as a public health measure to reduce TB transmission and the development of drug resistance caused by poor adherence.

Contact tracing aims to further reduce TB disease by diagnosing secondary TB cases early, and identifying and treating latent TB infection.

All patients undergoing treatment for TB and latent TB infection in Western Australia have a case manager at the WA TB Control Program. 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.

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

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, networking and communication with hospital-based and private physicians; and infection control practitioners to ensure the early identification of patients with tuberculosis.

Coordination of timely contact tracing (see section 5.1. Contact Tracing) is required to detect cases of tuberculosis related to the index case, to detect and treat latent tuberculosis infection (LTBI) 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 un-identified source index case (cohort effect).

Assessment

The assessment involves gathering of information about the patient's disease and social circumstances to assist with the planning of TB treatment. Information should be gathered from the patient, 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 whether that occurs in an outpatient setting or in hospital. It may take place at the first clinic appointment or at the first home visit by the case manager. During the assessment phase the case manager should aim to assess and document the following:

- Previous medical history.
- Medication lists.
- Determine the period of potential infectiousness which will then guide contact tracing activities.
- Evaluate the patient's knowledge and beliefs about TB.
- Assess TB medication regimen prescribed.
- Identify barriers to treatment adherence e.g. difficulty swallowing tablets, transportation problems to attend appointments, issues that may require directly observed therapy.
- Develop an understanding of the patient's social circumstances that might impact on completion of treatment i.e. living arrangements, housing issues, employment, education, residency status, welfare issues, cultural background and presence of any drug or alcohol misuse.
- Collect and record surveillance data as a requirement for statutory medical notifications. Enhanced surveillance TB data is forwarded to the Health Department.

Patient assessment should continue throughout treatment in order to detect changes to the patient's circumstances that may affect treatment compliance e.g. social issues, communication and language difficulties, transport problems, medication side effects or interactions, travel plans etc.

Care Planning

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

provision. The plan should be developed in consultation with the patient and their medical team and it needs to be flexible to accommodate the patient's individual situation and may change depending on treatment progress.

Case Management Meeting

The WA TB Control Program regularly reviews the care of TB cases. The purpose of these meetings is to document new TB cases, discuss issues that may be a barrier to successful TB treatment completion, discuss the extent of contact tracing, and ensure that clinical outcomes are achieved.

Care Coordination

The case manager should act as the central point of contact for the TB patient for the duration of their treatment. The case manager is the coordinator of care and primary source of support for the patient and should be in continuous communication with the patient (via telephone, home visits or clinic attendances) throughout the treatment duration. Care coordination for drug sensitive uncomplicated TB can be structured as given in *Table 2.6*.

For extended TB treatment and MDR TB treatment, coordination follows the same structure for the duration of the treatment.

Table 2.6 Structure for Care Coordination in Uncomplicated TB Management

Diagnostic Assessment	Initial medical assessment and relevant investigations
Start of Treatment	Clinic visit – Seen by 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
Two weeks	Clinic visit – physician and case manager, supply one month's medications
Four to Six weeks	Clinic visit – physician and case manager
Two months	Clinic visit – physician and case manager – sensitivities reviewed, treatment changed from intensive to continuation phase, supply one month's medications
Three months	Clinic visit – physician and case manager, supply one month's medications
Four months	Clinic visit – physician and case manager, supply one month's medications
Five months	Clinic visit – physician and case manager, supply one month's medications
Six months	Clinic visit – physician and case manager – treatment ceased and outcome reported

Medication Management

An essential part of successful TB treatment is the completion of therapy. Case managers are essential to monitor adherence to prescribed medications, to support the patient through medication side-effects, and to identify and address promptly any barriers to medication adherence. The treatment can be either 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 to ensure that patients have an adequate and ongoing supply of TB medications including patients living in rural and remote areas. Drugs are dispensed via the WA TB Control Program, and can be sent via courier to remote and rural areas. Patients treated by physicians outside the WA TB Control Program can, and usually will, also receive their medications via the WA TB Control Program.

Patients Requiring First Line TB Treatment Regimens

The first line TB drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) are available and supplied by the WA TB Control Program. Moxifloxacin and adjuvant agents such as pyridoxine and prednisolone may also be supplied by the WA TB Control Program. When pyrazinamide is prescribed, medical staff must complete a Category C Special Access Scheme (SAS) form, which is then faxed or emailed to the TGA.

Patients Requiring Injectable or Non-First Line Oral Drugs

Injectable drugs and other non-first line oral TB drugs are usually obtained from Royal Perth (RPH) Hospital Outpatient Pharmacy with a RPH pharmacy prescription. Non-first line agents often require SAS approval. Medical staff must complete a Category A SAS form to ensure timely commencement of treatment and a Category B SAS form to ensure ongoing supply of the medication. The Category B SAS form needs to be renewed every12 months if the drug is continued. Patients requiring injectable drugs are initially hospitalised to establish treatment and once discharged, intravenous administration is arranged via an ambulatory service such as Silver Chain Hospital in the Home.

The WA TB Control Program provides all medications at no cost to the patient.

Non-Adherence and Directly Observed Therapy (DOT)

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

Adherence should be checked regularly by directly questioning patients, pill counts and prompt contact whenever a patient does not attend planned appointments. 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.

Directly observed therapy (DOT) 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.

DOT involves observing the patient swallow every dose of treatment.

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 case managers. The DOT is most commonly provided by the case manager, but with consent from the patient can be provided by a community nurse or service, local doctor, local pharmacist, correctional staff or hospital staff. The external DOT providers should be given information and instruction on DOT and a Directly Observed Therapy Log sheet (see *Appendix 2.4*). The log should be returned to the WA TB Control Program on a monthly basis. 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 should complete a Directly Observed Therapy Agreement (see *Appendix 2.5*) that clearly states the agreed time and location for DOT and includes the public health implications of not taking the treatment as prescribed. The contract should be added to the patient's records and the original given to the patient. The 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; however, this may not be possible for all patients. Community based DOT can be provided more efficiently by establishing partnerships with community based services.

The WA TB Control Program advocates for daily DOT especially during the intensive phase of treatment. It is common practice for some patients to self-administer medications on the weekends and send an SMS message to a designated number. Virtually observed therapy via internet based programs (TeleDOT) can be adopted for some patients.

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 make 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 make a test order in respect of a person where 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 can assist clients to take treatment and attend appointments by overcoming barriers such as transportation issues.

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 may:

- 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;

- Provide education on navigating the healthcare system and services to contact regarding non-urgent issues.

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 and friends regarding the nature of tuberculosis and its treatment.

The main advocacy of the case manager on behalf of the patient is with the patient's treating physician. This is especially important if the physician works outside the WA TB Control Program. The case manager ensures the physician is aware of difficulties or non-adherence with treatment, assists with patient's understanding and compliance with the physician's treatment recommendations.

When TB treatment is prescribed by a physician outside the WA TB Control Program 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 TB Control Program who will discuss the issues with the treating physician.

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. Being diagnosed with TB and the social stigma associated with the diagnosis can be a source of great distress for the patient. The case manager has an important role to help them through this difficult time. The aim of case management beyond the successful treatment of TB is to rehabilitate the patient to full pre-morbid health and function.

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 records.

Monitoring and Review

The case manager needs to determine if a patient is receiving and adherent with appropriate 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 the course of 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 for simple information e.g. confirming appointments, and not for collecting of personal medical details or conveying of medical advice. All contact with patients and other care providers should be recorded in the patient's record.

Home visiting: can be carried out 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 with patients on TB treatment a monthly basis, whether it be at home or in the clinic.

Case Closure

The process for discharge of patients from case management or 'case-closure' should be clear and defined in time. The aim for case management for tuberculosis should be the successful completion of medical treatment. The decision to discharge a patient should be determined by the case manager and the treating physician.

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 or the patient had extensive disease. The decision on follow up and case closure is made by the treating physician and the case manager.

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Appendix 2.4 Directly Observed Therapy (DOT) Log

WESTERN AUSTRALIAN TUBERCULOSIS CONTROL PROGRAM Directly Observed Therapy Log Chart No ..... of	DOT Month:	Case Manager:	Case Manager Phone:	REGION:
Adverse Drug Reaction Label	PATIENT DETAILS UMRN First Name Given Name DOB Sex: M F	DOT Start Date:	DOT Expected Completion Date:	
		DOT Site: ☐ Home ☐ Work ☐ Clinic ☐ Pharmacy ☐ Other:_____ If Work/ Pharmacy/ Other Details: Name: Contact Details:		
	Patient Contact Details HOME: WORK: MOBILE:	PPE Required? ☐ Yes ☐ No Details: Location		

Day of Month	Time DOT observed	DOT OBSERVED SIGNATURE / SELF TICK		COMMENTS Please note any side effects E.g. Abdominal discomfort rash/itch, visual disturbance, changes to appetite, fatigue. Joint pain	Case Manager notified of adverse reaction?	Day of Month	Time DOT observed	DOT OBSERVED SIGNATURE / SELF TICK		COMMENTS Please note any side effects E.g. Abdominal discomfort rash/itch, visual disturbance, changes to appetite, fatigue. Joint pain	Case Manager notified of adverse reaction?
1			☐ Self		☐Yes ☐No	17			☐ Self		☐Yes ☐No
2			☐ Self		☐Yes ☐No	18			☐ Self		☐Yes ☐No
3			☐ Self		☐Yes ☐No	19			☐ Self		☐Yes ☐No
4			☐ Self		☐Yes ☐No	20			☐ Self		☐Yes ☐No
5			☐ Self		☐Yes ☐No	21			☐ Self		☐Yes ☐No
6			☐ Self		☐Yes ☐No	22			☐ Self		☐Yes ☐No
7			☐ Self		☐Yes ☐No	23			☐ Self		☐Yes ☐No
8			☐ Self		☐Yes ☐No	24			☐ Self		☐Yes ☐No
9			☐ Self		☐Yes ☐No	25			☐ Self		☐Yes ☐No
10			☐ Self		☐Yes ☐No	26			☐ Self		☐Yes ☐No
11			☐ Self		☐Yes ☐No	27			☐ Self		☐Yes ☐No
12			☐ Self		☐Yes ☐No	28			☐ Self		☐Yes ☐No
13			☐ Self		☐Yes ☐No	29			☐ Self		☐Yes ☐No
14			☐ Self		☐Yes ☐No	30			☐ Self		☐Yes ☐No
15			☐ Self		☐Yes ☐No	31			☐ Self		☐Yes ☐No

Appendix 2.5 Directly Observed Therapy (DOT) Agreement

WA Tuberculosis Control Program Directly Observed Therapy Agreement

(Please note- MEDTECH DOCUMENT Active Tuberculosis (TB) Disease)

Patient Name:……

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.

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

The nurse will come to my home or I will attend the …… between……hours so I can take my medicine. The nurse will come to my home on the following days:

Monday Tuesday Wednesday Thursday Friday

Saturday Sunday

If I am required to take my medication unsupervised I will take my medication at the following time …… and then send a SMS message to the following phone……..

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.

TB Nurse Signature ……Date……

Patient / Guardian Signature…… Date……

Interpreter Signature…….....Date……

Copy for patient and Scan to notes

Chapter 3: Latent Tuberculosis Infection

3.1 Latent TB Infection – Diagnosis

Introduction

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

Following infection, the lifetime risk of TB disease is estimated at 5%-10% with the majority of cases occurring within 5 years of initial infection (Northern Territory Centre for Disease Control, 2016).

Rationale for Testing for LTBI

The majority of TB notifications in Australia are in the overseas-born population (92% of 2016 cases in Western Australia). This combined with evidence of low local transmission indicates that most of TB cases in Australia are the result of reactivation of LTBI acquired prior to immigration to Australia. (Stock & NTAC, 2017; Tuberculosis notifications in Western Australia, 2016). This highlights the importance of detecting and treating LTBI in high risk populations as a fundamental strategy in TB control to achieve the goal of TB elimination.

Indications for LTBI Testing

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

Risk Factors for High Pre-test Probability of TB 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, in countries that have a high incidence of TB (>40/100 000 per year (e.g. Africa, Asia). For country based tuberculosis incidence refer to the WHO website https://www.who.int/tb/country/data/profiles/en/index.html (World Health Organisation 2018).
- LTBI testing should be prioritised for recent arrivals (within 5 years) and those individuals staying permanently especially:
    - Migrants (from any country) with a history of TB contact within the last 2 years or
    - Migrants from countries with a high incidence of TB as stated above, aged 35 or under; or aged over 35 with one or more risk factors for reactivation (see next section)
- Certain occupational groups or residential settings (*Table 3.1*).

Table 3.1 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 correctional facilities and detention centres
Mycobacteriology laboratory personnell and mortuary staff performing autopsies

Risk Factors for Progression of LTBI to TB Disease

Once infected with MTB the majority of 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 MTB (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 (*Table 3.2*).

Table 3.2 Co-morbid Conditions that Increase the Risk of TB Disease.

Co-morbid conditions that increase the risk of developing TB disease.
HIV infection
Immunosuppressive therapy such as anti-tumour necrosis factor alpha (TNFα), post organ transplantation immunosuppressant therapy and immunosuppressant therapy equivalent to prednisolone 15mg/day for > 1 month
Silicosis
Chronic renal failure and haemodialysis
Leukemia or lymphoma
Cancers of the head, neck or lung
Individuals who have had gastrectomy or jejunoileal bypass

Tests for Latent Tuberculosis Infection

The screening tests available for LTBI in Western Australia are:

- Tuberculin skin test (TST), also called Mantoux test.
- QuantiFERON-TB Gold Plus Test (QIFN).

Both tests are indirect and reflect cellular immune response to previous sensitisation with mycobacterial antigens and cannot distinguish between individuals with LTBI, TB disease or past TB infection.

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

The result of either TST or QIFN 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 LTBI can be made on the basis of a positive screening test.

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

Both TST and QIFN are acceptable for the diagnosis of LTBI (WHO. 2018, Stock & NTAC, 2017), therefore either test can be used, except in the following two circumstances:

- Screening of household contacts: testing performed immediately and if negative, repeated after 8 – 12 weeks.
- Serial surveillance testing of health care workers with high probability of TB exposure.

In both of these circumstances a TST conversion as well as a positive result are indications for LTBI treatment (see below- *Interpretation of the TST*).

Tuberculin Skin Test (TST)

The TST has been used in the management of tuberculosis since the 19th century. The form of tuberculin used in Western Australia is 'Tubersol', a tuberculin purified protein derivative (PPD), which is a protein derived from cultures of MTB. 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 MTB, a hypersensitivity reaction occurs at the injection site. It is this hypersensitivity reaction that is measured. A dose of 5 International Units of human PPD in 0.1ml is used.

Indication for TST

(See section above *Indications for LTBI 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 MMR, varicella or yellow fever vaccines within the last month as the risk of a false negative result increases (Department of Health New South Wales, 2009)
- 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 appropriately trained and accredited to administer and interpret the TST. A dose of 5 International Units of human PPD in 0.1ml is injected intra-dermally. 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. The measurement should be in mm, 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 3.3*) 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 3.3 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 (American Thoracic Society, 2000; Department of Health New South Wales, 2009).

