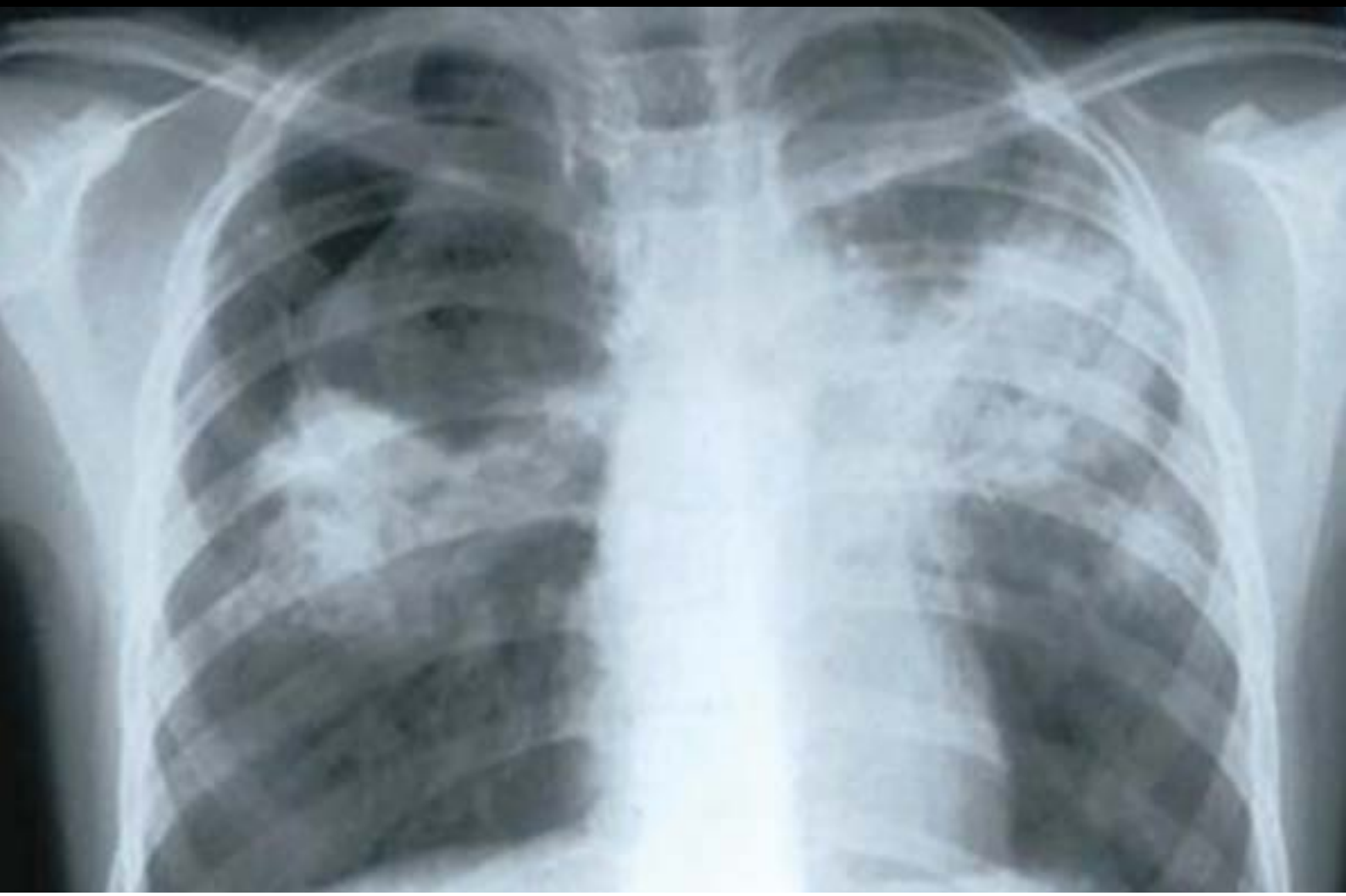
Management, control and prevention of tuberculosis

Guidelines for health care providers



Department of Health & Human Services

State Government Victoria

Management, control and prevention of tuberculosis

Guidelines for health care providers

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To receive this publication in an accessible format phone 1300 650 172 using the National Relay Service 13 36 77 if required, or email <infectious.diseases@dhhs.vic.gov.au>.

Authorised and published by the Victorian Government, 1 Treasury Place, Melbourne.

Available at: <http://ideas.health.vic.gov.au/publications.asp>

Printed by Digital House, South Melbourne on sustainable paper (1411005)

Acknowledgments

In addition to the contributing authors listed above, the Department of Health & Human Services thanks those who authored chapters in previous versions of the guidelines, because these formed the basis for many chapters in this version. The Department of Health & Human Services also wishes to thank the following people for their time and contribution to the guidelines:

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Chapter 1 Introduction

Tuberculosis (TB) continues as a global public health threat predominantly affecting low- and middle-income countries. In 2012, 8.6 million people became ill with TB (including an estimated 450,000 cases of multidrug-resistant TB) and 1.3 million people died from TB.[3, 4] In May 2014, the World Health Assembly adopted the WHO's post-2015 global TB strategy, which aims by 2035 to reduce global TB incidence by 90 per cent and TB deaths by 95 per cent. To support these goals, the WHO and others have developed a framework to target pre-elimination and, ultimately, elimination of TB from low TB-incidence countries such as Australia.[4] These guidelines can be used as a practical tool to support clinicians and public health staff in the quest to reduce and ultimately eliminate TB from Victoria.

Active TB is primarily a disease of human stress due to overcrowding, poverty, poor living conditions, malnutrition, associated illnesses such as HIV co-infection and/or AIDS, malignancies, diabetes and the stress of migration, relocation and family disruption. In contrast to the current world situation, Australia is fortunate in having a low but relatively constant pattern of TB. In the last decade, there have been 1062–1384 (median 1,241) new TB cases notified each year in Australia and 322–436 (median 365) new cases notified each year in Victoria (National Notifiable Diseases Surveillance System). Nearly 90 per cent of Australia's TB notifications occur in people born overseas, with 30 per cent of these cases reactivating in the first two years of residence in Australia.[2] There is evidence of only a low level of person-to-person transmission within Australia, mainly in specified risk groups.

Following inhalation and deposition of infected droplet nuclei on the bronchial mucosa, the *Mycobacterium tuberculosis* organisms are ingested by macrophages and transported into the pulmonary lymphatic system. In the majority of people exposed to infected droplet nuclei, their pulmonary macrophages do not destroy the organisms by phagolysis, but rather the organisms are able to inhibit the phagolytic process, and thus replicate within the macrophages while being transported to regional lymph nodes or to the pleura.

This replication occurs prior to the development of effective cell-mediated immune responses, which normally take 6–12 weeks (currently demonstrated by tuberculin skin test conversion). However, in highly susceptible persons, extensive lymphatic and haematogenous spread can occur in this period, resulting in widespread seeding of TB, particularly in children and in those who are immunosuppressed for whatever reason. This seeding occurs through lungs, brain, lymph nodes and other organs such as bones and kidneys. Miliary TB, TB meningitis and TB septicaemia are life-threatening consequences and still represent major causes of death from TB around the world today. It should be noted that over the past couple of centuries, when previously unexposed indigenous populations have been exposed to TB infection, high mortality rates from TB disease would follow, due to a rapidly progressive, septicaemic illness of only a few weeks duration in a manner similar to typhoid fever.

In most exposed people, however, the pulmonary macrophages remain contained at the site of infection and in the local regional lymph nodes. This results in the development of a primary granulomatous lesion (Gohn's focus), including a local area of pneumonitis and swelling of regional lymph nodes, healing by resolution and scarring, with eventual deposition of calcium within the scar tissues. Within this scar tissue, residual infected macrophages can be identified containing bacilli that have gone into a state of 'dormancy' or latency, and which are maintained in this state by the individual's normal cell-mediated immunity. This state of latency can last for many decades, more often than not until the death of the host, unless some event occurs which results in impairment in the cell-mediated defence mechanisms. It is this ability of *M. tuberculosis* to change its metabolic state to that of dormancy over many decades that accounts for the persistence of the organism within the macrophage environment, and the potential for reactivation at any time, resulting in possible onwards transmission to other individuals.

When impairment of cell-mediated defence mechanisms occurs, the bacilli may become metabolically active again, replicate and move outside the macrophage into the surrounding tissues. This event is known as 'reactivation', and is the usual pattern of disease development in most cases of active TB seen in our community at this time. In general terms, only 5–10 per cent of all those who have been infected with TB actually develop active disease at some time in their lives, with the greatest period of risk being in the first two years after infection. What has dramatically changed the world TB situation is the advent of HIV co-infection which has transformed a 5–10 per cent lifetime risk of reactivation of latent infection into a ten per cent annual risk of reactivation. In addition, the individual's risk of direct infection following re-exposure to active disease is dramatically increased. The frequency of unusual clinical presentations increases sharply as a result.

Tuberculosis therefore should always be considered as a potential differential diagnosis in any person who has come from overseas, especially from high-risk countries, or who might otherwise be in compromised situations (the aged, diabetics, those on steroid therapy, who are immunosuppressed, those who presents with cough, have weight loss, sweats, general ill health, unusual pneumonias or infections and so on) and investigated accordingly.

In short: 'THINK TB'.

These guidelines replace the *Management, Control and Prevention of Tuberculosis: Guidelines for Health Care Providers (2002–2005)* published by the Victorian Government Department of Human Services in 2002. Each chapter in these guidelines was revised by a Victorian TB expert, and the revised chapter was then reviewed by a second independent expert. The revised guidelines were approved by the Victorian Tuberculosis Advisory Committee in August 2014.

For advice regarding TB not covered in these guidelines, readers are advised to seek expert advice or consult the Victorian Tuberculosis Program (phone 03 9342 9478).

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Chapter 2 Testing for latent tuberculosis infection

The two most widely used tests for diagnosis of latent tuberculosis infection (LTBI) in Australia are the tuberculin skin test (TST) and the Quantiferon Gold-TB In-Tube (QFN-GIT) test, an interferon gamma release assay (IGRA). Neither test has perfect sensitivity or specificity. The following sections describe TST and QFN-GIT and their advantages and disadvantages and interpretation, including when to initiate testing and how to interpret discordant results.

2.1 Who needs a test?

A test for LTBI should be performed to identify any person who might be at an increased risk for TB and who might benefit by treatment of latent TB infection. Thus, it is desirable to undertake testing programs among those who are at risk for infection, and those who are at increased risk for progression to active TB. Routine screening of low-risk persons is not encouraged, with the exception of initial testing of those low-risk persons whose future activities might place them at increased risk of exposure, such as health care workers (HCWs).

In summary, consider testing for LTBI in these situations:

- recent contacts of persons known to have, or who are suspected of having clinically active TB. Casual contacts (for example, visitors at home, at work or at clubs) should be tested only if the source case is considered highly infectious (laryngeal disease, strongly smear positive cavitary pulmonary disease, or endobronchial tuberculosis). If the initial test is negative, consider retesting at eight weeks
- persons with HIV infection
- persons with abnormal chest X-rays suggestive of previous TB
- persons expected to be at substantially increased risk of TB disease (for example, in preparation for renal transplant or significant immunosuppression)
- groups at high risk of recent infection with *M. tuberculosis,* such as refugees and asylum seekers. Other groups, including immigrants from Asia, Africa, Central America, Oceania, Eastern Europe and the former Soviet Union, medically under-served populations, personnel and long-term residents in some hospitals, nursing homes, mental institutions, and correctional facilities do not require routine screening, but may be considered for testing on an individual basis
- HCWs at risk of infection with *M. tuberculosis* (see Chapter 7 Preventing TB Infection and disease among health care workers).

2.2 Tuberculin skin test (TST)

Tuberculin purified protein derivative (PPD) is derived from human strains of *M. tuberculosis,* and consists of several antigenic components. A variety of tuberculins produced from different strains using different methods exist and are now subject to international standards: an international unit (IU) for tuberculin is a unit of biological activity in a defined amount of a standard preparation.

All available tuberculins are subject to significant cross-reactivity with other species of mycobacteria, including BCG-bovis, and many environmental mycobacteria such as *M. avium* complex (MAC). This results in a significant reduction of both sensitivity and specificity. A positive response on skin testing is therefore a measure of previous exposure/infection potentially to several mycobacterial species.

Tuberculin PPD can be delivered into the skin by the Mantoux test, the Heaf test and the tuberculin tine test. These are all variants of the tuberculin skin test (TST). In Australia, the Mantoux test is used virtually exclusively. The Mantoux test is subject to variability in both injection technique and reading technique, but many of the inherent variations in the administration and interpretation of the test can be avoided by careful attention to detail. It is most desirable that persons performing and reading the test are appropriately trained and educated about the test.

Disadvantages of TST

Poor specificity: false positive TST results

TST is known to have high rates of false positives. Factors that lead to a false positive TST include:

- previous BCG vaccination. A single BCG vaccination at birth usually leads to a positive TST that wanes over the next decade. However, BCGs given after age 2, and repeat BCGs can lead to prolonged (false) positive TST
- exposure to non-tuberculous mycobacteria (NTM). Geographically clustered in tropical and subtropical regions, exposure to these environmental mycobacteria can lead to a false positive TST.

Poor sensitivity: false negative TST results

Immune dysfunction and other factors cause false negative TST results. Examples include:

- HIV, and other immunosuppressive disease or therapy
- inadequate nutrition
- malignancy
- active TB, especially severe/miliary TB
- concurrent viral infection
- children and the elderly.

Tuberculin reversion

Reversion from a previous positive to a negative reaction occurs in 2–20 per cent of people over 2–20 years and is more likely in those with an initial reaction of 10–14 mm; that is, not a strongly positive reaction. With continuing TB exposure a large tuberculin reaction tends to be maintained.

Individual and interpreter variability

The TST response in an individual is highly variable. Two tests done at the same sitting by the same operator on different arms may show a 15 per cent discordance. The same tuberculin reaction in an individual measured by two different experienced operators may also show 15 per cent discordance in the readings. Under-reading of a positive TST was common in one study: 33 per cent failed to identify a positive reaction.

Booster reactions

In patients with previous mycobacterial infection (either BCG vaccination, TB or NTM), an initial TST may be negative, but if this is followed by a second TST, the protein from the first TST boosts the immune response and can lead to a positive second test if performed from one week to one year (and possibly longer) later.

The implication of this is that when people have multiple TSTs (for example, serial testing in high-risk HCWs, or screening before and after travel to a country with a high TB incidence), a positive result on a second or subsequent TST following an earlier negative result could be erroneously interpreted as indicating TB exposure and infection in the interval between the tests; whereas the result is really due to boosting of a waned immune response to a previous mycobacterial infection. This issue is not relevant if serial testing is performed with IGRA.

Interpretation of TST in the absence of BCG vaccination

Based on the sensitivity and specificity of the Mantoux test and the prevalence of TB infection in different subgroups of the population, three cut-off diameters have been recommended for defining a positive reaction: ≥ 5 mm, ≥ 10 mm and ≥ 15 mm (see table below). For persons at highest risk for developing TB disease, if they become infected with *M. tuberculosis*, a cut-off of ≥ 5 mm is recommended (for example, HIV-positive or otherwise immunosuppressed persons, all close contacts of active smear-positive cases). A reaction of ≥ 10 mm should be considered positive for those with an increased risk of recent infection (for example, recent immigrants and IV drug users), and ≥ 15 mm for all others.

Table 2.1 Criteria for Tuberculin Positivity, by Risk Group (adapted from ATS/CDC, 2000)

Reaction ≥ 5 mm	Reaction ≥ 10 mm	Reaction ≥ 15 mm
Recent contacts of active TB case patients Fibrotic changes on CXR consistent with prior TB Patients with organ transplants and other immunosuppressed patients (including those on oral steroids ≥ 15 mg/d prednisolone Infants under one year of age	Recent immigrants from high TB prevalence countries Injecting drug users Residents and employees of correctional facilities, nursing homes, hospitals and homeless shelters Mycobacteriology laboratory personnel Children 1–5 years of age, or older children and adolescents exposed to adults at high risk Persons with clinical conditions that place them at higher risk for TB disease	Persons without a history of risk factors for TB

2.3 Interferon gamma release assays

Interferon (IFN) gamma release assays (IGRAs) are whole blood ex-vivo T-cell-based assays for the detection of LTBI. The principle of the assay is that T-cells of individuals previously infected with *M. tuberculosis* will produce IFN-gamma when they encounter TB-specific mycobacterial antigens. Thus, a high level of IFN-gamma production is presumed to be indicative of TB infection. The antigens used in IGRAs (ESAT-6, CFP-10 with or without TB 7.7) are encoded by *M. tuberculosis* genes that are not shared with *M. bovis*-BCG or most NTM, and hence they are called 'region of difference' (RD) antigens.

There are two methods for detecting the IFN-gamma released by the T-cell: an enzyme-linked immunosorbent assay (ELISA, for example, QFN-GIT), and an enzyme-linked immunospot assay (ELISPOT, for example, T-SPOT. TB). The QFN-GIT is the more widely used of these tests in Australia. In both tests a control mitogen and a nil sample are tested in parallel with the *M. tuberculosis* antigens. IGRA tests are reported as positive, negative or indeterminate. Indeterminate tests may represent a low response to the control antigen or high response to the nil control. Currently there is a single cut-off at which the test is regarded as positive.

Advantages over TST:

- better specificity in the setting of BCG vaccination and NTM exposure (most common in tropical and subtropical regions)
- similar sensitivity to TST in most cases, although IGRAs may be more sensitive in the setting of immune suppression; for example, in haematology and HIV-infected patients
- single blood test, not requiring return visit
- automated interpretation of QFN-GIT eliminates problems with inter-user reliability
- no booster phenomenon, because the individual does not encounter antigen in this in-vitro test (results of studies of whether IGRA response can be boosted by TST are inconsistent).

Disadvantages:

- IGRAs are more expensive than TST, although this cost may be mitigated by the single clinical visit.
- IGRAs may not perform as well in children as in adults, and currently the CDC suggest that in children < 5 years TST is preferred, although QFN-GIT is an acceptable alternative.
- IGRAs require a phlebotomy and correct specimen handling and processing.
- There is relatively limited data concerning the ability of a positive or negative IGRA test to predict the subsequent development or absence of TB (although such data are accumulating and indicate at least equivalent predictive performance to the TST).

Interpretation of QFN-GIT:

- A single cut-off value (TB antigen minus nil control ≥ 0.35 IU/mL) is used to define a positive result. Some experts have suggested applying different cut-off values for high- and low-risk populations (as is done with TST), or defining a 'borderline' range, but this is not current practice.
- An indeterminate result can be due to a low positive control or a high negative control.

Factors affecting sensitivity:

- As with TST, IGRAs are less sensitive in the setting of significant immune suppression. However, studies in HIV infection indicate they are less likely to be falsely negative than TST.

Factors affecting specificity:

- False positives may occur in the presence of three NTM: *M. marinum, M. szulgai* and *M. kansasii.*

Management of indeterminate QFN-GIT result

Indeterminate QFN-GITs should be repeated (once). An indeterminate QFN-GIT due to a high nil control value (reflecting elevated background T-cell activity) may well lead to a more definitive result in the second test. An indeterminate result due to reduced mitogen activity is more likely to remain indeterminate. After two indeterminate results, judge the situation by epidemiology and risk of progression. A TST can be done in cases where:

1. the patient has no risk factors for false positive TST (no BCG and/or low likelihood of exposure to NTM)
2. the TST is expected to be positive if LTBI exists (not significantly immunosuppressed)
3. a positive TST would lead to a decision to treat the patient. Examples include recent significant TB exposure in an Australian-born person, or someone about to undertake TNF-a inhibition therapy.

2.4 Discordant test results

Should a second test be performed?

If a patient has already had a TST, a QFN-GIT should only be done if interpretation of the TST result is unclear and the result of the QFN-GIT would affect management. There is no indication for performing TST where an QFN-GIT is already available.

The following guidelines will assist in deciding whether to perform QFN-GIT, but do not cover every conceivable situation. In practice, epidemiology (pre-test probability), risk of progression to disease and risk factors for false positives (especially prior BCG) and negatives all have to be taken into account.

- If the TST is ≥ 15 mm, IGRA is not indicated.
- If the TST is ≥ 10 mm and < 15 mm:
  a) if the person has a history of TB exposure or has suggestive X-ray changes (for example, > 1 calcified nodules, upper lobe fibrosis) or is immunosuppressed: regard TST as positive and IGRA not indicated. This recommendation is stronger if the person has not had a BCG.
  b) if the person has none of the risk factors in (a): regard TST as indeterminate and IGRA indicated. This recommendation is stronger if the person has had a BCG.
- If the TST is < 10 mm, IGRA not indicated, unless the person has risk factors for LTBI and progression to active TB (for example, patient from TB-endemic country with HIV, or patient with abnormal CXR about to start infliximab).

Interpretation of discordant test results

On occasion, both tests may have been performed prior to review. The following considerations are not definitive, but may help guide interpretation of discordant results.

In immune-competent adults, sensitivity of QFN-GIT and TST are both estimated to be approximately 70–80 per cent. TST specificity is high (over 90% if 15 mm is used as a cut-off) in those not vaccinated with BCG or exposed to NTM. QFN-GIT is 93–99 per cent specific in immunocompetent people, whether or not they are BCG vaccinated. In patients with a low risk of exposure, discordant TST+/IGRA– results are common, especially in those previously vaccinated with BCG.

In HIV-positive patients, TST is more likely than the QFN-GIT assay to produce a false negative result, and the lower the CD4 cell count the more likely this is to occur. QFN-GIT has higher rates of indeterminate tests due to negative mitogen control response when the CD4 cell count is ≤ 100 per microlitre compared with when CD4 cell count is > 100 per microlitre.

In the elderly, TST is more likely to be falsely negative; whereas QFN-GIT is less affected by age.

Comparative studies are less common in children. QFN-GIT has been found to be less sensitive than T-SPOT.TB in children with active TB.

Following treatment of active or latent TB, reversion from a positive to a negative result can occur with both TST and IGRAs. The significance of this is unknown, in particular whether it indicates eradication of all *M. tuberculosis* organisms.

Meta-analyses have shown that IGRA specificity is consistently high in those with and without prior BCG vaccination; whereas TST specificity is diminished by prior BCG vaccination. A fully integrated statistical meta-analysis, which included latent class and mixed effects, estimated that sensitivity for IGRAs was 64 per cent and specificity was 99.7 per cent. TST specificity was similar

to IGRA in those without prior BCG, but fell to 50 per cent in those with prior BCG.

IGRA positive, TST negative

It is most likely that this discordance represents a falsely negative TST, because data show that for groups such as the elderly and the immunocompromised IGRAs are more sensitive than TST.

IGRA negative, TST positive

This pattern of discordance is relatively common, and is usually due to a falsely positive TST. If the patient has risk factors for a false positive TST, such as recent BCG, multiple BCGs, BCG at older age or exposure to NTM, the probability that this is a false positive TST is high.

If the TST reaction is large (> 20 mm); however, it is rarely a false positive. In such cases, the IGRA may be a false negative, particularly if the TB mitogen result is close to the positive cut-off.

2.5 Information for service providers

The Victorian Tuberculosis Program offers a training program in the performance and reading of tuberculin skin tests for service providers who are able to satisfy certain criteria. Training in the administration of BCG vaccination may be offered when required. For further information please contact the Victorian Tuberculosis Program on 03 9342 9478 or by email at vtpadmin@mh.org.au.

Mantoux tests can be performed at several locations, such as:

- local public hospitals (the infection control practitioner can advise if the service is available)
- pathology providers (remember that TST for purely screening purposes without a specific clinical indication does not attract a Medicare benefit)
- local general practitioners who have been trained in the technique.

If in any doubt, contact the Victorian Tuberculosis Program on the number / email above.

Availability of Human Tuerculin (Tubersol) for Tuberculin Skin Testing (TST): Supplies of Tubersol can be ordered via the Victorian Government funded vaccine order form located at http://docs.health.vic.gov.au/docs/doc/Government-funded-vaccine-order-form. Note: supplies of Victorian Government-funded Tubersol are not available to travel clinics for the purpose of pre-travel testing for adults, hospital pharmacy departments, pathology providers or student health services. These groups can access Tubersol through the pharmaceutical wholesaler Clifford Hallam (phone 03 9554 0500).

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Chapter 3 Laboratory diagnostic services for tuberculosis and other mycobacterial diseases

3.1 Introduction

TB control programs are dependent on laboratory services for the reliable and timely confirmation of the presence of *Mycobacterium tuberculosis* complex (MTBC) or other, non-tuberculous mycobacteria in clinical specimens.

The minimum necessary laboratory functions available to the state should include:

- microscopy using acid-fast (Ziehl-Neelsen or Auramine Rhodamine) stain
- culture on appropriate mycobacterial media
- definitive speciation of significant isolates
- anti-tuberculous drug susceptibility testing.

Large reference laboratories, such as the Victorian Mycobacterium Reference Laboratory (MRL), can supply additional services and provide information to assist with TB diagnosis and control.

This includes:

- provision of nucleic acid amplification (NAA) testing for MTBC and other pathogenic mycobacteria (for example, *Mycobacterium ulcerans* and *Mycobacterium leprae*) on respiratory specimens, aspirates, swabs and fresh or fixed tissue
- molecular techniques for speciation when required
- molecular genetic typing for epidemiological purposes
- maintenance of a laboratory TB database and collation of statistics
- maintenance of a mycobacterial culture collection for epidemiological and research and development purposes
- provision of training, and a consultation and advisory service available to other laboratories and health professionals
- ongoing research and development in mycobacteriology
- provision of veterinary and environmental mycobacteriology services as necessary to assist with the investigation and control of human mycobacterial diseases.

3.2 Level of laboratory service – mycobacteriology

Not all pathology laboratories need to provide comprehensive services. A three-tiered classification of laboratories performing mycobacterial tests has been proposed for adoption in Australia.

Patients with tuberculosis may present anywhere in the state, and all respiratory specimens referred for bacterial culture should be handled as if they potentially contain MTBC, including resistant strains. If a laboratory cannot comply with biosafety level PC2, they should not be processing respiratory specimens and should not attempt ZN staining.

Level 1

These are the majority of general bacteriology laboratories, as would be found in small hospitals and private pathology laboratories. Direct acid fast microscopy should be available at short notice, but culture for mycobacteria should not be attempted. Specimens are referred to a higher-level facility for both confirmatory microscopy and culture. These smaller laboratories should seek advice from the state MRL on less common requests, such as optimum specimen collection for the diagnosis of non-tuberculous mycobacterial infections.

Level 2

These are larger laboratories (both public and private), which would receive regular requests for the diagnosis of mycobacterial infections, especially tuberculosis and *Mycobacterium avium* complex (MAC) infections. Such laboratories perform both acid fast microscopy and mycobacterial culture. Definitive species identification is not generally performed.

Recently, NAA tests such as the Cepheid GeneXpert® MTB/RIF assay have become available which can both identify MTBC and detect most genetic mutations leading to rifampicin resistance within three hours. Published literature to date suggests these assays perform well in a Level 2 lab setting. However, this assay is not a substitute for microscopy, culture and phenotypic susceptibility testing, which should always be performed.

It is imperative that all new isolates of MTBC as well as any potentially pathogenic atypical mycobacteria be forwarded to a Level 3 laboratory for further testing. If specimens are received for mycobacterial culture for pathogens that require special culture media or conditions, it may be more cost-effective to refer these specimens directly to a Level 3 laboratory.

Level 3 (mycobacterium reference laboratories)

Level 3 laboratories provide drug susceptibility tests, and full speciation of isolates. Culture for less common mycobacteria that require special media or conditions is best performed by Level 3 laboratories. Some mycobacteria causing serious infections in immune-compromised patients (for example, *Mycobacterium genavense)* grow poorly in culture, and *M. leprae* will not grow ex-vivo. These species are best identified by NAA methods; if AFB are seen on stain or histology in specimens from an untreated patient, but not recovered by culture, NAA (both for mycobacterium genus and individual species assays should be considered. Because NAA diagnostics is a rapidly advancing field, it is best to contact the Mycobacterium Reference Laboratory (MRL) for advice.

Support should also be available to lower-level laboratories in the form of advice, training and provision of reference methods and mycobacterial strains. Statistics, particularly those dealing with new diagnoses of TB and antibiotic susceptibility patterns, should be collated and provided to public health authorities.

Level 3 laboratories should also be involved in the development or evaluation of new tests such as those involving molecular procedures for rapid diagnosis, speciation, susceptibility testing and molecular typing of isolates. Environmental mycobacterial outbreak investigations are best coordinated by the MRL.

Level 3 laboratories should also communicate with other interstate MRLs to provide highly specialised, but infrequently required tests such as mycolic acid analysis by HPLC, and also exchange epidemiological information and mycobacterial strains as necessary.

Currently, the only Level 3 facility in Victoria is the MRL at VIDRL.

3.3 Quality assurance

It is essential that all clinical laboratories performing diagnostic mycobacteriology at any level carry current National Accreditation and Testing Authorities (NATA/RCPA) accreditation for these procedures. This includes maintenance of appropriate biosafety and participation in proficiency testing programs appropriate to the level of service provided by the laboratory.

3.4 Standards

It has been a goal of the Special Interest Group in Mycobacteria of the Australian Society for Microbiology to standardise methods in use in major diagnostic mycobacteriology laboratories throughout Australia. Although some differences remain, most of the methods used in these laboratories are now similar, and have comparable sensitivity and outcome, as shown by the results of collaborative quality assurance projects. Efforts are being made to standardise protocols for identification and susceptibility testing of atypical mycobacteria and to exchange information about new molecular techniques under development.

Microscopy

Microscopy should be routinely performed on all specimens submitted for AFB examination except blood and urine, using Ziehl-Neelsen and/or fluorochrome (Auramine/Rhodamine) staining. An attempt should be made to quantitate the number of AFB present in any positive smear.

Culture

Culture should be performed using a validated automated commercial liquid media system, egg-based solid media or a combination of these. Special media are also required for mycobacterial blood culture. Certain species such as *M. bovis, M. haemophilum, M. marinum, M. genavense* and *M. ulcerans* have special requirements in media and/or temperature and length of incubation. To ensure that appropriate cultures are performed, communication between clinicians and the laboratory is required. All cultures should be read at weekly intervals for at least six weeks (and for up to 18 weeks for *M. ulcerans).* Culture in liquid medium remains the most sensitive and preferred isolation technique for *M. tuberculosis.*

Identification

Level 3 facilities should have the expertise to identify all human pathogens. Members of the MTBC may be identified by traditional criteria, such as niacin production, nitrate reduction, cord formation, lack of growth at room temperature and drug susceptibility. Recently a direct MPT-64 antigen detection test has become available to rapidly identify MTBC growing in liquid (or on solid) media, and this test is now used in some Level 2 labs (any culture tubes flagging positive should still be forwarded to the MRL regardless of MPT-64 Ag result). MPT-64 Ag detection has partly replaced commercial DNA probes for the detection of MTBC, but probes are still required for certain non-tuberculous mycobacteria. Isolates not identified by the above methods should be identified by sequencing. (The Victorian MRL uses 16S rRNA gene and 16S–23S ITS region sequencing targets, and has other assays for speciating members of the MTBC).

All isolates of atypical mycobacteria likely to be pathogens should be identified, for example, repeat isolates from sputum, isolates from sterile sites, tissues and wounds. Adequate clinical data is essential for determining the pathogenic role of such isolates. Authoritative texts and recently published studies provide adequate reference sources for procedures and identification strategies.

Susceptibility testing

Susceptibility testing should be performed only in Level 3 facilities.

All initial isolates of MTBC, as well as repeat isolates from relapse cases or 'treatment failures' should be tested for susceptibility to at least isoniazid, ethambutol, rifampicin and pyrazinamide. Additional drugs will be tested when resistance to first-line agents is found.

The value of susceptibility tests on slow-growing atypical mycobacteria remains controversial. Most MRLs do not perform drug susceptibility testing of slowly growing species such as MAC routinely, because clinical correlates between in-vitro test results and clinical responses have been poor for some drugs. Susceptibility testing may be useful to compare sequential isolates from the patient following clinical relapse or treatment failure, but should be discussed with the MRL. Some species (for example, *M. kansasii)* have such uniform susceptibility patterns that there is nothing to be gained from testing individual isolates. Rapidly growing species such as *M. fortuitum* should be tested by broth dilution against a range of drugs, including tetracyclines, amino-glycosides and sulphonamides. Occasional surveys of drug susceptibility may be performed on stored isolates of some atypical mycobacteria, such as *M. marinum*, as an aid to clinical management.

3.5 Other issues

New NAA procedures, such as polymerase chain reaction (PCR), are now well established, but in most cases, the sensitivity is still not as high as modern culture methods. MTBC specific PCRs targeting repetitive insertion sequences (for example, IS6110) may provide higher sensitivity than single target or generic mycobacterial PCRs.

Specimens are still required for culture, because an isolate is essential for sensitivity testing and genetic typing. Mycobacterial NAA testing is not yet covered by the Medicare Benefits Schedule or health insurance companies, and should be reserved for cases where there are problems with standard diagnostic methods, a pressing need for rapid information or difficulty with the collection of suitable specimens for culture.

It should be noted that NAA methods have no further role once the diagnosis of TB is made, because dead mycobacteria may persist in human tissues for months following successful treatment.

Molecular typing of strains of *M. tuberculosis* by mycobacterium interspersed repetitive unit/variable number of tandem repeat (MIRU/VNTR) is an important tool in epidemiological studies of TB. To date it has been very useful for defining chains of TB transmission in the community and investigating potential nosocomial transmission, or episodes of laboratory cross-contamination. All Australian *M. tuberculosis* isolates submitted to the Victorian MRL are typed.

Chapter 4 Treatment of active tuberculosis

4.1 Introduction

Patients with TB have a cure rate of approximately 98 per cent if managed with appropriate treatment regimens. Treatment of patients with alternative regimens is associated with poorer outcomes. In Victoria TB should only be managed in close consultation with specialists with experience and training in treating TB. The treatment regimens in this guideline are based on current international evidence-based guidelines.

In Victoria, all primary TB drugs are provided free of charge to patients that have been notified to the Department of Health & Human Services.

4.2 Drug-susceptible versus drug-resistant TB

Bacterial confirmation of the diagnosis with drug susceptibility testing should be strenuously pursued because of concerns about drug resistance. Regimens including multiple antibiotics are necessary in all cases to cover the possibility of initial drug resistance and to prevent emergence of resistant organisms.

Isoniazid resistance is found in 7–10 per cent of *Mycobacterium tuberculosis* isolates in Australia, predominantly in patients born overseas and in those with a history of treated TB. Standard initial treatment regimens assume isoniazid resistance. These regimens are then altered according to susceptibility results.

Multidrug resistance (MDR) (resistance to at least isoniazid and rifampicin) remains uncommon in Australia (approximately 1–3 per cent of isolates). MDR-TB is important to recognise as early as possible because it is associated with high rates of failure with standard drug regimens. MDR-TB should be suspected in:

- migrants from high-risk areas (for example, China, Eastern Europe, Indian subcontinent, Papua New Guinea, Russia, South-East Asia, sub-Saharan and South Africa)
- patients who have previously failed treatment
- patients who are failing to respond within two to three months of treatment, either clinically or bacteriologically
- contacts of patients with MDR organisms.

Patients with suspected MDR-TB may require alternative empiric treatment regimens and must be discussed with a specialist experienced in managing MDR-TB prior to empiric TB treatment commencing (see Section 4.5 Drug-resistant tuberculosis).

Extensively-drug resistant tuberculosis (XDR-TB) is MDR-TB that is also resistant to a fluroquinolone and at least one injectable anti-TB medication such as amikacin. It is very rare in Australia; however, reports from around the world of cases have been increasing.

4.3 Initial (intensive) standard daily regimen

The initial (also called intensive) phase of TB treatment for patients where there is no drug resistance suspected is with four antibiotics (see Table 1). This treatment phase is often commenced prior to antibiotic sensitivities being available. The duration of the initial intensive phase is for a minimum of two months or at least until sputum is smear-negative for pulmonary TB and, in culture positive cases, drug susceptibilities are known, whichever is longer.

Table 4.1 Initial (intensive) standard daily regimen.

Isoniazid(H):	300 mg (child 10 mg/kg up to 300 mg) orally daily
PLUS	
Rifampicin(R):	600 mg (adult less than 50 kg: 450 mg; child 10 mg/kg up to 600 mg) orally daily
PLUS	
Ethambutol(E):	15 mg/kg orally daily (up to 1200 mg; in adults and children 6 years or older)
PLUS	
Pyrazindamide(Z):	25 mg/kg (up to 2 g) orally daily
+Pyridoxine:	25 mg orally daily

Ethambutol can be ceased as soon as the TB isolate is confirmed to be fully sensitive to first-line agents, even if this is before two months, and can be omitted if the isolate is known to be fully sensitive to first-line agents before treatment is commenced. The more common side-effects and interactions of the agents in the standard regimen can be seen in the table below.

Table 4.2 TB drug side-effects and drug interactions

TB drug	Side-effect	Drug interaction
Isoniazid (may need to reduce dose)	Hepatitis Giddiness Rarely, mental symptoms Convulsions Peripheral neuropathy (preventable with pyridoxine – vitamin B6) Mild drowsiness Hypersensitivity reactions	Anti-convulsants
Rifampicin	*Intermittent or daily use* Hepatitis Gastrointestinal upset Skin rashes Thrombocytopaenia Renal failure Haemolytic anaemias Orange discolouration of urine, tears, saliva, semen, contact lenses (harmless) *Intermittent use* Flu-like symptoms	Interaction with oral contraceptives, anti-coagulants, hypoglycaemics, theophylline, anti-arrythmics, dapsone, anti-convulsants, anti-fungals, corticosteroids, anti-retrovirals
Pyrazinamide	Hepatitis Arthralgia Flushing Gout Lability of blood glucose in diabetics	
Ethambutol	Optic neuritis (avoid use in children younger than 7 years of in cases of impaired renal function)	

4.4 Continuation (sterilisation) phase of treatment for fully-sensitive TB

Fully-sensitive TB

Treatment is continued after the initial (intensive) phase for at least another four months with rifampicin and isoniazid, for a total treatment course of six months (2HRZE/4HR), otherwise known as 'short-course' treatment. This treatment course is suitable for most forms of TB sensitive to the first-line antibiotics. The six-month treatment short-course is NOT suitable if:

- the patient has not received rifampicin or isoniazid for the complete treatment course or has not received two months of pyrazinamide during the initial (intensive) phase
- there is evidence of extensive disease, including extensive cavitation on CXR
- the patient is not fully adherent to medications; for example, treatment interruption requires consideration of longer therapy
- there is a delayed clinical response to treatment, including persistent positive sputum smears two months into treatment
- there is evidence of disseminated, central nervous system or skeletal disease
- the organism shows resistance to isoniazid, rifampicin or pyrazinamide (see Section 4.5).

Fully-sensitive TB not suitable for six-month short-course treatment

For patients with fully susceptible TB who have not responded well to the intensive phase, consideration should be given for extending the intensive phase of treatment. For example, for patients still smear positive or with extensive cavitation, pyrazindamide could be continued for longer (for example, one additional month, to a total of three months of pyrazindamide). Patients who have not received rifampicin and isoniazid for the full treatment course, have not received pyrazindamide for the two-month intensive phase, have extensive or cavitary disease, have a delayed clinical response to treatment or have not been fully adherent to medications should have the continuation phase extended to at least seven months, meaning a nine-month total duration.

Disseminated, central nervous system or skeletal TB.

The recommended minimum total duration of treatment (including initial and continuation phases) for these forms of extrapulmonary TB is:

- disseminated (including miliary): 9–12 months
- central nervous system (including meningitis): 12 months
- skeletal: at least 6–9 months, possibly longer.

Note that there are no good prospective data supporting these recommended durations, which are based on international guidelines. With expert advice, where there is extensive disease or a slow clinical response, longer durations may be required.

4.5 Drug-resistant TB

Isoniazid-resistant TB

The recommended regimen is two months of the initial standard daily regimen, as per Section 4.3 (assuming resistance discovered after initiation of standard treatment), and then seven months of rifampicin, pyrazinamide and ethambutol (2HRZE/7RZE). If pyrazinamide is not tolerated, then rifampicin and ethambutol alone can be used in the continuations phase but for 10 months (2HRZE/10RE).

Some isolates are reported as exhibiting 'intermediate-level' isoniazid resistance (resistant at 0.1 mcg/mL but sensitive at 0.4 mcg/mL). It is unknown if isoniazid maintains clinical efficacy in treatment of such TB cases. Given the good efficacy of the above regimens for isoniazid mono-resistance, isoniazid should not be used for these cases.

Multi-drug resistant TB and extensively-drug resistant TB

MDR-TB is challenging for patients and treating clinicians. Good outcomes depend on early clinical suspicion, rapid and accurate laboratory diagnosis and the timely administration of appropriate combinations of drugs with close monitoring. Treatment regimens involve prolonged courses of multiple second-line anti-tuberculous agents that can be difficult to tolerate. Administering inappropriate treatment regimens can lead to further drug resistance.

The ‘second-line’ anti-tuberculous drugs that are used for the treatment of MDR-TB include fluoroquinolones, amikacin, prothionamide and PAS. Where possible, these drugs are often used in combination with drugs from the standard regimen which are confirmed to have sensitivity. Regimens are at least 18–24 months in duration. A detailed discussion of the management details of MDR-TB and XDR-TB is beyond the scope of this guideline.

Given the complexity of management, only specialist clinicians with appropriate experience should carry out treatment of drug-resistant TB, and clinicians should discuss the management of specific cases with the Victorian TB Advisory Committee.

4.6 Culture-negative TB

Culture-negative TB can occur because of lack of appropriate culture specimens, a low-burden of disease or inactive TB. In patients where TB is clinically suspected and there is a clinical or radiological response to empiric treatment but cultures are negative, it is recommended to treat, assuming isoniazid resistance but continuing isoniazid. The continuation phase therefore includes an extra antibiotic, and is extended to at least seven months. For example, the treatment of culture-negative pulmonary TB would be 2HRZE/7HRE.

4.7 Intermittent TB treatment regimens for DOTS

Many international guidelines recommend routine use of directly observed intermittent short-course therapy (DOTS). Intermittent (three times a week) regimens are only recommended if directly observation of dosing is available and patients are HIV negative. In Victoria, DOTS is provided on a case-by case basis for patients with anticipated or demonstrated compliance problems.

An initial intensive 2–8 weeks of a daily regimen is always used prior to intermittent therapy. As in standard therapy, ethambutol is used until drug-susceptibility is confirmed, and pyrazinamide is used for at least the first two months during the intensive phase.

Table 4.3 Drug doses for intermittent therapy for DOTS

Isoniazid	15 mg/kg (up to 900 mg) orally 3 times a week
Rifampicin	15 mg/kg (up to 600 mg) orally 3 times a week
Ethambutol	30 mg/kg orally (up to 2.4 g) 3 times a week
Pyrazinamide	50 mg/kg (up to 3 g) orally 3 times a week

4.8 Adjunctive corticosteroid treatment in TB

Corticosteroids can be given as an adjunct to anti-tuberculous drugs in certain TB infections in an attempt to decrease the adverse effects of inflammation associated with TB infection and its treatment. Corticosteroids are definitely indicated for TB meningitis and TB pericarditis. They are also indicated where a HIV-associated immune-reconstitution syndrome has resulted in a worsening clinical status in a patient with active TB.

There are other situations where adjunctive corticosteroids have been used with anecdotal success, but where there is limited evidence as to their role. These include ureteric TB, extensive pulmonary TB, pleural TB, vertebral TB and paediatric intrapulmonary lymph node TB.

Doses of corticosteroids (as prednisolone) studied are 60 mg/day (child 1–2 mg/kg) weaning over 6–12 weeks.

4.9 General principles of treatment

Never use monotherapy, except when treating latent TB (see Chapter 10 Treatment of latent TB infection (chemopreventative therapy)).

Never add only a single drug to a failing regimen.

Compliance is essential to the success of treatment regimens. Patients and carers must be educated and repeatedly reminded about their medications and the importance of compliance and have supportive written information in the appropriate language provided. They must have contact details of treating doctors and public health nurse allocated to them. Check compliance with the patient, their carers and their public health nurse and by reconciling prescriptions and pills.

Take care with elderly patients, who are at higher risk of treatment intolerance. Medications can be introduced step-wise in these patients with breaks of 5–7 days between each new medication to ensure tolerance. A suggested regimen is commencing rifampicin with ethambutol, then one week later isoniazid then one week later pyrazinamide, checking liver function in between.

Given the increased risk of optic neuritis, ethambutol should be avoided or used with caution in patients with renal failure, significant pre-existing ocular disease or where ocular toxicity cannot be monitored. Alternatives such as moxifloxacin should be considered in these cases under specialist guidance.

Patients with chronic liver disease may also require modification of their treatment regimen; however, this depends on the specific clinical situation.

Patients with pulmonary TB should have monthly sputum samples monitored until culture negative. A CXR should be performed at 2–3 months of treatment (that is, at the end of the intensive phase) to ensure radiological response and then again at the completion of treatment.

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Chapter 5 Directly observed therapy

5.1 Introduction

Successful completion of treatment is an essential component of any TB control strategy. It is also crucial in preventing relapse and development of secondary drug resistance. Studies have shown that compliance with TB treatment cannot be predicted – it is not related to socio-economic status, severity of disease, presence of drug side-effects or the patient's educational level or understanding of disease.

5.2 DOT short course in global and Australian TB control

The World Health Organization (WHO) has campaigned strongly for all National Tuberculosis Programs (NTP) to implement the DOTS strategy in an effort to achieve global TB control. In 2007, DOTS programs had been implemented in 182 countries. Population coverage was complete in 16 of 22 high-burden countries (HBCs), almost complete in five others, and reaches 98 per cent of the population in these countries.[1] By 2004, more than 20 million patients had been treated in DOTS programs worldwide, and more than 16 million of them had been cured. Mortality due to TB has been declining, and its incidence diminishing or stabilising in all world regions except sub-Saharan Africa and, to some extent, Eastern Europe. The Stop TB Strategy was launched in 2006 and builds on the successes of the DOTS Strategy. The Stop TB Strategy aims to: halt and begin to reverse the increasing incidence of TB by 2015; reduce prevalence of TB by 50 per cent (compared with a baseline of 1990) by 2015; reduce deaths due to TB by 50 per cent (compared with a baseline of 1990) by 2050; and to eliminate TB as a public health problem. A high quality DOTS expansion and enhancement program remains at the heart of the Stop TB Strategy, with a focus (among other things) on case detection through quality-assured diagnostics, standardised treatment with supervision and patient support, and ensuring supply of TB medications.

The original DOTS programs included a range of strategies to improve TB detection and treatment outcomes, including:

- directly observed administration of drugs
- short-course (six-month) treatment
- reliable, affordable supply of drugs
- case detection (laboratory confirmation, particularly smear positive pulmonary tuberculosis)
- reliable surveillance including recording and reporting
- government commitment to tuberculosis control.

In its most simplistic form, DOTS relates to the supervised swallowing of medication and is advocated as the preferred method of TB treatment by WHO, the Centre for Disease Control (CDC) and the Australian National Health and Medical Research Council (NH&MRC). In Australia, administration of TB medication by directly observed therapy (DOT) has been implemented in three of the eight states and territories TB programs and covers about 37 per cent of the Australian population. Despite recommendations for universal DOT, treatment completion rates of over 90 per cent have been reported in both the United States and United Kingdom using self-administered medication regimens and selective DOT for at-risk patients. Similarly, 98 per cent of Victorian patients diagnosed in 2007 successfully completed treatment using standard supervised, but self-administered medication regimens, with DOT reserved for identified at-risk patients. This was in a year where the outcome of therapy was recorded for 97 per cent of patients, including only three patients who defaulted on treatment.