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 QIFN 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 MTB infection are (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 MTB infection are (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 non-tuberculous mycobacteria.
- 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 of health care workers 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, or
- An increase of 5mm in the TST diameter (Menzies, 1999).

TST conversion indicates the development of a hypersensitivity reaction to infection with MTB or non-tuberculous mycobacteria, 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.

Interferon Gamma Release Assays (IGRAs)

Interferon gamma release assays (IGRAs) are blood tests that detect cell mediated immune responses to TB specific antigens secreted by MTB. The QuantiFERON-TB Gold Plus test is used in Western Australia. This test measures the gamma interferon secretion by T cells in response to in-vitro exposure to TB specific antigens. These antigens are present in all MTB but are absent from BCG vaccine strains and most non tuberculous mycobacteria with the exception of *M.kansasi, M.szulgai and M.marinum*.

The QIFN test should not replace the standard diagnostic investigations of TB disease (See section *1.1. Diagnosis of Tuberculosis – Laboratory*). A positive QIFN may not indicate disease and a negative result does not rule out disease.

Table 3.4 Advantages and Disadvantages of TST versus QFT-Plus

	Tuberculin Skin Test	QuantiFERON-TB Gold In-Tube test
Advantages	Has been used for >100 years and its 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 In-Tube 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. There is limited data available on the use of IGRAs in immunocompromised patients, children and populations from TB endemic countries (Mazurek et al, 2010; Denkinger et al 2011). 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).

Selection of LTBI Test

The selection of test(s) for the investigation of LTBI infection should take into account 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 QIFN specimens need to reach the laboratory in Perth within 16 hours of collection).

3.2 Latent TB Infection - Treatment

Introduction

The treatment of LTBI, also known as preventive therapy reduces the risk of developing TB by up to 90%. (WHO, 2018; Northern Territory Centre for Disease Control, 2016). One person can be prevented from developing TB for every 35 people taking isoniazid for six months (Smeja, Marchetti, Cook, & Smail, 1999).

Rationale for LTBI Treatment

The rationale for treating LTBI is to kill dormant bacilli in order to prevent later reactivation and consequent TB disease. Treatment for LTBI can either be (NICE, 2011):

- 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, exposed to tuberculosis
- Secondary: treatment after latent infection has occurred.

Indications for LTBI Treatment

The decision to treat LTBI 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.

Precautions for LTBI Treatment

Caution should be exercised in prescribing preventive therapy 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 group.

Although isoniazid hepatotoxicity increases with age and underlying disease, most international guidelines recommend no absolute age limit for treatment of LTBI because the risk of severe or fatal hepatotoxicity is considered low, with an acceptable risk-benefit ratio even in those aged over 35. (NICE, 2016; Long & Ellis, 2007, 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 (Canadian Tuberculosis Standards, 2014).

In pregnant women treatment can be delayed until after delivery unless there is a high risk of progression to TB disease (see section *4.3. TB in Pregnancy*).

These are not absolute contraindications to preventive therapy 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.

Contraindications for LTBI Treatment

Preventive therapy is *not* recommended in:

- Patients with a history of previously completed treatment for TB.
- Previously completed treatment for LTBI. CXR follow up for 2 years is preferred in this group.
- Suspicion of TB disease.

Primary Preventive Therapy

Individuals at high risk of developing primary TB infection following exposure to an infectious case require special consideration. Commencement of preventive treatment immediately following the exposure to prevent the development of primary TB infection 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).

Pre-Treatment Investigations

Treatment of LTBI 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 therapy:

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 acid-fast bacilli examination are required and preventive therapy 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 prior history of previous completed TB treatment.

Baseline blood tests

Liver function tests (LFT) 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 therapy, with further testing after this as indicated (e.g. abnormal baseline LFTs, high risk of hepatotoxicity, advanced age).

Treatment Regimens

The doses for drugs used in preventive therapy are given in *Table 3.5*

Table 3.5 Doses of Drugs Used in Treatment of Latent TB Infection

Drug	Dose
Isoniazid	> 40kg body weight: 300mg daily
	≤ 40kg body weight: 5mg/kg daily
Rifampicin	≥ 50kg body weight: 600mg daily
	< 50kg body weight: 450mg daily NB. Rifampicin 450mg is preferably given as 3 x 150mg capsules.

The regimens used at the WA TB Control Program are given 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 making include:

Length of treatment

Pill burden

Potential adverse effects

Drug interactions

Risk of inadvertent monotherapy in TB

Isoniazid Monotherapy (6H)

Single agent isoniazid has been used to treat LTBI for at least 35 years (Smeja et al, 1999). In most instances isoniazid monotherapy for 6 months is adequate treatment for LTBI 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 out-weighed by the poorer adherence associated with prolonged length of treatment. There is also a small increased risk of hepatic toxicity.

Rifampicin Monotherapy (4R)

Recent evidence supports a four month course of rifampicin monotherapy. This treatment has equivalent efficacy to 9 months isoniazid (Menzies et al, 2018). It is also the recommended treatment option for individuals who are known contacts of patients with TB resistant to isoniazid, and for patients intolerant of isoniazid e.g. hepatic toxicity. Rifampicin should be used with caution in HIV- infected individuals on certain antiretroviral drugs and joint management with an HIV specialist is essential.

Combination Therapy (3HR)

Combination therapy with rifampicin and isoniazid for three months (3HR) has been shown to be equivalent to isoniazid monotherapy in terms of effectiveness and safety (National Institute for Health and Clinical Excellence (NICE, 2016; 20. Zenner et al, 2017).

Weekly Combination Therapy (3HP)

A short-course combination regimen of once-weekly isoniazid and rifapentine for 12 weeks (3HP) is another acceptable regimen for LTBI treatment. This regimen is not currently available at the WATB Control Program but may be offered in the future.

This combination treatment was shown in an open-label study (CDC, 2011) as non-inferior to 9 months of daily isoniazid treatment for LTBI. CDC recommends 3HP by either DOT or self-administered therapy for the treatment of LTBI in adults, children aged 2–17 years and for HIV positive patients on antiretroviral medications with acceptable drug-drug interactions with rifapentine (Borisov et al, 2018).

Notwithstanding this advice, the WATB Control Program recommends that weekly preventive therapy should be given with supervision e.g. SMS reminders and Webster packing.

Drug Side Effects

Side effects of isoniazid and rifampicin are presented in details in section *2.1. TB Treatment - Medical*.

Pyridoxine Administration

Pyridoxine at a dose of 25mg daily should be given concurrently to persons on isonaizid who 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 or for individuals on preventive therapy.

Special Treatment Groups

HIV Co-Infection

Co-infection with HIV increases the lifetime risk of progression of LTBI to TB disease from 5-10% in non-HIV infected individuals to a 10% annual risk in HIV positive individuals (World Health Organisation, 2018). Preventive treatment needs to be extended to 9 months. Isoniazid monotherapy is the preferred treatment regimen and pyridoxine 25mg daily should be prescribed concurrently. For further details on TB in HIV-affected individuals see section *4.4. HIV Co-infection*.

Pregnancy

The preferred regimen in pregnancy is isoniazid 300mg daily for 6 months with pyridoxine 25mg 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 LTBI 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 LTBI.

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 4.1. Paediatrics and 4.3 TB in Pregnancy.

Isoniazid resistance

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

Multidrug resistant TB (MDR-TB)

Contacts of MDR-TB can and should be given preventive therapy 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 MTB isolate of the index case. Consultation with a specialist physician experienced in TB management should be sought. (WHO, 2018; Stock & NTAC, 2017)

Preventive Therapy Not Given: Refusal or Otherwise

Patients who are eligible for treatment of LTBI 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 above *Indications for LTBI Testing*).

Clinic Management and Follow up

Follow up at the WA TB Control Program is essential to ensure adherence and to manage any 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 therapy. More frequent biochemistry should be considered in HIV-infected individuals, pregnant women or women within three 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 there have been concerns with adherence.

Treatment Completion

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

Table 3.6 Criteria for Completion of Treatment of Latent TB Infection

Treatment Regimen	Criteria for Completion
6 months daily isoniazid	180 doses within 8 months
4 months daily rifampicin	120 doses within 6 months
9 months daily isoniazid	270 doses within 12 months

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

Follow-up after LTBI 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 LTBI 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 LTBI therapy or

in immunocompromised individuals (e.g.HIV-infected, children < 5 years); then it is prudent to recommend a full course of LTBI therapy (Canadian Tuberculosis Standards, 2014).

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Chapter 4: Tuberculosis in Special Populations

4.1 Paediatrics

Introduction

The basic principles for the diagnosis, treatment and prevention of TB in adults discussed in other chapters apply to children and adolescents. Please refer to those sections for details of TB management in children and adolescents.

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

Clinical, diagnostic and management differences between TB in children and TB in adolescents and adults are:

- Children are at higher risk of TB disease following primary infection compared with adults, especially the 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 paucibacilliary 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 cavitatory disease, is similar to adults.
- TB disease in children usually occurs within 12 months of infection. Paediatric tuberculosis is an indicator of recent transmission in the community.
- The majority of children are infected by a household index case, usually one of the parents, but extended family members and any other caregivers should also be considered as the possible source.

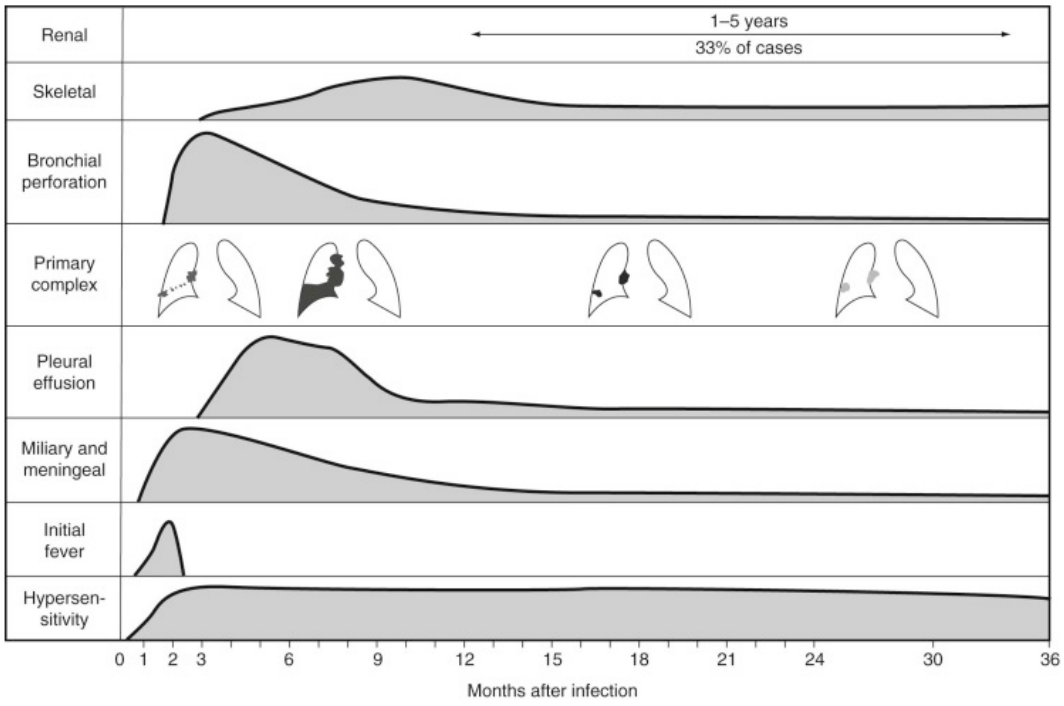
Presentation of Tuberculosis

The type of TB disease in children is dependent on the effectiveness of the immune response to contain a recent *Mycobacterium tuberculosis* infection. The immune response improves with age as the immune system matures (Graham, Marais, & Gie, 2009). Therefore, infants and younger children are at higher risk of developing TB disease and more severe disease (TB meningitis and disseminated disease) after primary infection. The majority of disease manifestations occur in the first 6-12 months following primary infection (Marais and Donald, 2009).

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

The majority of children infected with MTB do not develop disease.

Figure 4.1 Timetable of TB Infection in Children and Adolescents.



Source: Cruz, T., and Starke, J. Tuberculosis. In Feigin and Cherry's Textbook of Pediatric Infectious Diseases Seventh edition. Elsevier, 2014.

Symptoms and Signs of TB

Early in the disease, the majority of 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 unable to express their symptoms, and respiratory specimens for examination are difficult to obtain from young children. 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 (Marais, Wright, Gie et al, 2006; Marais, Gie, Schaaf et al, 2006):

Common symptoms

- A persistent non-remitting cough, more often non-productive,> 2 weeks' duration. Failure to resolve completely with standard antibiotic therapy increases the suspicion.
- Weight loss or failure to thrive.
- Reduced playfulness or increased tiredness.
- Enlarged, non-tender cervical lymph nodes (> 2cm x 2cm) with/without overlying skin changes or fistulae.

Less common symptoms

- Respiratory distress (uncommon and more likely in neonates and infants).
- Haemoptysis (uncommon and more likely in older children and adolescents).
- Unexplained and persistent fever.

- Excessive night sweats.
- Lethargy, headache, irritability +/- progressive neurological signs (suggestive of TB 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). Data available at use https://www.who.int/tb/country/data/profiles/en/ or http://www.who.int/tb/publications/global_report/gtbr2017_annex2.pdf?ua=1.

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 TB meningitis or military TB is highest in infancy (see *Table 4.1*).

Table 4.1 Age-Specific Risk for TB Development 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%
	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

(Marais, Gie, Schaaf et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era, 2004)

Differential Diagnosis

The differential diagnosis for tuberculosis is broad. Useful investigations to consider when there is uncertainty include bronchoalveolar lavage. Discussion with a paediatric infectious diseases specialist and/or clinical microbiologist is recommended.

Investigations for Tuberculosis

Direct microscopy for acid fast bacilli, culture and nucleic acid amplification testing of clinical specimens are the first line investigations for tuberculosis. As treatment for TB is prolonged, complex and with the potential for drug side effects, diagnostic specimens should be collected on all children before treatment is initiated. Culture is also important because drug susceptibility testing for *M. tuberculosis* isolates ensures the appropriateness of treatment.

Due to the paucibacillary nature of TB in children, mycobacterial culture is frequently negative even in the presence of TB disease. Given this, diagnosis should be based on clinical and/or radiological signs of TB. A history of contact with tuberculosis and/or results of tests indicating previous *M. tuberculosis* infection (e.g. TST or IGRA test) may assist in the diagnosis but also may be absent.

Microscopy and Culture of Respiratory Specimens

Microscopy and culture of respiratory specimens is the most reliable and cost effective method of diagnosing infectious cases of pulmonary tuberculosis. The optimal method of specimen collection in children depends on the age, location and skill of the available staff. Appropriate respiratory specimens in children include:

Three Induced Sputum Samples:

Inpatients at Perth Children's Hospital:

These can be organised with the assistance of the physiotherapy team, who are able to perform induced sputum in children >3 months of age after a period of fasting. Pre-treatment with inhaled bronchodilators (to protect against bronchospasm) and hypertonic saline (to encourage sputum expectoration) should be given as follows:

- Salbutamol: 6 puffs x100mcg (<6 years) or 12 puffs x100mcg (≥6 years) via spacer OR 2.5mg neb (<6 years) or 5mg neb (≥6 years)
- 6% Hypertonic saline neb (10mLs)

Outpatients at the Anita Clayton Centre:

The paediatric team may be asked to oversee the nursing staff inducing sputum in the negative pressure room at the WATB Control Program located at the Anita Clayton Centre. The above medications need to be charted for this to occur.