A 2003 Cochrane systematic review of six random controlled trails (RCT) found that patients allocated to DOT compared to self-administered treatment had similar outcomes in relation to cure and treatment completion. A Victorian RCT that compared a family-based program of DOT with supervised but non-observed therapy, (which is standard in Victoria) found there was no significant difference in relation to treatment completion or non-adherence. In addition, it is recognised that there are limitations to implementing a universal DOT program within a given community. DOT is resource intensive and expensive. Patients may find it difficult to cooperate

with clinic attendances or home visits for supervised administration of medication. This is particularly the case in developed countries, where many patients are in full-time employment or study. Strategies to manage supervised pill taking need to be creative and flexible, and must involve participation by both patient and care provider in any decisions about the arrangements. In order to be successful these must be acceptable and practicable for everyone involved.

5.3 Supervision of treatment in Victoria

In Victoria, adherence to treatment is monitored by treating physicians and the Victorian Tuberculosis Program public health nurses. Adherence to therapy is the single most important determinant of treatment outcome, with poor adherence being strongly associated with treatment failure and relapse. Evidence of successful completion of therapy is demonstrated by low rates of relapse (< 1 per cent per year). All TB patients in Victoria are provided with varying levels of support and supervision by the Victorian Tuberculosis Program, depending on a progressive risk assessment for their ability to adhere to treatment.

Levels and methods of supervision vary from patient to patient, and may change during the course of treatment. Most supervised therapy in Victoria is unobserved and involves monthly review by the treating physician or clinic, and questioning about pill taking. The Victorian Tuberculosis Program nurses monitor patients during home visits, telephone calls and clinic attendances; however, medication is mostly self-administered.

Strategies implemented by the Victorian Tuberculosis Program nurses to support compliance and maintain adherence to treatment include:

- the issue of an 'adherence pack' at initial notification. This pack includes a medication-dispensing box ('dosette'), language-specific information about medications and drug side-effects, pill recording chart and contact information details for the public health nurse. Comprehension and ability to use the 'dosette' box is monitored closely during the initial phase of treatment
- encouraging family support and enlisting a relative or significant other to supervise pill taking
- weekly visits to fill the 'dosette' box
- ensuring adequate drug supplies by arranging scripts and/or delivering medications
- reminders via text messages, emails and telephone calls
- use of enablers and incentives such as taxi, food and gift vouchers.

5.4 DOT in Victoria

Adherence to therapy should be assessed on an ongoing basis. All patients should have an initial risk assessment for adherence to therapy and DOT should be implemented routinely for some patients including those with a history of non-adherence and relapse, mental health issues and MDR-TB. Occasionally the treating physician and/or the Victorian Tuberculosis Program nurse will consider a patient at risk of non-adherence, either at diagnosis or during the course of treatment. In this event a case conference should be instigated and attended by the patient, clinician and public health nurse. A plan for directly observed therapy must be negotiated and a decision made on the most appropriate intermittent therapy regimen, which is agreeable to all parties. In most instances medications will be given three times a week. Twice-weekly therapy is no longer recommended in Victoria. It is uncommon for DOT to be administered daily, particularly after the initial, sterilising phase of treatment. Supervision of pill taking may be undertaken by the Victorian Tuberculosis Program nurse, however in some circumstances, other health care providers or lay personnel could be approached to supervise medications (with Victorian Tuberculosis Program support). These could include the Royal District Nursing Service (RDNS), local community health care or general practitioner clinics, campus nurses or personal care attendants. More recently, the use of social media and new communication technologies have enabled selected patients to be monitored via videotelephony (for example, 'Face Time') and video conferencing.

The most important consideration is commitment to the arrangements by both the patient and supervisor – a missed thrice a week dose has a greater impact on treatment outcome than missing a daily dose of medications. Any indication that a patient is not committed to their DOT program will require additional counselling and negotiation. Sometimes, changing times and days may be sufficient to overcome any problems, or the use of enablers and incentives may further encourage patient adherence to treatment.

If a patient fails to comply with the above intensified measures to assist medication adherence, and the Chief Health Officer is satisfied that the public's health is jeopardised, the Victorian *Public Health and Wellbeing Act 2008* allows the detention of a patient for the purposes of directly observed therapy. This is rarely employed in practice, because a suitable alternative can usually be negotiated.

References

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Chapter 6 Hospital care of tuberculosis

6.1 Introduction

TB is transmitted in airborne droplets, and particularly by droplet nuclei that are generated by persons with pulmonary or laryngeal TB when they sneeze, speak or sing. Droplet nuclei are particles which remain after fluid from droplets evaporates. They are approximately 2–10 microns in diameter, and remain suspended in an indoor atmosphere until they are vented from a room or breathed in.[1] Normal air currents can keep infectious particles airborne for prolonged periods of time and spread them throughout a room or building. For this reason, a patient in hospital with 'open' (infectious pulmonary or laryngeal) TB represents a potential infectious hazard to other patients, carers and visitors. Tuberculosis involvement of other organs (for example, lymph glands, bone, kidneys, liver, gastrointestinal tract or meninges) does not pose a significant risk of transmission unless associated with aerosolisation of the infected material. This chapter focuses on methods of reducing the risk of hospital cross-infection including patient isolation, engineering requirements of the isolation room, and personal respiratory protection.

It should be noted that in the hierarchy of control measures, evidence suggests that the following are more efficacious than personal respiratory protection, and should not be neglected:[2, 3]

- early recognition of proven or suspected infectious patients
- regular education of health care workers to help facilitate this
- isolation of infectious patients in appropriate rooms
- prompt laboratory diagnosis and subsequent communication with clinicians caring for the patient
- prompt institution of effective treatment
- environmental controls, particularly including airborne infection isolation (AII) rooms, air filtration (where necessary) and (possibly) ultraviolet germicidal irradiation.

Where previous nosocomial outbreaks of TB were successfully contained by hospitals, several administrative and environmental controls, and personal respiratory protection, were usually instituted simultaneously, making it difficult to designate which measures were most efficacious.[4, 5]

6.2 Identification of patients with confirmed or suspected active TB

TB should be considered, and a decision made about isolation, in any patient who has:

- a cough persisted for three weeks or longer
- other symptoms or signs compatible with active TB, for example, weight loss, fever, night sweats, bloody sputum or haemoptysis (fever, sweats and haemoptysis are less common in older patients)[6]
- CXR changes consistent with pulmonary TB (often, previous X-rays need to be reviewed to look for new changes).

Active TB should be even more highly suspected if the patient has previously lived in a TB endemic country. The techniques used to establish the diagnosis of TB are discussed elsewhere; however, a microbiological diagnosis should be thoroughly pursued in all patients, where this is safe and practical to do so.

6.3 Guidelines for the management of hospitalised patients with confirmed or suspected active TB

Infectiousness of pulmonary TB declines rapidly once treatment begins. In some situations, patients with active pulmonary TB may be able to have anti-TB therapy commenced at home[7, 8, 9] and avoid admission to hospital, which carries the risk of infecting previously unexposed people, providing that:

- a microbiological diagnosis is confirmed, or if not, treatment at home does not compromise the ability to obtain appropriate microbiological samples for diagnosis
- the patient is commenced on treatment promptly
- the patient is likely to adhere to the prescribed medication and side effect monitoring requirements, including subsequent TB clinic appointments
- a public health nurse with experience in TB control, and who is in close contact with a consultant physician experienced in treating TB, can visit the home within 24 hours of diagnosis to start treatment and provide appropriate education to the patient and household contacts

- there are no other indications for hospital admission, for example, not systemically unwell, hypoxic
- the patient agrees to limit their movements to the home, and not to visit venues where there are previously unexposed people
- visits by previously unexposed people are minimised (and all visits by children should be discouraged) until the patient is smear negative
- the patient wears a mask during visits to the house by previously unexposed people (if these occur) and the public health nurse
- household members undergo contact tracing promptly
- there is no marked increased risk of serious side-effects (for example, the very elderly, underlying liver disease)
- any coexisting medical or psychiatric illnesses are not significant enough to make it difficult for the patient to be able to cope with the requirements of TB treatment, and do not require admission in their own right.

Any patient with confirmed or suspected active pulmonary or laryngeal TB requiring admission to hospital, or who are current inpatients in whom this diagnosis is confirmed or suspected should be placed in an Class N (airborne infection isolation, or AII) room that has currently recommended ventilation characteristics.[10]

Patients requiring inpatient care in hospitals without an AII room should be transferred to a hospital where one exists. Isolation may sometimes be required in patients with non-pulmonary TB in whom aerosol generating procedures such as wound irrigation are required.

While the patient is within the hospital and awaiting transferred to an AII room, and following explanation, they should be separated from other patients, fitted with a surgical mask and instructed to cough or sneeze into tissues, if this is occurring.

Paediatric patients with confirmed or suspected active TB should be evaluated for potential infectiousness according to the same criteria as adults (that is, on the basis of symptoms, sputum AFP smears, radiological findings and other criteria). Although TB in young children has been considered to be rarely contagious, if sputum is smear positive, transmission of infection to others can occur.[11] If the child is admitted to hospital, and if there is any doubt as to whether family members or other close contacts have active TB, and may be the source of infection for the child, then the child should be put into isolation to reduce the risk of subsequent spread of TB from an unrecognised family member/close contact to members of staff, other patients or visitors within the hospital.

Patients with confirmed or suspected active pulmonary TB in intensive care units should be treated the same as patients in noncritical care settings. They should be placed in an AII room and have respiratory secretions cultured and examined for AFBs. In patients who are intubated and mechanically ventilated, a suitable particular filter should be placed in the exhalation side of the respirator circuit. For further advice on infection control relating to respiratory units, see the document *Guidelines on Infection Control in Anaesthesia.*[21]

Patients with extrapulmonary TB (for example, lymphadenitis) and no pulmonary involvement may be managed in the general ward environment. If any open wounds are present such as a draining suppurative wound, these secretions should be managed with care as for any potentially infected bodily fluids. This includes covering wounds with dressings and disposing of waste in appropriate infectious bins.

6.4 General isolation practices for patients with confirmed or suspected TB

Patients with confirmed or suspected active TB and their visitors should be educated about the mechanisms of TB transmission, including the requirement to cover their mouth and nose when coughing or sneezing, to minimise the droplet spread of mycobacteria in expelled air.

Patients placed in isolation should remain in their isolation rooms with the door closed. When a patient needs to be transported outside the isolation room, they should wear surgical masks to cover their mouth and nose during transport. Where possible, investigative procedures for these patients should be scheduled at times when they can be performed rapidly and when patients are not held in crowded waiting areas for long periods.

The number of health care workers or visitors entering and isolation room should be kept to an absolute minimum. All persons entering an isolation room should wear a personal

respiratory protection device (see below). This includes kitchen and cleaning staff, family and visitors.

Although items contaminated with respiratory secretions are not usually associated with the transmission of TB, these items should be handled and transported in a manner that reduces the risk of transmitting microorganisms. Sputum specimens collected from TB patients should be transported to the laboratory in clearly marked bio-hazard plastic bags.

Separate crockery and bed linen are not required for TB patients.

6.5 Characteristics of the Class N room

For Class N Isolation rooms, the ventilation characteristics recommended by the Victorian Advisory Committee on Infection Control includes a minimum of 12 air changes per hour (ACH) for all rooms.[22]

Isolation rooms for patients with TB should be under negative pressure to promote the airflow from less contaminated (more clean, for example, corridors) to contaminated (less clean; that is, Class N) areas. The Victorian Advisory Committee on Infection Control document *Guidelines for the Classification and Design of Isolation Rooms in Health Care Facilities 2007* details minimum requirements for Class N rooms.[10] These include:

- minimal pressure differential pressure between the isolation room and adjacent ambient pressure of 30 Pa if the room has an airlock and 15 Pa if the room does not have an airlock
- pressure displayed on an appropriate pressure gauge
- recording of pressure daily by nursing staff when room is occupied
- auditing of negative pressure by qualified ventilation engineers at regular intervals
- reporting of results to the hospital's infection control committee
- a private bathroom.

Air should be exhausted to outside atmosphere and not recirculated into the hospital's general ventilation, unless first filtered by a HEPA filter. Attention should be given to exhaust airflow dynamics to ensure that potentially contaminated air does not re-enter the hospital's ventilation system.

Those seeking a more detailed description of the engineering requirements for TB isolation rooms are referred to the above document.[10]

Ideally, all acute care inpatient facilities should have at least one appropriately ventilated TB isolation room, depending on the size and location of the facility.[10] It is recognised that in some facilities, isolating the patient in an appropriate room may not be possible. In this case, the patient should be promptly transferred to a facility with this capability, and until transfer is arranged, the patient should be kept in a single room, with a surgical mask on their face, and staff entering the room should wear appropriate respiratory protective devices as detailed elsewhere in this document.

6.6 Cough-inducing and aerosol-generating procedures

Cough-inducing procedures include endotracheal intubation and suction, diagnostic sputum induction, aerosol treatments (for example, pentamidine therapy) and bronchoscopy.

Procedures that may generate infectious aerosols include irrigation of tuberculous abscesses, or laboratory techniques such as homogenising or lyophilising of TB infected tissue. Such procedures should be performed with gloves as well the appropriate masks. Such procedures should only be performed on patients who have confirmed or suspected infectious TB or on TB infected tissue, in an appropriate isolation area.

Health care workers exposed to potentially infectious aerosolised material should wear a suitable mask during the cough-inducing procedure or the period of potential aerosolisation. Such procedures should be performed in an appropriate isolation room. Patients should be retained in the isolation room until coughing has subsided. During this period they should be instructed to cover their mouth and nose with disposable tissue when coughing. Where a cough-inducing or aerosol-generating procedure takes place, sufficient time should be provided after departure of the patient from the room to allow for efficient removal of airborne contaminants. The duration of time required depends on the number of air changes per hour. For a room with a rate of 12 ACH, this will require approximately 35 minutes.[3]

6.7 Masks and 'respiratory protective devices' (RPDs)

Detailed information concerning the transmission of TB is incomplete in the sense that issues such as the smallest infectious dose of TB and the level of exposure to TB at which transmission occurs has not been defined conclusively, although it is generally assumed to be one viable bacillus.[2] In a patient with active pulmonary TB, 100 per cent of infectious particulates produced by natural coughing (not 'induced') are larger than 1.1 micron diameter.[12] In settings where the likely exposure to HCWs of airborne droplet nuclei containing TB are high, the use of personal respiratory protective devices may be of benefit; however, masks should be seen as an adjunct to the more important measures of prompt identification, isolation, treatment and environmental controls.[14] A detailed description of masks and RPDs can be found elsewhere.[3, 13]

Surgical masks are designed to protect the sterile field from contaminants generated by the wearer. Air leakage occurs around and through them, and they only provide minor protection to the wearer against airborne droplet infection.[15] The degree of penetration by one-micron particles is highly variable when challenge tested.[16] Routine surgical masks should be worn by patients suspected or known to have pulmonary TB when not in Class N rooms.

Other disposable RPDs

These include certain duck-bill surgical-style masks which have improvements in design making them more effective at filtering, and have improved face seal.

'P' class RPDs are oilproof. 'N' class RPDs are not resistant to oil.

'N-95' or 'P2' RPDs have the following properties:

- an effectiveness of particulate (0.1 micron) filtration (PFE) greater than 95 per cent (usually 99%)
- a bacterial (3 micron) filtration efficiency (BFE) greater than 95 per cent (usually 99%)
- a breathability (DeltaP / differential pressure) less than 5.0 mm water/cm^2.

Although the closeness of fit with N-95 or P2 masks is better than with standard surgical masks, this remains a potential problem with such masks, and wearers should take particular care to ensure optimum adjustment when wearing one. Staff with beards or facial hair will not be able to achieve an effective seal, and alternative protection (for example, a positive pressure HEPA filtered, hooded respirator) should be used.

RPDs with at least the filtering capacity of N95 or P2 disposable RPDs should be worn by all persons entering the room in which patients with known or suspected active TB are isolated.

In general, the infection control measures for a patient with suspected or proven MDR-TB remain the same as for a patient with drug-susceptible TB. Patient movement around the hospital and external visitors should be kept to a minimum.

The reliability of RPD supplier should be ascertained by each hospital to reliably provide these in the quantity required. An alternative RPD/s needs to be planned for in the event of supply failure.

6.8 Staff health monitoring

Health care institutions should have in place a strategy to prevent and monitor transmission of TB from patients to staff. Various strategies exist, and the most appropriate strategy depends on the number of TB patients seen in that institution and the TB epidemiology in that region. Victoria is an area of low TB endemnicity; however, various hospitals, and particularly departments within these hospitals, will see a very large number of patients with pulmonary TB. A strategy appropriate to institutions seeing a low number of TB cases is to perform baseline testing of staff upon recruitment for latent TB with TST or IGRA, and only repeat testing if there is a significant exposure from an infective patient, such as a patient with unrecognised pulmonary TB being nursed without respiratory isolation. A strategy suitable for institutions caring for moderate to high numbers of TB patients is to routinely retest all initially negative staff at regular intervals, for example, annually or biannually. Staff members who convert from negative to positive on either TST or IGRA should be offered preventive therapy. Another strategy for moderate- to high-risk institutions is to regularly test only staff who are at increased risk for having close contact with patients who have infectious TB, and who have previously had a negative test for TB infection. These staff may include,

for example, respiratory ward health care workers or bronchoscopy suite staff. Such testing has the benefit of monitoring TB transmission among health care workers (and the adequacy of the institutions TB infection control program), and detects health care workers who may need treatment for latent or (less likely) active TB.[3, 4] Again, if this policy is adopted, it is important to measure the baseline TB status of staff for a comparison with periodic testing. Many staff may be positive from distant prior exposure (for example, in their country of origin), and are therefore not at increased risk for TB reactivation as compared with a staff member with a recent test conversion. Once a test for latent TB (TST or IGRA) has become positive, this is considered positive for life, based on our current understanding of these tests.

6.9 Discontinuing TB isolation

For patients placed in isolation because of suspected infectious TB, isolation can be discontinued when infectious TB is subsequently considered unlikely and either:

- an alternative diagnosis has been made which explains the clinical syndrome

  or
- the patient has three consecutive negative AFB sputum smears on different days.[17, 18, 23]

For patients in isolation with infectious TB who have commenced treatment, isolation can be discontinued when the patient is no longer likely to be infectious. Traditionally, this has been when the following are achieved:

- the patient has received a minimum of two weeks of effective therapy; and
- the patient understands and tolerates the medications, and is improving clinically, including improvement of cough; or
- three consecutive daily negative sputum AFB smears.

With the exception of patients with MDR-TB, the requirement for these patients to have three consecutive negative sputum AFB smears before being able to be released from TB isolation has been strongly questioned.[19]

Some patients continue to discharge non-viable organisms in sputum for some weeks after commencement of effective therapy. However, the fact that they are nonviable can only be established with certainty when cultures become available six to eight weeks later. Judgment as to when to release such patients from isolation is difficult, and should be made in close consultation with a physician experienced in treating TB. Patients with smear-negative pulmonary TB that is subsequently culture positive have also been shown to cause a proportion of secondary cases.[24] This emphasises the need for clinical judgment in determining which patients to step down isolation precautions.

Continued respiratory isolation of patients with proven pulmonary MDR-TB is recommended for the duration of their hospitalisation.

6.10 Discharge from hospital

As soon as possible after diagnosis, and certainly prior to hospital discharge of any patient with active TB, the patient must be notified to the Department of Health & Human Services and the appropriate follow-up with TB public health nursing arrangements made.

Patients should not be discharged from hospital earlier than is usual if they will be in regular contact with young children, unless the children are already on isoniazid therapy.

Patients should not be discharged from hospital earlier than is usual if they will be having new social contacts.

Note: Assuming directly supervised administration of therapy while in hospital, the most common reason for patients remaining infectious during treatment in hospital are the presence of cavities on chest X-ray, numerous AFB seen on smear of sputum[20] or MDR-TB.

For patients with proven or highly suspected MDR-TB, continued isolation throughout the period of hospitalisation should be strongly considered, regardless of the factors noted above, due to the tendency for treatment failure and/or relapse in these cases.

Patients who may be infectious at the time of discharge should not be discharged to their homes if they will have contact with immunosuppressed persons or children under five years of age.

6.11 Management of patients with confirmed or suspected active TB in ambulatory care settings and emergency departments

Emergency departments should review the need to be equipped with an appropriately ventilated isolation area (an airborne infection isolation room) suitable for patients with confirmed or suspected active TB. This decision should be guided by the general principles set out in the department of Human Services *Guidelines for the Classification and Design of Isolation Rooms in Health Care Facilities.*[10] Such patients should be identified at the time of presentation, triaged to the airborne infection isolation room and given a surgical mask to wear. In addition, if they are known to be presenting, a friend or relative should first obtain a mask from the department for the patient to wear prior to entry and while awaiting transfer to an isolation room. They should be instructed to keep their masks on, and to cover their mouths and noses with disposable tissues when coughing or sneezing, until a clinical decision regarding the likelihood of TB has been made.

If there is no airborne infection isolation room onsite for a patient in the ED with confirmed or highly suspected infectious TB, the patient requires immediate transfer to a facility with one. While awaiting transfer, staff should place the patient in a single room with the door closed, place a surgical mask on the patient, use a P2 or N95 face mask themselves when entering the room, and inform the patient, relatives and ambulance staff of the patient's diagnosis. The patient's mask should be left on during transfer.

Patients with confirmed or suspected active TB must be managed in a separate area to those patients known to be infected with HIV.

Institutions should ensure there are strategies in place so that patients with confirmed or suspected active pulmonary tuberculosis prior to the commencement of treatment attending outpatient appointments can be assessed in areas that separate them from the general outpatient population. A surgical mask should be placed on the patient and staff attending the patient should use a P2/N95 mask.

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Chapter 7 Preventing tuberculosis infection and disease among health care workers

7.1 Introduction

This chapter provides a framework for employers, staff, and other personnel to minimise the risk of transmission of TB within health care facilities. It should be used as a guide rather than a directive, because a 'one-size-fits-all' approach to guidelines is not appropriate when different health services have different levels of risk of exposure to cases of active TB disease. All facilities need a program to ensure prompt detection, institution of airborne precautions, and treatment of persons confirmed or suspected of having active TB disease. Such programs are based on a hierarchy of controls including administrative, environmental and respiratory protection.[1]

While the overall rate of TB in the Australian population remains low by global standards, there has been a modest increase in rate in recent years. In 2014 there were 445 new cases of TB in Victoria, at a rate of 7.8 per 100,000 population.[2]

In 2001 in Australia there were 17 cases of TB in overseas-born HCWs, rising to 83 cases in 2008. This increase was due to the recruitment of HCWs from high-burden countries in whom disease reactivated. There have been no recent reports of TB transmission to patients from HCWs; however, the possibility of this occurring when there is a potentially high rate of TB infection in the migrant workforce needs to be recognised.[3]

The occupational risk of HCWs acquiring TB, although mentioned in the 19th century literature, and in retrospect obviously higher than that of the general population, was not seriously acknowledged (and often underrated by eminent physicians) until the 1920s.[4] The resurgence of TB in the United States in the 1990s, including reports of HCWs infected with drug-resistant TB, refocused attention on the necessity to identify TB cases quickly, and implement appropriate strategies to reduce the risk of transmission of TB to HCWs.

The incidence of HCWs becoming infected with TB from occupational exposure varies between health services according to the prevalence of TB in the population served and the degree of contact by health care workers with TB patients.[5, 6]

The incidence of newly acquired TB infection by HCWs in Victoria is unknown. One study found that the odds ratio for having a positive tuberculin response in staff with direct patient contact compared to staff from the same institutions who had minimal patient contact was 1.5 (95% CI 1.3–1.7).[7] However, a positive tuberculin response is a poor proxy for recent tuberculous infection, because it could be due to other factors, including previous BCG (Bacille Calmette-Guérin) vaccination, or prior infection with TB or non-tuberculous mycobacteria. The study found that the following factors were all significantly associated with a positive response: age, country of birth (high versus low TB prevalence), history of BCG vaccination, years since last BCG, occupation (health care versus non-health care worker) and years of hospital employment. However, rates of positive responses among employees varied greatly between hospitals (6–35%). These differences were not explained by employee characteristics, hospital TB patient load or percentage of hospital patients from countries with high TB prevalence, and from this we may infer that a possible contributing factor to HCW infection was the variability in infection prevention practices for TB within each health service. The study identifies the need for hospitals to have appropriate screening programs for TB infection and sufficient negative pressure isolation rooms for the number of suspected or confirmed TB cases at the institution.