Three Early Morning Gastric Aspirates:

In infants, consecutive early morning gastric aspirates obtained via a nasogastric or orogastric tube is frequently performed.

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 but can be performed by visiting nurses (e.g. Hospital in the Home).

Three Expectorated Sputum Samples:

In older children productive of sputum, expectorated sputum samples can be obtained.

Bronchoalveolar Lavage (BAL) Sample:

BAL samples may be indicated in specific situations however should be performed by an experienced operator with appropriate infection control precautions. Given the increased risk of TB exposure to the operator, BAL should only be considered if a respiratory sample cannot be obtained by an alternative method.

Getting at least three respiratory specimens using any combination of the most feasible options available is recommended. Primary TB infection in young children is often paucibacillary and so the yield from microscopy and culture for acid-fast bacilli is low even when samples are available for examination. A negative culture should not be used to exclude TB in a child.

Direct Nucleic Acid Amplification Testing (NAAT)

For detail on laboratory methods of diagnosing tuberculosis see section 1.1. *Diagnosis of Tuberculosis - Laboratory*.

Chest X-ray (CXR)

CXR is useful in the diagnosis of pulmonary tuberculosis 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 coexist. A lateral CXR may be useful, but should not routinely be performed given the significant increase in radiation exposure.

CXR appearances suggestive of pulmonary tuberculosis 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).
- Cavitatory disease 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.

Chest CT (HRCT)

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

Tuberculin Skin Test (TST) and Interferon Gamma Release Immunoassays (IGRAs)

Information on TST and IGRAs is provided in section *3.1. Latent TB Infection - Diagnosis*.

Other Diagnostic Tests

The diagnosis of extrapulmonary tuberculosis 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, GeneXpert and microscopy/culture and if positive, arrangement of neuro-imaging. Abdominal USS in infants <1 year is also recommended to exclude disseminated TB.

An HIV test should be performed in all children with TB and considered in those with suspected TB.

Tuberculosis Disease

The main objectives of anti-TB treatment in children and adolescents are 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.

Standard Treatment of TB in Children and Adolescents

Standard therapy for TB in children and adolescents uses the same drugs as in adults. Combination regimens are used and treatment is divided into an intensive phase to rapidly eliminate the majority of organisms and prevent drug resistance, followed by a continuation phase using a lesser number of drugs to eradicate dormant organisms.

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). A basic regimen of 6 months of isoniazid (H) and rifampicin ® with pyrazinamide (Z) added in the first 2 months intensive phase cures over 99% of cases of drug susceptible pulmonary TB in children (Starke, 2004).

First line treatment regimens for TB in children are given in *Table 4.2*.

Table 4.2 Treatment Regimens for Children Recommended by WHO

TB Disease	Intensive Phase	Continuation Phase
Pulmonary TB or TB lymphadenitis and HIV negative	2HRZ	4HR
Extensive pulmonary disease	2HRZE	4HR
Pulmonary TB and HIV positive	2HRZE	4HR
TB meningitis*	2HRZE	10HR
Osteoarticular TB	2HRZE	10HR
MDR-TB	An individually constructed regimen based on known resistance and with agents from all classes (see section below).	

*In addition to anti-tuberculous therapy, treat TB meningitis or pericarditis with corticosteroids.

The WHO recommends the following dosages of anti-tuberculosis medicines in children (World Health Organisation, 2017; World Health Organisation, 2014; Graham S., 2011):

Table 4.3 WHO Dosages of Anti-Tuberculous Medication for Children

Anti-TB Medicine	Dosage
Isoniazid (H)	10mg/kg (range 7-15 mg/kg); Maximum dose 300mg a day
Rifampicin (R)	15mg/kg (range 10-20 mg/kg); Maximum dose 600mg a day
Pyrazinamide (Z)	35mg/kg (30-40 mg/kg); Maximum dose 2000mg a day
Ethambutol (E)	20 mg/kg (15-25 mg/kg); Maximum dose 1600mg a day

Children's weight should be monitored frequently during treatment and medication doses adjusted accordingly.

Treatment Issues in Childhood TB Include:

- Doses should be calculated according to the child's weight.
- Doses should be recalculated as the child gains weight and condition improves.
- The method of delivery needs to be considered in young children and advice provided to ensure child can take medications (e.g. crushed pills, suspensions).
- Where possible daily regimens are preferred to intermittent dosing.

- Children are dependent on care-givers for treatment adherence. If concerns with adherence, discuss with case manager the role for directly observed treatment.
- If there is no MTB isolate available from the patient then treatment regimens should be based on proven or probable drug sensitivities of the index case.
- Pyridoxine supplementation is not routinely offered to children but is considered in breastfeeding children, children with nutritional deficiencies or milk and meat deficient diets; and HIV infection.
- Round dosing to the nearest appropriate tablet / capsule size as needed:
    - Isoniazid (H) comes as powder for suspension and 100mg tablets that can be split and crushed. Max dose 300mg per day.
    - Rifampicin (R) comes as syrup (100mg/5mL in 60ml bottles) or 150mg and 300mg capsules. Max dose 600mg per day.
    - Pyrazinamide (Z) comes as 500mg tablets.
    - Ethambutol (E) comes as 100mg and 400mg tablets. The 100mg tablets require an SAS form.

Drug Toxicities in Children and Adolescents

The following are the minimum adverse effects that the patient should be aware of, and which should be screened for during follow up visits:

- Hepatitis (H, R, Z): anorexia, jaundice, malaise, nausea, vomiting, epigastric or right upper quadrant pain/tenderness, hepatomegaly
- Rash (H, R, Z): macular, pruritic on trunk extending to limbs
- Optic neuropathy (E): loss of visual acuity, red/green colour blindness
- Neuropathy/paraesthesia (H)
- Rifampicin will turn the urine, tears and other secretions orange/red due to a pigment in the medication. It is not harmful.

Significant drug side effects including symptomatic hepatitis (ALT >5x upper limit of normal) may require treatment interruption.

After a severe drug adverse effect has resolved TB drugs are reintroduced in a stepwise fashion to re-establish treatment and to identify which drug is responsible. This should be individualised on a case-by-case basis by a consultant physician with TB expertise. The principles underpinning this include:

- Re-introduction of the most effective drugs (isoniazid, rifampicin) first.
- Avoidance of treatment with one drug alone for more than 1 week.
- Starting with a low dose and increase to full dose if tolerated.
- Ensure appropriate tests (e.g. LFTs) are done frequently enough to associate the adverse effect with a specific drug.

Ethambutol Use in Children

There have been concerns about the use of ethambutol in young children due to the potential for optic neuritis, but a comprehensive review by WHO indicates that ethambutol is safe to use in children at recommended doses (Graham S., 2011).

Limiting ethambutol to the initial intensive phase of treatment decreases the potential for toxicity. Children requiring ethambutol for longer than 2 months should have regular vision assessment and/or ophthalmology review. Monitoring of colour vision using the Ishihara chart and visual acuity using the Snellen's or revised Snellen charts for children who are not familiar with the English alphabet, should occur at all clinic visits for children on ethambutol.

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 (World Health Organisation, 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 four drugs in the initial intensive phase of TB treatment (Cotton, Graham, Jaspan et al, 2010) and followed by at least four 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. A ten-month continuation phase is recommended for TB meningitis or osteoarticular TB. 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).

The risk of immune reconstitution inflammatory syndrome (IRIS) is highest in patients with TB-HIV coinfection and who are on ART. ART should be initiated within the first two weeks of TB treatment with CD4 cell counts <50/mm3 and by 8 weeks of TB treatment for patients with CD4 cell counts > 50/mm3. However, patients with TB meningitis SHOULD NOT start ART before 8-10 weeks of TB treatment is completed, regardless of CD4 count (Nahid, Dorman, Alipanah et al, 2016). 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.

MDR-TB

MDR-TB should be managed by a paediatrician familiar with efficacy and side effects of second line anti-tuberculosis agents. For more detailed information on MDR and XDR treatment, see section *2.1. TB Treatment - Medical*.

Preventive therapy for MDR TB can and should be considered following high-risk exposure. The choice of drugs will depend on the agents the index case's TB isolate is sensitive to. There is limited evidence on the efficacy of this potentially toxic therapy. The alternative management to preventive therapy involves contacts of MDR TB to be monitored clinically and by CXR at regular intervals for at least five years. Longer follow up may be justified and is at the discretion of the treating physician.

Follow-up of TB Disease

All children and adolescents on TB treatment should be reviewed regularly. The initial review is after 2 weeks of commencement of treatment for clinical assessment and liver function testing. Subsequent to this, reviews can be conducted monthly either at the WA TB Control Program or via telehealth (if child or adolescent lives in a rural or remote location).

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.

All children diagnosed and treated for TB should be reviewed in clinic following completion. In children with fully susceptible tuberculosis and where adherence is adequate, a single review at 3 months is sufficient.

In children with inadequate adherence or if a nonstandard regimen was used (due to resistance or intolerance), follow up for at least one year is recommended.
Follow up for children with MDRTB should be for a minimum of 5 years.

Treatment Interruptions

Accidental or necessary treatment interruptions are common. Each case needs to be considered individually and therapy modified, if necessary. In general, if a treatment interruption occurs, calculate the number of days missed in the total regimen and add these days to the end of the regimen to compensate for any missed doses. If treatment interruption > 2 weeks in intensive phase or > 2 months in continuation phase, the TB treatment regimen should be restarted (See *Table 4.4*).

Table 4.4 Treatment interruption management

Time point of interruption	Details of interruption	Approach
Intensive phase	Lapse <14 days	Continue treatment (Rx) to complete planned total number of doses
	Lapse >14 days	Restart Rx from the beginning
Continuation phase	Received ≥80% of doses & smear negative at baseline	Further Rx may not be necessary
	Received ≥80% of doses & smear positive at baseline	Continue Rx until all doses are completed
	Received <80% of doses and accumulative lapse <3 months	Continue Rx until all doses are completed unless consecutive lapse >2 months
	Received <80% of doses and lapse ≥3 months	Restart Rx from the beginning of intensive phase

Adapted from Table 6 Nahid et al IDSA guidelines
https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

Latent Tuberculosis Infection (LTBI)

The majority of children seen at the WA TB Control Program have LTBI. They are referred from Health Undertakings (HUT), Humanitarian Entrant Health Screening (HEHS), GPs and medical colleagues. In addition, children identified as household contacts of TB cases may also have LTBI.

The identification and treatment of LTBI in children is important to reduce the risk of developing TB disease in the short term, and also to reduce the lifelong risk of TB reactivation.

This incorporates:

- early identification of paediatric contacts of TB cases and
- post-migration screening and treatment of high-risk groups as detailed in other Western Australian TB Control Program policies.

LTBI Treatment

The preferred regimen for preventive therapy in children at the WA TB Control Program is:

3 months of combined isoniazid and rifampicin (3HR)

OR

6 months isoniazid monotherapy (If needed due to underlying liver disease, drugs which may interact with rifampicin [e,g. antiretrovirals] or other tolerability issues) (6H)

OR

4 months of rifampicin monotherapy (4R)

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

Recommended TB drugs dosages are:

- Isoniazid (H) – 10mg/kg (range 7-15 mg/kg); Max dose 300mg a day
- Rifampicin (R) – 15mg/kg (range 10-20 mg/kg); Max dose 600mg a day

Alternative approaches are required in the setting of intolerance or if an index case has isoniazid resistant disease. Rifampicin monotherapy for 4 months may be considered as an alternative therapy.

Pyridoxine supplementation is not routinely offered but it is considered in breastfeeding children, children with nutritional deficiencies or milk and meat deficient diets, and HIV infection. 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 - 12.5-25mg daily

LTBI Follow-up

Children and adolescents on LTBI treatment are reviewed after 2 weeks of commencement for clinical assessment and liver function testing.

Subsequent reviews are scheduled after 6 and 12 weeks respectively from commencement of treatment. If adherence is adequate, the child or adolescent can be discharged from the WA TB Control Program with a letter to their local doctor. Patients and their families should be advised on discharge that their risk of developing TB is now <1% providing they do not return to an endemic country. If symptoms occur in the future of cough for >3 weeks, weight loss, night sweats or persistent fevers, they should be reassessed for TB.

Primary Preventive Therapy

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 or QIFN and a normal CXR. These children may rapidly develop TB before a contact tracing visit and before a TST or QIFN test can become positive.

All children under 5 years old and those who are immunocompromised, and a close or household contact of a case of infectious TB (adult or adolescent with bacteriologically confirmed pulmonary TB), should have a TST/IGRA performed and should be clinically and radiologically screened for TB disease.

If TB is excluded, children under 5 years old and children who are immunocompromised and exposed to household or close contacts with smear positive pulmonary tuberculosis should be started on preventive treatment.

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

These children should be reviewed at 2 weeks after commencement of therapy for a repeat clinical assessment and liver function testing. Subsequent reviews are at 6 and 12 weeks from commencement of treatment should also be undertaken. Repeat TST or QIFN testing at end of treatment is recommended but treatment should be completed regardless of test results.

Perinatal Tuberculosis

Transmission of TB from a mother to the foetus is most likely to occur when the mother has disseminated TB or develops infection in pregnancy. Babies born to mothers with sputum smear positive TB are at high risk of respiratory transmission post-delivery.

Perinatal tuberculosis encompasses tuberculosis acquired by the baby while i) in-utero, ii) intrapartum and iii) in the postnatal period.

Tuberculosis acquired by the fetus in-utero from haematogenous spread via the umbilical cord, or in-utero aspiration or ingestion of infected amniotic fluid is rare. TB in the infant should be considered if the mother is diagnosed with genital tract TB, especially if late in the pregnancy, and the neonate develops signs of sepsis. Tuberculosis infection after delivery occurs from airborne transmission from the mother, an adult family carer or another infectious adult with whom the infant has had contact (including health care workers).

The diagnosis of perinatal tuberculosis is difficult and frequently delayed. If the neonate exhibits any signs or symptoms of TB infection then a thorough assessment and investigation should be

undertaken for bacterial confirmation of MTB infection. (see above; *Investigations for Tuberculosis*).

Symptoms and signs that should raise suspicion of TB in a neonate born to a mother diagnosed with TB are fever, respiratory distress, hepatosplenomegaly, jaundice, lymphadenopathy or an abnormal CXR.

The clinical features can be subtle and difficult to differentiate from other congenital/ neonatal infections. Standard anti-TB therapy should be commenced after appropriate specimens have been collected.

After TB has been excluded in the baby, a neonate born to a mother with pulmonary, miliary or disseminated tuberculosis should receive primary preventive therapy (see above; *Primary Preventive Therapy*).

During the period of preventive therapy, if the infant develops clinical symptoms, signs or radiological appearances suggestive of TB; appropriate investigations should be performed to exclude TB and a complete course of anti-TB treatment considered.