Although the majority of cases of active TB in Victoria are treated by specialist units within a few major hospitals, all open pulmonary cases must be identified early (before or at the time of admission, if the patient is admitted) and appropriate precautions immediately instituted to prevent transmission of infection to staff, patients and visitors. In this context, the challenge is to provide appropriate and feasible strategies to protect health care workers, with particular attention to those HCWs most likely to be exposed to cases of TB.

Substantial guidelines have been published in the United Kingdom,[8] United States[9] and New Zealand.[10] They take slightly differing approaches despite similar hazards from TB faced by their respective general HCW populations.

Occupational health and safety legislation—duty of care of employers and employees

The Victorian *Occupational Health and Safety Act 2004* defines the duty of care of employers as being 'to eliminate risks to health and safety so far as is reasonably practicable' and if it is not reasonably practicable to eliminate them, 'to reduce those risks so far as is reasonably practicable'.[11] This duty extends to staff, students, patients, visitors, volunteers, contractors and others who enter the facility. Employers must assess and control health and safety risks, monitor the health of employees and provide information, instruction and training to enable their employees to perform their work safely and without risks to health. Employees have a duty to take care for their own safety and cooperate with the employer's actions to provide a safe workplace.

Strategies for health care institutions

Strategies to reduce the transmission of TB within health care institutions are effective. One study has shown that after appropriate infection prevention measures were implemented, there was a seven- to eightfold reduction in the number of TB exposures to HCWs, and in the rate of Mantoux / tuberculin skin-test (TST) conversion.[12] Another study demonstrates that after appropriate control measures were introduced in a hospital treating patients with MDR-TB, the rate of new infection (as evidenced by TST conversion rate) among HCWs assigned towards housing patients with TB decreased by 70 per cent, returning to a rate similar to that of HCWs assigned to hospital wards not housing patients with TB.[13] A meta-analysis has shown that the introduction of transmission control measures to protect HCWs may decrease the incidence of latent TB among HCWs as much as 49 per cent in populations with a low incidence of TB.[6] The incidence within Victoria and Australia falls within this level.

The following strategies should apply to all staff, students and volunteers in health care settings, including those in long-term care facilities and community-based care:

- policy and governance processes
- environmental controls
- respiratory-protection controls.

Policy and governance processes ('administrative controls') relating to the prevention and detection of TB infection in HCWs

Each health care institution must:[9]

- assign responsibility for control of TB infection within its organisation
- conduct a TB risk assessment of its individual settings
- develop and institute a documented infection prevention plan that directs the prompt detection of, institution of airborne precautions for, and treatment of persons with proven or suspected pulmonary TB disease
- implement effective work practices for the screening and prompt triage of patients, and the subsequent management of patients with proven or suspected pulmonary TB disease
- promptly place persons suspected or known to have infectious TB in a specifically designed airborne infection isolation (AII) / negative pressure room. The following factors increase the risk of infectiousness:
  - presence of cough
  - acid fast bacilli (AFB) seen on sputum smear ('smear positive')
  - cavitation on chest X-ray
  - cough-inducing or aerosol-generating procedures (for example, bronchoscopy, sputum induction, aerosolised medications).

While patients are waiting for placement in an airborne infection isolation (AII)/ negative pressure room, they should wear a surgical mask, observe strict respiratory hygiene and cough etiquette,[14] be located in a single room (if one is available) with the door shut, and staff attending the patient should wear an appropriate P2/N95 particulate respirator.

The contact of staff, students and volunteers with persons suspected or known to have infectious TB should be restricted to strictly necessary encounters only. All persons entering an isolation room should wear an appropriate P2/N95 particulate respirator.

Institutions should implement an ongoing training and awareness program appropriate for staff, students and volunteers regarding TB, including:

- its mode of transmission
- the natural history of TB infection, including the difference between latent and active infection
- when to suspect active pulmonary TB as a possible diagnosis using simple features from a patient's history (for example, any of the following lasting longer than three weeks, particularly if occurring in a patient from a demographic with an increased risk of TB:
  - cough
  - unexplained weight loss
  - bloody sputum or haemoptysis
  - fever
  - fatigue
  - chest pain[9]
- engineering and personal protective strategies available to minimise nosocomial transmission of TB
- the need for appropriate screening of HCWs for TB infection and management of HCWs found to be infected.

Staff induction or orientation on infection control is an appropriate context in which to provide TB education, but an ongoing awareness strategy should be in place in higher-risk areas. This must be conducted by suitably qualified personnel. In institutions with low TB risk, a simple pamphlet may suffice. Areas within institutions that may be at greater risk from TB must be specifically addressed by the institution in regard to education and raising the awareness of TB and the required actions related to this. These areas include accident and emergency departments, intensive care units, respiratory wards, bronchoscopy units and infectious diseases wards.

Institutions that regularly manage TB patients should also provide periodic in-service education on TB. Updates may address trends such as the admission of TB cases, the delay in isolation of cases and the outcomes of staff TB screening. Because the majority of patients with previously unsuspected active pulmonary TB will be admitted via a hospital's emergency department, and delays in considering the possibility of TB will increase its risk of nosocomial transmission, ongoing cyclical effective reminders to triage, nursing and medical staff to consider the possibility of TB should be strategically placed, physically or electronically, within emergency departments. For any ongoing training and awareness program to be effective, it should be consistent with published successful strategies regarding determinants of diffusion, dissemination and implementation of innovation within health service organisations.[15, 16]

Institutions should ensure the prompt availability and performance of appropriate laboratory and radiology testing for persons with suspected pulmonary TB, and the prompt reporting of results to the ordering doctor and infection-prevention team. Institutions should also coordinate efforts with the state or relevant health department.

7.2 Environmental controls

This involves preventing the spread and reducing the concentration of infectious droplet nuclei containing *M. tuberculosis* in ambient air. Droplet nuclei are the airborne 1–5 micron residues from potentially infectious aerosols (generated by sneezing, coughing, singing, talking) from which most of the liquid has evaporated, and are thus capable of staying airborne for long periods. There is strong evidence to demonstrate the association between ventilation, air movements in buildings and the transmission/spread of infectious diseases including TB.[17]

Primary environmental controls involve controlling the source of infection by ensuring high rates of ventilation, whether by artificial ventilation with high airflow rates to the room in which a patient is located (18 Nielsen) or natural ventilation.[19] Few, if any, health facilities in Victoria would have such high rates of natural ventilation.

Secondary environmental controls include prompt and appropriate use of airborne infection isolation (AII) / 'negative pressure' rooms to reduce the dissemination of droplet nuclei containing *M. tuberculosis* from infectious patients to adjacent areas. These rooms must be installed, operated and maintained correctly, including the routine measurement of air-pressure differentials.[9] Ultraviolet germicidal irradiation (UVGI) kills *M. tuberculosis* under experimental conditions,[20, 21] and has been used as an adjunct to other TB infection control and ventilation measures.

7.3 Respiratory protection controls / personal respiratory protection

Policy and governance processes ('administrative controls') and environmental controls are the two most important interventions to reduce the nosocomial spread of TB, because, if implemented appropriately, they assure rapid diagnosis, isolation and treatment of persons with pulmonary TB. Use of personal respiratory protection (PRP) may further reduce risk of exposure for HCWs to infectious droplet nuclei expelled into the air from a patient with pulmonary TB. Respirators capable of high-efficiency particulate air filtering that meet AS/NZS1716 are designed to provide respiratory protection to the wearer, unlike surgical masks. They are commonly called any of the following: N95/P2/submicron masks or respirators.

There is a lack of high-level epidemiological data demonstrating the effectiveness of PRPs in protecting HCWs from pulmonary TB,[9] and neither the smallest infectious dose of *M. tuberculosis* nor the highest level of exposure to *M. tuberculosis* at which transmission will not occur has been defined.[22] Additionally, the size distribution of droplet nuclei and the number of particles containing viable *M. tuberculosis* organisms that are expelled by patients with infectious TB disease have not been well defined. Accurate methods for measuring the concentration of infectious droplet nuclei in a room have not been developed.[9]

Supported by Level D evidence, the Australian NHMRC has recommended the use of particulate respirators that meet or exceed the N95 standards set by the United States Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health (CDC/NIOSH) or the European FFP2 standards when caring for patients or those suspected of having infectious TB.[23] HCWs should especially wear particulate respirators when undertaking high-risk aerosol-generating procedures associated with high risk of TB transmission (for example, bronchoscopy, intubation, sputum induction procedures, aspiration of respiratory secretions, and autopsy or lung surgery with high-speed devices).

The strongest evidence supporting PRP is based on mathematical modelling, laboratory testing using surrogate bacteria or particles and expert opinion.[24] In Australia, this PRP essentially is in the form of a variety of 'respirators' in conjunction with the training of patients on respiratory hygiene and cough etiquette procedures. Respirators may be either disposable or non-disposable elastomeric (rubber-like) with filter cartridges. While PRP may reduce the risk of infection in the face of suboptimal environmental controls,[25] it may also be inadequate in the absence of these controls.[26] A PRP program in isolation will fail because it cannot protect HCWs from exposure to unrecognised cases.

Respirators range from devices that cover only the nose and mouth (the majority of types in Australia) to those that cover the user's head, to those that have independent air supplies. There are nine types of non-powered particulate filter masks according to whether they are non-resistant (N) to oil, resistant (R) to oil, or oil proof (P), and their filtering efficiency in terms of the percentage of 0.3 micron particles that are filtered (95%—95, 99%—99, 99.97%—100). Using this categorisation, the most commonly used masked in Australia is a 'N95' respirator/mask.

Excessive face-seal leakage reduces the ability of respirators to protect HCWs from airborne materials. Factors contributing to excessive leakage include beard growth, incorrect facepiece size, failure to follow manufacturer's instructions, and perspiration or facial oils that lead to facepiece slippage.[9] A half-facepiece respirator, including an N95 disposable respirator, should have < 10 per cent leakage.[9]

There are several methods of 'fit-testing'. Fit characteristics often cannot be determined soley by physical appearance of the mask;[27] however, some data suggest that very well designed masks without fit-testing may provide better PRP than some masks with fit-testing.[28]

7.4 TB risk assessment

The purpose of TB risk assessment is to allow the implementation of the TB control strategies appropriate to a particular institution or situation.

Assessing the risk of TB at a health care institution involves:

- an overall assessment of the TB risk faced by the institution
- an assessment of the TB risk faced by particular groups of health care workers within the institution
- regular review of these risks.

Institutional risk

An assessment of the risk faced by the institution must consider:

- the number of persons with TB disease admitted to the institution each year
- the clinical activities of the institution
- the availability of appropriate isolation facilities for airborne diseases
- evidence of recent TB infection of health care workers
- populations served by the institution.

Institutions with evidence that they admit, on average, fewer than one patient with infectious TB per year may be considered to have a low TB risk.[5, 7] Many small and medium-sized health-care institutions in Victoria are in this category. One guideline[9] has set different criteria to satisfy 'low-risk' classification for inpatient health care settings:

- if < 200 inpatient beds—fewer than three patients with active pulmonary TB per year
- if 200 or more inpatient beds—fewer than six patients with active pulmonary TB per year.

It also provides criteria for medium- and higher-risk classifications. A review of this detailed reference should be made for further details.

HCWs' risk

Institutions that admit, on average, one or more patients with infectious TB per year should assess the TB risk faced by particular groups of HCWs within the institution. Prospectively measured local rates of newly acquired TB infection in different groups of HCWs are the ideal measure of this risk. In practice, such data, so far largely based on tuberculin skin testing in an extensively BCG-vaccinated population, are difficult to collect and interpret. The rarity of TB disease in local HCWs provides some evidence that infection of such persons is uncommon. Prospective data derived from serial screening of health care workers using interferon-gamma release assays (IGRA) may eventually help define the incidence of newly acquired TB infection.

Until such data become available, the following risk categories may serve as a guide to the risk to particular groups. The categories reflect historical experience of nosocomial TB transmission, and settings in which untreated TB patients are most likely to receive health care. Within many of these settings there will be a variety of medical, nursing, physiotherapy, paramedical, scientific, and non-clinical ward staff, the risk for whom may differ.

Relatively higher risk settings and HCWs with increased risk may include:

- mortuaries performing post-mortems[29–31]
- suites/theatres in which bronchoscopies are performed
- wards where patients with active pulmonary TB are treated
- laboratories dealing with potentially TB material (mycobacteriology, bacteriology, histology and cytology)
- inpatient and outpatient settings where persons with HIV or latent TB infection are managed (patients with known active pulmonary TB should not be managed in an outpatient clinic setting which involves exposure to other patients or staff, unless appropriate environmental and respiratory protection precautions are in place)
- emergency departments
- intensive care units.

While eight hours of cumulative time has previously been arbitrarily used as a guide to a minimum time to acquire TB infection when in the same environment as a person with active pulmonary TB, this is largely based on reports from transmission of TB occurring during long-haul flights. Given that the air handling/engineering conditions during these flights are quite different from those in standard clinical areas,[32] and that both cases of infection occurring with shorter exposures, and no infection occurring with longer exposures,[31] a direct extrapolation should not be

made. Lower thresholds should be considered where more susceptible people are involved or people participate in high-risk procedures.

Relatively lower-risk settings may include:

- all other hospital settings where direct patient care is provided
- community settings in which health care workers might occasionally encounter persons with TB
- ambulance service
- paediatric hospitals.

Settings where staff have no contact with patients or their clinical specimens, such as the kitchen and administrative areas, are unlikely to pose a greater risk of TB infection than is experienced in the general community.

Significantly immunocompromised HCWs, including those with HIV, must not be exposed to settings known or suspected to pose a risk of TB infection.

Regular review of TB risk

As part of the clinical governance of its infection prevention program, each health service/institution should regularly (at least annually) review:

- its incidence of admissions of patients with active pulmonary TB to inpatient beds
- performance indicators that reflect the effectiveness of its strategies to prevent the nosocomial transmission of TB. These should include the delay (in days) to the institution of appropriate isolation within an inpatient setting for patients who are subsequently proven to have pulmonary TB (or commenced on treatment for suspected pulmonary TB within an inpatient setting)
- compliance with the recommended schedule for screening of staff for latent TB who are new employees, or who work in high-risk areas for being infected with TB
- evidence of nosocomially acquired TB infection
- the outcome of follow-up of health care workers exposed to cases of TB

These data should be provided to the institutional committee/other body who reports to the board of the institution regarding occupational risk to infection (or in the absence of such a body, directly to the board).

7.5 Screening of HCWs

Protocols for TB screening of HCWs

The role of serial TB testing of HCWs in settings of generally low TB prevalence is unclear. The process is mandated in all but the lowest TB risk settings in the United States[9] and recommended in a recent British guideline, but which also concluded that the evidence for the benefit of such a process is lacking.[33] The yield from serial TB testing during employment is likely to depend on the institutional TB risk, and the risk to particular groups of health care workers of TB infection. The institution must provide screening for TB infection to appropriate staff freely, confidentially and at the employer's expense. Screening is preferable onsite, although an appropriate external provider is an alternative.

Institutions that admit, on average, fewer than three patients with infectious TB per year are unlikely to benefit from serial TB testing of staff. Rather, their efforts should be directed to establishing the entry or baseline TB status of all their staff, and to follow up testing in the rare event of a significant, uncontrolled TB exposure.

Institutions that admit, on average, three or more patients a year with infectious TB per year should assess the risk faced by workers in various settings to determine the need for serial TB testing.[9] Ideally, this risk would be determined by data from serial TB testing. In the absence of such evidence, institutions may choose to selectively target for serial TB testing HCWs in the settings likely to be associated with a relatively higher risk of exposure to TB (see above). The appropriate frequency of serial TB testing of such HCWs is also unclear. The recommendation in the United States is to screen staff in the highest risk settings annually, subject to information from risk assessments of these settings.

Screening of HCWs for TB infection aims to:

- identify all HCWs who may be infected with TB at the start of their employment
- identify all HCWs who may subsequently become infected with TB during their employment
- prevent HCWs infected with TB progressing to TB disease
- establish the TB status of HCWs as a point of reference for future screening.

Screening for TB infection may involve testing at several different stages during the course of employment. It is possible for this to be done via either tuberculin skin testing (TST) or interferon-gamma release assays (IGRAs), or a combination of both.

Screening for latent TB infection in a low-prevalence HCW population using TST may be associated with several problems:

- false positives due to previous BCG vaccination or other previous non-tuberculous mycobacterial infection
- false negatives due to a state of anergy (immune system unresponsiveness) to TST, even if previously infected with TB
- in some people with longstanding latent TB, their TST may revert to negative (a false negative result). Performing a TST will stimulate (boost) their sensitivity to tuberculin, and if given a second test a few weeks or months later, these people will correctly test positive. This may be incorrectly interpreted as evidence of recent infection with TB. To control for this 'boosting', phenomenon workplace surveillance programs should provide an initial two-step baseline screening process (two TSTs given 1–4 weeks apart).[34] In this context, a positive result for the second test following a negative result for the first should be interpreted as a boosted result rather than a true recent conversion. A HCW with a boosted test result should not be involved in a periodic retesting program.
- logistical problems with administration of TST, including correct administration technique, the need for the person tested to return for reading of the test, incorrect reading of the test
- serial TB testing by TST is contraindicated in persons with previous strongly positive tests or previously established TB infection or disease
- testing by TST should be rescheduled for persons on short-term immunosuppressive therapy and recent recipients of live viral vaccines
- BCG-vaccinated persons with a documented TST of 10–14 mm often demonstrate progressively larger TST reaction with serial tests. For such persons, the discomfort of serial TST may outweigh their diagnostic value; IGRA is an alternative.

Serial TB testing by TST involve a one-step TST for persons with a documented previous negative two-step TST.

Persons whose TST reaction exceeds their last TST reaction by 10 mm or more, or by more than 5 mm if a recent contact of a case with active pulmonary TB (a 'conversion') and persons with a reaction of 15 mm or more (if known to have had BCG) should be referred for further assessment. Typically, this will involve an IGRA, a chest X-ray, and clinical review by an appropriately qualified consultant.

The IGRA has better specificity in previously BCG vaccinated HCWs, and repeat testing has no associated booster effect. IGRAs therefore have some potential advantages over TST in HCW screening. However, the most appropriate use of IGRA in testing for latent TB is still currently unresolved. Some guidelines from high-income, low-incidence countries state that IGRAs may be used for serial testing of HCWs in place of TST;[35] whereas others do not recommend IGRAs for this purpose.[36]

From a cost-effectiveness viewpoint, there have been differing conclusions regarding the cost-effectiveness of using an IGRA only versus TST/IGRA strategy as screening programs for latent TB in high-risk groups including HCWs.[37] The 2012 recommendation of the Australian National Tuberculosis Advisory Committee was that TST remains the preferred test for HCW screening, with IGRAs used to increase specificity in the case of a positive TST.[38]

Testing on employment entry for latent TB infection

This should:

- apply to all medical, nursing, allied health and other staff who may have face-to-face contact with patients
- occur before or within four weeks of commencing employment
- be accompanied with a written explanation to staff about TB screening
- if positive, be followed up with a chest X-ray, looking for evidence of tuberculous infection/disease.

Notes:

1. Pre-employment testing may be waived if the HCW can provide a documented record of TB screening within the previous three months.
2. Pre-employment chest X-rays are necessary only if clinically indicated, or the TB screening test on entry (see above) is positive.
3. The method of screening for TB infection (TST or IGRA, or both) should be determined by the institution, after considering the particular situation for each individual HCW and the points above.
4. Tuberculin skin testing is contraindicated in persons who have previous strongly positive tests or previously established TB infection or disease, or who are on short-term immunosuppressive therapy, or within six weeks of live viral vaccines.
5. Persons with a first TST of less than 10 mm who have had previous BCG vaccination should have a two-step entry TST. A two-step TST aims to identify persons with a false negative or weakly positive TST result at the first test. Up to 10 per cent of persons with an initial negative or weakly positive TST will, when tested one to three weeks later, respond with a 'booster' reaction that is 5–10 mm larger. The reaction is most often seen in persons previously vaccinated with BCG. Identifying such persons as reactors reduces the chance that subsequent positive tests are misinterpreted as conversions.[39] Subsequent tests (if indicated) involve only a single TST. Two-step testing need not be performed if the initial test is greater than 9 mm.
6. Persons with an unexplained positive TST – typically greater than 15 mm in the presence of a BCG scar, or greater than 10 mm in the absence of a BCG scar – need to be referred for further assessment and support.
7. HCWs entering the local workforce from backgrounds of living and working in countries with high TB burdens must be carefully counselled and their past experience taken into account when evaluating their TST result.

'Catch-up' screening

It is recognised that many HCWs who are already employed do not have a record of their TB infection status. Screening should be performed on these HCWs, but for logistical reasons, this may assume secondary priority to new employees, and when undertaken, should be commenced with employees working in higher risk areas for becoming infected with TB (see above).

Regular screening following initial testing

The need for (if at all) and frequency of regular screening following initial testing should be determined by the likelihood of the HCW becoming infected with TB, as determined by the health institution's infection prevention advisors. It is recommended that HCWs judged to be working in 'high-risk' areas are screened annually with either a TST or IGRA, if these tests are not already positive. In general, HCWs working in TB, or general respiratory wards, bronchoscopy or induced-sputum rooms, TB laboratories, and post-mortem examination rooms should be considered at high risk of TB exposure.

For HCWs judged to be in medium-risk work settings, screening is recommended every two years. For HCWs in low-risk areas, regular screening is not recommended. If the TST and/or IGRA is already positive, the HCW should have a chest X-ray if suggestive symptoms of pulmonary TB develop (following prior communication with them regarding these possible symptoms by the institution).

Exit testing

All health care workers should be offered TB screening at the conclusion of their employment, and provided with copies of their TB screening results and related investigations and therapy to take to their next workplace.

Institutional records of TB testing

Institutions must securely and retrievably store institutional records of TB testing, referrals, investigation and treatment, and maintain confidentiality between the test provider and the HCW. This process must allow for access to records to facilitate follow-up of TB exposures, and for analysis of de-identified aggregate data on the performance of the TB screening program and conversion rates.

Institutions must provide each HCW with a serially updated personal record of their TB status and associated management to take from workplace to workplace. There must be a process for providing a copy of the TB screening and associated management to a nominated person at the HCW's next place of employment, on request of the worker. Health care workers have a responsibility to carry their personal record from one employment to another.

7.6 Contact management

If HCWs are significantly exposed to a person with potentially infectious TB for whom adequate infection control procedures cannot be assured, then they must be identified, advised and followed up according to contact tracing procedures. This situation typically arises when an unexpected diagnosis of TB is made some time after admission, and infection control measures for suspected and known TB cases were not used. Follow-up would consist of counselling, and if previously negative, repeating either a TST or IGRA as soon as possible after the contact, and again approximately 10–12 weeks later. If either the TST or IGRA was previously positive, the HCW should be counselled regarding the possible symptoms of active pulmonary TB, told to report these if they occur, and have a chest X-ray at that stage, or at an earlier asymptomatic stage if the HCW wishes, or if the infection prevention consultant judges this appropriate. For HCWs who have undergone a definite recent conversion following exposure to a patient with active pulmonary TB, commencement of treatment for latent TB is recommended, unless there are strong contraindications, and providing that active pulmonary TB has been excluded.

In post-exposure situations, the factors that contribute to an increased risk of nosocomial transmission to staff and patients must be carefully assessed, including the infectiousness of the index case, the duration of exposure, the proximity of contact and the susceptibility to infection of the contacts. Significantly exposed staff and co-patients should be managed the same way as household contacts.

Routine short-term contact of staff with infectious (that is, smear positive) TB patients (taking observations, administering medications, assistance with personal hygiene, clinical examination, minor procedures) before isolation does not pose a high risk. However, staff involved in expired air resuscitation without appropriate protection, prolonged care of a high-dependency patient, repeated chest physiotherapy or any aerosol-generating procedure such as sputum induction, nebuliser therapy, or certain post-mortem procedures should be managed as close contacts.

In general, co-patients in the same room or bay (within three beds either side of the index case) should be regarded as significantly exposed if the index case was coughing, smear positive and present in the room for (arbitrarily) more than eight hours before isolation, or if the exposed co-patient is known to be particularly susceptible to infection.

Smear-negative patients are approximately four- to fivefold less infectious than smear-positive.[40, 41] For such patients, staff members and co-patients with a cumulative exposure of 48 hours should be identified, assessed for particular susceptibility and followed up accordingly.

Patients identified as significantly exposed, but who have been discharged from hospital, should be notified by the hospital, advised of their exposure and will be provided appropriate investigation and follow-up.

Staff whose exposure to an infectious TB patient does not meet the criteria for urgent follow-up should be reassured of their safety. Routine serial TB testing of HCWs in settings with relatively frequent involvement with TB cases provides an opportunity to screen such staff.

Responsibility for contact tracing of hospital staff and patients significantly exposed to infectious TB rests with the infection prevention and occupational health units of the hospital.

Contact tracing within the health care institution requires a written contact tracing protocol, including processes to:

- assess the infectious risk posed by the TB case
- record the movements of patients and deployment of all staff (including agency staff and students)
- identify and record the names and contact details of all staff, parents, students, volunteers and contractors exposed to the TB case
- provide written advice to exposed persons, including details of their TB testing appointment (typically 10 to 12 weeks after their last exposure to the case)
- perform and document TB testing of exposed persons, follow-up positive tests, trace and complete follow-up of persons who miss their TB testing
- review and summarise the incident and follow-up, and provide feedback to the infection control unit, occupational health and safety committee and affected staff.

Contacts should not be isolated or restricted unless they have symptoms consistent with pulmonary TB, or smear positive pulmonary disease is confirmed. Symptomatic contacts should be isolated until active TB is excluded.

Persons with no record of their TB status are best managed with a TB test immediately after their exposure. These persons then require further TB testing 10–12 weeks later, unless the initial test indicates TB infection.

In BCG-vaccinated persons, an immediate post-exposure one-step TST (which may be negative), and another 10–12 weeks later, may elicit a booster response, which is difficult to interpret. An IGRA immediately after exposure and another 10–12 weeks later, may provide better evidence of the timing of any TB infection.

Immediate post-exposure TB testing is often impossible when the diagnosis of TB (typically by culture) is made four or more weeks after the last unprotected exposure of the HCW. In such circumstances, TB screening 10–12 weeks after the last exposure is the only feasible strategy. The results of such screening may be difficult to interpret unless a record of earlier TB screening is available.

Persons with new evidence of TB infection (a TST conversion or new strongly positive TST, or a positive IGRA), must be promptly referred to an appropriately qualified clinician for advice, assessment and management.

7.7 The role of BCG vaccination

A healthy non-BCG-vaccinated HCW who is recently infected with TB has an approximately 10 per cent lifetime risk of developing TB disease. The role of BCG vaccine in managing the TB risk to HCWs remains contentious. BCG vaccination does not prevent the transmission of TB to an individual; however, it may limit the spread of primary infection within an individual. Estimates of the degree to which previous BCG vaccination may reduce this risk of progression vary from 0–80 per cent.[42–44] Such differences are not readily explainable simply by the different BCG strains used,[45] and differences in methodology, age and genetic or immune factors may be involved. In contrast, others have reported lack of efficacy in preventing infection.[46] Data on the likely risk reduction conferred by BCG vaccination specifically in healthy HCWs in the developed world are scant.

The possible *benefits* of BCG vaccination of HCWs are that:

- If a worker is infected with TB, then BCG *may* moderately reduce the risk of developing TB disease.
- Where there is a significant risk of infection with drug-resistant TB, BCG may induce an immunological defence that reduces the risk of developing TB disease from these strains of *M. tuberculosis.* In contrast, treatment of latent TB infection due to such strains would not be expected to confer benefit if the *M. tuberculosis* strain has primary resistance to the drug(s) used to treat latent TB infection.

The possible *limitations* of BCG vaccination of HCWs are that:

- BCG may act as a disincentive for HCWs to participate in serial TB testing, by conferring a false sense of protection against infection. Missed opportunities to detect and treat latent TB infection may result.
- Most HCWs in Victoria are likely to be at very low risk of exposure to infectious TB cases. Accordingly, many such health care workers would need to be vaccinated with BCG to prevent a single case of TB disease.
- BCG confounds the interpretation of the TST and precludes this test from being used to diagnose TB infection in many BCG recipients. IGRA is a means to diagnose TB infection in BCG-vaccinated persons and monitor the incidence of new TB infection in BCG-vaccinated populations.

The use of BCG as a primary means of protection for HCWs is not recommended by current Australian national guidelines. These guidelines restrict the recommendation of BCG to specific subgroups and do not precisely define the role of BCG for HCWs; however, they state that BCG should be considered for HCWs at high risk of exposure to drug resistant TB.[47]

BCG vaccination should not be administered to HCWs who are immunocompromised, infected with HIV, pregnant or likely to become pregnant soon. If BCG vaccination is planned, HCWs should have a two-step TST prior (if not performed previously). BCG should not be given to an individual with a TST reading of 5 mm or more. It should not be administered unless consent has been obtained following a full explanation of the benefits and risks associated with vaccination. BCG revaccination is not routinely recommended, regardless of TST reaction. TST reaction size does not correlate with BCG vaccine efficacy.[52]

Pre- and post-deployment care of HCWs who work in overseas settings of high TB prevalence

The risk of TB infection faced by local HCWs when they work or volunteer in health care settings in countries with high TB burdens is considerable, and may be approximately one per cent per month.[48–50]

Many Australian HCWs are involved in such activities; infection of some is inevitable.[51] The cumulative exposure and associated risk to an individual mounts with repeated and prolonged stays. Such persons require careful advice on the strategies available to them to prevent TB disease. In deciding on their approach, they must consider the incidence of TB in the particular setting(s) where they will be, the prevalence of drug-resistant TB, the duration of their stay, the likelihood that they will make recurrent visits, the availability of timely screening for TB infection after periods of risky exposure and any particular personal susceptibility to TB. For single, brief spells in health care settings with high TB prevalence, particularly where drug-resistant TB is relatively uncommon, pre- and post-deployment TB testing may suffice. For longer and recurrent visits to health care settings in high-TB countries, particularly in the many countries where drug-resistant TB is now common, the potential benefit conferred by BCG becomes increasingly tangible. Post-deployment screening of BCG-vaccinated persons who have visited health care settings in high TB countries is absolutely crucial. Detection and treatment of latent TB infection in such persons reduces their chance of developing TB disease, and the possibility of transmitting TB in local health care settings.

Compliance and accreditation

All health care institutions must meet the accreditation standards and guidelines of various state and Commonwealth government departments and agencies. Compliance also helps health care institutions meet their legal responsibilities under occupational health and safety legislation.

The view of the Department of Health & Human Services is that the board of governance of a health care institution is responsible for providing a safe environment for patients, staff and visitors. Health services must also report to their communities annually on their infection control outcomes as part of their annual quality of care reports.

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Chapter 8 Prevention of tuberculosis in institutions, including aged care facilities, prisons, special accommodation homes

8.1 Introduction

Elderly residents of aged care facilities, special accommodation residents, prisoners, and the homeless are at higher risk for TB than the general community. Awareness of the possibility of active TB disease is the cornerstone of preventive measures in these situations. Risk is significantly increased by several factors, including:

- age
- alcoholism
- smoking
- HIV infection and other immunosuppressive conditions
- immunosuppression due to medication, for example, steroids
- diabetes
- silicosis
- general neglect
- malnutrition.

In these settings delayed diagnosis, sustained contact with the index case, inadequate ventilation and overcrowding can also contribute to the risk of TB transmission.

8.2 Administrative controls

Transmission of TB infection can be limited by having adequate controls in place for dealing with TB, including:

1. developing and implementing effective written policies and protocols to ensure the rapid identification of persons likely to have TB
2. developing protocols requiring physicians and other HCWs admitting to aged care facilities, hostels, special accommodation facilities and prisons to undertake and report pre-admission medical assessment, including previous history of TB, history of cough and baseline CXR where appropriate
3. education, training and counselling of HCWs about TB – refer to Chapter 7 Preventing TB Infection and disease among health care workers.

Guidelines for procedures to be followed in the event of a TB diagnosis:

- persons with suspected pulmonary TB should be transferred to an appropriate acute care facility until therapy is instigated and patient stabilised – refer Hospital Care of TB
- early investigation and treatment of persons likely to have TB
- immediate contact investigations – refer to Chapter 16 Contact tracing guidelines
- liaison with treating physician in acute care facilities to ensure that discharge criteria relating to cessation of TB isolation are met, before allowing return to pre-admission facility
- ensure adequate supervision of patients on anti-TB treatment to maintain compliance with therapy.

A high index of clinical suspicion of active TB disease must be maintained by HCWs involved with these high-risk groups and the appropriate clinical investigations undertaken as indicated – CXRs, sputum smears and culture.

The occasional situation where unrecognised active TB disease results in new infections and large-scale contact tracing in institutions highlights the need for medical officers and other HCWs in these settings to be especially vigilant. The possibility of TB infection should always be kept in mind for any person who presents with complaints of prolonged productive cough, weight loss, haemoptysis, prolonged fever and/or sweats.

Screening CXRs are not cost-effective and are not recommended, except where there is specific clinical indication or where other measures are unlikely to be effective (for example, treatment of LTBI in the immunosuppressed).

8.3 The prison population

Prisoners have a higher incidence of HIV infection and other TB risk factors than the general population. HIV co-infection is the most serious risk factor for developing active TB disease among those with LTBI. Screening HIV positive prisoners for LTBI identifies those who would benefit from treatment of LTBI (refer to Chapter 11 HIV infection and tuberculosis). Rapid assessment of prisoners with possible TB is essential. An HIV-positive inmate with possible active TB should be isolated and evaluated even if they have a negative TST and a clear CXR. Any therapy, either for LTBI or active disease, given to any prisoner, should be administered on a fully supervised basis. Arrangements should be in place to ensure continuity of care and supply of anti-TB medications if a prisoner is incarcerated, transferred between centres, or released into the community – contact the Victorian Tuberculosis Program (phone 03 9342 9478) to assist with planning for this.

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Chapter 9 BCG vaccination

9.1 Background and history of the BCG vaccination program in Victoria

Bacillus Calmette-Guérin (BCG) is the only licensed vaccine against TB. It is a live attenuated strain of *Mycobacterium bovis.* After its creation by Albert Calmette and Camille Guérin, and first use in humans in 1921, the vaccine was distributed worldwide. Continued subculture under different conditions led to the existence of different strains of BCG vaccine worldwide.[1–3]

Routine BCG vaccination was stopped in Victoria 1984–85. Prior to this, a school-leaving age vaccination program existed from 1950–52, a period when TB was responsible for about 30 per cent of deaths in the 20–40 year age group in Australia. The aim of the program was to improve immunity to TB during the latter half of adolescence and into early adult life while school-leavers were settling into the adult workforce and being exposed to adult patterns of TB infection.

The program was terminated following a review comparing TB incidence patterns in Victoria and New South Wales over the previous 30 years in the 15–29 year old age groups. A deliberate decision had been made not to use BCG vaccination in New South Wales since 1950, which therefore acted as a control for the school-leaving age program routinely being undertaken in all other Australian states and territories. No significant long-term protective effect from BCG was found in the Victorian Australian-born population by 1980[4].

Since 1985 there has been a progressive reduction in the incidence of TB in the Australian-born population (now generally fewer than one per 100,000 in adolescents and young adults). Although TB rates are higher in the overseas-born Australian population, there is no evidence to suggest significant transmission of infection between the overseas-born and Australian-born populations. BCG vaccine is therefore no longer included in the routine National Immunisation Program in Australia.

9.2 Efficacy of BCG vaccine

There is strong evidence that BCG vaccination in infancy provides approximately 80 per cent protection against the severe and disseminated forms of TB that occur in infants and young children, including miliary TB and tuberculous meningitis.[5] The vaccine is less effective in preventing pulmonary TB in adults (approximately 50% protection).[6] There is a wide variation in the reported protective efficacy of BCG and an apparent inverse correlation between efficacy and proximity to the equator.[6] Factors that might account for these findings include differences between BCG strains, age at vaccination, nutritional (for example, vitamin D) factors, and differences in exposure to environmental non-tuberculous mycobacteria.

The duration of protection following BCG vaccination is uncertain. Protection following infant vaccination is believed to wane after 10 to 20 years.

It is generally believed that BCG does not prevent infection with TB, or reactivation of LTBI, so BCG vaccination does not have a significant role in preventing transmission. BCG vaccination also has no role in the treatment of active TB.

BCG vaccination provides some protection against leprosy caused by *Mycobacterium leprae.* BCG has strong immunomodulatory properties which are exploited in its use for the treatment of bladder cancer. These 'non-specific' effects of BCG vaccine are of current interest and a recent focus of research[7, 8].

9.3 Tuberculin skin testing and BCG vaccination

BCG vaccination initiates a cell-mediated immune response that leads to tuberculin conversion in a large proportion of vaccinees. This tuberculin conversion can persist, to varying degrees, for many years. This complicates the interpretation of the TST.

BCG vaccination of individuals with LTBI is unnecessary, and is associated with an accelerated local reaction. Australian recommendations therefore state that 'all individuals, except infants < six months, have a tuberculin (Mantoux) skin test (TST) before BCG vaccination to exclude LTBI resulting from previous TB exposure'.

However, because the risk of exposure to TB in developed countries is low, a more targeted approach has been suggested that uses a risk assessment questionnaire to identify children who should have a TST before BCG immunisation.[9] This proposes that TST screening for LTBI or active TB disease is only necessary if a child meets one or more of the following criteria:

1. born in a country with an annual TB incidence > 40 per 100,000* population
2. previous travel to a country with an annual TB incidence > 40 per 100,000 population
3. exposure to an individual with active TB disease
4. contact with an individual with a positive TST or interferon-gamma release assay (IGRA) or an individual with symptoms compatible with active TB (see below)
5. current or previous household visitor from a country with an annual TB incidence > 40 per 100,000 population
6. symptoms compatible with active TB disease including persistent (> 2 weeks) cough, weight loss, fever or night sweats.

* Current annual TB incidence data available from the WHO: http://www.who.int/tb/country/data/download/en/index.html

It should be noted that a hypersensitivity reaction may also occur in those infected with other mycobacteria and those previously vaccinated with BCG. Also, the TST may be unreliable for up to a month after the administration of live viral vaccines, because these inhibit the response to tuberculin leading to a false negative TST result.

9.4 Indications for BCG vaccination

The National Health and Medical Research Council has reviewed the place of BCG vaccination in Australia, and current recommendations are published in the latest revision of *The Australian Immunisation Handbook.*[10] Reference should be made to Section 4.20 – TB, pp. 409–15 for further details regarding the currently available vaccines, transport, handling and storage of the vaccines, administration techniques and adverse reactions.

Given the low incidence of TB in Victoria, and the variable efficacy of the vaccine in adults, **BCG vaccination is not recommended for routine use in the adult Victorian population.**

BCG vaccination is recommended in the following groups of infants and young children:

- Aboriginal and Torres Strait Islander neonates in remote regions of Victoria where an increased incidence of TB has been demonstrated in that community
- infants born to parents with leprosy or a family history of leprosy
- children under the age of five years who will be travelling to high TB incidence (> 40 per 100 000 population per year) countries. BCG vaccination should ideally occur at least three months before departure, and therefore consideration should be given to future travel plans at birth. The TB incidence in the destination country, the cumulative planned duration of travel and the age of the child should all be considered when deciding on the need for BCG (see table below)
- infants and young children under the age of five years who live in a household that includes immigrants or unscreened visitors, recently arrived from countries of high TB incidence (> 40 per 100,000 population per year).

Table 9.1 Deciding on the need for BCG

TB incidence in country visited*	Duration of travel	Age of child		
		< 1 year	1–5 years	≥ 5 years
High (> 100/100 000)	≥ 4 weeks†	BCG	BCG	Consider BCG
	< 4 weeks	BCG	Consider BCG	No BCG
Intermediate (40–100/100 000)	≥ 4 weeks†	BCG	Consider BCG	No BCG
	< 4 weeks	Consider BCG	No BCG	No BCG

Table adapted from Ritz et al.[11]

Notes:

* Current annual TB incidence data available from the WHO: http://www.who.int/tb/country/data/download/en/index.html

† or if further travel planned such that cumulative duration of travel is > 4 weeks.

BCG vaccination should be considered on an individual basis for the following groups of children and adolescents:

- children and adolescents aged under 15 years who continue to be exposed to an index case with active smear and/or culture positive pulmonary TB, and where that child or adolescent cannot be placed on isoniazid preventive therapy
- children, adolescents and young adults to age 25–30 years who have been exposed to an index case with active multidrug-resistant pulmonary TB (organisms resistant to at least both rifampicin and isoniazid).

Other risk groups that may be considered for BCG vaccination include:

- HCWs who have a high risk of occupational exposure to TB, such as staff in public hospitals who may have frequent contact with pulmonary TB; for example, direct care medical and nursing staff working in specific chest or TB clinics or wards, physiotherapists, diagnostic laboratory staff and autopsy room staff, who are tuberculin-negative, and particularly if likely to be exposed to active cases of drug-resistant TB (see Chapter 7 Preventing TB Infection and disease among health care workers)

  Note: BCG vaccination is no longer routinely recommended for HCWs in Victoria.
- persons over the age of five years through to young adulthood who are living or travelling for extended periods (2–3 months or more) in countries of high TB prevalence.

9.5 Contraindications to BCG vaccination

BCG vaccination is contraindicated in the following clinical situations:

- individuals who are immunocompromised, because they are at greatly increased risk for disseminated BCG infection. This includes:
  - those with known or suspected (at high risk and HIV antibody status is unknown) HIV infection,
  - those on corticosteroid or other immunosuppressive therapy, including monoclonal antibodies against TNF-alpha (for example, infliximab, etanercept, adalimulab). Infants born to mothers treated with bDMARDS (for example, TNF-alpha blocking monoclonal antibodies) in the third trimester of pregnancy frequently have detectable antibodies for several months and they should not be vaccinated[36])
  - with congenital T-cell immunodeficiencies, including specific deficiencies of the interferon-gamma pathway
  - radiation or chemotherapy, or malignancies involving either bone marrow or lymphoid systems.
- pregnancy – although there is no evidence of BCG causing foetal damage, the use of live vaccines is not recommended during pregnancy (BCG can be given to breastfeeding women)

- individuals who are known to have TB disease in the past
- individuals with a positive TST (> 5 mm diameter induration)
- individuals with any serious underlying illness, including severe malnutrition.

For those who would otherwise be candidates for BCG, vaccination should be deferred in the following groups:

- neonates who are medically unstable, until the neonate is in good medical condition and ready for discharge from hospital
- infants born to mothers who are suspected or known to be living with HIV infection, until HIV infection of the infant can be confidently excluded
- persons with generalised septic skin disease and skin conditions, such as eczema, dermatitis and psoriasis
- persons being treated for latent TB infection, because the therapy is likely to inactivate the BCG vaccine
- persons who have recently received another parenteral live vaccine (for example, MMR, MMRV, varicella, zoster and yellow fever vaccines), until four weeks have elapsed, unless these vaccines are given concurrently with the BCG vaccine. There are no restrictions on the timing of BCG vaccine in relation to oral live vaccines
- persons with significant febrile illness, until one month after recovery.

9.6 Dose and administration

BCG is given as a single dose by intradermal injection. It is usually given in the left arm at the level of insertion of the deltoid muscle into the humerus.

Dose:

- newborns and infants < 12 months: 0.05 mL id
- children ≥ 12 months and adults: 0.1 mL id.

BCG revaccination is not recommended in anyone.

Accidental 'overdose' of larger quantities of BCG are associated with severe local reactions, and in this circumstance urgent specialist advice should be sought.[12]

9.7 Adverse reactions and complications

Adverse reactions and complications with BCG vaccination occur infrequently, provided that due care is taken to observe the recommended indications, contraindications and administration techniques. Anaphylactic reactions can occur, but are rare. The commonest adverse reaction is a localised abscess at the site of injection, especially if the vaccination is given too deeply. Regional (cervical or axillary) lymphadenitis is less common.

Accelerated BCG responses are seen when an already TST positive individual is vaccinated with BCG. These responses usually develop within five to seven days of vaccination, and take the form of an exaggerated BCG response, often resulting in gross local reactions and axillary lymphadenopathy. Unsightly keloid scars can result from vaccination, with or without an accelerated response. Ensuring BCG is not given higher than the level of insertion of the deltoid muscle into the humerus reduces the risk. Very rarely (approximately one case per million vaccinated), a potentially fatal disseminated infection can occur when BCG vaccination is undertaken in an immunocompromised individual.

Specialist advice should be sought for the management of severe local or systemic complications. There is little evidence on which to base treatment, and therefore no consensus on the optimal management of these complications. Severe complications of BCG vaccination are sometimes treated with anti-TB drugs, but there is no evidence to support this approach. Note that because BCG is derived from *M. bovis,* it is naturally resistant to pyrazinamide.

9.8 Availability of BCG vaccine

Due to the presentation of the BCG SSI vaccine in 100-dose packaging, the Victorian Government-funded supply of BCG vaccine is only available at the Royal Children's Hospital and Monash Medical Centre Paediatric Infectious Disease units until further notice. A referral from the GP is required. Please be aware there are currently waiting periods for appointments at these clinics. For enquiries regarding eligible patients in regional areas, please call the Victorian Tuberculosis Program on 03 9342 9478.

Victorian Government-funded BCG vaccine will only be supplied for babies and children aged five years and younger travelling to countries of high TB incidence (defined as in excess of 40 per 100,000 population). Countries of high incidence include India, China, other areas of Asia and sub-Saharan Africa. For further information visit www.who.int/tb/en/

Clinics that wish to purchase private stock of BCG vaccine should call Sanofi Pasteur on 1800 829 468.

For other recommendations and additional information refer to the Tuberculosis section in the current edition of the *Australian Immunisation Handbook* at http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home.

9.9 Conclusion

The general use of BCG vaccine in Victoria is no longer recommended. BCG vaccine is to be used only in specific individual cases where clear-cut risk factors can be identified either in the general community or in specific occupationally exposed groups[13]. Where uncertainty arises regarding the appropriateness of BCG vaccination in an individual, please contact the Program Manager, Victorian Tuberculosis Program (phone 03 9342 9478, fax 03 8344 0781), who can make further reference to appropriate consultant advice where necessary.

Information and recommendations for use of BCG vaccine in Australia from the Australian National TB Advisory Committee (NTAC)[14] are available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cdi3701h.

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Chapter 10 Treatment of latent tuberculosis infection (chemopreventative therapy)

10.1 Introduction

For a person who has been identified as having latent or inactive TB infection by virtue of their clinical/radiographic presentation and/or by the demonstration of a positive tuberculin skin test or QuantiFERON-TB response, the aim of therapy is to reduce the risk of progression to active TB disease. The benefits of treatment for latent TB infection, however, need to be carefully weighed against the risks of drug toxicity.

Since the 1950s it has been standard practice to use isoniazid as chemopreventative therapy. Several literature reviews indicate that isoniazid used as a single drug for 6–12 months (optimum nine months) on a daily or intermittent basis in an appropriate dose (5–10 milligrams per kilogram, to a maximum of 300 milligrams daily as a single dose) will significantly reduce the likelihood of TB disease for some decades, if not permanently. Patients should receive written information (in the appropriate language) about latent TB infection, treatment side-effects and contact details.