Contact Tracing

The principles and procedures for contact tracing in tuberculosis (TB) in Western Australia are discussed in section *5.1. Contact Tracing*. Below are salient points relating to contact tracing in children.

Child as the Index Case

Children with TB are generally less contagious than adults because they:

- Rarely produce sputum
- Have less cavitatory disease
- 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.

Child as a Contact of TB Disease

Table 4.5 Contact Tracing Based on Age of Child and Exposure

TB Contact	Household or close contact			All other contacts
	Smear positive Pulmonary TB	Smear negative culture positive Pulmonary TB	Extra-pulmonary TB	
< 5 years of age or immunocompromised	CXR Baseline TST* Outpatient clinical review (regardless of investigations) 3HR once TB disease excluded	CXR Baseline TST* Repeat TST† Outpatient clinical review (only if symptomatic, CXR or TST abnormal) # 	Baseline TST* Outpatient clinical review (only if symptomatic or TST abnormal)	Baseline TST† Outpatient clinical review (only if symptomatic, or TST abnormal)
≥ 5years of age	CXR Baseline TST* Repeat TST† Outpatient clinical review (only if symptomatic, CXR or TST abnormal)	Baseline TST* Repeat TST† Outpatient clinical review and CXR (only if symptomatic or either TST abnormal)	Baseline TST* Outpatient clinical review and CXR (only if symptomatic or either TST abnormal)	Baseline TST† Outpatient clinical review (only if symptomatic, or TST abnormal)

*TST preferred for contact tracing but if not possible or immunocompromised, consider QIFN

† minimum of 8 weeks following last contact to infectious TB contact or 10 weeks post commencement of index cases' TB treatment if ongoing contact

Outpatient clinical review for child < 5 years of age or immunocompromised should be considered if the exposure is considered high risk despite smear negative result (e.g. Cavitatory lung disease).

Household or Close Contact

Household contacts are children (or adults) who have had a cumulative eight hours or more of exposure (e.g. shared a bedroom, kitchen, bathroom or sitting room) to a smear positive case of TB. Exposed individuals to an index case for greater than eight hours within a restricted area equivalent to a domestic room are at similar risk to household contacts and should also be included for contact tracing (National Institute for Health and Clinical Excellence, 2011). This indication may apply to a school or institutional setting.

If a child is a named household or close contact of an index case of either pulmonary or extra-pulmonary tuberculosis, the child should be assessed for symptoms and signs indicative of TB disease.

Casual Contact

Casual contacts are those children (or adults) who have had minimal exposure to the index case and the total cumulative exposure time is less than 8 hours. For healthy low risk casual contacts, a single TST performed 8-12 weeks after exposure is sufficient to detect new TB infection. All symptomatic casual contacts should be medically assessed regardless of TST history. All casual contacts with a positive TST should be reviewed regardless of symptoms.

The components of contact tracing include:

- Interview: all contacts should be questioned for symptoms of TB. Other relevant history includes previous tuberculin skin test (TST) result, previous TB exposure or treatment, BCG immunisation and co-existing medical conditions of the contact.
- CXR should be performed in:
  - Any child, regardless of age, with symptoms compatible with TB disease.
  - All household or close contacts of smear positive pulmonary tuberculosis (irrespective of TST or QFN).
  - Household contact or close contact of smear negative culture positive pulmonary TB if child immunocompromised or <5 years of age.
  - Any child, regardless of age, with a positive TST reading or IGRA result.
- TST and/or IGRA should be performed in all contacts of TB. A TST or IGRA should not be done if there has been a previous positive result or documented past TB.
- Paediatrician review should be arranged for:
  - All immunocompromised children or children < 5 years who are household contacts of smear positive adolescents and adults.
  - All children with symptoms suggestive of TB.
  - All children with a positive TST and/or IGRA or TST/IGRA conversion.
  - All children with an abnormal CXR.
  - Household contacts (<5 years of age or immunocompromised) whose exposure is considered high risk despite negative smear result (e.g. cavitatory lung disease).
  - A positive TST reading of 5mm is considered indicative of MTB infection in a child less than 5 years old. For further information regarding TST interpretation please see section *5.1 Contact Tracing*.

BCG Disease

BCG disease can be categorised as (Hesseling, Rabie, Maris et al, 2005):

- 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, cerebrospinal fluid, 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-IRS, is defined as BCG disease that presents in an HIV infected child within 3 months after the initiation of anti-retroviral therapy (Hesseling, Rabie, Maris et al, 2005). 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. *Mycobacterium bovis* (including all BCG strains) is inherently resistant to pyrazinamide and treatment may require higher doses of other first-line TB or additional medications (World Health Organisation, 2016).

Bacille Calmette-Guérin (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 TB infection progressing to disease. If TB disease occurs, it lessens the chance of a severe outcome.

BCG vaccination is not offered routinely in Western Australian 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 the Department of Health Western Australia Information Circular IC 0062/09 *BCG Vaccination Schedule for Tuberculosis Control* and section *6.1. BCG Vaccination.*

Other Tips for Caring for Children and Adolescents at WA TB Control

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: ACC.admin@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.

Phlebotomy

The paediatric team are often required to collect their own blood tests. HEHS phlebotomists can be available on a Tuesday morning to assist after 10:30am.

School or Day-care Exclusion

Each case should be considered individually regarding the risk of infecting others based on the site of infection, disease burden and resistance profile. On the whole, children have paucibacilliary disease and are not considered highly infectious. School exclusion is not needed unless smear positive.

4.2 Prisoners and Immigration Detainees

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 centres' procedures may differ from these guidelines.

Effective TB control activities in this setting include:

- The early identification of persons with TB.
- Targeted screening for LTBI in those at risk of reactivation while in the correctional or detention facility. Completion of treatment regimens for TB and latent TB infection.
- 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.

Background

At 30 June 2017 the Department of Corrective Services managed 13,918 adult and young prisoners and detainees across public and private prisons in WA.

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). The incidence of TB in the Aboriginal Australian population was 4.6 cases per 100,000 in 2013 compared to an incidence of TB in Australian born non-Indigenous population of 0.8 cases per 100,000 (Tuberculosis Notifications in Australia 2012 -2013, Communicable Diseases Network Australia, June 2015).

As well as sentenced prisoners, the prison population consists of around 18% remand prisoners, which contribute to a high turnover of inmates. 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 on TST or QIFN testing. Similar results have been reported from NSW. This is higher than the estimated 1-3% in the general population (Latent tuberculosis infection (LTBI) screening in Western Australian correctional facilities, ASID 2012).

Prison populations may have higher levels of TB because transmission of TB infection is facilitated through prolonged and repeated exposure to *Mycobacterium 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 latent infection through:
- Co-existing pathology, particularly HIV and intravenous drug use
- Poor nutritional status

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 (Centers for Disease Control and Prevention, 2006).

Health Assessment on Entry - Active Surveillance

It is recommended that all persons upon entry to a prison facility and immigration detention facility be screened for TB. Those at highest risk include persons with recent close contact with TB, arrivals to Australia 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 2-3 weeks)
- Haemoptysis
- Unexplained fever
- Night sweats
- Weight loss
- Lethargy and tiredness
- Chest pain

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 Systematic Screening for Active TB, 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 AFB 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 WA TB Control Program on 08 9222 8500.

Other information which 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 tuberculin skin test TST, QIFN or CXR
- Medical conditions that increases the risk of TB i.e. 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.

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. a recent contact of TB, arrival to Australia from a TB endemic country within the last 5 years or Aboriginal Australians.

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; *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 AFB microscopy and culture.

In addition, the WA TB Control Program 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 WA TB Control Program does not need to wait until a positive test result is obtained. See *Appendix 4.1Flow Chart for the Management of a Prisoner Suspected of Active Tuberculosis.*

Effective Treatment of TB

The medical management of tuberculosis is discussed in detail in section *2.1. TB Treatment – Medical*.

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 directly observed therapy (DOT) is imperative and should be documented. This is necessary to ensure adherence and for vigilance regarding side effects.

Management in conjunction with the WA TB Control Program 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 two 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 WA TB Control Program 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; *Planning for Released Prisoners*).

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 WA TB Control Program regarding management of the case. TB isolation procedures can be discontinued if the TB physician deems the prisoner or detainee is non-infectious.

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 (Prevention and Control of TB in Correctional and Detention Facilities; recommendations from 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 WA TB Control Program should be alerted as soon as possible to coordinate admission to hospital for initiation of treatment and to begin contact tracing activities.

Contact Tracing

Contact tracing can prove 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 WA TB Control Program 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. (Prevention and Control of TB in Correctional and Detention Facilities, CDC 2006).

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

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 WA TB Control Program 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 WA TB Control Program 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 WA TB Control Program in order 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 general practitioner or case worker and the WA TB Control Program.

Routine follow up after completion of TB treatment requires a CXR and medical review three months post therapy. This can be organised via the WA TB Control Program 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 WA TB Control Program can assist with this process.

Screening for Latent Tuberculosis Infection (LTBI)

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

Universal screening for LTBI 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 LTBI in these targeted groups.

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

Employee screening

All Department of Corrective Services employees (health care workers, non-clinical staff, custodial staff, etc.) in Western Australia and staff working with immigration detainees should have a TB risk assessment and be screened for TB as appropriate.

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 section *Infection Control*

Contact Anita Clayton Centre (WA TB Control Program)

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

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 therapy in consultation with WA TB Control Program 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

4.3 TB in Pregnancy

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 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 (Ormerod, 2001, Adhikari & Jeena, 2009). 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.

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 also occur in 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 sections *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 50mGy is not associated with significant health risks and the amount of exposure to the foetus from a maternal two-view CXR is <0.01mGy. This is comparable to 10 days of natural background radiation. (Prenatal Radiation Exposure, Department of Health, September 2012, http://www.health.gov.au/internet/publications/Content/ohp-radiological-toc. CXRs in pregnant women are performed with lead shielding to the abdomen and usually not in the first trimester of pregnancy to reduce the radiation risk to the foetus.

Therefore, if tuberculosis 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 tuberculosis.

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 the WA TB Control Program chapter 2.1 Medical Treatment of Tuberculosis (adults) sections 5.0 and 6.0.

Pyrazinamide

Although in some jurisdictions (American Thoracic Society, CDC and Infectious Diseases Society of America, 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 PZA. 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 PZA in short course TB chemotherapy, pyrazinamide is recommended for routine use in pregnant patients in WA (Therapeutic Guidelines Antibiotic Version 15, 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 nine 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, CDC and Infectious Diseases Society of America, 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 Vit 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 (Ormerod, Thorax 2001):

- Aminoglycosides (kanamycin and amikacin)
- Streptomycin (ototoxic to the foetus),
- Ethionamide (CNS defects) and
- Capreomycin (use with caution if absolutely required)

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 (World Health Organisation, 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 25mg per day (Centers for Disease Control and Prevention, 2016).

Breastfed infants of mothers taking isoniazid should be given pyridoxine 5 mg daily on the days that the mother receives her isoniazid dose (Therapeutic Guidelines Antibiotic Version 15, Limited, 2014).

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 preventive treatment. Contact tracing procedures are followed as per usual.

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 (World Health Organisation, 2009, Centers for Disease Control and Prevention, 2008). The concentration of TB medications found in breast milk is too small to be an effective treatment for TB or latent TB in the nursed baby. Neonates born to mothers with TB should receive their own treatment for either TB or preventive therapy, with pyridoxine supplementation.

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 tuberculosis encompasses tuberculosis acquired by the baby while in-utero, intra-partum and in the postnatal period.

Tuberculosis 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.

Tuberculosis can be spread to the neonate during delivery by aspiration or ingestion of infected amniotic fluid or cervicovaginal secretions. Tuberculosis 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 health care workers).

Medical management

A paediatric specialist should always be involved in the management of children at risk of or suspected to have neonatal tuberculosis. The diagnosis of perinatal tuberculosis 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 *4.1 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 with either 6 months isoniazid (10mg/kg) and pyridoxine supplementation (5-10 mg daily), or 3 months combination therapy of isoniazid (10mg/kg) and rifampicin (15mg/kg) with pyridoxine supplementation (World Health Organisation, 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 tuberculosis.

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.

Latent Tuberculosis in Pregnancy

Screening

Routine screening for LTBI 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 World Health Organisation tuberculosis country profile website http://www.who.int/tb/country/data/profiles/en/index.html.
- HIV infected patients (and other profoundly immunocompromised patients).

TST is the test of choice and tuberculin reactivity is not affected by pregnancy. It is considered both a valid and safe test to use in pregnancy. The IGRAs are also safe to use in pregnancy as a screening test, but they have not been validated for pregnant women.

It is recommended that asymptomatic pregnant women with positive TST or QIFN *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 300mg daily for 6 months with pyridoxine 25mg 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 LTBI.

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

4.4 HIV co-infection

Introduction

This chapter addresses differences in the approach to the assessment and treatment of tuberculosis in patients co-infected with the human immunodeficiency virus (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 latent TB infection to 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, 2016). This risk increases with increasing immunosuppression.

Diagnosis

Clinical Features

The clinical presentation of tuberculosis in HIV infected persons is influenced by:

- The degree of immunosuppression in the person; and
- The rate of HIV disease progression.

Pulmonary TB is the commonest 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 one week rather than three 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 (World Health Organisation, 2010).

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 (Centers for Disease Control and Prevention (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 nucleic acid testing.

Patients who are highly immunocompromised may return a negative result on sputum microscopy despite clinical and/or radiological appearances suggestive of TB. Non-tuberculous mycobacterial infections may be present in patients with advanced immunodeficiency and nucleic acid testing can help to differentiate these from tuberculosis 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 nucleic acid testing. For a list of suitable clinical specimens please 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 4.6 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 show 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

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 anti-retroviral treatment;
- Drug interactions between TB medication and anti-retroviral treatment;
- Immune reconstitution inflammatory syndrome (IRIS) after anti-retroviral treatment initiation; and
- 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 (World Health Organisation, 2010; Australasian Society for HIV Medicine, 2016).

Therefore, standard short-course therapy for TB is two months intensive phase of isoniazid, rifampicin, ethambutol and pyrazinamide followed by a four-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. TB meningitis, bone or joint disease spinal TB. For further information on various drug regimens and drug doses please see section 2.1 *TB Treatment - Medical*.

Daily TB treatment should be used, rather than intermittent therapy, as intermittent regimens are associated with a higher rate of relapse and failure (World Health Organisation, 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; Nahid et al 2017; Department of Health and Human Services, 2017):
    - TB meningitis
    - Severe tuberculosis associated immune reconstitution inflammatory syndrome.

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 Anti-Retroviral Therapy

Anti-retroviral therapy (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 TB meningitis. Caution is needed in patients with TB meningitis where early initiation of ART is associated with more severe adverse events than delayed ART therapy (World Health Organisation 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, 2016; World Health Organisation, 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 tuberculosis associated immune reconstitution inflammatory syndrome (TB-IRIS);
- Drug interactions; and
- 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, non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc and raltegravir. 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 (Centers for Disease Control, 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 (Centers for Disease Control, 2013).

However, rifamycins are important for the success of tuberculosis 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 with 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 tuberculosis and HIV please see the references given.

Tuberculosis Associated Immune Reconstitution Inflammatory Syndrome

Tuberculosis associated immune reconstitution inflammatory syndrome (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 (Centers for Disease Control and Prevention, 2017).

Paradoxical Tuberculosis Aassociated 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 (Centers for Disease Control and Prevention, 2017). Central nervous system TB-IRIS can be severe and in patients

with profound immunosuppression and TB-IRIS can involve multiple sites (Australasian Society for HIV medicine, 2016).

Paradoxical tuberculosis-associated 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 (Centers for Disease Control and Prevention, 2017).

Most cases of paradoxical tuberculosis-associated 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 (Centers for Disease Control and Prevention, 2017). If TB-IRIS should occur, neither TB therapy nor ART should cease.

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.

Tuberculosis paradoxical reactions can also occur in HIV negative individuals and in HIV positive patients not receiving anti-retroviral therapy but this occurs less frequently compared to those on anti-retroviral therapy.

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 anti-retroviral therapy and may be the result of a missed diagnosis prior to anti-retroviral therapy, 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 anti-retroviral therapy is started.

Unmasking tuberculosis-associated 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 (Centers for Disease Control and Prevention, 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 (Centers for Disease Control and Prevention, 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 *2.2 TB Treatment – Case Management*.

Latent TB Infection in HIV

Diagnosis

The TST relies on a competent immune response to identify people with latent *M. tuberculosis* infection and therefore in HIV infected patients have a lower cut-off of 5mm diameter reaction

which is deemed a positive result (versus 10mm in the general population). HIV related immunosuppression can be associated with false negative results. False negative and indeterminate QFN results increase with advancing immunodeficiency and low CD4+ counts (World Health Organisation, 2011).

On balance QIFN is the preferred test for LTBI in HIV patients. The routine use of both a TST and QIFN test to screen for LTBI is not recommended.

All individuals should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk (Centers for Disease Control and Prevention, 2017). Patients with advanced HIV infection (CD4+ count <200 cells/µL) may initially return a negative screening test for LTBI and should be retested once ART commences and the CD4+ count increases above 200 cells/µL (Centers for Disease Control and Prevention, 2017).

All individuals returning a positive screening test for LTBI should be assessed for TB disease by screening for symptoms e.g. cough, fever, sweats, weight loss etc, and a CXR. Once TB has been excluded, all HIV infected persons with a positive screening test for LTBI should receive treatment for latent TB. If there is a history of TB exposure e.g. contact with a person with infectious TB, then treatment for latent TB 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, 2016):

- Have a TST reaction of ≥5mm in diameter or positive QIFN test and no prior history of treatment for TB or latent TB infection.
- Negative TST or QIFN test but is a close contact of infectious TB.
- Radiological evidence of past TB infection (e.g. fibrotic change on chest radiography).

The treatment recommended by the WA TB Control Program is 9 months of isoniazid monotherapy, at a dose of 5-10mg/kg to a maximum of 300mg daily. Pyridoxine at a dose of 25mg daily should be given concurrently to minimise the risk of peripheral neuropathy.

Primary Preventive Therapy

Individuals with HIV infection are at high risk of developing primary TB infection following exposure to an infectious case. Commencement of LTBI treatment immediately following the exposure aims to prevent the development of primary TB infection. These patients should be offered preventive therapy regardless of TST or QIFN result. For individuals who are a contact of infectious drug resistant TB, the choice of medication should be made in conjunction with a TB physician.

Pregnancy

The investigations and principles of management of TB and latent TB infection in HIV infected pregnant women are no different from that in HIV negative women. However, the following should be considered (Centers for Disease Control and Prevention, 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 LTBI 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.
- Drug resistant 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.

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 e.g. 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 tuberculin skin test despite having TB and so caution is needed in interpreting results.
- Bacille Calmette-Guérin (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 *4.1 Paediatrics*)

BCG Disease

BCG is a live attenuated vaccine derived from *Mycobacterium 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 tuberculosis. BCG disease can be categorised as (Hesseling & al, 2005):

- 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, cerebrospinal fluid, 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. *Mycobacterium bovis* is inherently resistant to pyrazinamide and treatment may require higher doses of other first-line TB medications (World Health Organisation, 2014).

BCG immune reconstitution syndrome, BCG-IRS, is defined as BCG disease that presents in an HIV infected child within 3 months after the initiation of anti-retroviral therapy (Hesseling & al, 2005). It can occur with local, regional, distant or disseminated disease as described above.

Mycobacterium avium complex

Mycobacterium avium and *Mycobacterium intracellulare* are two non-tuberculous mycobacteria that collectively form a group of organisms known as the *Mycobacterium avium* complex (MAC). MAC infection is important in the differential diagnosis of acid-fast bacilli present in specimens from HIV-infected individuals. MAC infection is seen in patients with very low CD4+ counts. There is a strong relationship between CD4+ cell count and the presence of disseminated MAC infection, with nearly all cases of disseminated MAC occurring at a CD4+ cell count of <50 cells/µL (Australasian Society for HIV medicine, 2016).

Clinical manifestations of MAC infection are similar to *M.tuberculosis* infection, although disseminated disease is more common than pulmonary forms. Diagnosis is confirmed through the isolation of MAC from culture or identification by molecular techniques.

In cases where MAC is in the differential diagnosis, and a histological diagnosis of mycobacterial infection is made in the absence of diagnostic cultures, empirical therapy should cover both MAC and *M. tuberculosis* infections. Clarithromycin should be added to the standard four-drug TB regimen until the identification of the mycobacterial species is available, either by NAAT or culture (Australasian Society for HIV medicine, 2016).

4.5 Country Patients

This guideline relates to the care of patients that are resident outside of Perth and are receiving TB treatment or are otherwise referred to the WA TB Control Program.

Referrals

All referrals received by the WA TB Control Program are triaged by medical staff and provided with appropriate appointments. All regional patients are offered a telemedicine review or alternatively they can attend the TB clinic in person.

TB Patients

The overarching document for the process of delivering TB and leprosy care to patients in regional WA is the Memorandum of Agreement between the WA TB Control Program and WA Country Health Service that came into effect May 2017. 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.

The WA TB Control Program provides direction to ensure appropriate clinical management is maintained for each patient in consultation with the local primary care provider (such as General Practitioner/local Public Health Unit/Nurse Practitioner/District Medical Officer).

For a detailed explanation of the roles and responsibilities of the WA TB Control Program and WACHS please refer to the Memorandum of Agreement between the WA TB Control Program and WA Country Health Service.

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Chapter 5: Active Surveillance for Tuberculosis

5.1 Contact Tracing

Introduction

Effective contact tracing is an important strategy for TB control in Australia (CDNA, 2002). The aims of contact tracing are to detect:

- Another individual with TB disease that transmitted TB to the index case (source case)
- LTBI 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.

Background

Governance

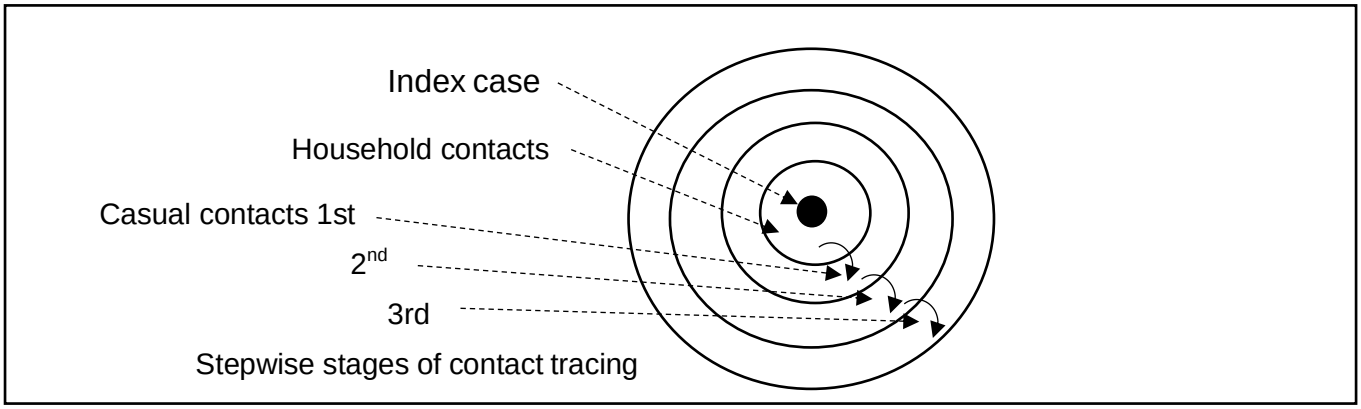
TB contact tracing is undertaken by the TB Control Program. Primary oversight is provided by the TB case manager for the index case, who in turn reports to and seeks advice from the Medical Director for TB Control. Occasionally, contact tracing is undertaken by other agencies, in which case it is carried out in consultation with the TB Control Program. This is especially important when contact tracing is required in a hospital (see below *Hospitals and other Health Care Settings*) or rural and remote areas, where it is coordinated between WACHS and WATBCP by the WACHS Regional TB and Leprosy Program Coordinator in consultation with the TB case manager.

Principle of Contact Tracing

Contact tracing for tuberculosis is conducted based on the "stone in the pond" principle (see *Figure 5.1*) where contacts are identified and tested in a logical (temporally & spatially) 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 no positive cases of TB infection are found as evidenced by negative screening tests (TST or QFN).

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 5.1 Stone-in-a-pond Principle of Contact Tracing



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 contacts are people who share a bedroom, kitchen, bathroom or sitting room with the index case and have prolonged exposure. Prolonged exposure is a cumulative total exposure exceeding 8 hours. Other contacts that spend greater than 8 hours within an enclosed area (e.g. shared hospital room, dormitory, other residential institution, but not a school room or work space) with the index case are considered close contacts and thus equivalent to household contacts. These individuals need to be included in the contact tracing exercise in addition to household contacts. (National Institute for Health and Clinical Excellence, 2011).

Casual Contacts

Casual contacts are those who have less exposure to the index case, but the total cumulative exposure time is 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.

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 5.1* (CDC, 2005).

Table 5.1 Characteristics of the index case that influence TB infectiousness

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 chest x-ray 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 can have chest x- ray 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	Certain medical procedures that increase respiratory droplet production can increase the risk of transmission of TB e.g. chest physiotherapy, nebuliser, intubation, airway suction, induced sputum, CPR, 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 5.2*.

Table 5.2 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 <2 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 immunosuppressant therapy and immunosuppressant therapy equivalent to prednisolone 15mg/day for > 1 month • Silicosis • Chronic renal failure/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.

Extent of contact tracing

Timeframe

Contact tracing should begin as soon as possible after an index case has been diagnosed with tuberculosis. 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. If the index case is asymptomatic, usually only household contacts are contact traced.

Who to Contact Trace

All household or close contacts of pulmonary tuberculosis 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 *Tables 5.1 and 5.2* above.

In cases of extra-pulmonary tuberculosis, 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.
- Drug resistant 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.

Procedure for Contact Tracing

The procedure for contact tracing in household contacts and casual contacts of tuberculosis 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 5.1*).

Stratification of Contact List

Contacts should be stratified into groups according to the "stone in a pond" principle (see above *Figure 5.1*) 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

All contacts should be questioned for symptoms of TB. Other relevant history should include any previous TST or QIFN result, previous TB exposure or treatment, history of or BCG vaccination scar, and co-existing medical conditions.

CXR

- All household contacts over 10 years old (irrespective of result of test for LTBI).

- All contacts with positive test for LTBI 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 LTBI

The preferred screening tool when sequential testing is required is the TST. This applies to household 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 QIFN are considered equivalent tests and either can be used.

A detailed summary of the pros and cons of the TST and QFN can be found in section *3.1 Latent TB Infection - Diagnosis* and section *5.3 Health Care Workers*.

More detail on the standard operating procedure of contact tracing can be obtained from the WA TB Control Program. 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 QIFN (consider preventive treatment irrespective of age).
- All contacts <5 years old are referred for paediatrician review according to *table 4.5* (See section *4.1 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 *Treatment of latent tuberculosis infection.* Individuals who decline or cannot take preventive treatment are followed up with CXRs every six months for 2 years. Contacts of MDR TB with a positive test for LTBI 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 or WACHS Regional TB and Leprosy Program Coordinator completes a report summarising the extent and results of the contact tracing. The details of this reporting are described in the WA TB Control Program contact tracing standard operating procedure.

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 (World Health Organisation (WHO), 2008). The risk of transmission of *M. tuberculosis* on board aircraft is low and limited to persons in close contact with an infectious case for 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 tuberculosis, 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, and exposed to 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 at-risk passengers (or friends of the case) who moved from being seated elsewhere in the aircraft to spend large amounts of flight time near the index case are also considered for contact tracing.

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 Medical Director of the WA TB Control Program. The WHO Tuberculosis and air travel guidelines for infection prevention and control 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 WA TB Control Program.
- 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 health care workers 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 WA TB Control Program 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 (National Tuberculosis Advisory Committee, 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 tuberculosis.

HIV

High risk contacts with immunosuppressive conditions (including HIV infection) may show a negative tuberculin response despite infection. They should be referred to a physician experienced in TB management, irrespective of the result of the LTBI screening test or CXR.

Children

All children < 5 years old, who are close contacts of pulmonary TB, are at higher risk of progression to disease (Marais, Schaaf, & Donald, 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 WA TB Control Program chapter *4.1 Paediatrics* for further details regarding TB management in children.

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, Western Australia Mandatory Policy 0010/16 Patient Confidentiality Policy (Department of Western Australia 2016) Department of Health, Western Australia Operational Directive OP 2050/06 (Department of Health Western Australia, 2006).

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 six 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 WA TB Control Program 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 WA TB Control Program.