Several alternatives to isoniazid are available. Rifampicin for four months (4R) is an acceptable alternative if there is significant toxicity to isoniazid or if the index case has known isoniazid-resistant TB. There are no head-to-head long-term efficacy studies comparing 4R with nine months of isoniazid (9H). The use of short-course therapy (12 weekly doses) with rifapentine and isoniazid has been demonstrated to be non-inferior to 9H; however, it is not currently licensed for use in Australia. Other previously used regimens include the combination of rifampicin and pyrazinamide, which is no longer recommended due to higher rates of severe hepatotoxicity.

Compliance with treatment is essential for a useful long-term effect, with treatment courses extended until patients receive the intended number of doses. If it is not possible to ensure compliance, it is preferable not to give treatment for latent TB infection.

10.2 Adverse effects related to isoniazid chemoprophylaxis

Hepatitis

Abnormal LFTs are common in patients following commencement of isoniazid therapy, and baseline screening of liver function is desirable. Elevations of AST or ALT occur in 10–20 per cent of people on isoniazid; however, clinical hepatitis is infrequent and is directly related to increasing age – a very low risk below the age of 35, but a significant risk in those over the age of 50. The risk of hepatitis is increased in those with pre-existing liver disease and increased alcohol intake. While hepatitis is more common in the first two months of therapy, approximately 50 per cent of elevated LFTs occur after this date. The late development of hepatic toxicity progressing to hepatic failure, at times requiring liver transplantation, is an uncommon but well-recognised and potentially fatal complication.

Peripheral neuropathy

Peripheral neuropathy occurs in < 1 per cent of people on isoniazid, and is preventable with pyridoxine (vitamin B6) supplements of 25 mg/day. Pyridoxine is indicated for people older than 65 years, pregnant women, people with diabetes, daily alcohol users, people with chronic renal failure, poorly nourished people (frequent in recently arrived immigrants and refugees) and anyone with any other predisposition to peripheral neuropathy; otherwise, we do not prescribe pyridoxine routinely.

Other, less well characterised, isoniazid adverse effects include allergic rash, neuropsychological effects such as minor difficulties with concentration and dizziness, acne, minor alopecia and gastrointestinal upset. Isoniazid has few drug interactions, but may result in increased serum levels of phenytoin and disulfuram.

10.3 Special situations

Immunosuppression

People with a significant degree of immunosuppression, including those with HIV infection or long-term use of immune-suppressing medication, are at higher risk of progressing to active disease. A diagnosis of latent TB infection in people who have, or who are expected to undergo, significant immunosuppression should prompt consideration of chemoprevention according to normal protocols.

Exposure to MDR-TB

Chemoprevention with isoniazid or a rifamycin would not be expected to have activity against multidrug-resistant strains of tuberculosis. Where a known exposure to MDR-TB has occurred, clinicians may opt to tailor a chemopreventative regimen to the known drug susceptibilities of the initial case; however, little prospective evidence currently exists regarding the effectiveness of various strategies following MDR-TB exposure.

10.4 Notification

Treatment for latent TB infection is not notifiable in Victoria, but it is desirable to take note of patient details, the treatment plan, side-effects and the outcome. Currently, only isoniazid used for this purpose can be provided free of charge through hospital pharmacies on indent to the TB Program (as for the drugs used in standard treatment regimens), or provided on standard Pharmaceutical Benefit Scheme prescriptions, where usual pharmacy dispensing charges apply. All persons undergoing treatment for latent TB infection should receive written treatment plans, with information covering drug use, drug side-effects and follow-up.

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Chapter 11 HIV infection and tuberculosis

11.1 Importance

Globally, tuberculosis (TB) is the most important opportunistic infection complicating human immunodeficiency virus (HIV) infection, and is the leading cause of AIDS-related deaths. In 2011, 13 per cent of the world's estimated 8.3 million cases of TB (and 31% of the estimated 1.4 million deaths) occurred in HIV-infected people; in some countries in sub-Saharan Africa, more than 50 per cent of patients with TB have HIV infection.

In Australia, dual infection with HIV and *M. tuberculosis* is much less common than in developing countries and less than 5 per cent of Australian AIDS patients develop active TB. However, among Australian AIDS patients who were born in TB-endemic countries in Africa and Asia, 10–20 per cent present with TB as their AIDS-defining illness.

Tuberculosis is one of the few HIV-related opportunistic infections that can be transmitted from person to person. Community and nosocomial outbreaks of TB (the latter affecting HCWs as well other HIV-infected patients) have occurred overseas, some involving MDR-TB.

11.2 Interactions between HIV and TB

The interaction between HIV and *M. tuberculosis* infection is bidirectional. Of HIV-infected individuals with pre-existing latent TB infection, 1–7 per cent progress to active TB each year, and the ultimate risk of developing TB is 21–35 times higher than in those without HIV infection. HIV-infected patients who become newly infected with *M. tuberculosis* are also much more likely to develop symptomatic primary infection. Tuberculosis also impacts on the course of untreated HIV infection: HIV-infected patients with TB in developing countries who do not receive antiretroviral therapy develop more opportunistic infections than patients at a similar stage of HIV infection but without TB.

11.3 Clinical manifestations

The clinical presentation is influenced by:

- the patient's degree of immunosuppression and
- whether TB has arisen from recently acquired infection or reactivation of latent infection.

Patients with relatively well-preserved immunity (as indicated by a CD4 T lymphocyte count greater than 200 per microlitre) and pre-existing latent TB infection usually present with pulmonary TB and manifest the expected clinical, radiological and microbiological findings.

In contrast, HIV-infected patients with primary TB, and those with reactivation TB and impaired immunity (CD4 cell count fewer than 200 per microlitre) often have atypical manifestations of pulmonary TB, or present with extra-pulmonary or disseminated TB. Radiological features of pulmonary TB in these patients include absence of cavitation, non-specific infiltrates in the mid and lower zones, hilar lymphadenopathy, pleural effusion and occasionally even a normal chest X-ray.

11.4 Diagnosis

Latent TB infection

Testing for latent TB infection should be part of the routine evaluation of every newly diagnosed HIV-infected person. The basis of this recommendation is that the incidence of TB in people living with HIV infection in Australia is estimated to be more than ten times higher than the incidence of TB in the general population.

The decline in cell-mediated immunity that is a hallmark of HIV infection reduces the sensitivity of latent TB tests, but interferon gamma release assays (IGRA) are less affected than the tuberculin skin test (TST) (however, IGRAs may be indeterminate when the CD4 cell count is fewer than 100 per microlitre). If the TST is used, a reaction of 5 mm or greater is considered to indicate infection with *M. tuberculosis.*

Patients with a CD4 cell count of less than 200 per microlitre who have a negative TST or a negative or indeterminate IGRA should undergo repeat testing when the CD4 cell count rises above 200 per microlitre after antiretroviral therapy is started.

Tuberculosis

Pulmonary TB should be strongly suspected in any HIV-infected patient presenting with fever and chest X-ray opacities who has epidemiological risk factors for TB (most importantly birth or residence in a TB-endemic country) or clinical features such as subacute or chronic symptoms, weight loss or haemoptysis. In contrast to the 'classic'

HIV-related opportunistic infections such as *Pneumocystis jiroveci* pneumonia, TB may occur when the CD4 cell count is greater than 200 per microlitre.

As already indicated, the chest X-ray may not demonstrate classical TB changes. Chest CT scanning is useful for identifying intrathoracic lymphadenopathy, early disseminated disease and small cavities.

Patients with HIV-associated pulmonary TB have a lower rate of sputum smear positivity than non-HIV patients. If acid-fast bacilli (AFB) are visible in a sputum specimen, the patient must be assumed to have TB (and not disseminated *M. avium* complex infection), and should be managed accordingly, pending sputum culture or nucleic acid amplification test results.

Nucleic acid amplification testing platforms such as GeneXpert (Cepheid) enable prompt identification of *M. tuberculosis* in AFB smear-positive sputum specimens (and in some smear-negative, culture-positive specimens as well), and detect mutations associated with rifampicin resistance with a high degree of sensitivity and specificity. This technology is becoming more widely used, both globally and in Australia.

Mycobacterium tuberculosis can sometimes be cultured from blood, and may provide a more rapid diagnosis than sputum specimens; special mycobacterial culture systems, obtainable from most microbiology laboratories, must be used.

Diagnosis of extra-pulmonary TB is more difficult. CT imaging is usually required, and can detect abnormalities such as mass lesions, intra-abdominal lymphadenopathy and disease of bones. AFB smear and culture of fluids such as CSF, joint fluid, pericardial fluid and pleural fluid are insensitive, and tissue biopsy is often needed for diagnosis.

Unsuspected HIV infection

Tuberculosis is occasionally the initial manifestation of previously unrecognised HIV infection, because TB may occur with relatively well-preserved immune function. Patients with TB in Australia are a distinct risk group for HIV infection; their rate of underlying HIV infection is at least 10 times that of the general population. Therefore, all patients with newly diagnosed TB should be asked about HIV risk factors, and should be advised to undergo HIV testing after appropriate pre-test discussion.

11.5 Prevention

Treatment of latent TB infection

All patients with a positive test for latent TB infection should be assessed for active TB by history, examination, chest X-ray and (if necessary) by examination of sputum or other specimens for AFB.

Patients with no evidence of active TB should be treated with a nine-month course of isoniazid (Chapter 10 Treatment of latent TB infection (chemopreventative therapy)). Pyridoxine should be prescribed routinely, and liver function tests monitored monthly.

Patients who are intolerant of isoniazid or who are likely on epidemiological grounds to be infected with isoniazid-resistant *M. tuberculosis* can be treated with a four-month course of rifampicin, but care must be taken with interactions with antiretroviral therapy (discussed in more detail below).

Other measures

BCG is contraindicated in HIV-infected persons.

HCWs with HIV infection should be advised of their heightened susceptibility to TB, and should not be permitted contact with potentially infectious TB patients.

Infection control considerations

Any patient admitted to hospital with suspected pulmonary TB must be placed in respiratory isolation, as described in Chapter 6 Hospital care of tuberculosis.

Treatment

The treatment of TB in an HIV-infected patient is not straightforward, chiefly because of the complex interactions between antiretroviral, antituberculous and other medications. Patients with TB who are HIV-infected should only be managed by a doctor or doctors with special expertise in HIV medicine and TB. If more than one doctor is involved, close collaboration is essential to ensure optimal treatment coordination. Support from other members of the treatment team, particularly clinic and public health nurses and social workers is essential.

Antiretroviral drugs

Antiretroviral agents used for initial therapy[1] belong to four major classes:

- nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) – tenofovir, abacavir, lamivudine (3TC), emtricitabine (FTC)
- non-nucleoside reverse transcriptase inhibitors (NNRTI) – efavirenz, rilpivirine, nevirapine
- protease inhibitors (PI) – lopinavir/ritonavir, ritonavir-boosted atazanavir
- integrase inhibitors – raltegravir.

Regimens that allow once-daily dosing and use fixed-dose combinations are the standard of care. A typical combination comprises two NRTIs and either a NNRTI or a ritonavir-boosted PI; examples in current use are tenofovir + emtricitabine + efavirenz (Atripla) and ritonavir-boosted atazanavir combined with either tenofovir + emtricitabine (Truvada) or abacavir + lamivudine (Kivexa).

Interactions between TB and antiretroviral drugs

Rifampicin lowers blood levels of NNRTIs and PIs (through induction of hepatic cytochrome P450 oxidases, chiefly 3A4) and raltegravir (through induction of UDP glucuronyl transferase); rifabutin has a less marked effect. Rifabutin is a substrate for cytochrome P450 and its metabolism is affected by PIs and NNRTIs (see table below). There are no significant interactions between rifampicin or rifabutin and NRTI agents, or between other first-line TB medications and any antiretroviral agents.

1 Antiretroviral drugs no longer used widely for initial therapy in Australia, or only used after failure of the initial regimen, are not included.

Table 11.1 Interactions and dosing with rifamycins and selected antiretroviral (ARV) agents or classes

	Rifampicin		Rifabutin (RBT)			
ARV agent/class	ARV levels	ARV dose	ARV levels	ARV dose	RBT levels	RBT dose
Efavirenz	↓	600–800 mg daily	→	600 mg daily	↓	450 mg daily
Rilpivirine	↓↓↓	Contraindicated	Contraindicated			
Nevirapine	↓↓	Relative contraindication	→	200 mg BD	→	300 mg daily
Protease inhibitors	↓↓↓	Contraindicated	↓	Standard dosing	↑↑	150 mg daily
Raltegravir	↓	800 mg BD	→	400 mg BD	→	300 mg daily

Key:

↑ blood levels increased

→ blood levels unchanged

↓ blood levels lower

Adapted from: Street, McBryde, Denholm, Eisen Eds. *Management of Tuberculosis,* VIDS, 2012.

11.6 TB treatment regimens

Empiric therapy

In general, antituberculous therapy is withheld until there is definite or highly suggestive radiological, microbiological or histological evidence of TB. However, patients with HIV-associated TB (especially those with a low CD4 cell count) are at high risk of early death, so empiric TB therapy may need to be considered in the absence of such evidence. Examples include:

- suspected TB meningitis (notoriously difficult to diagnose and associated with a high mortality if not treated promptly)
- suspected disseminated TB (for example, unexplained fever in a patient from a TB-endemic country who is deteriorating clinically)
- pulmonary opacities in a patient from a TB-endemic country with negative sputum or bronchoscopy AFB smears and no alternative diagnosis
- some forms of extra-pulmonary TB where non-specific histology on tissue biopsy does still not exclude TB for example, TB pericarditis.

Drug-sensitive infections

- Isoniazid, ethambutol and pyrazinamide are used in standard doses.
- Rifampicin can only be given with efavirenz (some authorities recommend a higher efavirenz dose of 800 mg daily for patients > 65 kg) and raltegravir (given at twice the normal dose, 800 mg twice daily); rifampicin is contraindicated with other NNRTIs and all PIs.
- Rifabutin dose is 150 mg daily with ritonavir-boosted PIs, 300 mg daily with nevirapine and 450 mg daily with efavirenz (see table).

Treatment follows the same principles as for non-HIV patients (see Chapter 4 Treatment of active tuberculosis), with a four-drug intensive phase for two months followed by isoniazid and rifampicin (or rifabutin) given in the continuation phase. Treatment duration for uncomplicated pulmonary infections is six months unless clinical or microbiological response is delayed, in which case treatment should be continued for at least four months after sputum becomes culture negative. Most forms of extra-pulmonary TB can be managed in the same way, except that treatment should be prolonged for CNS and disseminated TB.

Drug-resistant infections

These infections require longer courses of treatment. Multidrug-resistant (MDR) TB (resistance to at least isoniazid and rifampicin) only occurs in 1–2 per cent of all notified TB cases in Australia, but is much more common overseas, especially in patients treated for TB in the past; second-line agents such as aminoglycosides, fluoroquinolones and thioamides must be used to treat these patients (see Chapter 4 Treatment of active tuberculosis).

11.7 Timing of initiation of antiretroviral therapy

In patients with HIV-associated TB who have not previously been treated with antiretroviral therapy, TB is the treatment priority. Initiation of antiretroviral therapy is generally delayed to avoid the introduction of an unmanageable number of tablets at the same time, to avoid confusion with overlapping drug toxicities and to reduce the risk of immune reconstitution inflammatory syndrome (see below). However, this has to be balanced against the increased risk of death in the early phase of TB treatment, especially in patients with a low CD4 cell count.

The following recommendations for initiation of antiretroviral therapy (ART) in patients with TB, based on the results of three studies, are adapted from US HIV/TB treatment guidelines:

Table 11.2 Recommendations for initiation of antiretroviral therapy

CD4 cell count/μL	Timing of ART in relation to starting TB treatment
< 50	Within 2 weeks
> 50, clinically severe disease*	Within 2–4 weeks
> 50, no clinically severe disease	Within 4–12 weeks

* Low Karnofsky score, low body mass index, low haemoglobin, low albumin, organ dysfunction, extent of disease.

11.8 Monitoring

Monitoring should be as for non-HIV-infected patients (see Chapter 4 Treatment of active tuberculosis). Patients should be seen at least monthly, and sputum should be collected from those with pulmonary TB to document conversion to smear and culture negativity.

Treatment is usually well tolerated. However, drug-induced hepatitis may be more common than in HIV negative patients, so routine laboratory monitoring of liver function is recommended.

Reduced absorption of anti-TB drugs has been demonstrated in some AIDS patients, but the clinical significance is unclear.

11.9 Immune reconstitution inflammatory syndrome

Initiation of antiretroviral therapy results in a heightened pathogen-specific immune response (including against *M. tuberculosis),* which may manifest clinically as the immune reconstitution inflammatory syndrome (IRIS). One form of TB IRIS is seen in patients who have recently started anti-TB treatment; soon after introduction of antiretroviral treatment, these patients may develop a paradoxical reaction, characterised by fever, lymph gland enlargement or worsening pulmonary opacities. A second form of TB IRIS, an unmasking reaction, also occurs after starting antiretroviral therapy, but in patients with previously latent (not active) TB. Risk factors for TB IRIS are a low CD4 cell count (especially < 50 cells per microlitre), and for paradoxical reactions, a short interval between introduction of anti-TB and antiretroviral therapy, and extensive or disseminated TB.

The reaction usually resolves with time, and anti-TB treatment should be continued. Glucocorticoids can be used if the reaction is particularly severe or prolonged.

11.10 Post-treatment

Reinfection with a different strain of *M. tuberculosis* is well documented after successful completion of TB treatment, usually in countries of high TB endemicity such as in sub-Saharan Africa. There may be a role for ongoing 'secondary' isoniazid prophylaxis after completion of TB treatment in these countries, but this approach is not necessary in countries such as Australia.

11.11 Outcome

Patients with drug-sensitive infections who adhere to their treatment regimen respond well to treatment, with failure and relapse rates comparable to non HIV-infected patients. Widespread use of combination antiretroviral therapy has dramatically reduced the incidence of other opportunistic infections, which were chiefly responsible for the high mortality rate of HIV-associated TB in the past. In addition, patients on combination antiretroviral therapy who have latent TB infection and experience an increase in their CD4 cell count are at a much lower risk of developing future TB than untreated patients.

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Chapter 12 Tuberculosis in children and adolescents

12.1 Introduction

The WHO *Global TB Report* in 2012 estimated that children represent approximately 6 per cent of the total burden globally, but recognised this as an underestimate. It is difficult to estimate the true burden of tuberculosis (TB) in children due to difficulties with diagnosis, particularly with confirming diagnosis in children in TB endemic settings, and due to the widespread problem of under-reporting of child TB cases by TB control programs. In low TB endemic countries such as Australia, however, it is likely to be lower than in high burden countries due to very limited transmission in the community. In Victoria, 6–25 cases of active TB disease in children (0–15 years) were reported each year from 2008 to 2011.

The clinical presentation of TB in children differs markedly from that in adults. Following infection with *Mycobacterium tuberculosis,* there is an immune response that involves the regional lymph nodes. A positive tuberculin skin test (TST) is considered an immunological marker of the response to infection. The primary complex comprising the site of infection and the involved regional lymph nodes may heal, or complications may develop from enlargement or rupture of the regional lymph nodes or the spread of tubercle bacilli into the bloodstream, giving rise to disseminated disease. Most children contain the infection resulting in what is commonly referred to as 'latent TB infection' (LTBI), but the risk of developing disease remains lifelong. Some children progress to develop disease (that is, 'active' TB) following infection, and in almost all of these cases, TB will present within 24 months following infection. TB in young children is usually paucibacillary, but infants and young children are at particular risk of disseminated TB, which is associated with a poorer outcome than localised disease. The increased likelihood of dissemination also explains why the presentation of extra-pulmonary TB is more common in children than adults. Adolescence is also an age group associated with an increased risk of TB, and the presentation of TB in adolescents is more similar to that which occurs in adults.

12.2 Risk of disease following primary infection

Data from studies in the pre-chemotherapy era in children followed for two years after infection, indicate that following primary infection the risk of development of *radiological changes* in the chest consistent with TB infection is greatest in the first two years of life and progressively decreases thereafter (see table below).

Table 12.1 Risk of disease following primary infection

Age at primary infection	Risk of active TB disease in immune-competent children[a]
< 2 years	No disease 50–70%
	Pulmonary disease 10–30%
	TBM or miliary disease 2–10%
2–10 years	No disease 95–98%
	Pulmonary disease 2–5%
	TBM or miliary disease < 0.5%
> 10 years	No disease 80–90%
	Pulmonary disease 10–20%
	TBM or miliary disease < 0.5%

a The risk is greatest in the first 12 months after infection.

These historical figures are related to the general health, nutrition and other disease states. Currently in Australia the risk is probably much less than these figures suggest.

For children who have a normal CXR at the time a positive TST is first detected, the lifetime risk of developing active TB disease is 2–10 per cent.

12.3 Infectivity

Childhood TB is rarely contagious because:

- children with latent or active TB usually have a low bacterial load
- children are less able to generate the tussive forces needed to aerosolise bacilli
- young children with pulmonary TB rarely have cavitating disease
- young children swallow rather than expectorate sputum.

Older children and adolescents (> 10 years) may present with cavitatory TB and be infectious.

12.4 Diagnosis

Infection with *M. tuberculosis*

The standard indicator of infection with *M. tuberculosis* is a positive TST. The interpretation of a positive test may be modified by the risk of infection which is influenced by the contact history, the infectiousness of the source case and the closeness and duration of contact, by the medical history and age of the child, and by their BCG vaccination status. The TST is an imperfect test that can yield both false positive and false negative results. Its interpretation and subsequent clinical management depends on the prior probability of the test being positive and on the clinical and epidemiological circumstances of the individual or family – see Table 2.1 Criteria for Tuberculin Positivity, by Risk Group (adapted from ATS/CDC, 2000).

Active TB disease

The care of a child suspected of having TB should involve a physician experienced in the management of childhood TB. Diagnosis of active TB disease is based on clinical symptoms and signs, chest X-rays or other investigations, smear microscopy, culture and molecular tests of infected body material. Lateral chest X-rays increase the yield for detecting lymphadenopathy, as do CT scans. However, the latter requires a volumetric scanning protocol, and should not be performed routinely because of the high radiation dose.

Even though the yield from cultures is low in children, microbiological confirmation of TB should be sought. Treatment should be started as soon as samples have been obtained.

12.5 Collection of specimens for demonstration of tubercle bacilli

Pulmonary

In younger children when it is not possible to obtain sputum, gastric aspirates should be collected on three consecutive days. Approximately 50 mL of gastric contents should be aspirated via a nasogastric tube early in the morning after the child has fasted for 8–10 hours, preferably while the child is still in bed. This is best performed in hospital, but can be undertaken through some hospital in the home programs. Smear microscopy, culture and PCR should be performed on the aspirate.

If there is radiological evidence of focal disease such as lobar, segmental or subsegmental collapse or clinical evidence of bronchial obstruction, a flexible fibreoptic bronchospcopy with broncho-alveolar lavage may be indicated in addition to gastric aspiration. Otherwise, there is no advantage of bronchoscopy over gastric aspiration.

Inhalation of nebulised sterile hypertonic saline (3–6%) via an ultrasonic nebuliser can be used to induce sputum in those unable to expectorate sputum. However, the cough produced by this technique may be of sufficient force to aerosolise tubercle bacilli and infect HCWs. Thus, induced sputum should only be performed in areas with high-efficiency particulate air filters, and qualified personnel should wear appropriate respiratory protection. For this reason it is not the procedure of choice for obtaining respiratory samples in children.