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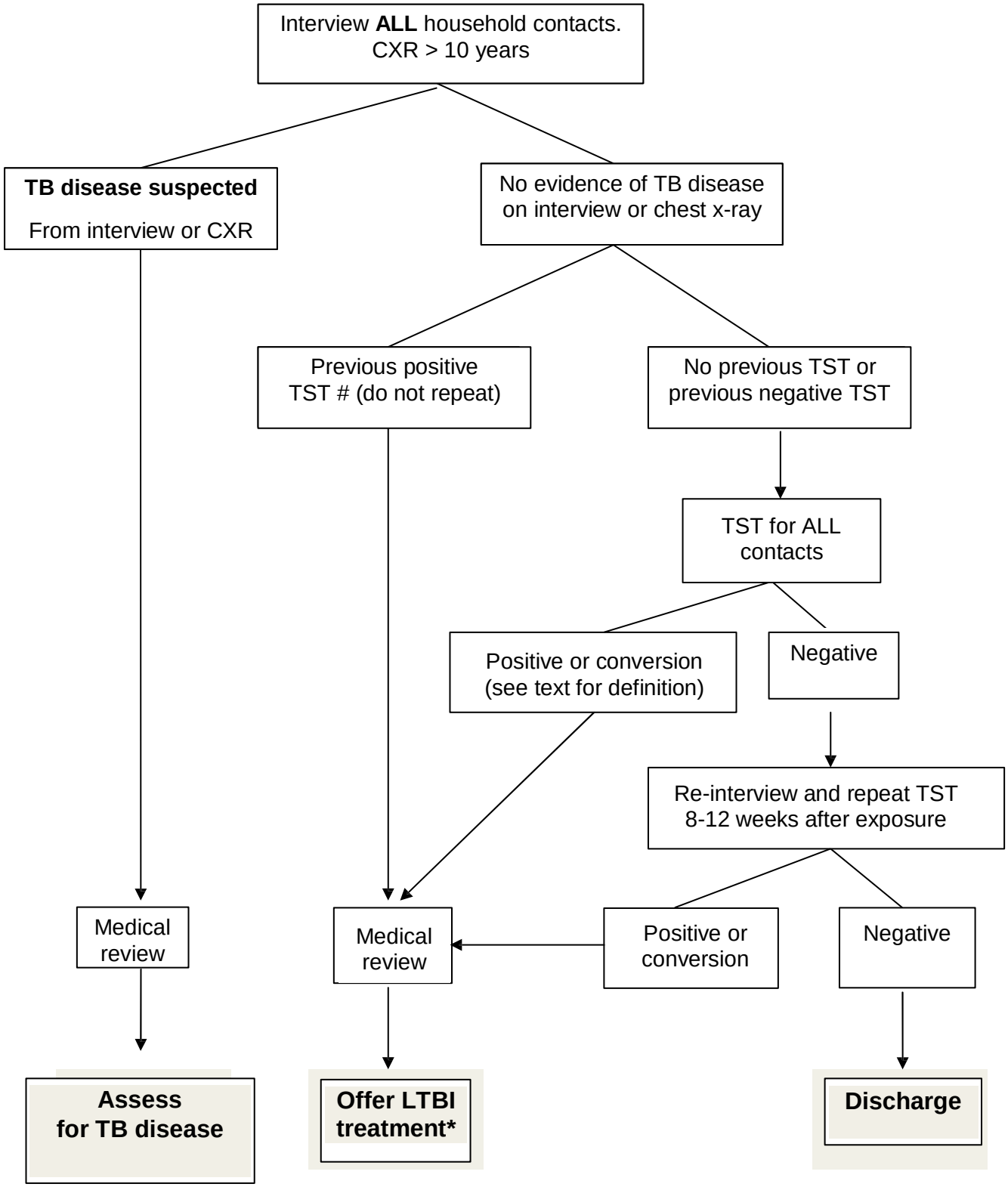
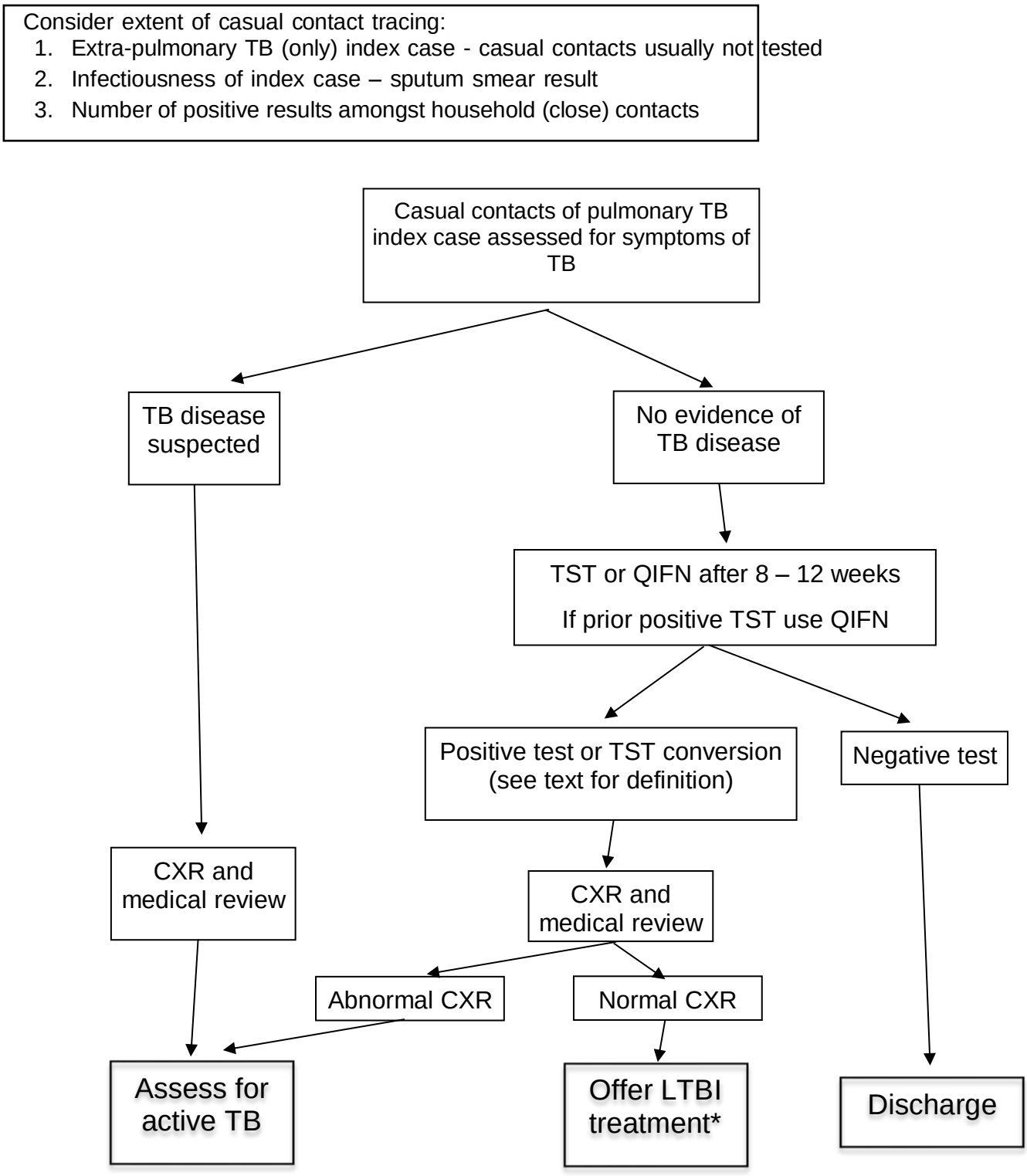
Appendix 5.1 Algorithm for Investigation of Household (Close) Contacts of TB.

NOTE:
For age > 5 years (for younger contacts see Table 18)
In high-risk contact, a highly infectious index case or pre-disposing conditions in the contact, consider treatment for latent TB infection.
* For those who decline treatment for latent TB infection, then follow up for 2 years.



CXR = chest x-ray TST = tuberculin skin test LTBI = latent TB infection

Appendix 5.2 Algorithm for Investigation of Casual Contacts of TB



NOTE:
In high-risk contact, a highly infectious index case or pre-disposing conditions in the contact, consider treatment for latent TB infection.
* For those who decline treatment for latent TB infections, then chest CXR follow up for 2 years
CXR = chest x-ray TST = tuberculin skin test LTBI = latent TB infection

5.2 Post-migration Screening

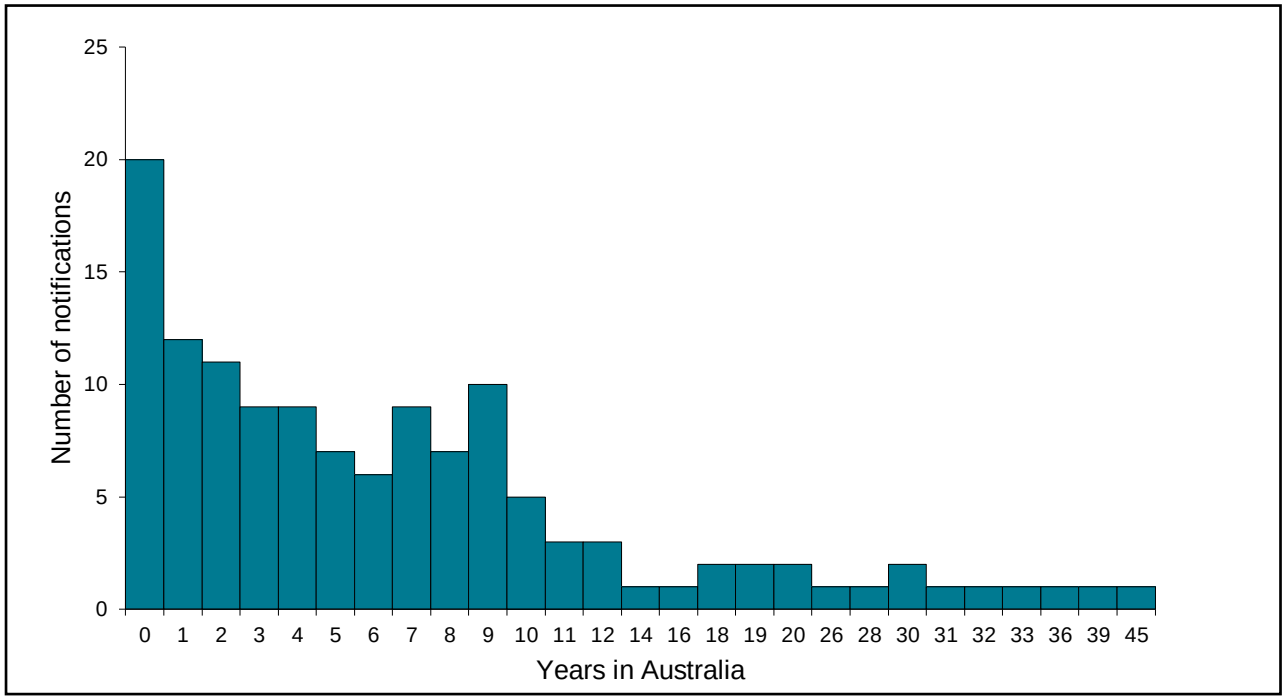
Introduction

Most TB diagnosed in Australia occurs in migrants. Of the 1,339 cases of TB notified in Australia in 2014, 86% (n=1,151) of cases occurred in overseas-born people with their rate being 17 times the rate of TB in the Australian born population (19.1 per 100,000 versus 1.1 per 100,000 population). The rate of TB in overseas born cases has remained relatively stable since 2010 (CDNA 2015).

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. Strengthening migrant TB screening programs is an area of particular focus. Secondary and tertiary students from TB endemic countries as well as health care workers born overseas are important subgroups to target.

Almost 30% of TB diagnosed in overseas-born people in WA occurs within the first two years of arrival (*Figure 5.2*), therefore screening for TB in this population must be done in a timely fashion.

Figure 5.2 Tuberculosis Notifications in the Overseas-born Population in Western Australia, 2016 by number of years since arrival in Australia.



Rationale

The purpose of screening recently arrived migrants from TB endemic countries is:

- To detect individuals with TB disease who require treatment, and also to prevent secondary TB cases.
- To detect LTBI in order to offer latent TB treatment, especially in those under 35 years of age.

Screening, investigation and treatment for both TB and latent TB infection in migrants should be provided at no cost to the patient regardless of their visa status.

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 tuberculosis incidence refer to the WHO website http://www.who.int/tb/country/data/profiles/en/index.html* (WHO 2018).

LTBI testing should be prioritised for:

- Migrants (from any country) with a history of TB contact within the last 2 years or
- Migrants from countries with a high incidence of TB as stated above who are:
    - Aged 35 or under or
    - Aged over 35 with one or more risk factors for reactivation (see section *3.1 Latent TB Infection – Diagnosis*)

Migrant Screening

Pre migration

Migrants, refugees, irregular maritime arrivals (IMA) 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 (“Immigration”) and may take place off-shore, where the testing and assessment is delegated to authorised “panel physicians”; or on-shore, where the process is contracted to non-government health assessment companies.

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 three sputum samples for AFB smear and culture, they are reassessed clinically and have a repeat CXR in 3 months. For on-shore applicants in WA, this testing takes place at the WA TB Control Program.

In applicant children under 10 years of age a TST or Quantiferon test is performed, and CXR (as well as sputum tests) are only required if there is clinical evidence of TB or a positive LTBI test. If the test for LTBI 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 (see below).

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 on-shore, 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 WA TB Control Program in the following circumstances:

- TB Health Undertaking (TBU): A TBU is required for individuals identified on pre-migration as having had past TB, those who have a suspicious CXR (but no proven TB) or those not fully screened (e.g. due to pregnancy). The TBU, although not legally binding, requires the migrant to contact the Department of Home Affairs soon after their on-shore arrival and to declare their residential address. This prompts referral to the nearest jurisdictional TB service (TB Control Program in WA). The further assessment and management, including any subsequent follow up is entirely at the discretion of the physician seeing the migrant at the WA TB Control Program. The primary objective remains exclusion of post-migration TB, but testing and treatment for LTBI should be considered.
- 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 Quantiferon test in individuals aged between 2 – 35 years. Those with a history or CXR changes of possible or treated TB, or a positive Quantiferon test; are referred to the WA TB Control Program for further assessment and LTBI treatment.
- Opportunistic screening: Any migrants referred to the WA TB Control Program should be assessed for TB and testing and treatment for LTBI offered; 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.

Active surveillance for TB, including testing for LTBI, is not currently done systematically in WA, apart from in refugees attending HEHS.

Clinical assessment

Assessment of TB risk in migrants from high incidence countries includes the following:

- Country of origin or recent residency.
- Past history of TB

- History of TB treatment
- Contact with TB cases
- Any recent CXR or tests for TB pre-migration e.g. sputum examination, TST, IGRA

Investigations

Tuberculosis

If TB is suspected in a migrant, the clinical assessment, investigation and treatment of the disease should not differ from the general population. See section *1.2 Diagnosis of Tuberculosis - Clinical*.

Latent TB Infection

Both TST and Interferon Gamma Release Assays (IGRAs), such as the Quantiferon test, are acceptable for the diagnosis of LTBI in migrants. See section 3.1 Latent TB Infection - Diagnosis.

Management

The treatment and management of TB or latent TB infection 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 LTBI please see the relevant preceding sections.

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.

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5.3 Health Care Workers

Background

TB is uncommon in Australia and rare in staff members 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 among health care staff (Stuart et al 2001, Menzies et al 2007). In addition, increasing numbers of staff 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 (National Tuberculosis Advisory Committee (NTAC), 2009). The most recent national TB notification report for Australia described 77 cases in health care staff in 2013, of which 24 were working in health care at the time of diagnosis (National Tuberculosis Advisory Committee (NTAC), 2015).

Pre-employment Surveillance for Tuberculosis

Rationale

- Future staff members may be exposed to TB in the course of their work. Baseline assessment of TB status is useful in the post-exposure assessment.
- Future staff members may have LTBI, 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.
- Future staff members may have tuberculosis.

Risk Assessment

All staff of health care facilities, or students undertaking tertiary education that involves clinical work, should be assessed for risk of TB prior to starting clinical work. 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 staff member with written documentation of prior TB assessment moves to a new health care facility or re-starts work in health; pre-employment TB assessment does not need to be repeated. Repeat TB assessment may be considered if a staff member has had TB exposure subsequent to 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 staff 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 staff working in health care facilities.