Extra-pulmonary

Table 12.3: Diagnostic approach according to site of tuberculosis

Site	Imaging	Biopsy	Culture
Lymph node		Node	Node or aspirate
Bone/joint	Plain X-ray and computed tomography (CT) Magnetic resonance imaging (MRI)	Site of disease	Biopsy or paraspinal abscess Site or joint fluid
Gastrointestinal	Ultrasound CT abdomen	Omentum Bowel	Biopsy Ascites
Genitourinary	Intravenous urography Ultrasound	Site of disease	Early morning urine Site of disease Endometrial curettings
Disseminated	CXR High-resolution CT thorax Ultrasound abdomen CT brain	Lung Liver Bone marrow	Blood Bronchial wash Liver Bone marrow
Central nervous system	CT brain MRI	Tuberculoma	Cerebrospinal fluid
Skin		Site of disease	Site of disease
Pericardium	Echocardiogram	Pericardium	Pericardial fluid
Cold/liver abscess	Ultrasound	Site of disease	Site of disease

Role of interferon-gamma release assays in children

Interferon gamma release assays (IGRAs), like TST, can be used as an indicator of infection with *M. tuberculosis.* IGRA were developed and licensed for assisting in the diagnosis of LTBI. However, like TST, these assays are often used as an adjunctive test to help in the diagnosis of TB in addition to clinical, radiological and other investigations. The sensitivity of the currently available IGRA in children with culture-confirmed TB disease in children is not high enough for these assays to be used alone to rule out TB in children. In most studies IGRA and TST yield equivalent results for the detection of latent TB infection in children, once adjustment is made for interpretation of the TST based on differing cut-offs. Limited data suggest that IGRA may prove useful in situations where the value of TST is greatly reduced, for example, the immunocompromised.

In Victoria, the QuantiFERON-TB Gold assay is funded currently on the MBS scheme only in the context of HIV infection or immunodeficiency, and should be used as an adjunct to TST in such children to increase sensitivity. Other specific situations where the test might be indicated are:

- if the child has been vaccinated with BCG and the TST is low positive or borderline
- as a replacement for TST, where repeat testing with TST is likely to result in a booster phenomenon
- if TST testing is considered likely to result in a blistering or a large painful response (for example, where active TB is strongly suspected or there has been a large reaction to TST in the past)
- if the child is unable or unlikely to return at 48–72 hours for reading of the TST.

What is indicated by a positive IGRA (for example, QuantiFERON-TB Gold) response in children?

Like the TST, IGRAs do not distinguish individuals with LTBI from those with active TB disease. Interpretation of the test is made in the context of contact history, symptoms, signs and radiology according to established guidelines. A recently positive assay is likely to indicate a greater likelihood of progression to active disease. The significance of a positive IGRA may be greater in small children because of their greater risk of progression to active disease compared with adults. Furthermore, a positive result from an IGRA can add support to the diagnosis of active TB disease when the clinical suspicion is high.

What is indicated by a negative IGRA response in children?

Although a positive test confirms infection with *M. tuberculosis* due its high specificity, a negative test does not rule out the possibility of either LTBI or active TB disease, due to the low sensitivity of the test in children, especially in those under five years.

What is indicated by an indeterminate IGRA response?

Indeterminate responses are more common in children, especially in infants and young children under five years. If the result is indeterminate, no interpretation can be made, and the test should either be repeated or excluded from the process of evaluating the diagnosis.

What is indicated by an IGRA result that is discordant with a TST result?

In some children the IGRA and TST results are contradictory; that is, TST+ / IGRA– (more commonly) or TST– / IGRA+. It is safest to assume that a negative IGRA or TST in this situation does not exclude TB infection. Also, there remains controversy about whether an IGRA is necessarily more specific than a TST in BCG-immunised children. Most experts therefore recommend that a discordant result is regarded as a positive result when making treatment decisions.

12.6 Treatment of latent TB infection

Treatment of children with LTBI and no evidence of active disease is indicated for two reasons:

- first, to reduce the risk of developing disease in the years immediately after acquiring the infection, particularly in children under the age of five
- second, there is a lifelong risk of developing disease, and this can be reduced substantially by the use of isoniazid therapy for six months, which in children and adolescents has few side effects.

Therefore, a minimum of six months of isoniazid preventive therapy (10 mg/kg, up to max of 300 mg) once daily is recommended for otherwise healthy children and adolescents who have a positive TST or IGRA as defined above and no evidence of TB disease (that is, asymptomatic with a normal CXR), and is strongly recommended in the following risk groups:

- ethnic communities with a high rate of TB
- HIV infected children
- children in whom corticosteroid or immuno suppressive therapy (including DMARS) is contemplated
- those with diabetes or other chronic diseases associated with malnutition (for example, coeliac disease)
- children under five years who have been in close contact with a case of sputum smear-positive TB, who are TST negative on initial screening, pending further review of their tuberculin status at three months from break of contact.

The incidence of liver toxicity in children is extremely low, and routine monitoring of liver function is not recommended.

Prophylactic pyridoxine is not normally recommended with isoniazid in children.

12.7 Treatment of pulmonary TB disease

Children with active TB disease are usually treated with daily therapy with four drugs: isoniazid, rifampicin, pyrazinamide and ethambutol for two months, and then generally two drugs: isoniazid and rifampicin for a further four months. Normally, these drugs are given daily, but supervised therapy given on three days a week is sometimes necessary when treatment adherence with daily therapy is considered to be poor. In those where culture sensitivity from an index case is unknown, or the child has migrated from a country where there is a low prevalence of drug-resistant TB, ethambutol can be omitted and a three-drug regimen used for the first two months of treatment in those under 12 years. Because optic neuritis is extremely rare in children receiving recommended doses of ethambutol, an ophthalmology review is not necessary before or during treatment.

Such short-course therapy (six months) has been shown to be effective in children with primary TB and complicated primary TB limited to the respiratory tract, but there are insufficient data to recommend it for CNS, bone or joint TB infections. The WHO currently recommends eight months' continuation phase (10 months' total treatment duration) in these cases. Management of these require multidisciplinary specialist input.

12.8 Treatment of extra-pulmonary TB disease

Table 12.1 Treatment of extra-pulmonary TB disease

Meningeal	Minimum 12 months treatment using a four-drug regime for initial two months and two drugs for the rest of the course. Corticosteroids are indicated (1–2 mg/kg prednisolone, maximum 40 mg with gradual withdrawal starting within 2–3 weeks of initiation).
Peripheral lymph node	Minimum six months standard treatment even in those who have had an affected gland surgically removed.
Bone and joint	Minimum six months treatment. If there is spinal cord involvement management should be as for those with meningeal tuberculosis.
Pericardial	Minimum standard six months regimen. Corticosteroids are indicated (1–2 mg/kg prednisolone maximum 40 mg with gradual withdrawal starting within 2–3 weeks of initiation).
Miliary	Minimum standard six months regime. Brain scan (CT or MRI) and lumbar puncture are indicated to assess for central nervous system involvement. If CNS involvement is detected, treat as for meningeal TB.
Genitourinary	Standard six-month regime.

12.9 Strategies to improve adherence

Strategies to enhance adherence to treatment (see DOT chapter) are generally relevant to treatment in children. Wherever possible, liquid preparations should be prescribed or made readily available. Patients and their families should have easy access to follow-up.

Chapter 13 Tuberculosis and pregnancy

13.1 Effect of pregnancy on TB

Pregnancy has no adverse impact on TB if there is no significant delay in diagnosis. With adequate treatment, a pregnant woman with TB has a prognosis equivalent to that of a comparable non-pregnant woman. Most cases of TB associated with pregnancy occur in the last trimester or in the early post-natal period. However, infant and maternal mortality from untreated active TB are 30–40 per cent.[12]

Although the clinical manifestations of pulmonary TB in pregnant women are similar to those in non-pregnant women, the diagnosis of TB may be delayed because pregnant patients are more likely to have non-specific symptoms and also to experience a delay in obtaining a chest X-ray than non-pregnant women with tuberculosis.[3] In addition, pregnant women with pulmonary TB are more likely to be asymptomatic at the time of diagnosis compared with non-pregnant women with pulmonary tuberculosis.[2]

The site of TB and therefore likelihood of extrapulmonary TB is not altered by pregnancy. The symptoms of extrapulmonary TB are frequently non-specific, and may be attributed to physiological changes of pregnancy. A high index of suspicion is therefore required when pregnant women develop symptoms, particularly women that are from TB endemic countries.

13.2 Effect of TB on pregnancy

Maternal and foetal outcome in pregnancy varies with the site of the TB and the timing of diagnosis in relation to delivery. In patients with a late diagnosis of pulmonary TB, obstetric morbidity is increased fourfold and preterm labour ninefold.[5] There is some evidence that infants born to pregnant women receiving treatment for TB might have an increased risk of low birth weight and be small for gestational age,[8] but this has not been confirmed in other studies.[13] In sub-Saharan Africa, the dual epidemic of tuberculosis and HIV infection is regarded as a major factor in an eightfold increase in maternal mortality.[1] In addition, there is emerging data that maternal TB is a risk factor for perinatal HIV transmission.[6]

Early diagnosis and treatment of TB is essential for optimal pregnancy outcome. In fact, untreated TB represents a far greater hazard to a pregnant woman and her foetus than does treatment of her disease.

Congenital infection may occur by transplacental spread, by aspiration/ingestion of infected amniotic fluid in utero or aspiration/ingestion of infected genital secretion during birth. These routes of infection are extremely rare. Most cases of neonatal TB occur as a result of airborne spread after delivery from contact with someone with pulmonary TB.

13.3 Anti-TB drugs in pregnancy

Isoniazid and ethambutol are both category A drugs, and are safe in pregnancy.

Rifampicin (category C)

Current consensus is that rifampicin is not teratogenic, and is recommended as a component of treatment for TB during pregnancy.

Administered in later pregnancy, there is a theoretical concern that rifampicin can be associated with haemorrhagic disease in the newborn baby in an unknown proportion of cases. There are very little data to support this. While some authorities prescribe supplemental vitamin K 10 mg/day for the last 4–8 weeks of pregnancy, this is not routinely recommended.

Pyrazinamide (category B2)

Compared with other first-line anti-TB agents, there is less safety data for pyrazinamide. However, there is no clear evidence that it is teratogenic, and so it is recommended by the World Health Organization for all pregnant women with TB, during all trimesters of pregnancy. Other authorities recommend it in certain scenarios such as:

1. when multidrug resistance is suspected
2. when the pregnant woman is HIV infected
3. tuberculous meningitis, especially when isoniazid resistance is a possibility.

Streptomycin (category D)

Streptomycin is contraindicated in pregnancy.

Pyridoxine

Supplement in pregnancy should be at a dose of 50 mg/day (instead of 25 mg/day).

Second-line agents

Drug-resistant TB can affect women of child bearing age; however, experience with second-line agents is limited in this group. Gaps in knowledge, limited data and a paucity of experience means that management may be controversial. Some clinicians recommend termination of pregnancy in the setting of MDR-TB, but this is highly controversial. Others recommend treatment with second-line agents. A small case series (n = 38) report comparable success rates when MDR-TB treatment is continued during pregnancy.[10]

13.4 Breast feeding and anti-TB drugs

Anti-TB drugs are excreted in breast milk. It is estimated that breast-feeding infants receive no more than 20 per cent of the usual therapeutic dose of isoniazid for infants, and less than 11 per cent of other anti-TB drugs. Potential toxic effects of drugs delivered in breast milk have not been reported. Women receiving anti-TB treatment should be encouraged to breastfeed.

13.5 Management of the newborn after delivery

Adult physicians managing pregnant women with TB need to consider the risk of congenital TB and/or exposure after birth. The risk to the neonate depends on the mother's site of disease, timing of diagnosis and duration of treatment in relation to delivery.

All neonates considered at risk for congenital infection or exposure in the post-partum period should be referred to a paediatrician for assessment and follow up.

Scenario 1 Mother's TB is likely to be associated with haematogenous spread (for example, miliary TB, tuberculous meningitis) or in the setting of active genital/pelvic TB during pregnancy

- Send the placenta for histology, microscopy and culture and PCR.
- The infant has a definite risk of having or developing congenital TB. The onset of congenital TB occurs at an average of 2–4 weeks (range a few days to a few months) after birth.
- Assess neonate for clinical evidence of congenital TB, and treat with multiple drug therapy if clinically suspected.
- Separate only if mother is extremely ill.
- Perform chest X-ray and gastric washings for smear and culture at birth. Lumbar puncture is indicated if there is suspicion of congenital TB.
- The tuberculin skin test is likely to be negative at birth; it should be done at 4–6 weeks after birth. If negative initially, repeat the tuberculin skin test at 12 weeks and six months. Repeat the chest X-ray at 4–6 weeks. The tuberculin skin test is frequently non-reactive at the onset of clinical congenital TB. A negative tuberculin skin test (or IGRA) cannot exclude infection – and nor does a positive test confirm disease; rather, it provides evidence that the baby was infected.
- Repeated clinical evaluation is necessary in these high-risk infants during the first six months.
- In the absence of active disease, commence isoniazid (10–15 mg/kg/day) at birth. This should be continued for at least six months. If the tuberculin reaction is greater than 5 mm, and there is no evidence of pulmonary or extra-pulmonary disease, continue isoniazid for a full nine months. If the chest X-ray is abnormal, regard it as evidence of congenital TB and treat accordingly. If there is any doubt about the diagnosis of congenital TB, consider empirical treatment for active disease.

Scenario 2 Mother has active pulmonary TB and is infectious at time of delivery

- Assess neonate for clinical evidence of congenital TB, and treat with multiple drug therapy if it is present.
- Separate only if the mother is extremely ill.
- Maximise infection control measures, including admission to an isolation room and wearing of a respiratory face mask.
- In the absence of active disease, give isoniazid (10–15 mg/kg/day) to the newborn. Daily isoniazid can protect the newborn from developing TB if infected.
- After 4–6 weeks of isoniazid, perform a tuberculin skin test and do a chest X-ray.
  1. If tuberculin skin test is negative and chest X-ray normal, continue isoniazid and repeat these at 12 weeks and six months.

     If tuberculin reaction is greater than 5 mm (at six weeks, 12 weeks or six months), investigate thoroughly for pulmonary and extra-pulmonary disease. If evidence of disease is present, treat with multiple drug therapy.
  2. If tuberculin reaction is greater than 5 mm (at six weeks, 12 weeks or six months), and there is no evidence of pulmonary or extra-pulmonary disease, continue isoniazid to complete a nine-month course. Some authorities recommend a 12-month course of isoniazid in this situation.
  3. If tuberculin reaction is negative and the chest X-ray is normal at six months, discontinue isoniazid if the mother is smear negative and give BCG to the newborn.

     The reason for repeating tuberculin skin test at six months and giving isoniazid up to this time even if the reaction is negative is that in infants infected at birth tuberculin conversion may be delayed for up to six months.
  4. If tuberculin reaction is negative at six months and mother is still smear positive, this is a difficult situation. The mother should be investigated for treatment failure, and drug resistance is to be excluded. The baby should be continued on isoniazid unless isoniazid resistance is thought to be likely or confirmed. If so, rifampicin and isoniazid would have to be given. A strong case now exists for BCG.
- If BCG is given to the baby, watch for accelerated response (see document on BCG reactions).
- An accelerated response suggests that the baby has been infected, follow action outlined above in (2) and (3).
- If there is no accelerated response, a tuberculin skin test can be done 2–4 weeks later. A tuberculin reaction at this early stage suggests that it is due to a natural infection and not to the BCG.

Scenario 3 Mother is still on anti-TB treatment, but is no longer infectious (sputum culture is now negative)

- Assess neonate for clinical evidence of congenital TB, and treat with multiple drug therapy if it is present.
- Separation of mother and baby is not required.
- Examine the infant at monthly intervals.
- Evaluate TB risk in family members
- Do a tuberculin skin test at six weeks, 12 weeks and six months (see above for further action).
- There is a case for isoniazid preventive therapy for six months even if the mother is now sputum negative because:
  1. Mother might have had haematogenous or genital spread thereby spreading infection the infant.
  2. Mother might still be infectious.
- Give BCG to the newborn if isoniazid preventive therapy not given, or once preventive therapy ceased.

Scenario 4 Mother completed anti-tuberculous treatment during pregnancy and is no longer infectious

- Separation is not required.
- Evaluate TB risk in family members.
- Recommend BCG to the newborn.
- If BCG is not given, do the tuberculin skin test at six weeks, and at 12 weeks.

Scenario 5 Another member of the family is being treated for TB

- If the family member with TB has completed treatment:
  - evaluate the family member before the baby returns home
  - recommend BCG to the newborn.

- If the family member is on treatment:
  - no contact with patient for eight weeks after being culture negative
  - give BCG.
- If the family member is infectious:
  - the best course of action is to have no contact with the infectious person for at least eight weeks after being culture negative
  - if exposure is unavoidable or likely, give isoniazid until the index case is culture negative for eight weeks
  - an alternative is to give BCG before returning to the household.

Scenario 6 Baby has been exposed to a HCW with infectious TB while in the nursery

- Infection is rare under nursery conditions, but it can and does occur.
- Investigate for TB and treat as needed.
- If no evidence of active TB, give isoniazid to newborn for three months.
- After three months of isoniazid, repeat tuberculin skin test and do a chest X-ray.
  1. If tuberculin reaction is negative and the chest X-ray is normal, discontinue isoniazid.
  2. If tuberculin reaction is greater than 5 mm, investigate thoroughly for pulmonary and extra-pulmonary disease. If evidence of disease is present, treat with multiple drug therapy.
  3. If tuberculin reaction is greater than 5 mm, and there is no evidence of pulmonary or extra-pulmonary disease, continue isoniazid to complete a six-month course.

13.6 Screening for TB during pregnancy

All women with symptoms suggestive of active TB need to be fully investigated. Routine screening for latent TB during pregnancy, however, is not recommended, but may be considered in several groups of pregnant women. The performance of interferon gamma release assays for detecting latent TB have been evaluated in pregnant women and compared with tuberculin skin tests.[14] These tests have been shown to perform equally well in each trimester of pregnancy with comparable results to non-pregnant females.[7]

Table 13.1: Screening for tuberculosis during pregnancy

At risk group	Test
HIV-infected patients	TST/QFN* and chest X-ray#
Profoundly immunocompromised	TST/QFN* and chest X-ray#
Close contact of infectious TB	TST/QFN* (chest X-ray# if TST significant)
Recent arrival from high-prevalence country who has not been screened previously	TST/QFN* (chest X-ray# if recent infection suspected)

* Tuberculin skin test/QuantiFERON-TB test

\# In asymptomatic pregnant women with a reactive tuberculin skin test, chest X-ray should be delayed until 12 weeks of gestation and be performed with proper abdominal shielding. Chest X-ray may be omitted in the last two groups if the risk of active TB is considered to be low.

13.7 Latent TB infection in pregnancy

The risk of developing disease in a pregnant woman who is tuberculin skin test positive with a normal chest X-ray is the same as a non-pregnant woman. There is no evidence that pregnancy increases the chance of TB developing in either HIV positive or negative women.[4]

There is no evidence of fetal toxicity from INH. The risk of INH hepatitis is higher in women compared with men, and may be higher in the post-partum period. Fatal isoniazid-related hepatitis has been reported in pregnant and post-partum women, although it is not clear if this is increased compared to non-pregnant women of comparable age. Given this, treatment for latent TB is usually withheld until after pregnancy unless the patient has been recently infected (within the last two years), is HIV infected or has a medical condition that increases the risk for reactivation of inactive TB. For these women, treatment for latent TB can usually be delayed until the second trimester. In the case of post natal treatment for latent TB, careful patient selection (including age), education and close monitoring (monthly follow-up) is recommended to minimise risk.

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Chapter 14 Tuberculosis and air travel

14.1 Introduction

This chapter is aimed particularly at general practitioners, public health nurses and respiratory and infectious diseases specialists. Readers are referred to the WHO *Tuberculosis and air travel: guidelines for prevention and control (3rd edition)* for detailed guidelines on this issue. The following two scenarios set the scene for the guidelines in this chapter.

Scenario 1: Patients taking treatment for TB may wish to undertake air travel. How do you decide whether they pose a public health risk by doing so?

Scenario 2: Your patient has recently been diagnosed with active pulmonary TB after being investigated for a six-month history of chronic cough. He mentions that he flew to England to visit relatives two months ago. What should you do now?

Patients who are under treatment for TB may tell you that they intend to travel overseas, or may make travel arrangements without consulting their treating physician. Approximately 90 per cent of new TB cases seen in Victoria are in foreign-born persons. Many of these cases are on short-term visas and are likely to want to travel during their 6–12 month treatment period. Issues of concern are the risk of transmission of TB to other passengers, as well as continuity of anti-TB treatment for the patient.

14.2 Risk of transmission of TB

There have been several documented cases of patients with pulmonary TB travelling on airlines, some of which have produced evidence to suggest transmission of TB to susceptible passengers and flight crew,[2, 3, 10] and some of which have failed to demonstrate transmission.[1, 5, 6, 7, 9] To date, there have been no reported cases of active TB disease following exposure during air travel. The likelihood of transmission of TB depends on several factors, including the infectiousness of the index case, susceptibility and vulnerability of those exposed, degree of exposure (duration and proximity) and adequacy of cabin ventilation.

The characteristics of the index case

Pulmonary and laryngeal TB are infectious; whereas extrapulmonary TB (such as lymph node, genitourinary, bone or meningeal TB) carries negligible risk of transmission. In addition, the level of infectivity of a case of pulmonary TB is determined by whether the sputum is culture positive, whether the sputum is smear positive, the degree of smear positivity (indicating bacterial load) and whether a cavity is present on chest radiograph (CXR). Culture positive, smear positive, cavitating pulmonary disease and laryngeal disease are highly infectious.

Table 14.1 Score for infectivity used to classify cases

0	Negligible	Extrapulmonary TB
1	Low	Sputum culture and smear negative pulmonary TB
2	Medium	Sputum culture positive and smear negative, bronchial washings smear positive, no cavitation on CXR
3	High	Sputum smear positive and/or cavitation on CXR

An infectious case of active TB is defined as a case scoring 1 or more; a non-infectious case has a score of 0.

In general, a patient with pulmonary TB who complies with therapy and who is shown not to have drug resistant disease should become non-infectious after two to three weeks of appropriate anti-TB therapy.

14.3 The degree of contact with the case

People in casual contact with infectious patients are at low risk. Continuous, close contact (such as living in the same household) is associated with high risk. Therefore, a long flight poses more risk than a short flight. Total flight duration of more than six to eight hours' duration is associated with increased exposure and therefore a risk of transmission of *M. tuberculosis* (WHO, 2008). Total flight duration includes the flight time and any ground delays after boarding and before disembarking the flight. There is also evidence that the risk of transmission is related to proximity to the infectious case.[3] Contact tracing can be limited to passengers sitting in:

1) the same row
2) the two rows in front of
   and
3) the two rows behind the TB index case.

It is not necessary to perform contact tracing of passengers who are separated from the index case by a solid bulk-head. Where the index case is a passenger, contact tracing of cabin crew is generally not required, except in unusual circumstances such as when a cabin-crew member has been designated to look after a passenger subsequently diagnosed with infectious TB. If the index case is a member of the cabin crew or flight-deck personnel, contact tracing should include all work colleagues who were potentially exposed, but generally does not include passengers.

14.4 Recommendations

Infection risk and fitness to travel

A person with untreated infectious TB should not travel by aircraft on a flight of any duration. A person with drug-susceptible pulmonary or laryngeal TB should have at least two, and preferably three, weeks of effective anti-TB treatment, clinical improvement and three consecutive negative sputum smears (performed on separate days) before being allowed to fly. A person with MDR-TB or XDR-TB will require a longer period of effective anti-TB treatment, satisfactory clinical response to treatment, and sputum-culture conversion to negative before being allowed to fly. Patients with extra-pulmonary TB carry negligible risk of infectivity, but should also be commenced on effective anti-tuberculous treatment before travelling.

What to do if a patient informs you that they intend to travel

The decision to allow a patient on anti-TB treatment to travel should be made on an individual basis, and should be discussed with the Victorian Tuberculosis Program (phone 03 9342 9478).

The patient should not travel until the above 'fitness to fly' criteria have been met. In addition, they should be encouraged to postpone travel until at least one month of treatment has been successfully completed so that antibiotic sensitivities are available and any adverse reactions to medications have been identified.

Patient compliance and commitment to therapy should be assessed, and patients who are at risk of non-compliance should be discouraged from travelling, especially early in their course of treatment. Patient education and counselling is important to ensure maximal compliance.

If a patient on anti-TB treatment advises you that they intend to travel, it is important that the Victorian Tuberculosis Program be informed (phone 03 9342 9478) to ensure continuation of treatment, including appropriate medication supplies and follow-up. Arrangements should be made for overseas follow-up, if possible. A letter from the treating clinician outlining the person's clinical condition and required treatment is helpful. The Victorian Tuberculosis Program has a list of suitable medical contacts for many countries.

Contact tracing

The risk of *M. tuberculosis* transmission on an aircraft is low. Approximately two or three cases of active TB with recent air travel are notified to the Department of Health & Human Services each year. The Victorian Tuberculosis Program undertakes contact tracing to identify persons who may have been infected by the index case and who require medical evaluation, treatment and follow-up. There are several barriers to successful contact tracing on airflights, including difficulty in obtaining passenger lists and/or contact details, a poor response rate from individuals contacted and difficulty interpreting a positive Mantoux or IGRA screening test in contacts.

Recent air travel by cases of TB (within 3–6 months prior to diagnosis) should be reported to the Victorian Tuberculosis Program on 03 9342 9478.

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Chapter 15 Migrant screening for tuberculosis

15.1 Introduction

People who want to migrate permanently, or stay in Australia temporarily, must satisfy the health requirement specified in the Migration Regulations of the Australian Government. All applicants for permanent visas must be assessed against the health requirement. Applicants for a permanent visa are asked to undergo a medical examination, a chest X-ray if 11 years or older and an HIV/AIDS test if 15 years or older, as well as any additional tests requested by the Medical Officer of the Commonwealth. Where chest X-ray shows possible evidence of TB, the applicant is asked to provide sputum for smear and culture, and may be asked to provide serial chest X-rays over six months. If active TB is found, Australian migration law does not allow a visa to be granted until the person has undergone treatment and been declared free of active TB. This is documented by repeat chest X-ray and sputum examination.[1, 2] Applicants for temporary visas may be required to undergo a medical examination, chest X-ray and/or other tests depending on how long they propose to stay in Australia, their intended activities in Australia, their country's risk level for TB and other factors.[3]

If the chest X-ray shows evidence of previous but now inactive TB, the applicant may be asked to sign a health undertaking at the time of visa grant. A health undertaking is an agreement that is made with the Australian Government, which obliges the applicant to attend an appointment with a health authority clinic for a follow-up health examination.[4] By signing the health undertaking the applicant also agrees to undergo any course of treatment or investigation that the health clinic directs. Issue of a health undertaking indicates that a Medical Office of the Commonwealth is satisfied that, while the chest X-ray may be abnormal, the applicant does not have active TB. Applicants outside Australia also agree to contact the Health Undertaking Service on a free call number within four weeks of arrival in Australia. At the time of signing a health undertaking applicants from within Australia will have already been referred to an Australian health clinic for follow-up where required. The visa is not at risk, once in Australia, no matter what status of TB is diagnosed as a result of the monitoring.[4] Most health undertakings originate from visa applications lodged outside Australia (offshore), with a smaller number from inside Australia (onshore). Both offshore and onshore health undertakings include permanent and temporary residency immigrants, refugees and other humanitarian entrants.[5]

15.2 Screening of migrants in Victoria

In Victoria, the Department of Health & Human Services has contracted the screening of all migrants on health undertakings and onshore applicants with abnormal chest X-rays to The Western Hospital, Footscray. At the Migrant Screening Clinic, immigration chest X-rays are reviewed and repeated in selected cases. The radiological activity of any abnormality that could represent a TB infection is assessed from chest X-rays taken at least six months apart. The patient is assessed clinically for symptoms or signs of active TB.

Tuberculin skin testing (TST) is offered to selected migrants including those aged under 35 years with an abnormal chest X-ray, and refugees.[6–8] TST is performed with five tuberculin units of tuberculin purified protein derivative (Tubersol®, Sanofi Pasteur Limited, Toronto, Ontario, Canada). Most TSTs are read at 72 h; however, some are read at 96 h to provide TST at all clinics. Supplemental interferon-γ release assay (IGRA) may be used to confirm a positive TST.[9]

The clinic acts as a triage service,[10] seeing each person once and referring those who need further assessment to other health services. Persons with symptoms suggestive of TB, or one or more chest X-rays suggestive of active TB, are defined as suspected active TB and referred to other specialist clinics. Those without such features, but with a history of TB diagnosis, positive TST or one or more chest X-rays thought likely to represent previous TB, are defined as inactive TB. Migrants with a positive TST who wish to accept treatment of latent TB infection are referred at the discretion of the clinic physician. Migrants are not required to comply with treatment of latent TB. Those aged over 35 years thought to have inactive TB are either discharged or referred for further radiographic surveillance, depending on the extent of the radiographic abnormality

and the period of radiographic observation already undertaken. Any person with a chest X-ray suggestive of TB and less than six months' radiographic observation is also referred. The remaining persons are defined as either normal or an abnormal chest X-ray due to a non-TB problem. Persons who do not attend an appointment are notified to the Australian Government to check for a change of address.[4] The Victorian Tuberculosis Program is advised of non-attendees with chest X-ray suggestive of active TB; TB program nurses are asked to contact the person, and may make a home visit.

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Chapter 16 Contact tracing guidelines

16.1 Introduction

Tuberculosis is an airborne communicable and preventable disease. TB case finding has long been one of the mainstays of TB control efforts. Contact tracing is a form of active case finding and it is an integral component of any TB control program.

The aim of contact tracing is to identify transmission of infection and evaluate for the presence of latent infection and disease in the contacts of all notified cases of infectious TB. Tuberculosis remains a stigmatised and emotive issue, particularly among some population subgroups, who, in Australia, contribute the majority of annual TB cases. These subgroups constitute the overseas born from high TB prevalence countries. In Victoria, the proportion of notified cases in the overseas-born has increased from 37 per cent in 1970 to 87 per cent in 2013. The highest region-specific incidence rates are in the Vietnamese, Indian, Filipino and African born populations. This reflects the pattern of disease in their countries of birth. Of the overseas-born patients, almost 50 per cent present within five years and 30 per cent within two years of their arrival in Australia. It is therefore opportune in contact tracing activities to target testing for TB infection in family contacts of all notified cases of TB, infectious or non-infectious if they have recently arrived in Australia from a high (TB) prevalence country (HPC). Those identified with latent TB infection can be assessed and offered treatment if appropriate. These public health interventions of contact tracing, identification and treatment of latent infection and early detection and prompt, effective treatment of active disease are fundamental to the eventual elimination of TB in a low-prevalence country such as Australia.

Conventional contact tracing processes, as shown in recent studies, have some limitations in accurately identifying all cases of transmission of TB infection and disease. Improved techniques utilising molecular technology such as strain genotyping and social network modelling can assist in developing more refined and targeted activities to identify local transmission.

16.2 Role of the Victorian Tuberculosis Program

The Victorian Tuberculosis Program has statewide responsibility for the public health management, prevention and control of TB. This involves the provision of case management for all patients notified with TB, education of patients, contacts, health professionals and the community and the planning, implementation and evaluation of contact tracing activities.

Successful contact tracing requires well developed interpersonal, interviewing and counselling skills, patient assessment, and a good clinical knowledge of TB. The Victorian Tuberculosis Program public health nurses have been responsible for contact tracing and investigation since the inception of the State TB Control Campaign in the 1950s. Case management and contact investigation are guided by internal protocols, as well as national and international policies and guidelines. Over the past several years, in a move to ensure consistency of practice across Australia, the Communicable Diseases Network of Australia (CDNA) has undertaken the publication of a Series of National Guidelines (SoNG) that outline the public health management of various communicable diseases. The TB SoNG was written by a subcommittee of the National TB Advisory Committee (NTAC) and was recently endorsed by CDNA and the Australian Health Protection Principal Committee (AHPPC) in 2013. The SoNG has now been published for reference at http://www.health.gov.au/cdnasongs

The principles of contact tracing are evidence based, determined by a thorough risk analysis of all contributing factors, including index case, contact and environmental features that are outlined in the TB SoNG, and form the basis for the Victorian TB guidelines.

The Victorian Tuberculosis Program is responsible for coordinating contact tracing activities and identifying individual contacts, but on occasions may seek assistance from other health professionals, for example, in rural Victoria, to carry out testing on its behalf. A contact investigation may be undertaken in a patient's home, a school, child care centre, university, workplace, hospital or

aged care facility. Specialist skills are needed to tease out and identify the conditions and contacts that are most at risk of acquiring TB infection. Doctors in the community or in hospitals who are requested by family or other contacts of the index case to be screened should not undertake screening themselves, but should refer such requests to the Victorian TB Program to ensure a consistent screening process. Review of notified cases and the extent, timing and circumstances of contact investigations are carried out on a weekly basis.

All contact tracing and testing is provided free of charge by the Victorian Tuberculosis Program.

16.3 Definitions

In understanding contact investigations, the following definitions will apply:

- Contact tracing is the process of conducting an epidemiological investigation into a confirmed/suspected case of TB.
- The 'index case' is the individual with active TB.
- The 'contact of TB' is an individual who has a risk of acquiring TB because the person has shared the same environment with the infectious case of TB.

Reasons for contact tracing:

- to identify people who have been exposed to the index case
- to identify people who have become infected as a result of exposure to the index. Recently infected people are at greater risk of developing TB. They should be assessed for the presence of clinical TB and managed accordingly
- to identify a 'source case' where the index case is a child. This is particularly important where there are no identified risk factors for TB, for example, overseas born, recent travel to an HPC
- to identify environmental factors that may be contributing to the transmission of TB.

Initiation of contact tracing

Upon notification of a suspected/confirmed case of infectious TB, initiation of contact investigation should be prompt. This is based on the possibility of other infectious TB cases related to the notified case. Initiation of contact investigation should not wait for positive culture if the history and other clinical findings are compatible with a diagnosis of TB. The estimated risk of transmission should guide the priority, rapidity and thoroughness of the contact investigation.

Data collection

All available information about the notified case from various sources (such as the reporting doctor, hospital records and laboratory) should be collected and collated in a case/client record. Data collection is progressed by interviewing the 'patient' about the details and history of their illness. This interview is conducted as soon as possible by a Victorian Tuberculosis Program public health nurse and may take place in the hospital or at home.

Identification of index case characteristics:

- the clinical presentation of cough, whether it is productive/non-productive
- the duration of symptoms
- the site of disease
- the bacteriological results for sputum/bronchial washings: AFB smear/culture, susceptibility testing results, nucleic acid amplification testing (PCR), bacteriological examination of biopsy material and so on
- the radiological reports: chest X-ray description of extent of pulmonary disease (cavitary/non-cavitary), chest CT scans and the like.

Table 16.1: Degree of infectiousness of TB cases based on clinical, radiological and laboratory findings

Degree of infectiousness of case	Clinical, radiological and laboratory findings
High	sputum smear positive or laryngeal involvement and/or cavitation on CXR or evidence of transmission to other contacts
Medium	smear negative sputum but sputum culture positive or nucleic acid test positive or pleural disease without pulmonary involvement or bronchial washings smear positive
Low	sputum culture and smear negative or smear positive and clinically unlikely to be TB
Negligible or none	extra-pulmonary TB (without associated pulmonary disease; that is, pulmonary TB has been actively excluded by CXR and sputum tested for *M. tuberculosis* and for NTM disease

NTM – non-tuberculous mycobacteria

16.4 Identification of contact characteristics

Contacts identified by the index case or self-identified can be placed in high-, medium-or low-risk categories (see SoNG).

High risk contacts are either:

1. people who have had frequent, prolonged and close contact in an enclosed environment with an infectious case, such as:
   - all people living in the same dwelling
   - relatives and friends who have frequent, prolonged and close contact
   - work colleagues who share the same indoor work area on a daily basis, following an individual risk assessment

   or
2. people who have not had as frequent, prolonged and close contact, but are more susceptible to TB infection due to age (< 5 years) or are immunosuppression related to disease or therapy.

Medium-risk contacts:

- people who have had frequent but less intense contact with an infectious case. This group may include:
  - other close relatives, neighbours
  - friends, schoolmates, work colleagues.

Low-risk contacts:

- includes other contacts at school or in the workplace or social environments not included in the high- or medium-risk groups.

Obtaining details of low-risk contacts is not necessary initially, and need only be pursued if there is evidence of transmission in the high- and medium-risk groups.

Extent of tracing

There is a need to set priorities and limits for contact tracing. Without a systematic approach, the investigative efforts may be wrongly directed to delivering services to people who are not at demonstrated risk of TB infection or disease.

In setting priorities for contact screening, the infectiousness of the index case is the most important determinant. There is clear indication for rapid contact tracing when the TB case has a productive cough, X-ray evidence of cavitary disease and sputum smear for AFB is positive. However, each contact tracing activity needs to be assessed and developed on an individual basis. After the investigation has been carried out in each risk group, an analysis of the results should be undertaken to determine if transmission has occurred and further testing is required in lower-risk groups.

Who should be investigated?

It is important to take into consideration the risk of progression from latent infection to active TB. The risk of progression is highest in young children (< 5 years), HIV infection, other immunosuppressive conditions or therapies such as cancer chemotherapy, high-dose steroids and tumour necrosis factor (anti-TNF alpha) antagonists. Therefore:

- High risk (close contacts, young children under five years and the immune compromised), should be investigated first, commencing within seven days of notification of diagnosis.
- Where no evidence of transmission of infection has occurred, the contact investigation need not extend beyond this group.
- Where evidence of infection has taken place in the close contacts (high-risk group), the contact survey should be extended to include medium- or low-risk contacts.

Management of contacts

1. Clinical evaluation

- Clarify history of exposure – time, duration and environment.
- Assess for any symptoms that are consistent with TB and ensure early referral.
- Consider host factors such as diabetes, HIV (or risk of HIV infection) and other immunosuppressive conditions/therapies.

2. Tuberculin skin test (TST) and/or interferon gamma release assay (IGRA)

- TST remains the test preferred by Victorian Tuberculosis Program for latent TB infection (LTBI) in most patient groups who are tested after TB contact. IGRA testing may be useful as a confirmatory test in the event of a positive TST in immune competent contacts who have had previous BCG vaccination.
- IGRA may be used as a replacement for TST in some circumstances, including contacts with known previous positive tuberculin reactions.

Interpretation of reaction and subsequent action

Contacts, regardless of age who demonstrate a positive IGRA and/or a positive TST reaction with no evidence of prior Bacillus Calmette-Guerin (BCG) vaccination, and have a normal chest X-ray (CXR) should be referred to a physician experienced in the management of TB, or to a hospital TB/infectious diseases unit for further assessment and consideration of treatment for LTBI.

Any contact – regardless of age – who demonstrates a positive IGRA and/or a TST reaction of 15 mm and more, with evidence of previous BCG, and has a normal CXR should be referred to an appropriate physician or hospital for assessment and consideration of treatment for LTBI.

All contacts with a positive IGRA and/or TST and an abnormal CXR must be referred to exclude active tuberculosis.

For immunosuppressed contacts and young children, a TST reaction > 5 mm is significant and these people should be referred for assessment. Note that IGRA is not recommended for use in children.

Repeat tuberculin skin tests

If the TST reaction is negative in the first round of testing, the test should be repeated 8–12 weeks later. If the first skin test is delayed until 8–12 weeks after the last contact with the index case, or since the index case commenced treatment, then repeat testing is not required. (Refer to Chapter 2 Testing for latent tuberculosis infection.)

Booster phenomenon

The booster reaction is not generally considered in routine contact tracing. It is of importance where serial testing to detect tuberculin conversion is conducted for health care workers. (Refer to Chapter 2 Testing for latent tuberculosis infection.)

16.5 Chest X-ray

All IGRA/TST positive contacts should have a CXR.

Contacts with negative IGRA and or TST reactions should be considered on an individual basis. (Refer to section on false negatives in Chapter 2 Testing for latent tuberculosis infection.)

Children – refer to Chapter 12 Tuberculosis in children and adolescents.

Action

All contacts with abnormal CXRs are referred for assessment.

16.6 Follow-up of contacts

All contacts identified to be free of tuberculosis infection are discharged from follow-up.

All contacts identified to be infected by the index case will be followed up with CXR surveillance for a period of 1½–2 years if they are unable to tolerate, or decline treatment for LTBI.

BCG vaccination

BCG vaccination is no longer routinely recommended for contacts of TB. Vaccination may be offered to contacts five years or less on demonstration of a second negative TST test 'at break of contact' if they are likely to travel to high-incidence countries for extended periods in the future.

(Refer to Chapter 9 BCG vaccination and the *Australian Immunisation Handbook* (http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home) for further information.)

Special categories

1. Neonates

This group is very susceptible to TB infection and progression to disease. It is important that neonates are appropriately managed by paediatric physicians with experience in treating TB. For a detailed account of the management of neonates whose mothers are under treatment for TB, refer to Section 13.5 Management of the newborn after delivery.

2. Children

All children under 5 years who are household contacts of a smear-positive case of pulmonary TB should be referred as a priority to an appropriate paediatric TB/ID clinic or physician experienced in the treatment of TB. Regardless of their TST status, these children, who are highly susceptible to progression to disease if infected, will be assessed and may be offered a primary course of preventive therapy.

All other children who demonstrate a positive TST result (see Table 2.1 Criteria for Tuberculin Positivity, by Risk Group (adapted from ATS/CDC, 2000)) should be referred to an appropriate paediatric TB/ID clinic or physician experienced in the treatment of TB.

CXRs will be performed at the time of appointment. (Refer to Chapter 12 Tuberculosis in children and adolescents.)

3. Pregnancy

A TST/IGRA test can be safely performed.

CXRs are withheld unless the woman is symptomatic, in which case referral is necessary.

CXR is offered following delivery. (Refer to Chapter 13 Tuberculosis and pregnancy.)

4. Immunocompromised contacts

In immunocompromised individuals, particularly those infected with HIV, sensitivity of both TST and IGRA is reduced, and either or both tests may be negative despite TB infection. Contacts are to be referred to their treating physician irrespective of their IGRA/TST reaction or CXR appearance.

5. Contacts of multidrug-resistant (MDR) cases

MDR-TB does not appear to be more virulent or infectious than TB that is susceptible to first-line anti-TB drugs, but the consequences of acquiring this form of infection and disease are far more serious. Contacts of cases with MDR disease are screened according to the same criteria as all other contacts. Referral and follow-up is also carried out according to the same criteria, but the duration of follow-up should be extended, up to five years subsequent to exposure. It is important that the treating physician is made aware of the drug susceptibility profile of the index case as soon as it becomes available. In addition, the contact's family doctor should be made aware of the seriousness of MDR-TB, and of the need to assess for presence of active disease whenever the contact presents with symptoms.

Further prospective studies are required to evaluate the effectiveness of various chemotherapeutic regimens directed at preventing disease amongst close contacts of MDR-TB. However, retrospective and observation reports from a variety of settings, including local Victorian data, consistently demonstrate substantial reduction in active disease amongst contacts treated with directed chemopreventative therapy. Such therapy is by definition not standardised, but typically involves the use of fluoroquinolones for prolonged durations. The Victorian TB Advisory Committee has formed a consensus view that, on current evidence, a regimen consisting of a nine-month course of moxifloxacin alone or combined with either ethambutol or pyrazinamide is appropriate for documented recent close contacts likely to have acquired MDR LTBI, provided the index isolate is susceptible to these agents. This should only be undertaken by a clinician expert in the management of TB, and in consultation with the Victorian Tuberculosis Program.

6. Large-scale contact investigations such as in a school, workplace, nursing home or prison

Although contact identification and investigation follow the same principles as general contact tracing, clients in these settings may be more vulnerable to infection or at increased risk for progression to disease. In addition, an index case in these settings will lead to increased family, staff and community anxiety and stress. Key messages to be communicated include the low communicability of TB, the lack of risk for contacts to transmit infection, and reassurance about standard public health policy to identify and investigate contacts for evidence of infection. Obtaining information on contacts from other agencies or organisations must be done in compliance with privacy laws; therefore, it may be necessary to utilise the powers under the *Public Health and Wellbeing Act 2008* and Regulations (2009).

7. Contacts on aircraft

Occasionally, contact tracing of airline passengers may be required. The risk of TB transmission is increased if:

- the patient was symptomatic at the time of travel
- sputum specimens are smear positive for acid-fast bacilli
- the flight had a duration of eight hours or more.

Passengers who travelled in the same row and two rows fore and aft of the index case should be advised by letter of their possible exposure to TB and offered appropriate testing. Letters are sent at 8–10 weeks after the flight to coincide with the optimum time for skin test conversion if infection has occurred. The same principles of contact investigation apply to airline contacts (see Chapter 14 Tuberculosis and air travel).

Refer to the CDNA *Revised guidelines for the follow-up of communicable diseases reported among travellers on aeroplanes* for the follow-up of communicable diseases reported among travellers on aeroplanes: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-cdna-gl-airtravlers.htm

8. Contact tracing in a hospital setting

Nosocomial transmission of TB does occur, particularly in cases where diagnosis is delayed. It is important that a high index of suspicion for TB is maintained, particularly in patients with respiratory symptoms and belonging to a high-risk group for TB; that is, overseas born from high-prevalence countries, immune-suppressed patients, the elderly (both Australian and overseas born) and so on. All suspected and active cases of TB must be placed in respiratory isolation and appropriate infection control measures implemented, including use of submicron or particulate filter masks for HCWs and surgical masks for patients during transport within the hospital.

In the event that staff and patients are exposed to an undiagnosed case of TB, appropriate contact tracing must be implemented. The hospital will assume responsibility for conducting the contact investigation for staff and inpatients, and will provide letters to those patients who have been discharged, informing them of their exposure to TB and arrangements for follow-up testing. In the event that patients deemed to be at risk of exposure are unable to be contacted for follow-up, details for such patients will be compiled by the hospital and forwarded to the Victorian Tuberculosis Program for assistance with arranging appropriate follow-up. Once completed, a copy of the results of the screening should be forwarded to the Victorian Tuberculosis Program so that they may be linked to the index case.

Extrapulmonary TB

Contact tracing in cases of extrapulmonary TB is undertaken for the following reasons:

- to identify a source case if the index case is a young child, for example, with miliary tuberculosis or TB meningitis
- if the contacts belong to a high-risk ethnic group, to identify previously infected persons who may benefit from treatment for LTBI.

Acronyms and Abbreviations

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-Guérin 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
DHHS	Department of Health & Human Services, Victoria
DMARS	disease-modifying anti-rheumatic drugs
DOTS	directly observed therapy short-course
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
HPC	high TB-prevalence country
id	intradermal
IFN	interferon
IGRA	interferon gamma release assays
IRIS	immune reconstitution inflammatory syndrome
IU	international unit
IV	intravenous
LTBI	latent tuberculosis infection
MAC	mycobacterium avium complex
MDR-TB	multidrug-resistant tuberculosis

MIRU/VNTR	mycobacterium interspersed repetitive unit/variable number of tandem repeat
MMR	measles mumps rubella vaccine
MMRV	measles mumps rubella varicella vaccine
MRI	magnetic resonance imaging
MRL	Mycobacterium Reference Laboratory
MTB	Mycobacterium tuberculosis
MTBC	Mycobacterium tuberculosis complex
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
PRP	personal respiratory protection
QFN-GIT	QuantiFERON® Gold-TB In-Tube test
R	rifampicin
RBT	rifabutin
RCT	randomised controlled trial
RDNS	Royal District Nursing Service
RIF	rifampicin
RPD	respiratory protective devices
SoNG	Series of National Guidelines
TB	tuberculosis
TBM	tuberculous meningitis
TNF	tumour necrosis factor
T-Spot	T-SPOT®.TB test
TST	tuberculin skin test
Tuberculin PPD	purified protein derivative (tuberculin)
WHO	World Health Organization
XDR-TB	extensively-drug resistant tuberculosis
Z	pyrazinamide
ZN	Ziehl-Neelsen