Pre-employment TB risk assessment includes three components:

1. History indicating risk of prior TB infection, which includes:
   - Having been born in a high TB incidence country (rate > 40 / 100 000 population, for tuberculosis country profiles (see http://www.who.int/tb/country/data/profiles/en/)
   - Residence and/or work in a high incidence country for more than 6 months;
   - Past history of TB disease or treatment; and
   - Past history of contact with TB (work or personal).

Staff who have any of the above in their history are considered to have high risk for LTBI, and referred to as Group 2 in the Proforma (see *Appendix 5.3* and *Appendix 5.4)*. Staff who have none of these have a low risk for LTBI and are referred to as Group 1 in the Proforma (see *Appendix 5.3* and *Appendix 5.4)*.

2. Predicted probability of future occupational exposure

The probability of future TB exposure should be categorised according to staff members' likely contact with TB (see *Table 5.3*). Note that this does not refer to the risk of latent TB infection in any particular individual (assessed in risk assessment above), or the risk of transmission of TB when contact tracing is undertaken (discussed in section *5.1 Contact Tracing*) but rather an assessment of the likelihood of exposure to TB from patients in particular staff member roles. High & medium probability groups are distinguished because the staff in the high probability group must also be considered for routine follow up screening in addition to pre-employment screening (see *Routine Follow-up Tests* below).

Table 5.3 Predicted Probability of Future Occupational TB Exposure

High probability	Medium Probability	Low probability
Staff 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,	Staff with regular contact with patients that are not in a high probability category.	Staff who do not usually have contact with patients (e.g. clerical, administrative, non-microbiological laboratory staff)

3. Other useful information, which includes:
    - Previous TST results;
    - Previous BCG vaccination;
    - Medical history and medications that may compromise immune response; and
    - 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 QIFN) is available, tests do not need to be repeated i.e. 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 staff working in a clinical setting:

- 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), and do not have any history indicating likely TB exposure, are not required to have any test.

There should be no financial impediment to staff undertaking TB screening or any necessary treatment. Institutions should provide these free of charge to employees and students as outlined in section *8.1 Fees and Charges Related to the Diagnosis and Management of Tuberculosis and Leprosy*.

The result of the test must be given in written form to the employee or student. A record of the pre-assessment and results of tests must be kept by each Health Service Provider.

Which Screening Test for LTBI Should Be Used?

The tests available for screening for LTBI in staff are the tuberculin skin (TST) and the QuantiFERON TB assay (QIFN). The National TB Advisory Committee (NTAC) has recently changed its recommendation (NTAC 2017, *in press*) to state that TST and QIFN are equivalent tests for LTBI in staff working within health other than those staff requiring annual testing.

This guideline recommends that either test can be used to screen for LTBI in staff. The important exception to this recommendation is those staff working within health requiring annual testing i.e. identified in the “High probability of future occupational exposure” in *Table 5.3* above. This group should be screened at baseline with a TST, as detailed below in subsection *Routine Follow-up Tests*.

The advantages and disadvantages of the two tests are summarised below:

Tuberculin Skin Test (TST)

Advantages:

- Cut-offs for a positive result and conversion are well supported by research data; and
- 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. 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 Assay

Advantages:

- Convenience - a blood sample for QIFN 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 non-tuberculous mycobacteria (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 QIFN testing (Mazurek et al, 2005); and
- Results are recorded and easily retrieved from a results database such as iSoft.

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 staff that have routine follow up screening (see below subsection *Routine Follow-up Tests*); and
- 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 WA Tuberculosis Control Program does not routinely provide pre-employment screening testing, however this can be provided in certain circumstances and only by prior arrangement with the TB Nurse Manager.

WA TB Control Program nursing staff are available to train practitioners in the provision of TST testing. This training can be arranged through the TB 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 staff member
- A record of the TST (including date of the test and the reading) must be kept by the health service provider, with a copy given to the staff member
- 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 a algorithm given in *Appendix 5.3B*.

Staff with a positive TST, or a positive or indeterminate QIFN, require a CXR and medical evaluation by a medical practitioner experienced in TB management. The WA TB Control Program 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.

Management of TB in a Health Care Setting

A staff member suspected of, or diagnosed with, TB should be urgently referred (appointment within 1 week) to a TB physician at the WA TB Control Program, 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 staff member before disclosure of details of the infection to the employer;
- The practitioner making the diagnosis is required, under the *Public Health Act 2016* to notify the Communicable Disease Control Directorate;
- The staff member is to be excluded from the workplace, if diagnosed with pulmonary TB, until cleared by the medical supervisor nominated by the institution in consultation with a medical practitioner experienced in TB management; and
- The staff member must complete a satisfactory course of treatment and follow up, with appropriate certification provided to the institution by the treating doctor.

Post Exposure Follow-up

When a hospital inpatient, other clinical setting resident or staff member is diagnosed with TB, follow up of other staff 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 this 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 contact", 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 an patient with pulmonary TB and sputum that is smear positive for acid fast bacilli (AFB), who has not been isolated or where a breach of airborne precautions has occurred. See 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 that have 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 that have contact with an index case (either patient or staff) 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.

- Staff that have contact with an index case (patient or another staff member) are considered casual contacts.
- All contacts of a staff member 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 QIFN was performed initially, a repeat QIFN should be done; if the baseline test was a TST or there is no baseline, a TST should be done; and
- If the TB test is positive or converts (as compared to the baseline test), a CXR is required and the staff member should be referred to a medical practitioner experienced in TB management (as described above).

The responsibility for contact tracing of staff 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 WA TB Control Program, 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 hospitals, 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 staff members of possible occupational TB exposure is given in *Appendix 5.7*;
- Communication with Senior Health Service Executive or other 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 WA TB Control Program through the Communications Department, NMHS;
- Ensuring the privacy and confidentiality of the index case.

Routine Follow-up Tests

Repeat TB screening tests or CXR are not recommended routinely. However, testing is warranted in certain staff 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 5.3*).

These staff should have a baseline TST, rather than a QIFN test for reasons described above. If the baseline TST is negative, these employees should be offered an annual TST. If the TST is positive, then annual CXR can be considered. Any change in the TST result should prompt referral to the WA TB Control Program or an appropriate alternative TB specialist for assessment.

BCG Vaccination

BCG vaccination is not recommended for staff working within health in Western Australia.

Responsibilities for TB Infection Control

Health care facilities

Health care facilities should:

- Periodically review a TB infection control policy for the facility and ensure that all staff 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;
- 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* (National Tuberculosis Advisory Committee 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); and
- Supply appropriate personal respiratory protection. 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 staff.
- Ensure staff receive appropriate training on donning and performing a fit check or fit test for all types of P2 and 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 (National Tuberculosis Advisory Committee, 2006);
- Educate staff 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; and
- Exclude staff who are HIV positive, or otherwise immune-compromised or immunosuppressed form work in an environment with known or suspected infectious TB patients.

Western Australian TB Control Program

The Western Australian TB Control Program can be contacted for further information on any aspect of TB management, and to provide:

- Specific advice to the Health Service Provider about pre-employment screening, post-exposure contact tracing and maintenance of infection control infrastructure and policy;
- Training in TB infection control and health staff TB risk management. This includes training in TST if this is the screening test chosen by the institution; and
- A consultative service for review of staff with positive tests for LTBI 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: _____
Employee or student number: _____

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 http://www.who.int/tb/country/data/profiles/en/index.html*

What is the risk of TB contact from work?

What is the proposed area in which you will be working 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: _____
Have you had a BCG vaccination? ☐ No ☐ Yes - When: _____
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 ☐Yes - Visa expiry date: _____

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: _____

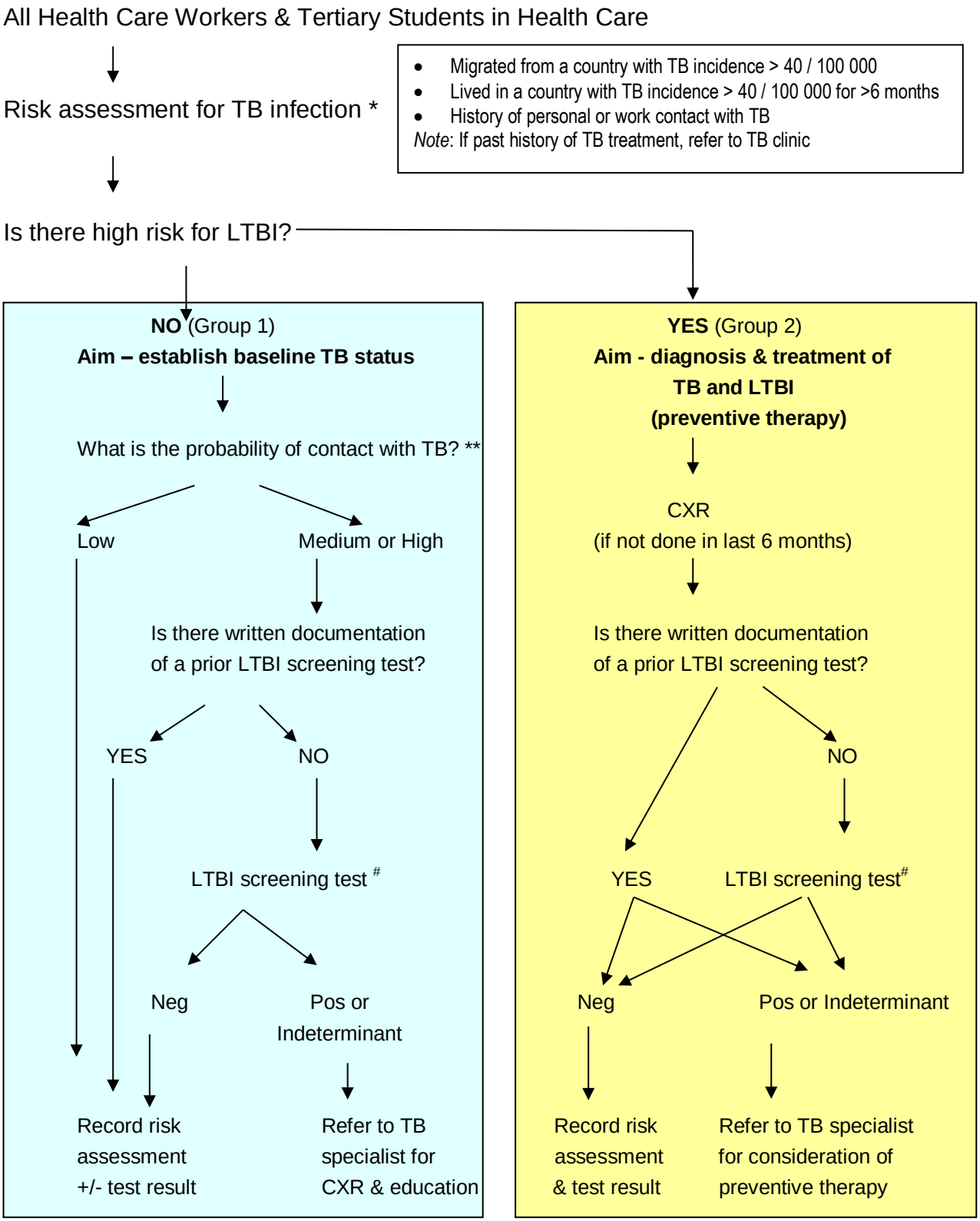
Test used: ☐TST – result: _____ mm

☐QuantiFERON – result: _____

CXR done? ☐ No ☐Yes Result: _____

Referred to TB specialist? ☐ No ☐Yes Where: _____

Appendix 5.4 *Algorithm for Pre-employment TB Screening Tests*



Notes

*	See text and *Appendix 5.3*, for definition
**	See text for definition
LTBI	Latent TB Infection
CXR	Chest x-ray
#	TST or QIFN.

Appendix 5.5 TB Fact Sheet for Future Health Care Staff or Students

Pre-employment tuberculosis screening fact sheet for future health service staff members 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 because 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 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 TB) and to see a TB specialist doctor who will discuss with you what the result means and what can be done about it.

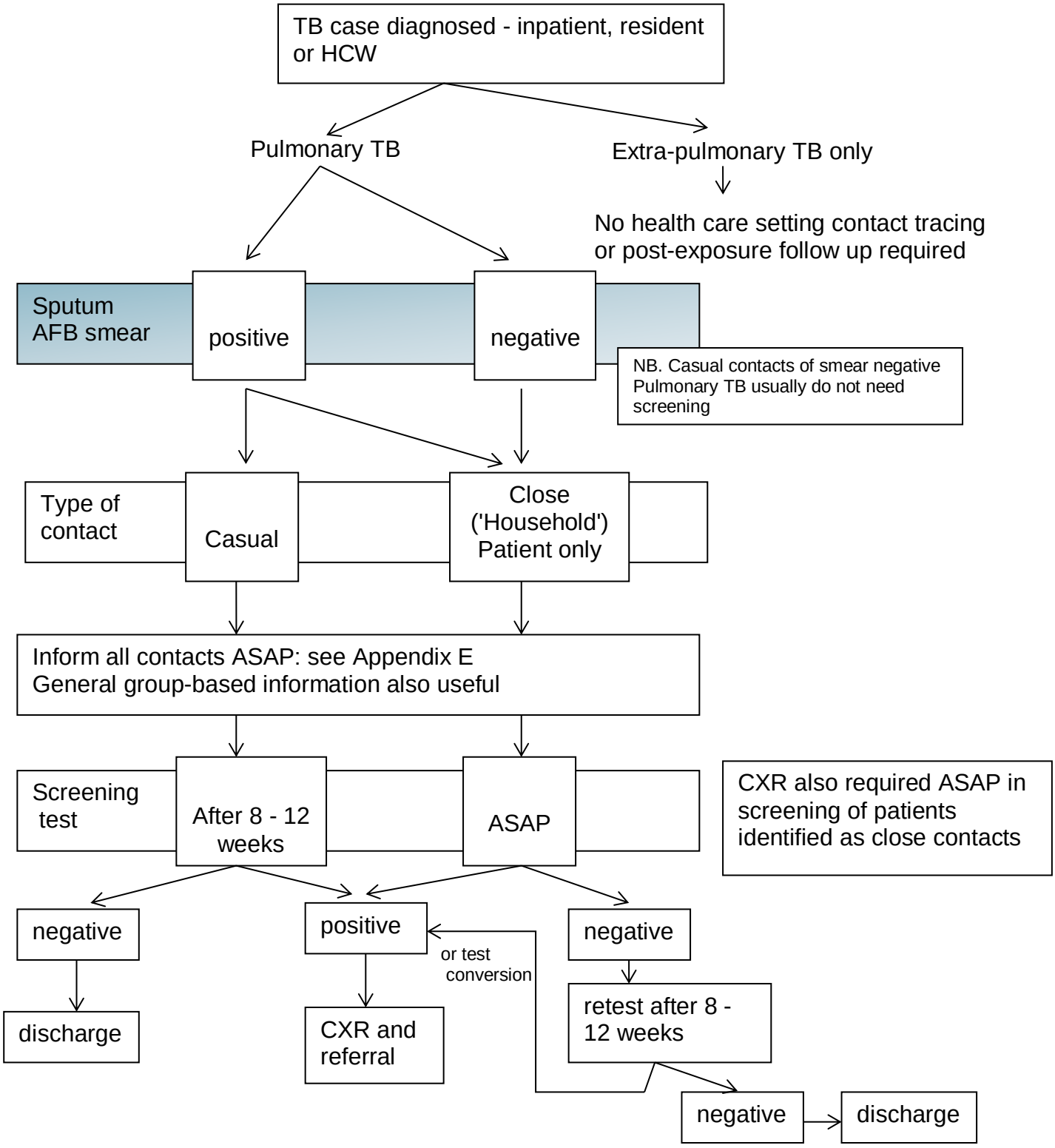
What if you think you have TB?

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 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 90222 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 attended to this 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

Introduction

Tumour necrosis factor alpha (TNFα) antagonist therapy is increasingly being used in rheumatology, dermatology and gastroenterology for disorders such as rheumatoid arthritis, psoriasis and inflammatory bowel disease. The TNFα antagonist agents currently available in Australia are:

- Etanercept (Enbrel)
- Adalimumab (Humira)
- Infliximab (Remicade)
- Certolizumab (Cimizia)
- Golimumab (Simponi)

TNFα antagonist therapy is associated with an increased risk of TB acquisition and reactivation of LTBI. Tuberculosis, either disease or latent infection, is not a contraindication to TNFα antagonist therapy. 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.

Non-antiTNF drugs (e.g. Abatacept, Rituximab,Tocilizumab) have the same recommendation from the American College of Rheumatology(2015), although these agents tend to have no increased risk of TB reactivation (Cantini, F., Nannini, C., Niccoli, L., & al, 2017). Therefore, this policy applies specifically to TNFα antagonist therapy only. The risk of TB reactivation should still be considered in other patients treated with non- anti TNF drugs.

Role of TNFα

The release of tumour necrosis factor alpha (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 (Gardam & al, 2003; Wolfe & al, 2004). The presence of granulomas is protective to the host and limits tissue damage. Therefore, any 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 and cause necrotising reactions and damage to tissues and organs (Gardam & al, 2003). TNFα mediates systemic inflammation, which manifests clinically as cachexia.

Tuberculosis and TNFα Antagonist Therapy

Patients on TNFα antagonists have an increased risk of reactivation LTBI and an increased susceptibility for acquisition of primary TB (Keane, Gershon, Wise, & 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 & al, 2009).

TB may develop soon after the initiation of TNFα antagonist therapy with the median time to onset being 3 months (Keane & al, 2001). Patients who develop tuberculosis have a higher proportion of extra-pulmonary and disseminated forms of TB compared to the non-immunosuppressed population (Keane & 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.

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. health care workers

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 two 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 Latent TB Infection (LTBI)

The assessment of a patient for TB infection involves:

- Taking a good history to assess risk of TB infection and exclude TB disease
- A latent TB infection 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 LTBI?

The Australian Rheumatology Association and other guidelines (Gupta, Street, & Macrae,2010) recommend a test for LTBI in all patients starting TNFα antagonist therapy. The American Thoracic Society (2011) recommends that a screening test for LTBI be done only if there is an identifiable risk factor for LTBI. The WA TB Control Program recommends testing for LTBI in all patients starting TNFα antagonist therapy because of the potential serious

consequences of TB reactivation in this immunosuppressed population if LTBI is not treated. Some patient 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 LTBI 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 LTBI?

Either TST or QIFN can be used, but the WA TB Control Program recommends the QIFN. QIFN has a positive control that reduces the chance of false negative results due to anergy, which is more common in patients with autoimmune conditions receiving immunosuppressive therapy. A falsely negative TST due to anergy is indistinguishable from a genuinely negative TST, whereas a QIFN test will be indeterminate in a strongly anergic patient.

TB Management and TNFα Antagonist Therapy

Any patient with symptoms or signs of TB or those with a positive or indeterminate QIFN 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 LTBI screening test was negative or treatment for LTBI has been given.

Patients with TB detected after the commencement of TNFα antagonist therapy should cease their biological therapy, minimise the use of other immunosuppressants and be referred for TB treatment. Pulmonary and extra-pulmonary TB diagnosed, either before or after commencement of TNFα antagonist therapy, should be treated with standard TB treatment (see section *2.1 TB Treatment - Medical*). It is preferable to delay further TNFα antagonist therapy until completion of the full course of TB treatment. However, if this is not possible, TNFα antagonist therapy should be withheld until at least 2 months after initiation of TB treatment. TNFα antagonist therapy can then be commenced provided the patient is adherent to TB therapy, drug susceptibilities are known and there is good evidence of response to TB treatment (British Thoracic Society Standards of Care Committee, 2005).

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 tuberculosis 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 LTBI 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 LTBI e.g. isoniazid monotherapy in this circumstance is not recommended. If the prior treatment was adequate there is no need for further LTBI treatment.

If prior TB treatment is considered inadequate but there is no current evidence of TB, assessment for further treatment prior to the start of TNFα antagonist therapy should be made by a physician experienced in TB.

Latent TB Infection

Patients with LTBI should be given standard preventive treatment before commencing TNFα antagonist therapy (see section *3.2 Latent 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 & al, 2006).

TNFα antagonists can be commenced in patients with LTBI once they are established on preventive therapy and do 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 LTBI 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 LTBI test results would be reasonable, as is the case in HIV infected individuals.

TB Re-infection after Preventive Therapy whilst on TNFα Antagonist Therapy

Re-infection after prior treatment for TB or latent TB infection 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 QIFN are likely to be positive from previous TB infection. 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.

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Chapter 6: BCG Vaccination

6.1 BCG Vaccination

Introduction

BCG (Bacille Calmette-Guérin) vaccine is a suspension of a live attenuated strain of *Mycobacterium 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 TB meningitis (BCG vaccines: WHO position paper – February 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).

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). BCG should be given 2 – 3 months prior to departure. For country specific incidence rates see the World Health Organisation TB country profile website http://www.who.int/tb/country/data/profiles/en/index.html
- 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 or a family history of 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 all individuals 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 WA TB Control Program Medical Director or Clinical Nurse Manager can be contacted to assist.

BCG Contraindications

Immunisation service providers should undertake a comprehensive pre-vaccination health screen on all individuals pre- vaccination. Refer to the Australian Immunisation Handbook for a detailed explanation of the required pre-vaccination checklist. Other contraindications and precautions to consider for BCG vaccination are outlined below:

- Anaphylaxis following a previous dose of BCG vaccine
- Anaphylaxis following any component of BCG vaccine
- Infants with a body mass < 2.5kg
- Individuals who are immunocompromised (increased risk for disseminated BCG infection)
- 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 is 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 or eczema, dermatitis and psoriasis. Vaccination should be deferred until the condition clears.
- Individuals who have received a live vaccine (MMR,Varicella,Yellow Fever) until 28 days have elapsed, 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.

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 as follows and 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 >40/100,000
- Previous travel to a country with an annual TB incidence >40/100,000
- Exposure to an individual with TB disease
- Contact with an individual with a positive TST or IGRA or an individual with symptoms compatible with TB (see N 6 below).
- Current or previous household visitor from a country with an annual TB incidence >40/100,000
- Symptoms compatible with TB disease including persistent (>2 weeks) cough, weight loss, fever or night sweats.

In individuals with LTBI or TB disease, BCG can be associated with an increased risk of an accelerated reaction with development of induration at the injection site of 5mm or more within 24 – 72 hrs. (Ritz et al, 2012)

The use of IGRA pre BCG is not recommended as there is insufficient data on the predictive value of IGRA in children and none in the setting of screening prior to BCG vaccination.

General Considerations

- Repeat BCG vaccination is not recommended.
- BCG vaccination should only be administered by appropriately trained health care providers. The WA TB Control Program 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 has a result which is < 5mm induration.

BCG Vaccine Administration

- The vaccine should not be exposed to direct sunlight or heat and should be stored between 2^0C and 8^0C.
- 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^oC and 8^oC 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 vaccine must be entered in AIR.
- Please refer to the WA TB Control Program - Intradermal BCG Injection Guideline for further information on how to administer BCG.

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 (BCG vaccines: WHO position paper).
- 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 when BCG vaccination is given to an immunocompromised individual.
- BCG immune reconstitution inflammatory syndrome (IRIS) occurs in association with HIV infection (BCG vaccines: WHO position paper – February 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)

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 (> three 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 WA TB Control Program Paediatric TB clinic for medical review and consideration for preventive therapy to minimise the risk of progression to TB disease.

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Chapter 7: Notification of Tuberculosis and Enhanced Surveillance

7.1 Tuberculosis Notification and Enhanced Surveillance

Introduction

It is a legal requirement for clinicians and laboratories to notify TB cases in children and adults to the WA Department of Health. Latent tuberculosis infection (LTBI) does not need to be notified. This chapter is a guide for clinicians on the process of mandatory notification of tuberculosis and enhanced surveillance requirements.

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*. As per section 94 of the Act, medical, nurse practitioners and pathology laboratories are legally required to report the diagnosis of notifiable infectious diseases, including *M. tuberculosis* infection, 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 or nurse practitioner that 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 two 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.

Case Definition of Tuberculosis

Only confirmed cases of tuberculosis should be notified to the Department of Health. A confirmed case of tuberculosis is defined by the Communicable Diseases Network Australia (CDNA) for state and national surveillance in *Table 7.1* below.

TB should be notified whenever diagnosed, even if it is not confirmed 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 tuberculosis.

Table 7.1 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.

Laboratory definitive evidence

1. Isolation of *Mycobacterium tuberculosis* complex (M. tuberculosis, M. bovis or M. africanum, 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.

Clinical evidence

A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis, including clinical follow –up assessment to ensure a consistent clinical course.

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 Communicable Disease Control Directorate (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: Notification Form. 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 WA TB Control Program. 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 WA TB Control Program. These are immediately faxed to CDCD for data entry. Conversely, notifications received by CDCD, once entered into WANIDD are faxed to the WA TB Control Program to ensure the program is aware of the newly identified case. The fax is received and processed by the Clinical Nurse Manager

at the WA TB control program or their delegate. The Mycobacterial Reference Laboratory, in addition to sending electronic notifications to CDCD, also notifies the WA TB Control Program of all new positive *M. tuberculosis* microbiology results by fax.

Cases of TB treated in WA but diagnosed in another state or country are not notifiable. The WA TB Control Program is responsible for providing surveillance data back to the notifying state or country as required and where possible.

Enhanced Surveillance

For tuberculosis, additional information such as risk factors, site of disease and antibiotic sensitivities 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 WA TB Control Program. The definitions of the data fields for enhanced surveillance are provided by the Australian Government Department of Health and Ageing (DoHA).

Enhanced surveillance data for tuberculosis are maintained as a separate module in WANIDD, with staff of the WA TB Control Program 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. 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 tuberculosis. Treatment outcome is classified according to *Table 7.2* below.

Table 7.2 Tuberculosis Treatment Outcome Classification

Outcome	Definition
Cured	A pulmonary sputum smear positive and culture positive case who was culture negative in the last month of treatment and on at least one previous occasion and completed treatment.
Completed treatment	Case who has successfully completed treatment but who does not meet the criteria to be classified as a cure or a failure.
Interrupted treatment	Case whose treatment was interrupted for two months or more but completed treatment.
Died of TB	Case died prior to treatment commencing OR during the course of treatment as a result of TB disease or the effects of TB treatment.
Died of other causes	Case died during the course of treatment of a cause other than TB disease or an unknown cause.
Defaulter	Case defaults from treatment
Treatment failure	A case who is sputum culture positive at 5 months or later during treatment.
Transferred out	Case who has been transferred overseas and treatment outcome is unknown.
Still under treatment	Case currently under treatment in Australia.
Not followed up; Outcome unknown	Case should have completed treatment in Australia but outcome is unknown.

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 3 months should be sent from the receiving jurisdiction back to the jurisdiction that originally notified the case. The WA TB Control Program 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 two weekly basis by designated staff at CDCD who then request staff of the WA TB control program 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 Department of Health and Ageing and the National Tuberculosis Advisory Committee. Requests to complete missing data fields are emailed to the WA TB Control Program prior to submission.

In May each year, TB notifications reported during the entire previous 12 months are reviewed at the WA TB Control Program, 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 WA TB Control Program. This report is presented to the WA Tuberculosis and Leprosy Advisory Council (WATLAC) and made available to WA TB Control Program clinical staff and other relevant stakeholders. It is not published publicly, but it is available upon application to the Medical Director of the Tuberculosis Control Program.

National Notifiable Diseases Surveillance System (NNDSS)

The National Notifiable Diseases Surveillance System (NNDSS) was established in 1990 and is maintained by the Australian Government Department of Health and Ageing (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 on a daily basis 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.

A sub-committee of CDNA, the National Tuberculosis Advisory Committee (NTAC), which has representatives from State and Territory tuberculosis control programs, provides guidance on public health management and surveillance of tuberculosis in Australia, and has oversight of the enhanced surveillance data collection. In addition to the daily electronic transmission of core surveillance data on notified tuberculosis 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.

Access to data from outside the WA TB Control Program

Occasionally individuals or groups that do not work within CDCD or the WA TB Control Program will request access to TB data from WANIDD or the enhanced surveillance dataset. These individuals will be required to provide a written submission to 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.

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Chapter 8: Fees and charges

8.1 Fees and Charges Related to the Diagnosis and Management of Tuberculosis and Leprosy

The WA TB Control Program's policy states that individual patients should not incur any financial cost for the investigation of possible TB or leprosy, and 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: 2016 - 2020 [National Tuberculosis Advisory Committee].

All fees and charges associated with TB and Leprosy management within WA Health are to be waived by the Health Service managing the care of the patient. However, 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). If WA Health is requested to take on extra work by other parties, WA Health may issue invoices to the other parties for the goods and services provided. These invoices may include fees and charges for, but are not exclusive of, radiology, pathology, pharmacy and inpatient services.

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, and should therefore be dispensed free of charge.

Accounts for tests or inpatient charges to individual patients diagnosed with TB or leprosy should be waived. This policy also applies to patients that are not Medicare eligible. Individual patients that receive accounts for these services 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.

Individual patients may be referred to the WA Tuberculosis Control Program 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 2019/20* under section *2.5 Treatment of Patients with Notifiable Infectious Diseases* and section *7.2 Medical Services and Treatment Exempt from Charges.*

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Policy Sponsor	Director Public Health MHPHDS NMHS				
Policy Contact	Medical Director WA Tuberculosis Control Program				
Date First Issued:	30/10/2019	Last Reviewed:	N/A	Review Date:	30/10/2022
Approved by:	WA Tuberculosis Control Program			Date:	25/10/2019
Endorsing Committees	WA Tuberculosis and Leprosy Advisory Council Public Health Policy Committee Public Health Executive Committee			Date: Date: Date:	22/10/2019 22/10/2019 25/10/2019
Endorsed by:	Director Public Health MHPHDS NMHS			Date:	30/10/2019
Standards Applicable:	NSQHS Standards (V2.0):				
Printed or personally saved electronic copies of this document are considered uncontrolled					

The health impact upon Aboriginal people have been considered, and where relevant incorporated and appropriately addressed in the development of this health initiative (IS29P1019).

Document Version Control			
Date	**Version**	**Author**	**Notes**
30/10/2019	V1.0	Medical Director WATBCP	Initial endorsement. Previous policy documents merged into one document.

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